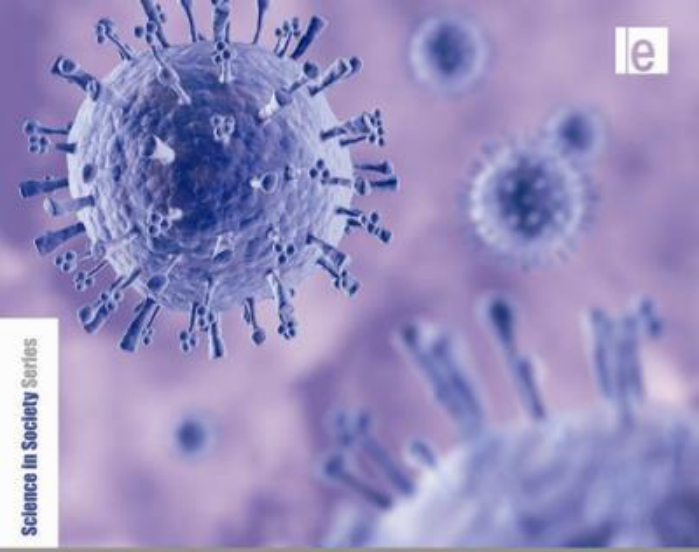

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LEARNING FROM PAST PANDEMICS

EDITED BY
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WITH JENNIFER GUNN

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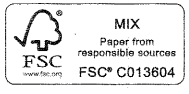

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Foreword

It is a great pleasure to introduce this collection on the comparative history of pandemic influenza for many reasons. Pandemic influenza has been of critical importance in human history. Particularly in light of the current H1N1 influenza pandemic, we are acutely aware of the spectre of 1918, the infamous 'Spanish' flu that killed more people than did combat during World War I. The impact of this pandemic was considerable, causing millions of deaths, precipitating both hunger and famine in certain parts of the world, wreaking political havoc and weakening certain states. It also altered national public health systems throughout the world. Virologists and epidemiologists have been warning us for several years that another global flu pandemic would strike. We are now confronting the H1N1 influenza pandemic, although pandemics – influenza or other – remain a threat at any time. And each pandemic unfolds in a different way. Nevertheless, past epidemics, particularly evaluated comparatively, can provide us with information on a range of ways that a future one might unfold, and it therefore remains important to reflect critically upon past pandemics as well as the present one, so as to prepare ourselves in the broadest possible ways for future epidemic events.

Much historical work has already been published about the 1918 influenza pandemic, including books by John Barry and Alfred Crosby, which reveals to us how this deadly pandemic unfolded. Other historians have examined local or national experiences of this pandemic and others, and are beginning to identify their longer-term consequences.

This collection by Giles-Vernick and Craddock is different: it is an interdisciplinary effort, bringing together social scientists, biological scientists and public health practitioners in order to think critically about influenza's past so as to develop plans to tackle future pandemics of influenza, but also of other infectious diseases. It seeks to bridge the gap between theory and practice, to begin a dialogue between the social sciences, sciences and public health about past experiences of influenza for future planning.

To be sure, we know that much has changed in the world since 1918, 1957 or even 1968. Yet we must mine historical knowledge of past epidemics in new ways

in order to deepen our understanding of them. It is important, I think, that we examine the political and economic dilemmas and decisions that guided attempts to manage these epidemics, and to investigate both the ethical implications of these decisions and the social responses to them. Such efforts will help us to revise current efforts under way, but also to prepare for the future.

Alice Dautry, Director General, Institut Pasteur
1 December 2009

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Jennifer Gunn made important intellectual contributions from the original conception of our project to the expanded form that it takes here. We are grateful for her wise insights, challenging questions and critical eye, not to mention her warm hospitality.

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And finally, we both thank our families for their unstinting support in the face of our late nights and trips away from home while we prepared the book.

List of Acronyms and Abbreviations

BSAC	British South Africa Company
BSE	bovine spongiform encephalopathy
CAFO	confined animal feedlot operations
CDC	American Centers for Disease Control
CIC	Interministerial Crisis Committee
CP	Charoen Pokphand
CPS	Commission of Public Safety
FAO	Food and Agriculture Organization
FDA	US Food and Drug Administration
FDI	foreign direct investment
FNRS	Fonds de la Recherche Scientifique
GISAID	Global Initiative on Sharing Avian Flu Data
GNRR	Great Northern Railroad
GSK	GlaxoSmithKline
H	hemagglutinen
IHR	International Health Regulations
InVS	Institut de Veille Sanitaire
IPR	intellectual property rights
MARD	Ministry of Agriculture and Rural Development (Vietnam)
MHSSA	Minnesota Historical Society and State Archives
N	neuraminidase
NIAID	National Institute for Allergies and Infectious Diseases
NAIs	neuraminidase inhibitors
OFFLU	FAO network on avian influenza
OIE	World Organisation for Animal Health
PloS	Public Library of Science
PSOE	Socialist Party of the Spanish Workers
RRP	Republican Radical Party (Barcelona)
SARS	severe acute respiratory syndrome
TRIPS	Trade Related Intellectual Property Agreements

TVE	township and village enterprises
UGT	Union General de Trabajadores
VNA	Vietnam News Agency
WHO	World Health Organization, UN
ZNA	Zimbabwe National Archives

Introduction

Susan Craddock and Tamara Giles-Vernick

Since the first cases appeared in California and Mexico in April 2009, swine flu has been exhaustively tracked across regions by public health and news organizations alike. By 11 July, the World Health Organization (WHO) declared the H1N1 outbreak a pandemic, the first one since the Hong Kong influenza outbreak of 1968. Conceding that further spread of the virus was 'inevitable', WHO Director General Margaret Chan stated that although the flu was moderate in severity, it transmitted easily from person to person and across regions, having already spread to at least 74 countries in a matter of 2 months (Chan, 2009; Cumming-Bruce and Jacobs, 2009). As of 30 August 2009, 254,206 cases and 2837 deaths had been reported from regional WHO offices. Although the first wave of H1N1 never went away entirely, the predicted second wave moved across the globe in the autumn of 2009, affecting most countries of the world, albeit unevenly. The WHO, the American Centers for Disease Control (CDC), the French Institut de Veille Sanitaire (InVS) and other national surveillance institutions stopped attempting to count individually confirmed cases of H1N1 because of the practical difficulties of doing so. But as of late December 2009, the WHO estimated that the pandemic had spread to 208 countries, with some 12,220 deaths (WHO 2009).

Before novel H1N1 occupied media and medical attention, H5N1 (avian influenza) was gaining notoriety as a virus predominantly found in birds in China and Southeast Asia, but which occasionally transmitted to humans with devastating results. Whereas H1N1 has proved to be easily transmitted between humans but relatively mild, H5N1 is the opposite. So far, adaptation of the virus for efficient human-to-human transmission has not happened, but if it does, public health officials are concerned that a virulent pandemic will result, with mortality rates not seen since the 1918–1919 influenza outbreak. The Chinese government warned in November 2009 of the dangers of a reassortment (mixing) of the avian H5N1 and novel H1N1 viruses, contending that the result could produce 'a disaster' (McIntyre, 2009).

The multilateral attention focused on these influenza viruses and the questions raised over their definition, transmission, virulence and containment provided

the impetus for this volume, and for our insistence on involving contributors from fields including virology, bioethics, medicine, public health and history. Namely, it is clear from H5N1, novel H1N1 and other recent outbreaks such as SARS that pandemics cause more than sickness, fear and confusion when they spread across regions. They mobilize public health surveillance networks, environmental studies, virological detective work, preparedness plans, laboratories and vaccine manufacturing plants. They also galvanize questions about who should get access to scarce medical resources, whether quarantine is necessary or effective, what constitutes vulnerability and how much individual freedoms should be sacrificed for the public good. Many of these questions have been raised for centuries in the midst of disease outbreaks, while others have been generated more recently by new technologies that enable greater understanding of each new virus or greater capacity for viral spread.

We approach this book with the premise that current and future epidemics can be better understood in their social, epidemiological, ecological and political entirety by careful examination of past influenza epidemics. Many public health analysts have called for more attention to previous pandemics for the lessons they might provide, and this book is a partial response to that call, but with caveats. We offer below a discussion of how we approach history, but a few quick points here are in order. First, we could not aim to be comprehensive in this book, but we sought to produce a volume combining the breadth and depth of perception gained from multiple analytical angles and multiple pandemics. Incorporating examinations of different influenza outbreaks allows specific attention to be paid to the numerous factors particular to each epidemic, but also to the issues cutting across time, geography and pathogen. As one of our contributors, the historian Ilana Löwy, suggests, comparative case studies demonstrate 'unexpected differences and/or surprising similarities', as well as elucidating complexities of response, understanding and decision-making that single site studies cannot provide (Löwy, 2007, pp466–467).

A related caveat is that both history and epidemics are complex and do not lend themselves to simple insights or prescriptive lessons. What Wallace et al (this volume) claim in explaining influenza in southern China today we extrapolate to all current and future influenza episodes, that they are 'neither effortlessly remade independent of history, nor enslaved to a static past'. The purpose of this book, then, is not to provide a roadmap for public health practitioners, a list of easy steps to follow for current and future preparedness plans or intervention measures. Such a list, like all simple how-to enumerations, would be detrimental in its simplicity and overgeneralization. It would also be a betrayal of the careful and nuanced insights of our contributors, and the more complicated relationship between history and the present, and histories of the present.

Instead, in the introduction that follows and in the conclusion, we outline points that we think are of critical importance in past and current epidemics, and

make connections not always obvious between social and economic factors and epidemic events. We also argue for particular areas that public health needs to target to mitigate effectively any future epidemic given longstanding histories of unequal burdens of suffering, and given the acceleration of population and livestock mobility, ecological change and pathogenic transfers often subsumed under the rubric of globalization.

History, multi-disciplinarity and public health

Using the analytical tools of history and of other disciplines simultaneously may seem somewhat contradictory, but history is not simply the purview of professional historians; it can cut across a range of disciplines that situate certain phenomena in terms of their past, present and future, and interpret change over time (Prakash, 1990; Tonkin, 1992). Contributors to this volume approach history very broadly, so that any development in the past, even recent, may be interpreted through an historical lens. Thus, the chapters by van der Werf and Hannoun (virology), Wallace, Bergmann, Hogerwerf and Gilbert (geography), Ali and Cassier (sociology) all reflect such concerns as much as those by contributors who are historians in this volume (Eyler, Rodríguez-Ocaña and Rasmussen).

Just what history can contribute to contemporary public health policymaking has been much disputed (Zylberman, 2009), but recently, Virginia Berridge suggested that history can:

> *offer a form of analysis which in its ability to segment and analyse the issues comprehensively and dispassionately over time is matched by no other discipline. Health policy specialists have pointed to failure to learn from experience as one of the main reasons for organizational failure in health... If evidence-based policy and evidence-based medicine are on the agenda, then history should be part of that process. Its ability to open up options is underdeveloped at the policy level. History can provide policymakers with great insight, interpretive richness, and a sophisticated understanding of the past.* (Berridge, 2008, p326)

This volume thus reexamines past pandemics in light of today's to afford critical insights into possible transmission patterns, experiences, mistakes and interventions that in turn could be useful in planning more effective responses to epidemics in the future.

There are significant limits, of course, to what history can offer to public health specialists and policymakers. We cannot make predictions based on our analyses of the past. Nor, as Patrick Zylberman reminds us, are we in the business of saving lives. Mobilizing the tools of virology, epidemiology, sociology and geography enable the authors in this volume to privilege particular questions that most

historians would not necessarily ask, nor be equipped to answer: What antigenic shifts have transpired in influenza viruses to produce new pandemic strains? In what ways have epidemiological tools changed over time? How have changing human activities and viruses interacted to produce multiple human-specific influenzas? In what ways did the AIDS epidemic and the threat of an avian influenza pandemic usher in a new era of conflict over intellectual property, drug patents and generics? This book raises questions about epidemiological, virological, environmental, social, economic and political changes that occurred during and after influenza pandemics in order to highlight the central dilemmas and successes or failures of past pandemic understandings and measures. It encourages reflection on the ways in which the past – while not predictive – might illuminate better the dilemmas and priorities embedded in public health decision making and implementation of particular pandemic interventions in the present.

Influenza – and in particular the 1918 Spanish influenza pandemic – has occupied a singular place in histories of infectious disease. The 1918 pandemic has generated a plethora of book- and article-length studies (Phillips, 1987; Patterson and Pyle, 1991; Davies, 2000; Afkhami, 2003; Kolata, 2001; Johnson and Mueller, 2002; Crosby, 2003; Phillips and Killingray, 2003; Barry, 2004; Johnson, 2006). Some of this scholarly interest can be directly traced to outbreaks of avian flu, and that interest intensified with the eruption of the novel H1N1 pandemic. More recently 1918 has become the comparative basis for the diverse aspects of the present novel H1N1 pandemic and of pandemic policymaking, partly because of similarities between the two viruses (see, for instance, Mathews et al; 2009; Stern et al, 2009). Zylberman (this volume) has observed that recollections of 1918 have an even longer history, having been revived as a historical comparison during the 1976 swine flu scare. Such comparisons require further interrogation: Why has 1918 so singularly served as the basis for comparative analysis and policymaking? Why not 1968, or another pandemic? More than one analyst has argued that 1918 has been used to mobilize political leaders and citizens to support and pay for pandemic preparedness (Michael Osterholm, pers. comm., 2006; Zylberman, 2009).

Viewed through the prism of a contemporary pandemic, 1918 rallies national and international public health authorities and politicians to demonstrate an effective response. It also appears to fan diffuse, and perhaps eschatological fears, to prompt criticism of failed government responses or of medical or public health expertise, or to elaborate stories of conspiracies about vaccination or the genesis of viruses. 1918 evokes dramatic images of widespread sickness and cataclysmic death, including famous photographs of makeshift military hospitals housing stricken soldiers, or descriptions of city morgues so overwhelmed by fatalities that the corpses of victims were piled on sidewalks (see Crosby, 2003; Barry, 2004). These images can produce fear among a wide array of constituencies. Several scholars in this volume have emphasized the role that fear has played and continues to play in pandemics. Some fear is productive, while other fears are not. Fear during past pandemics has been fruitful, for example, in generating new epidemiological and surveillance tools (Eyler, Hannoun); scientific innovation (van der Werf and Rasmussen); and social and political reform (Rodríguez-Ocaña, Guénel and Klingberg).

But 1918-induced fear also fits well into what Denis Duclos (2009) has described as a deep-seated, almost obsessive desire to live a secure existence amid the larger, contradictory forces of globalization with which international institutions, states and populations must contend. In Europe and North America, says Duclos, popular interpretations of the 2009 novel H1N1 influenza pandemic reflect these obsessions, and both state authorities and media respond to and feed such anxieties.

If we seek to demonstrate the usefulness of historical analysis of influenza pandemics for policymaking, a single, cataclysmic pandemic should never constitute the sole historical model on which to base pandemic preparedness. This collection highlights the questions, dilemmas and problems that cut across pandemics over time, including the race to understand new viruses as they emerge; epidemiological uncertainties about numbers of people affected, where and why; appropriate prophylaxis, containment and treatments; management, prioritization and distribution of scarce medical resources; continuity of basic economic and social functions and the prevention of massive economic losses. In this volume we acknowledge previous historical works that have examined epidemics comparatively (McNeill, 1976; Bourdelais, 2003), but extend this approach to scrutinize the continuities of pandemic responses over time.

Certain chapters in this collection do re-examine the 1918 pandemic (Rasmussen, Rodríguez-Ocaña, Giles-Vernick, Craddock, Gunn), but several chapters analyse past influenza epidemics whose mortality profiles differed considerably from that of 1918: 1889 (Rodríguez-Ocaña), 1957 (Eyler), 1968 (Hannoun), as well as various 21st-century epidemics (Ali, Cassier, Guénel and Klingberg). A few chapters (van der Werf, Wallace et al, Eyler) examine influenza epidemics over an extended time period, and nearly all chapters explore past pandemics in their own terms, but also in light of the 2009 novel H1N1 pandemic. None of the past epidemics achieved the scope and scale of the 1918 pandemic, but our contributors show that critical insights emerge nevertheless from examining even those epidemics that garnered less attention.

This volume also includes thematic analyses of epidemiological and scientific developments that are not moored to particular epidemic episodes, but are vital to understanding shifts over time of how epidemics are conceived as biological, epidemiological or social events (see particularly the contributions of Part 2). Focusing on a single pandemic threatens to elide efforts and developments that began with particular disease outbreaks, but which developed more slowly over decades in conjunction with changes in the scientific and political landscape.

By incorporating case studies from a wide range of geographic areas, including Barcelona, Vietnam, China, the rural Midwestern USA, colonial Zimbabwe and France, certain contributors show the interrelations between regional decisions and broader circulations of knowledge. When models of epidemic preparedness focus on one country or assume broad application of interventions across geographic regions, it becomes essential to highlight the variability across and within regions of epidemic experience, understanding and response.

Pandemic definitions, technologies and inequalities

Even the definition of pandemic can prove controversial, as evidenced during the first wave of novel H1N1 in spring 2009. By 12 June, the WHO declared novel influenza A/H1N1 a level-6 pandemic as defined by a virus with sustained community-level outbreak in at least two countries in one WHO region and at least one country in another WHO region (WHO, n.d.). One of the main debates emerging from this declaration was that the WHO's categorization of pandemic levels recognized only the degree of geographic spread, not the degree of severity. Yet a declaration of a level 6, or highest level pandemic in the WHO schemata, was a conscious step meant to galvanize multisectoral responses that could mitigate the social and economic impacts of the epidemic and initiate vaccine and pharmaceutical production. Some have questioned the wisdom of mobilizing extensive resources to intervene in an outbreak with the comparatively mild symptoms and relatively low mortality rates of the spring and fall waves of the 2009 H1N1 pandemic. At the same time, critics pointed out that the announcement of a level-6 pandemic by the world's leading public health organization inevitably led to panic among populations and governments alike and consequently to misguided actions. Egypt, for example, slaughtered thousands of pigs belonging to Coptic Christian minorities, despite admonitions that this measure was not epidemiologically justifiable; and USA lawmakers early on raised the spectre of tighter border controls with Mexico even though the lag time between infection and the onset of symptoms would have made this measure equally ineffective in stopping transmission (McNeil, 2009; Wong, 2009).

Other complications arise as well from attempting to define the parameters of any pandemic, as Chapter 7 by Hannoun demonstrates. In the 1968 influenza pandemic, accurate counts of morbidity and mortality were hindered by the very different modes of data collection that various governments had implemented, as well as the uneven presence of reliable diagnostic laboratories. Some regions simply did not have the capacity to isolate the virus to confirm cases, and many countries used substitute indicators such as work absenteeism or emergency room visits to supplement diagnostic confirmations. During the initial spring 2009 H1N1 outbreak, the WHO and several countries counted as official cases of influenza only those that were laboratory-confirmed. But they moved away from this designation when more cases appeared, because many individuals suffering from influenza were only mildly afflicted, and thus never visited a clinic but rather waited out the illness at home. The available diagnostic tests also proved labour-intensive and expensive. Moreover, many specimens collected were also found to have false positives or other quality problems (Reed et al, 2009). A team of CDC researchers and one Harvard researcher subsequently employed a probabilistic multiplier model to derive a more accurate assessment of influenza transmission; they estimated that the number of influenza cases during the first 4 months of the epidemic was more than 100 times the official estimate, or 5.7 million, with 1300 deaths, rather than the official 302 (Reed et al, 2009).

Definitions of pandemic do not stop with numbers and regional spread, however. The contributors to this volume make clear that the meaning of epidemics and what constitutes important questions about them can vary significantly, depending upon the discipline of the observer. For the virologist Sylvie van der Werf, explaining the virulence of different influenza viruses means studying the behaviour of viral mechanisms such as polymerase chains or surface proteins and ascertaining the role each or a combination have in regulating virulence. For the historian Patrick Zylberman, the conditions of pathogenic spread and virulence are determined by the convergence of factors such as war, mobilization of troops or collapsed economies. For Rob Wallace and his collaborators, 'perfect storm' conditions for a virulent influenza epidemic have emerged over thousands of years of linked Chinese human and viral histories that include transitions in agriculture, and duck and industrial stock breeding. John Eyler's chapter outlines epidemiologists' attempts since the 1918 pandemic to explain the variability of virulence in populations, finding significance in age, poverty or antibody production. Rather than attempt to reconcile these perspectives, we argue that our understandings of pandemic are made richer for their analytical divergence.

Despite continued debate over actual numbers of H1N1 cases, an unprecedented level of knowledge continues to evolve over the genealogy and structure of this and past influenza viruses. As van der Werf outlines in her chapter, advances in genotyping combined with coordination among various scientists from ornithology to veterinary to virology has meant the ability to determine the precise glycoproteins – that is the hemagglutinin (H) and neuraminidase (N) – characterizing each different influenza virus from the 1918 H1N1 virus to the 2009 novel influenza A/H1N1, and major influenza viruses in between. Van der Werf and Wallace and his collaborators (this volume) all suggest that one important part of better elucidation and intervention would focus on the role of the environment, in particular the precise avenues for reassortment of human, swine and avian viruses.

The stark contrast between scientific knowledge of influenza viruses and the continuing difficulties of counting the numbers of infected persons or achieving comprehensive intervention measures points to the contradiction brought out in

this volume, that scientific capacity to reveal the precise nature of a pathogen has advanced at the same time that public health measures to assess and intervene in pathogenic spread remain hindered by logistical, political and technological obstacles. This observation is not to suggest that scientific advances have no impact on public health interventions, but rather it highlights that interventions may come up against enormous complexities, even when scientific understanding has improved.Public health surveillance, for example, constitutes an area of significant gain but persistent roadblocks. As Ali describes in his chapter comparing SARS and H1N1, the Chinese government had the technological capacity to know relatively quickly that a new and potentially dangerous pathogen was causing deaths within its borders, but fearing political fallout, the government kept secret the initial cases of what turned out to be SARS. Once the WHO discovered the cases, it quickly galvanized interventions such as travel advisories that probably helped to stop further transmission of SARS across the globe. These measures, however, had adverse economic effects on affected countries, diminishing both tourist and business trade. As Heymann notes in his assessment of the SARS epidemic (2007), China's reluctance to alert the WHO about infectious cases within its borders prompted revisions to the existing International Health Regulations (IHR); such revisions shifted away from sole reliance on individual governments to conduct surveillance, and towards a global surveillance conducted through multiple sources of notification, 'even though such an action represents a potential infringement on national sovereignty' (Heymann, 2007, p43).

Current public health surveillance networks thus continue to improve, in terms of their technological capacity to speed notification at multiple geographic scales, and in their ability to increase on-the-ground sources of alert and infectious case confirmation. Systems such as the Global Outbreak Alert and Response Network, the European Centre for Disease Prevention and Control, Canada's Global Public Health Intelligence Network, France's InVS and the US Department of Defense-controlled Global Emerging Infections System maintain constant vigilance for any cases that warrant further inspection and for new or expanded outbreaks. Yet these systems are only as good as their technological coverage, which means that sizeable areas of the globe do not possess effective surveillance networks, including much of Africa and parts of Asia (Ortu et al, 2008; Oshitani et al, 2008). These gaps are especially worrisome, given that the development of influenza viruses often occurs in the same regions that lack sufficient surveillance capabilities (Butler, 2009a).

Other areas of surveillance transcending technological limitations also deserve more attention than they have thus far received. New modes of surveillance monitor possible outbreaks by following increased purchases of pharmaceuticals like Ibuprofen, and they raise questions about how intrusive surveillance should be. Is it appropriate, for instance, to track people's everyday activities? These new modes of surveillance invite scrutiny into the types of information that

surveillance systems glean from tracking consumption patterns, how useful or accurate that information is (King, 2008), and the multiple purposes to which it can be put. Bronwyn Parry has suggested that some modes of surveillance are collecting increasingly person-specific data, including DNA, opening up opportunities for other, deeply problematic uses. In the UK, for instance, biodatabases not only collect data to determine disease patterns, but also to determine genetic bases of criminal activity among minority populations (Parry, forthcoming).

Beyond current technological limitations and ethical questions of public health surveillance, concerns linger over the interventions that are mobilized as a result of surveillance data, and their consequence for affected countries. One such consequence can be economic, as in the case of SARS, when the WHO issued travel advisories warning travellers not to visit affected countries. And while these affected countries protested against these advisories, public health authorities have generally acknowledged that the WHO's actions were well-founded. But there have also been cases in which the most severe economic blow results not from well-advised public health interventions, but from individual governments' measures. Such was the case during the bovine spongiform encephalopathy (BSE) outbreak in the UK, when many countries banned imports of meat and meat products from the UK, even though the British government had taken extensive measures to redress the problem. The economic fallout for the UK was substantial, and probably unnecessary (Heymann, 2007). Similarly, Guénel and Klingberg explain that in the case of H5N1 (this volume), the Vietnamese government supported industrial chicken farming but cracked down on small family poultry production, even after it became apparent that industrial production was a greater incubator of H5N1. Financial incentives for maintaining the large-scale poultry industry and media encouragement of 'safe' supermarket versus local market shopping proved compelling, and rural families lost their livelihoods.

The politics of surveillance and intervention thus go well beyond pitting public health against individual rights, a concern often highlighted in public health analyses. While robust public health surveillance systems and well-considered global policies are critical, analysts have paid less attention to the social and economic consequences of surveillance and public health interventions for countries at the centre of epidemic outbreaks. Some of these consequences remain impossible to predict or to prevent, since no international public health agency can intervene in individual countries' decisions about trade, industry or national border closings. But as multiple contributions to this volume demonstrate (Rodríguez-Ocaña, Guénel and Klingberg, Giles-Vernick, Craddock and Gunn), many different factors, and not simply epidemiological ones, can shape both the interventions and their wide-ranging consequences.

Even scientific advances made during recent epidemics have come with serious limitations. Precise elucidation of the viral or other pathogenic mechanisms of reproduction have opened the way for research into better pharmaceuticals or

vaccines to prevent that reproduction. Yet these efforts have encountered stumbling blocks in manufacturing and distribution. Vaccines have been particularly beset by obstacles at multiple levels, including production methods. In the 2009 pandemic, it became evident that vaccine production was running 30 per cent below prediction, in part because the H1N1 virus was growing so slowly in fertilized eggs (Pollack and McNeil, 2009). Obtaining more fertilized eggs, however, can also pose problems. One USA company, Protein Sciences, was awarded a contract to develop a vaccine using a newer method that infected caterpillar cells with a baculovirus carrying genetic material from the influenza virus (Medicine and Health, 2009). Protein Sciences managed to develop an H1N1 vaccine much more rapidly, but ultimately failed to win FDA approval for its new technology (Fox, 2009). As some critics have pointed out, the more efficient method of vaccine production might have been the norm had governments invested in new vaccine technologies earlier. As it was, once the pandemic broke out, there was 'no choice, zero choice but to go with the reliable but fragile egg-based technology', as Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases, conceded (Pollack and McNeil, 2009, p1).

Equitable distribution of vaccines and antivirals is another problem only partially related to snags in supplies. One facet of this problem is the nature of vaccine contracts. By summer 2009, news sources began to predict that government contracts with vaccine manufacturers could be abrogated if the pandemic proved particularly virulent. Wealthy governments of countries where vaccine producers were headquartered, in other words, could respond to intense political pressure to protect their own citizens during a severe epidemic regardless of their pharmaceutical companies' long-standing contracts with other nations (Parekh, 2009). Though the 2009 H1N1 pandemic did not provoke such a situation, it revealed the vulnerabilities of even high-income countries such as the USA and the UK, which manufacture only 20 per cent and 0 per cent of their vaccines, respectively. A critical question left uninterrogated by the media, however, was why the USA and the UK have so little vaccine manufacturing capacity. This question is a complex one, but in part, the pharmaceutical industries accord low priority to vaccines, because in comparison to blockbuster drugs, vaccines offer far less promise of lucrative financial returns. They also increase liability risks: fast-mutating influenza viruses can increase the potential for a mismatch of vaccine to virus, thus rendering a vaccine obsolete; and tainted or weakened batches or slow production, not to mention government cancellations of manufacturing contracts when demand for vaccines is weak, can also mean financial loss to the manufacturer. Vaccine manufacturers now mitigate liability by shifting the risk of financial loss onto countries purchasing the vaccine (Enserink, 2009), a move that disadvantages poor countries disproportionately.

Liability, however, is just one facet of the most critical problem plaguing vaccine (and drug) production and distribution: the insufficiency – or outright lack – of supplies for poor countries. Martin Enserink has noted in a recent *Science* review that years of negotiation among higher income countries have done little to resolve the inequitable distribution of vaccines and drugs (Enserink, 2009, p782). Under the current system, poor countries rely upon donations from several sources. GlaxoSmithKline (GSK) has pledged 50 million doses of its H1N1 vaccine, while Sanofi Pasteur has pledged 100 million. The USA and Australian governments have committed 10 per cent of their own supplies, while other countries have made more vague promises. Given the issues of delayed production and delivery delineated above, however, donations from countries can be tenuous in the details and degree of commitment. The USA, for example, gave conflicting statements in Fall of 2009 about when it would donate its 25 million doses of vaccine, and whether it would even follow through with its promise because of delays in obtaining sufficient supplies for its own citizens (Enserink, 2009). The World Health Organization orchestrates the distribution of donations that do materialize, but as of March 2010 only 180 million doses had been procured and shipments had just begun to 17 low-income countries out of the 95 countries requesting vaccine donations. As the WHO spokesman Gregory Hartle indicated, there would be enough vaccines for each country to cover approximately 10 per cent of their populations (Schlein 2010; Enserink, 2009). In contrast, France, the UK and Japan – having ordered enough vaccines from GlaxoSmithKline, Sanofi Pasteur and Baxter to cover their entire populations – ended up cancelling millions of doses because of the mildness of the influenza pandemic, and because significant proportions of their populations refused vaccination due to safety concerns (Reuters 23 March 2010; Kyodo News 26 March 2010; UK Department of Health Bulletin 6 April 2010). The USA in turn, according to a recent CDC report, had only administered 91 million doses out of 229 million ordered, with some speculation that over 70 million doses would eventually go to waste (Roos 2010).

Reasons for the persistence of such remarkable inequities of vaccine and antiviral distribution need further scrutiny. Critiques of current donation systems are needed, but our historical analyses also reveal that they miss the mark. It is not that the donation system should be improved; rather, we need to ask why poor countries remain dependent upon the largesse of other countries or companies for essential treatments. One reason can be found in the role of recent global regulatory mechanisms that arguably have been instrumental in producing and maintaining inequities in the distribution of most new pharmaceuticals. As Maurice Cassier discusses in this volume, pharmaceutical production is governed by global treaties regulating the global reach and duration of intellectual property rights, or IPR. Cassier notes that the current system is 'saturated with patents and material transfer agreements'. As a result, most poor countries during current epidemics cannot afford to meet their populations' needs for vaccines and medications, nor secure advance vaccine contracts. At the same time, middle-income countries like

India, Brazil and Thailand with robust pharmaceutical sectors engaged in generic production have sometimes lost the rights to manufacture generic drugs such as antivirals, even when they are in short supply.

Although pharmaceutical companies need guarantees on the return of their investments in new pharmaceuticals, Cassier and many others argue compellingly for greater flexibility in IPR arrangements. The AIDS epidemic first made especially visible the dire need for valuing human lives when negotiating pharmaceutical manufacturing agreements, even while respecting pharmaceutical industry profit. The 2009 H1N1 pandemic was relatively mild, but in the event of a much more virulent influenza pandemic, the stakes for more equitable distribution of treatments will be very high.

Disproportionate loss of lives in poor countries is the most important potential consequence in the event of failing to address this critical issue. David Heymann, former deputy head of the WHO, suggested another when he stated that 'an acute pandemic with high mortality and no vaccine in developing nations, and vaccine in industrialized countries, could cause various scenarios, and one of those could be an extreme destabilization of global security' (quoted in Bennett, 2009, p1). Protest against unfair intellectual property arrangements also comes in many guises, as evidenced by Indonesia's recent refusal to provide samples of the more virulent H5N1 virus to pharmaceutical companies. Indonesia understandably came under criticism for its actions, since quick genetic sequencing of viruses such as H5N1 and posting this information on the Global Initiative on Sharing Avian Influenza Data database can assist virologists around the world (Butler, 2009b). Yet it is curious that equal criticism was not aimed at the pharmaceutical industry's intractable focus on profiting from a virus at the expense of global health. If the goal is to develop and implement more effective responses to pandemics, then governments and global agencies, including the WHO, need to set parameters on the powerful financial and political mechanisms that enable some people to gain more effective treatment than others. Addressing the United Nations Global Assembly on 4 May 2009, Margaret Chan, Director General of WHO, stated that 'it is my job to do whatever is possible to ensure that developing countries are not left without protection' (quoted in Enserink 2009, p782). Renegotiating intellectual property rights would be a critical step in fulfilling this promise.

Inequalities do not just refract along north–south lines, however. In the H1N1 pandemic, as with all epidemics, some groups suffered disproportionate burdens of illness, even in high-income countries. Many countries do not gather their epidemiological data by ethnic or economic category, but those that do consistently show significantly higher rates of hospitalization and death among minority groups. One study analysed H1N1 morbidity and mortality data from Australia, New Zealand and Canada and found a three-to-sixfold increased risk of developing severe disease and of dying among indigenous populations (La Ruche et al, 2009). An American multidisciplinary workgroup, responding to this disturbing finding and the inadequacy of comparable USA data, compiled available surveillance data from 12 participating states in the USA. Their results showed mortality rates four times higher among American Indian and Alaska Natives than any other group combined (MMWR, 2009). A smaller study conducted on people hospitalized for swine flu in Anchorage, Alaska, found similar results: mortality rates among Alaska Natives were four and a half times the rates for whites (Shinohara, 2009). Another large-scale study showed a 35 per cent hospitalization rate for African Americans across 13 metropolitan areas in 10 states during the first wave of the H1N1 epidemic, even though African Americans represented only 16 per cent of the population in the study area (CDC, 2009).

Virtually all these studies acknowledge that the reasons for these disparities are unknown, but they offer similar speculations about possible explanations. First, most people experiencing more severe symptoms of the H1N1 flu or death have underlying conditions such as asthma, diabetes, obesity and chronic obstructive pulmonary disease (La Ruche et al, 2009). Many indigenous populations have higher than average rates of these conditions, suggesting an association of chronic illness with higher H1N1 risk. Poverty, crowded living conditions and suboptimal housing, followed by less access to health care round out the list of potential associations.

These suggestions do help to explain disturbing disparities in morbidity and mortality rates among indigenous populations during the current epidemic. The problem is that most studies examining ethnic-based discrepancies in disease vulnerability and outcome do not move beyond these suggestive associations. To do so would require, first of all, greater resources allocated for in-depth and large-scale studies that could elucidate the particular ways in which such factors as poverty or access to care affect influenza outcome. Even if such studies obtained funding, the thornier problem is that high rates of chronic illness, poverty, access to care, and the added factors of histories of institutionalized racism and continued modes of discrimination, do not have short-term solutions. They have developed over long periods of time and indicate a reciprocal relationship between social, political and biomedical factors (see Duster, 2003). Many factors, including poverty and substandard housing, are traditionally outside the purview of public health interventions, even though they have long since been associated with many infectious and noninfectious diseases.

This is precisely where historical studies may assist our reflections, since they sometimes reveal more readily the effects of poverty and oppression on infectious disease outcomes. During the 1918 pandemic in colonial Zimbabwe (see Giles-Vernick, Craddock and Gunn), for example, fraught relations between European and African were more visible and racialized epidemiologies more blatantly articulated. Finding higher mortality rates among Africans was not surprising, though, given labour conditions in the mines and lack of access to medical care in rural areas. A benefit of examining historical case studies that illuminate the broader

social and political contexts in which epidemiological and public health knowledge operates is that this can provoke reflection about current contexts of epidemiological understanding. More particularly, it shows that tackling the problem of discrepant illness and mortality rates among marginalized populations during epidemics does not just require better housing and health care. It also demands a better understanding of past and present ways in which discrimination has shaped the social, political and economic lives of the poor, and even informed epidemiological understandings.

Assessing impacts

Just as defining a pandemic and counting total numbers of people affected are difficult endeavours, so too is assessing the impact of a pandemic on entire populations. By most accounts, the influenza A/H1N1 2009 pandemic was mild relative to influenza pandemics of the 20th century. By the WHO's estimates, around 16,000 laboratory-confirmed deaths resulted from influenza A/H1N1 as of late February 2010. This statistic makes the 2009 pandemic far less severe than the previous three influenza epidemics of 1968, 1957 or 1918, or even than most seasonal flu epidemics as noted by Viboud and colleagues (2010). Yet Viboud et al make a compelling argument that mortality rates across pandemics are not effective measures of impact. First, they argue, statistics for the 2009 pandemic are an underestimation of all influenza-related deaths, and point out that mortality estimates for historic pandemics were based on attribution of excess all-cause mortality for the duration of the pandemic and are thus much more inclusive. But Viboud and colleagues also argue that mortality statistics alone cannot account for the greater impact of a pandemic that primarily affected the young: only the 1918 pandemic had a lower mean age of death than the 2009 pandemic, 27 years versus 37, respectively. Because a spike in deaths of young adults in the prime of economic life has much broader impact on society, Viboud et al argue that a calculation based on Years of Life Lost (YLL) is a more accurate assessment of pandemic impact. Using this measure, the impact of the 2009 epidemic more closely resembled that of the 1968 epidemic (Viboud et al 2010).

As the discussion of vaccines above suggests, accurate assessments of pandemic impact are a vital part of public health intervention given the association of vaccine acceptance and perception of pandemic severity. In one French study, researchers found that one reason for low vaccination rates among survey respondents was a disconnect between everyday experience of the pandemic and health messages that heightened perceptions of risk. Another important factor was whether primary care physicians recommended the vaccine (Schwarzinger et al 2010). In virtually all of the examples of high vaccine rejection rates, concerns about safety were also central (Quinn et al 2009; Sypsa 2009). How to communicate a vaccine's safety to a national population has no easy answers, particularly in the

context of beliefs (however erroneous) that childhood vaccines cause autism, and memories of past vaccine debacles such as the 1976 influenza vaccine and its link to Guillain-Barre Syndrome. In the latter instance, mass vaccination was recommended before the severity of the 1976 influenza could be assessed, as health officials in the USA chose to move ahead and be seen as responsible rather than adopt a wait-and-see stance. One health official's suggestion to stockpile vaccines as a contingency plan was thus rejected. As Andrew Lakoff notes, "this type of 'preparedness' measure was not at this stage, part of the tool kit of public health" (2008, 41). Better tools for assessing impact and tracking the direction of influenza viruses helps circumvent repeats of the 1976 mistake, but adopting the right balance of risk communication to populations in order to encourage acceptance of new vaccines clearly remains difficult to achieve.

Organization of this volume

This collection is organized around three broad thematic sections, accompanied by additional chapters that frame our historical and contemporary meditations on influenza pandemics in a larger context. Harris Ali opens the volume by situating influenza and other infectious diseases in the broader historical context of globalization. Framing pandemics as the convergence and interaction of biophysical and sociopolitical factors, Ali argues that contemporary globalization has probably accelerated the mobility of pathogens, ushering in a 'transformative epoch in the emergence of infectious disease'.

The first section of the book tackles the 1918 pandemic, but from new vantage points. Esteban Rodríguez-Ocaña's chapter focuses on two influenza pandemics in a single site, the city of Barcelona. He compares the epidemiology, scientific knowledge of, public-health approaches and popular responses to the 1889 and 1918 pandemics. His analysis illustrates beautifully that pandemics are not simply driven by the nature of the virus itself, but that the confluence of political, social and economic factors can profoundly shape the trajectory of an epidemic. Moreover, his comparison of Barcelona in 1889 and 1918 reveals the enormous creative impulses that a pandemic can generate, spurring social reform and new biomedical thinking. Anne Rasmussen's elegant analysis examines the intellectual changes in biomedical knowledge and the recognition of influenza as a public-health problem that the 1918 pandemic in France generated. Rasmussen situates her investigation in the context of World War I, and she shows that challenges in managing the widespread morbidity and high mortality created significant conflict between the Ministries of War and of the Interior. In the post-pandemic period, however, these conflicts spurred major institutional reorganizations, and particularly the development of the Ministry of Hygiene, Aid and Social Pensions. The pandemic generated substantial disarray in the biomedical sciences, but it also

provoked a shift away from monocausal explanations of disease towards an embrace of a multicausal framework that incorporated both pathogenic agents and environmental influences. The two extended commentaries at the end of the chapter underscore the limits of historical analysis of influenza pandemics. Patrick Zylberman evaluates the place of 1918 in the 1976 swine flu scare, warning against the pitfalls of false historical analogies. We should never mistake likenesses for likelihoods, and 2009, he has observed, 'is not 1918'. Ilana Löwy tackles the very difficulties that until a few decades ago impeded historical analyses of pandemics. She contends that it was difficult to produce 'constructive' histories of 1918 when this catastrophe so fundamentally questioned the narrative that biomedical and other health professionals had created for themselves, of continually expanding knowledge and capacities to intervene effectively in epidemics.

The book's second section primarily examines the changing virology and epidemiology of influenza epidemics over the 20th century, but within the historical context of dynamic human–viral–animal interactions. Geographers Rob Wallace and Luke Bergmann and their collaborators Lenny Hogerwerf and Marius Gilbert open this section with a complex and compelling analysis about why southern China constitutes such an important global source of human influenza viruses, and the role of multinational agribusiness in driving the development and global transmission of influenzas. For Wallace and his collaborators, the answer lies partly in long-term and recent transformations in southern China's agro-ecology: the millennia-long histories of poultry domestication and agricultural practices provided the 'crucial ingredients' for more recent influenza evolution, which in turn has developed rapidly since the 1970s with economic liberalization and the massive expansion of commercial poultry production. Recent economic crises ('the financial flu') have also geographically expanded and intensified poultry exports, and at the same time have reduced measures to protect animal health. Wallace et al hypothesize that since World War II, 'influenza may be entering a new global context and so a new phase. In influenza's Industrial Revolution, billions of livestock monoculture are now pressed up against each other, an effort for which humanity has employed itself as a major contractor.'

Within this broad historical scope, Sylvie van der Werf's chapter offers us a historical analysis of the changes that influenza viruses underwent over the 20th century. Specifically, along with analyses of H5N1 and the more recent novel H1N1 viruses, she examines the changes that transpired to create influenza pandemics in 1918, 1957 and 1968, and she lucidly explores what made these viruses so pathogenic. Paralleling part of van der Werf's historical scope, John Eyler traces the transformation in epidemiological tools from 1918 until the 1957 pandemic, a transformation catalysed by the unevenness of descriptive epidemiological analyses of mortality during the 1918 pandemic.

Eyler focuses on Thomas Francis's work to develop clinical epidemiology, an innovative approach that shifted focus from the 'herd to the individual', building

on developments in virology to isolate the viral agent of influenza and to create new tools to isolate a virus and measure antibody titers against it. Clinical epidemiology, Eyler explains, reflected a radical shift in the field, by bringing 'the laboratory to the individual', and measuring human antibodies, rather than reported deaths or illnesses, as earlier epidemiologists had done. And finally, Claude Hannoun's chapter takes up where Eyler leaves off, with an investigation of the 1968 pandemic. Despite the developments in clinical epidemiology that Eyler describes, epidemiologists remained puzzled both by the 1968 pandemic's uneven global transmission and its highly variable severity among geographic regions. Hannoun also signals the inadequacy of surveillance systems in 1968, one of many measures that have been further developed since then. Frédéric Keck's extended comment reflects upon the diverse ways in which the old and new coexist in histories of epidemiology and of influenza viruses themselves.

The final section of the book examines relations between governments, non-governmental organizations and public health management of pandemics and epidemic threats. These chapters all reveal the ways in which national government management of pandemic and epidemic threats are created in engagement with non-governmental institutions and organizations. Giles-Vernick, Craddock and Gunn open this section by returning to the 1918 pandemic, but this time with a comparative analysis of the implementation and response to containment measures in two rural regions: the upper Midwestern United States and colonial Zimbabwe. These rural areas suffered from a paucity of health-care personnel and resources, forcing state authorities to rely on a range of nongovernmental organizations. In the face of a dearth of knowledge about influenza's aetiology or transmission, and a shortfall of health-care resources, authorities mobilized epidemiological certainty to justify social distancing measures, but also to respond to particular economic, social or political pressures, to placate a doubtful and frightened public, or even to demonstrate that they were doing something even when they recognized that little could be done.

Maurice Cassier's chapter shifts our sights to a more recent era in which avian influenza has emerged as a pandemic threat, and to the national interests and global debates around intellectual property rights. Cassier's insightful piece traces the recent developments of increasing tensions around intellectual property rights to pharmaceuticals and vaccines. These tensions come from multiple sources, including major pharmaceutical companies, manufacturers of generic drugs, but also states like Indonesia, which supply viral samples and seek to gain a financial stake in the revenues generated from the production of influenza pandemic vaccines and antivirals. And finally, Annick Guénel and Sylvia Klingberg explore in a fascinating chapter the development of Vietnam's national avian influenza control strategy. The government's strategy, they argue, was shaped by global influenza governance, which itself was defined by three international agencies: the World Health Organization, the Food and Agriculture Organization of the

United Nations (FAO), and the World Organisation for Animal Health (OIE). But they also document the contributions of nongovernmental institutions, including the Vietnamese press and commercial poultry producers.

Finally, the concluding comments by François Bricaire, Jean-Marie Cohen, Jean-Claude Desenclos and Pierre-Dominique Lansard are excerpts of their comments concerning some of the presentations at a spring 2008 Institut Pasteur workshop on the history of influenza pandemics, but in some cases also reflect the authors' more recent observations. We have included them here for several reasons. First, they reflect the priorities and concerns of practitioners who are currently dealing with the challenges of the H1N1 influenza pandemic. They also touch upon valuable questions that individual chapters do not address: the continuity of key economic and social activities; a shift in defining the public health agenda as safeguarding and ameliorating the health of all people toward one in which health security is its primary objective; the double-edged role of media communications during a pandemic; and the phenomenon of post-pandemic amnesia – the process of forgetting that seems to take hold after a pandemic has passed.

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Globalized Complexity and the Microbial Traffic of New and Emerging Infectious Disease Threats

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Human-induced environmental shocks – overseas tourism, wetland destruction, a corporate 'Livestock Revolution', and a Third World urbanization with the attendant growth of mega slums – are responsible for turning influenza's extraordinary Darwinian mutability into one of the most dangerous biological forces on our besieged planet.

Mike Davis (2005)

Over the relatively short span of a quarter of a century, the world appears to have witnessed the proliferation of an unusually large number of what are referred to as 'new and emerging diseases' – that is, infectious diseases that are newly appearing in a population or that have been known for some time but are rapidly increasing in incidence or in geographic range (Morse, 1995). Examples of these are numerous and include HIV-AIDS, SARS, *E. coli* 0157:H7, *Clostridium difficile*, West Nile virus, lyme disease, antibiotic-resistant tuberculosis, the ebola virus and avian influenza (Garrett, 1994; Drexler, 2003; Levy and Fischetti, 2003; Nikiforuk, 2006). In this chapter, using SARS and influenza A/H1N1 (Swine flu) as illustrative examples, I examine through the lens of complexity theory the question of how historically specific processes related to intensified globalization have influenced the emergence and spread of new diseases. As will be discussed, the complexity perspective offers a conceptual framework that is especially well-suited for the analysis of the multiple social and ecological aspects of globalization associated with the contemporary origins and responses to pandemics.

Historical transitions and microbial traffic

A. J. McMichael (2001) has documented how significant changes in the relationship between human beings and the environment at particular junctures in history were accompanied by the concomitant rise of certain types of infectious diseases.

The first such shift involved a change in settlement patterns 10,000 years ago as hunter-gatherers adapted to agrarian-village living based on herded food and agriculture. This shift created new ecological opportunities for the spread of disease as it enabled countless novel strains of bacteria/viruses to make the jump from domesticated herd animals and rodents to relatively stationary human beings. The origin of many diseases including smallpox, measles, tuberculosis, leprosy, influenza, the common cold, malaria, dengue and bubonic plague could be traced to this period (McMichael, 2001). During the time span of the past 1000 to 2500 years, increased trade, travel and military movement led to a new phase in disease emergence. Examples here include the spread of smallpox and measles from the Indian subcontinent to Europe via Roman Empire troops returning from settling unrest in Syria in AD 2; trade along the Silk Route that subsequently spread these diseases from Europe to China; and the introduction of the bubonic plague to 14th-century Europe as the caravans and armies of the Mongol Empire entered the continent through the Black Sea. The colonialist period spanning the 17th–19th centuries represented a third major shift in disease spread, particularly in relation to the transoceanic spread of disease via European ships. McMichael (2001) concludes by speculating that we may be entering a fourth transitional period defined by globalization, as evidenced through dramatic increases in the volume and speed of human mobility, changes in food production practices and newer medical techniques, all of which have implications for disease emergence.

It is readily apparent that changes in the flow of individuals and pathogens are key aspects of disease emergence no matter the epoch under consideration. This emphasis is captured by the notion of 'microbial traffic' proposed initially by Morse (1993) and refers to the mobility of a pathogen and how that will vary according to characteristics associated with cross-species transfer, pathogenic evolution (including changes in the structure and immunogenicity of earlier strains), spatial diffusion and changes in the human–environment relationship (Mayer, 2000). In what follows, using the lens of complexity theory, I will refer to the above-mentioned dimensions of microbial traffic to make the case that globalization may indeed represent another transformative epoch in the emergence of infectious disease.

Globalization and microbial traffic globalization is defined in various ways (Held et al, 2002) but a fundamental aspect of most definitions is that of time-space compression (Giddens, 1990; Harvey, 2005). Time-space compression refers to the idea that, largely because of modern technologies, there has been a dramatic increase in the speed at which the movement of people, money, images and information occurs, thus resulting in situational circumstances in which distance is not as insurmountable or as significant a barrier as it once was in the past. Time-space compression has some obvious implications for the spread of disease. Notably, the effects become evident when considering the time horizons associated with air travel and disease incubation (i.e. the period between infection

and symptom onset). Thus, the 2–7 day incubation period of SARS and a similar incubation period for Influenza A/H1N1 (Picard, 2009c; Tuite 2009), has meant that those infected could easily complete a transcontinental flight before their symptoms developed, thereby increasing the potential for pandemic spread overall.

The enhanced and accelerated mobility of pathogens has also meant that a 'reterritorialization' of risk has occurred leading to the problematization of traditional territorially based strategies of disease control in which it was assumed that pathogens were biologically stationary targets that could be geographically sequestered (Garrett, 1996). This territorial notion of disease has immediate political and social implications for the manner in which disease spread is conceptualized by both the general public and the elites. It is in this context that King (2002) notes that the history of infectious disease control is very much influenced by the legacy of colonialism and territorialism in which the colonizers sought to protect themselves from disease through the creation of administratively cohesive and geographically bounded regimes. Yet, as we shall see, the rapid spread of SARS and Influenza A/H1N1 worldwide has dramatically demonstrated how the assumptions of territoriality no longer hold in an increasingly interconnected and globalizing world, despite response strategies that to some extent are still informed by territorializing assumptions. The highly mobile nature of new and emerging diseases, coupled with the advent of qualitatively different types of interactions between humans and animals have contributed to the emergence of pandemic as a unique and complex phenomenon distinct to our historical epoch – a distinctiveness which, as we shall see, is associated with changes in the scale and intensity of economic globalization. The analysis of contemporary pandemics therefore requires new tools, particularly those that emphasize the contingent and multifactorial causes of disease. In this light, the recent work in complexity theory may prove to be a useful starting point in the analysis of pandemics (Ali and Keil, 2007; Ali, 2008).

Complexity theory is a systems perspective that emphasizes the role of such features as: punctuated equilibrium, non-linearity, emergence, feedback loops and tipping points in the development of phenomena. It is of interest to us here because it enables a conceptualization of pandemic in terms of the interdependence of biophysical *and* sociopolitical factors, thus avoiding a tendency towards a narrowly defined essentialist stance that overemphasizes at either extreme the biological or the social. Furthermore, analysing pandemics through the complexity perspective may help us acquire a more critical position by directing analytical attention to the questions of how and why alterations in microbial traffic come about through human-induced (and therefore politically based) changes in society and the environment. For example, in considering the *longue durée*, we see that periods of social and economic stability are interrupted by changes in the relationship between human beings and the environment that dramatically alter the existent microbial traffic pattern. In this sense, the periods of stability interspersed with changes in microbial traffic patterns, some of which result in epidemics, may be thought of in terms of a series of punctuated equilibria. What is perhaps alarming is how, over the last few decades, the periods of relative calm and stability between the periodic changes in microbial traffic have shortened considerably. Thus, over the last decade alone we have faced a barrage of new and emerging diseases such as SARS, avian flu and influenza A/H1N1. Second, the extent to which the microbial traffic pattern now involves a global dimension is noteworthy.

To address the question of why in even greater detail than has been employed up until this point, it is useful to consider the notions of non-linearity and tipping points. Non-linearity refers to how small changes in a system may lead to sudden and dramatically disproportionate shifts, usually triggered by exceeding some critical parameter or tipping point. The tipping points represents the dramatic moment in an epidemic when everything can change all at once (Gladwell, 2002).[1] Often it is only a relatively minor change in the external environment that can have an unusually high and disproportionate impact on the way a biological and social system functions (Gladwell, 2002). In the case of SARS, for example, a tipping point in the pandemic spread occurred when an infected physician from Guangzhou stayed at the Metropole Hotel in Hong Kong, inadvertantly initiating the simultaneous spread of the disease to different global cities across the world.[2] The suddenness of the unknown diseases' arrival meant that hospital staff in the various affected cities were unprepared to protect themselves. Consequently, during these early stages, a positive feedback loop was established in which those infected would lead to even more becoming infected – an increase defined as multiplicatively geometric rather than incremental linear/arithmetic.

Another tipping point to consider in relation to pandemics involves the point at which the virus has evolved to such an extent that it is able to survive within a human host and then be transmitted between human hosts. During times of stability, the viruses which affect humans tend to evolve relatively slowly in a process referred to as *antigenic drift*. This leads to the eventual development of new viral strains that require new vaccines on an annual basis. In contrast, occurring much more infrequently (every human generation or so), is a much more revolutionary shift where a bird or pig type of influenza A will exchange genes with a human type of influenza, thus enabling the virus to vault over the species barrier in a process known as *antigenic shift* – a shift that signals the beginnings of a pandemic (Davis, 2005, p11). As alluded to above, it appears that the frequency of tipping point initiations through antigenic shifts have increased dramatically over recent times. To understand why requires us to enquire how the nature of the relationships between animals and humans, as well as those between humans themselves, have changed during the recent past.

One area of comparatively dramatic change is the increased global demand for meat and poultry, resulting in the imposition of immense stresses on the biophysical environment and animals through the intensification of livestock operations (also referred to as factory farming). Many of these negative effects (or externalities) are hidden from urban dwellers who rely on such operations to maintain their meat-based diets, yet they have real consequences for altering microbial traffic patterns and inducing disease outbreaks and pandemics. For example, the development and spread of a lethal strain of *E. coli* could be traced to factory farming practices involving the international cattle trade (Ali, 2004). Similarly, the development of avian and swine flu strains is related to the factory farming of poultry and swine where opportunities for animal-to-human transmission (or vice versa) abound. The likelihood that a more virulent strain will develop under the conditions of globalized agrocapitalist operations is amplified in numerous ways, including an increased risk that animals will become more susceptible to infectious diseases due to the stresses endured in over-crowded factory farms or from the development of antibiotic resistance resulting from widespread administration of sub-therapeutic doses to promote weight gain.

Other global developments that can impinge on the microbial traffic of new and emerging diseases and the associated ecology of disease are those associated with intensified urbanization. Increasing poverty, particularly in the last 30 years, has driven exponentially more dispossessed people from rural areas to the peripheries of megacities across the developing world (Davis, 2005). If globalized factory farming contributes to the development of new and emerging pathogens, then mega-slums provide them with an environment in which they can flourish. Underserviced slum areas often lack proper sanitation and basic amenities and are overcrowded with a large pool of available susceptible human hosts – settings that are especially favourable to the spread of disease. This potential for epidemics to flourish is especially noteworthy given that 95 per cent of the world future population growth will be in the poorer cities of the Global South (Davis, 2005, p56) and that for the first time in history, more than half the world's population is now residing in urban areas (United Nations Population Fund, 2007). At the same time, it should be noted that the conditions conducive to disease spread are not necessarily found only in urban settings, but are common to those areas more generally characterized by poverty and lack of health-related amenities. In this light, certain non-urban areas are just as prone (if not more) to disease outbreaks as revealed by the extent to which influenza A/H1N1 has become widespread on some First Nations Reserves in Canada.

The SARS pandemic

In November 2002, the city of Foshan, Guangdong Province, China experienced an outbreak of a mysterious and highly contagious respiratory disease, then referred to as 'atypical pneumonia'. The disease spread quickly to other cities in the province including Heyang and Guangzhou, then subsequently to others in the country, most notably Beijing (Kaufman, 2006). Although the Chinese government initially took steps to keep knowledge of the outbreaks secret, by late February 2003 news about the outbreaks travelled through informal channels on text messaging and the internet –a notable development considering that in the past, such information could not be transmitted so readily across the country in such a short period and could thus be controlled by government to a greater extent (Heymann, 2005). Once confirmations of the informal rumours were received, the World Health Organization (WHO) coordinated a network of scientists from around the world to work together to characterize the disease agent, originally suspected to be a strain of influenza (Abraham, 2004). Much to the surprise of many infectious disease experts, however, the identification and subsequent characterization of the causative agent – completed in the unprecedented span of a few weeks – revealed it to be a strain of the Coronavirus, a variant of the virus associated with the common cold. Changes in the pathogenic structure and immunogenicity of this type of virus, from one that was relatively benign to a more lethal form, was not expected and the definitive mechanism for these changes has yet to be discovered.

The fact that over a third of the early cases of SARS occurred in food handlers – persons who handled, killed and sold food animals, or those who prepared and served food – led investigators to search the live animal markets of southern China for the animal reservoir that hosted the virus (Guan et al, 2003). At first it was thought that the viral crossover to humans had occurred from infected civet cats found in these markets. However, later studies revealed that the original viral reservoir may have been infected horseshoe bats, which subsequently infected the civet cat, where the virus evolved and multiplied in public markets until eventually evolving into a form that could spread to humans (Lau et al, 2005; Li et al, 2005; Normille, 2005). This was a plausible mechanism as bats were already known to serve as the natural reservoir for many human viruses such as the Ebola, Hendra and Nipah viruses (University of California Museum of Paleontology, 2006).

The evolution of the virulence of the SARS coronavirus highlights the contingent, multifactorial and emergent qualities of pandemic onset. In particular, the causal chain involved in the viral crossover alludes to other interconnected dimensions of disease emergence, namely changes in the human–environment relationship and spatial diffusion. The case of recent emerging diseases such as West Nile virus and lyme disease, for instance, demonstrate how the expansion of human

activities into previously untouched natural environs, particularly through intensified urbanization, have changed the nature and degree of human contact with wild animals. This in turn increases the potential for disease emergence in the human population. Thus, deforestation may have led to the release of mosquitoes carrying the West Nile virus into the urban population while also increasing the chance of human contact with the deer ticks that carry lyme disease. In the case of SARS, it has been argued that increased wealth stemming from the development of the free market economy in China has triggered a change in culinary preferences; namely, as a traditional vegetable diet is increasingly replaced by a meat based one, interaction between human beings and animals in wet markets increases (Zhan, 2005; Jackson, 2008).

One of the major effects associated with contemporary globalization involves increased travel and changes in mobility patterns. Indeed, according to John Urry, air travel is an indispensable element of the emergent global order and 'Without the rapid development of the complex extended systems of mass air travel, what is now termed "globalization" would be utterly different, possibly non-existent' (2007, p149). SARS demonstrated how air travel was also central to the globalization of infectious disease, as it was the first pandemic of its kind in which airports and airlines were instrumental to such a degree in the spread of the disease in such a short period of time (Bowen and Laroe, 2006). Notably, the flow of SARS could be traced through the international airports of major global cities such as Beijing, Hong Kong, Toronto and Singapore and its subsequent diffusion through global city networks points to another dimension of globalization that is worthy of attention, namely the intensified and expansive interconnections among global cities through the flows of information, commodities, foodstuffs, ideas and capital (Knox and Taylor, 1995; Sassen, 2002), in addition to people and viruses (Ali and Keil, 2006; 2008). As the networked interconnections between the different types of flows increase with globalization, the potential also increases for the development of feedback loops, tipping points and non-linearity related to all kinds of complex emergent phenomena, including a pandemic. In light of the different types of interconnected flows between global cities that serve as the foundation for economic and cultural globalization, a deeper understanding of the basis of contemporary disease spread must go beyond mere mechanistic understandings of airline connections between airports to a broader analysis of the global political economic forces that channel these and the various other types of flows in certain directions, thereby ultimately influencing the flow of microbial traffic through particular sites such as cities.

The potential role that cities could play in converting a localized epidemic into a globalized pandemic has been recognized for a long time, as evidenced for centuries by the imposition of quarantines on incoming ships in port cities. What was noteworthy of the SARS pandemic was the speed at which the disease spread though the network of global cities – within a matter of days the disease spread

from Hong Kong to Singapore, Vietnam, Taipei and Toronto (NACSPH, 2003). In part, the rapidity of disease diffusion in the case of SARS could be attributed to certain biological characteristics of the virus itself, including the fact that individuals were most infectious when they were the most ill and were therefore more likely to admit themselves to hospital at the point at which the transmission threat was greatest; hence the large degree to which SARS outbreaks were occurring within a hospital setting (i.e. nosocomial transmission).[3] At the same time, the diffusion of SARS was facilitated by the mechanism of 'superspread', that is, the tendency of certain individuals to infect an unusually high number of people, possibly because of the production of higher viral loads or a greater amount of respiratory secretions that linger in the surroundings for extended periods (Centers for Disease Control and Prevention, 2003). The biological characteristics of the virus also meant that the transmission of SARS could (and was) effectively prevented by adherence to traditional public health measures involving mechanisms of social distancing, including rapid case detection, case isolation, contact tracing and good infection control such as hand washing and the use of personal protective equipment (NASCPH, 2003). As a result of the particular biological characteristics of the SARS coronavirus, including its basic reproduction rate, public health officials needed only to block viral transmission in about half the infected cases to halt an outbreak.[4] Notably, this is very different from the case of pandemic flu, where an almost 100 per cent containment rate would be required for the effective disruption of viral flow (Davis, 2005, p79).

The influenza A/H1N1 pandemic

Similar to the case of SARS, the emergence of influenza A/H1N1 involves the reterritorialization of risk through globalization and the complex changes in human-to-human and animal-to-human relationships. The earliest cases of Influenza A/H1N1 were identified in mid-March 2009 in the Mexican town of La Gloria, Veracruz state, in an area located near an intensified pig farming operation (Alphonso and Wingrove, 2009). The disease quickly spread to major cities and tourist areas in the country, including Mexico City which experienced a cluster of 120 cases (Ha and Laghi, 2009). International spread soon followed and within a month, influenza A/H1N1 cases had been reported in 17 countries across 5 continents (Picard, 2009a). By September 2009, the unfolding second wave of the pandemic had claimed more than 2800 lives worldwide (Boyle, 2009a).

The pathogenic evolution of the virus was a key concern from the start of the influenza A/H1N1 epidemic. Although most of the early cases appeared to be of a mild form, with the majority of those infected recovering through the use of antibiotics (Alphonso and Wingrove, 2009), concerns were raised that a second wave of the disease in the autumn could involve a more virulent strain of the virus

(Ha and Laghi, 2009; Jimenez, 2009), exactly as occurred with the 1918 Spanish flu pandemic. Subsequent genetic analysis mitigated these fears somewhat as the current strain was not found to have any of the markers for virulence that characterized the 1918 strain (Galloway and Alphonso, 2009).[5] Other experts, however, contend that the virus was indeed exhibiting the potential to mutate into a more lethal form, as indicated by the case of human-to-swine transmission involving a Canadian farm worker returning from holidays in Mexico, who was subsequently believed to have infected pigs on a farm in Alberta (Picard, 2009b). The fear is that as the virus jumps from pigs to humans and back to pigs the likelihood increases that resulting genetic mutations will lead to a strain more dangerous to both species (Picard, 2009b) because the constant exchange of the virus' segment genes essentially enables the ever-evolving virus to genetically adapt so that it can more effectively evade the human immune system response and penetrate the human host cell (which a virus requires in order to reproduce itself). The enhanced ability to circumvent the immune system defence mechanisms through genetic adaptation in turn increases the virulence of the virus. Furthermore, the characterization of the genetic code of the influenza A/H1N1 virus revealed it to be a strange hybrid of North American swine influenza, North American avian influenza, human influenza and swine influenza typically found in Asia and Europe (Picard, 2009b), thus indicating a strong potential for rapid evolution into a more virulent form, as the enhanced genetic diversity of multiple strains offers greater genetic resources upon which the evolving virus can draw, thereby facilitating natural selection pressures to induce a viral strain that is more capable of evading the human immune response. Such indications added to the concern about the evolving virulence of the pathogen because swine flu had already been reported in parts of Asia where avian influenza was already present, and where it was thought that the pandemic strains could mix into a lethal cocktail transmissible to and between humans (Picard, 2009b). At the same time, the potential for increased virulence and transmissibility through mixing of the influenza A/H1N1 virus with existing northern hemisphere strains of the *seasonal* virus was ruled out on the basis of the genetic evidence – it was concluded that H1N1 would dominate other strains when flu season began in the northern hemisphere in the autumn (Smith, 2009).

Although sharing some similarities, the spatial diffusion of influenza A/H1N1 varied somewhat from that of SARS. It is clear, for example, that air travel played an integral role in both pandemics, particularly in relation to the rapid spread of the respective diseases. Nevertheless, differences are discernible when considering the localized nature of the outbreaks associated with each pandemic. With SARS, outbreaks occurred in major urban centres, many of which had a relatively high level of public health resources at their disposal. In contrast, increasing evidence gained from the Canadian experience revealed that influenza A/H1N1 was not a disease confined to nosocomial transmission within the hospitals of large urban

centres, but, for as of yet unknown reasons, was taking hold in more rural areas. Notably, although these areas experienced a relatively greater degree of community spread, they had fewer available resources to address the impending pandemic. This is exemplified by the occurrence of influenza A/H1N1 outbreaks in First Nations reserves and summer camps. Particularly hard-hit were several remote fly-in reserves in Manitoba where dozens who became ill had to be flown over vast distances into major urban centres such as Winnipeg (White, 2009a). Furthermore, unlike the relatively mild cases experienced elsewhere, members of the First Nations communities were experiencing illnesses so severe that they required hospital and intensive care (Alphonso, 2009a); indeed about two-thirds of all flu victims on respirators in the province were of aboriginal descent (White, 2009b). The disturbing extent to which First Nations communities were affected by influenza A/H1N1 was not surprising given that the conditions on many reserves in Canada – limited availability of health-care resources, crowded living conditions and ongoing problems with water quality and sanitation (*Globe and Mail Editorial*, 2009) – make this group susceptible to infectious and respiratory diseases more generally.[6]

The community spread of influenza A/H1N1 was also in evidence in summer overnight camps in Ontario, as dozens of children in three such camps were found to have symptoms of swine flu (Alphonso, 2009b). These outbreaks, coupled with the tendency of influenza H1N1 to infect the young (Alphonso and Galloway, 2009) has led to increased concern over community outbreaks in schools and universities (Alphonso, 2009c). Such fears may have been warranted considering the fact that in September 2009, the pandemic strain was confirmed in at least four British Columbia schools (Boyle, 2009b).

Conclusion

The emergence of new pathogens into human communities is not a new phenomenon. The increased frequency of the globalized spread of infectious diseases such as we have seen with SARS and now influenza A/H1N1 may, however, be indicative of a changing pattern of pathogen development and transmission. In this light, it has been argued that certain social and ecological developments associated with globalization (that we are only just beginning to understand) are playing a central role in increasing the potential for a pandemic. Notably, as reviewed in this chapter, these developments include the highly mobile nature of people and microbes today, as well as other macro-level developments such as the intensification of livestock operations and urbanization. Developments such as these have led to a complex array of social and ecological interconnections that are difficult to discern, disentangle and study through existing analytical perspectives. Indeed, Urry (2007, p244) notes that contemporary conditions make it less useful to

conceptualize our world in terms of the traditional linear model of local, meso and global scales, as the world now seems to be made up of multiple systems with mobile connections. To deal with the types of analytical challenges that this fluidity poses with respect to contemporary infectious disease spread, I have suggested that complexity theory be used to focus in on how the dimensions of microbial traffic, including cross-species transfer, pathogenic evolution, spatial diffusion and human–environment relationships, are influenced by system properties and mechanisms, including punctuated equilibrium, non-linearity, emergence, feedback loops and tipping points.

I conclude here by noting that studying the relationships of human mobility, social organization and microbial traffic through the lens of complexity theory also promises to help us understand how historical factors influence the *response* to a pandemic. Pandemic responses have always been influenced by historically informed social, political and economic programmes from colonial imperatives to structural adjustment plans. In this light, what is perhaps worthy of future research is how the policies and programmes that define our globalized era – for example, globalized trade agreements, global public health initiatives and interventions to combat international terrorism – will influence pandemic response. In other words, globalization has not only had implications for the production and unfolding of pandemics but also for pandemic response. Certainly experiences with SARS and influenza A/H1N1 have raised many issues in this regard, including those related to sovereignty, surveillance and privacy, biosecurity, the social control of mobility, the distribution of vaccines and the role of international pharmaceutical companies. For example, David Fidler (2004) notes that with SARS, the domain of international public health entered a post-Westphalian era in which the WHO dared to violate for the first time, via the imposition of travel advisories, the long-held and diplomatically agreed upon norm that initiatives to manage infectious diseases should not interfere with the sovereign right of nation states to engage in trade and commerce. The WHO further intervened in matters of sovereignty by insisting that nation states adopt thermal screening and other initiatives in their major airports to help stop the spread of the disease. In fact, the WHO threatened that they would not lift the respective travel advisories unless their suggested actions were adopted. Notably, such imposed measures represent strategies through which mobility was socially controlled not by the sovereign state, but by an international agency.

However, in the case of influenza A/H1N1, the social control of mobility was overshadowed by concerns related to the shortage of vaccine doses required by the population. Public controversies around this led to the raising of such issues as the ethics behind the prioritization of certain groups to receive the vaccine first, as well as increasing awareness of the significant influence that the monopoly of a few vaccine manufacturers (many of which are owned by huge pharmaceutical companies) may have during a pandemic. It is also clear that advanced

information and communications technology (i.e. internet-based technologies) have played a key role in recent pandemic responses. Important questions remain as to how these political and technological interventions and factors will influence future patterns of microbial traffic and the effects they will have in either deterring or inadvertently amplifying the potential for pandemics in an era characterized by increasing complexity and the unintended consequences of emergent phenomena resulting from the economic, cultural and environmental forces brought forth through globalization.

Notes

1. John Urry (2007) gives other examples of tipping points in the modern era, that is, where apparent long-term stabilities unpredictably flip towards their opposite. These include the overnight 'collapse' of the Soviet Union and the astonishing growth of the Internet from no users to 1 billion users, the spread of mobile phones and the overnight emergence of global terrorism after 11 September 2001.
2. In late February 2003, this physician travelled to Hong Kong to attend a relative's wedding and stayed at the Metropole Hotel. Here the virus spread to 11 hotel guests who continued their respective travels to various cities around the world, including Toronto, Singapore, Taipei, Hanoi and to other parts of Hong Kong (Abraham, 2005). The exact mode of transmission in the hotel has not been conclusively determined as some of the guests who became infected may not have had direct contact with the index case. The prevailing theories propose that the virus contaminated an elevator or travelled through the ventilation system (NACSPH, 2003).
3. There were, however, two significant community outbreaks of SARS – in the Amoy Gardens apartment complex in Hong Kong (Ng, 2008) and the Pasir Panjang Wholesale Market in Singapore (Teo et al, 2008).
4. The basic reproductive rate refers to the average number of people a disease carrier infects, for SARS this was 2–5 and for Influenza A/H1N1 it was 1.5–2. By comparison, this rate is 1.5–3 for seasonal influenza; 5–7 for polio; and 12–18 for measles (Picard, 2009a).
5. Specifically, influenza A/H1N1 lacks several genes that code for certain proteins (i.e. PB1-F2 and NS-1) that increase the virus' lethality. All pandemic flues of the past, including Spanish, Hong Kong, Asian flues and H5N5 (avian flu) contained these specific genes (Galloway and Alphonso, 2009).
6. It is also for these reasons that the First Nations communities have very high rates of tuberculosis (Public Health Agency of Canada, 2007). Furthermore, such conditions have persisted over the duration, and fatality rates among the First Nations of Canada during past pandemics has been between 5 and 10 per cent, while entire First Nations towns succumbed to the Spanish flu in 1918 (White, 2009a).

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Part 1

Reframing 1918: States, Pandemics and Public Health

2

Barcelona's Influenza: A Comparison of the 1889–1890 and 1918 Autumn Outbreaks

Esteban Rodríguez-Ocaña

Preparations to confront pandemic threat are an explicit concern of the World Health Organization (WHO). The 2007 World Health Report, entitled *A Safer Future: Global Public Health Security in the 21st Century,* begins with a description of immediate prospects of infectious disease transmission through global commercial networks. It states that 'infectious diseases are now spreading geographically much faster than at any time in history' (p6). This chapter is part of a broader comparative social scientific and historical study of influenza, one that might well be understood as a by-product of anxieties about the swiftness of disease transmission and the threat of emerging and pandemic disease. To what extent can historical analyses help to develop preparedness for these health threats? Are there any lessons to be learned to lessen the impact of future outbreaks?

The history of epidemic diseases has been a mostly pragmatic and traditional endeavour of the history of medicine and public health (Perdiguero et al, 2001; Berridge, 2003, p516). In a widely read book, *Civilization and Disease* (Sigerist, 1943; Temkin, 1958), Henry E. Sigerist (1891–1957) – the key figure in the 1930s internationalization of the strongly German-based discipline of the history of medicine – inaugurated the contemporary concern for the necessary linkage of social and biological factors as a means to understanding past episodes of heavy mortality. In the 1960s, social historians, expanding upon Louis Chevalier's work (1958), which itself was subsequently encoded by Asa Briggs (1961), found in cholera a compelling historical subject of study. Cholera as the focus of historical analysis gained further momentum in the 1970s with the outbreak of the seventh cholera pandemic. For many historians, past epidemics were a window into ordinary social life. As McGrew (1960, p71) observed, 'Epidemics, and perhaps other major calamities, do not create abnormal situations, rather they emphasize normal aspects of abnormal situations'. New emerging viral diseases, particularly AIDS, have also increased attention to the history of epidemic diseases (Fee and Fox, 1988; Grmek, 1989; Rosenberg, 1989; Harden and Risse, 1991; Berridge and Strong, 1993, among many others).

This historical approach echoes the central questions of traditional public health, and it appears that public health interventions and historical enquiries work synergistically. The case of malaria is instructive. As an unsolved global public health problem, it has become one of the main concerns of new global health, involving both public and private institutions, and generating such international agreements and programmes as the Global Strategy for Malaria Control (1992), Roll Back Malaria (1998), Global Fund Against AIDS, TBC and Malaria (2002), Booster Program for Malaria Control in Africa (2005), Stop Malaria Now (2008). From a historiographical perspective, three elements have fostered historical research on malaria (Rodríguez-Ocaña, 2009): the need to evaluate the successes and failures of previous interventions; the centenary of the discovery of the crucial components of the present model of malaria transmission (1881–1898); and the enduring linkage between the history of malaria and social history, as evidenced in Frank Snowden's history of malaria in Italy. Medical sources, he notes, 'provided more insight into living conditions' (i.e. diet, housing, working conditions, education, social relationships, religious beliefs) compared to other sources more familiar to mainstream historians (Snowden, 2006, p2).

No wonder, then, that the emergence of SARS in 2002–2003 and subsequent fears about an influenza (avian or other) pandemic have provoked a concomitant interest in the history of influenza. As this collection has gone to press, the WHO and other public institutions, states and their populations have been coping with the 2009 H1N1 Influenza pandemic.

This chapter compares two influenza epidemic outbreaks in the past (1889–1890 and 1918) in the city of Barcelona on a qualitative basis, mainly focusing on the ways in which local events, the behaviour of local and regional institutions and public reactions played out differently. This comparison aims to provide valuable information that can enhance the ability of today's experts to grasp the complexity of any new episode. Even though each pandemic occurs within its unique context, a careful comparison helps to show the inner fabric of the social process that we call 'an epidemic'. Thus, a historical approach contributes to the understanding of the determinants of disease by clarifying relationships between social and political factors, biological factors and population health. While the patterns of disease were similar in both the 1889–1890 and 1918–1919 influenza episodes, the 1889–1890 epidemic in Barcelona (Spain) resulted in relatively low mortality rates. By contrast, the 1918 crisis produced the highest mortality rates of any Influenza pandemic during the century, but it must also be understood as the concurrence of severe economic and political troubles, including vast population migrations. The comparison between the two pandemics allows us to explore the failures of scientific governmentality, which some experts had depicted as the desire for a 'public health dictatorship' at a moment when available scientific tools and the public health infrastructure could not cope with the health needs of Barcelona's population.

I first examine briefly the historiography of influenza in Spain, and then compare the epidemiological and demographic consequences of the two epidemics, changing medical understandings of influenza over the two periods, approaches to preventive measures and the provisioning of health care, and finally public awareness. The scarcity of available archival sources made the city of Barcelona's daily press the most important source of evidence concerning both episodes (see Guillamet (2003), which analyses the political framework of various firms and accounts for the press's importance and development at the time). Because of source limitations, my exploration here of the 1889–1890 episode – the first on the subject to my knowledge – is not as rich from an evidentiary perspective as the 1918 episode and does not match the richness of the further one; thus, the conclusions reached are provisional.

Historiography of influenza pandemics in Spain

The history of modern influenza epidemics in Spain has focused almost exclusively on the great 1918–1919 pandemic. By contrast, historians have overlooked the previous outbreak of 1889–1890, despite its significance in a longer history of scientific consciousness of infectious disease.

A wealth of studies exists on the 1918–1919 influenza pandemic. Prompted by her interest in population history, Beatriz Echeverri wrote the most comprehensive (and recently updated) account of the mortality crisis created by influenza in 1918–1919 Spain and included a skilful review of related health policies (Echeverri, 1993, 2003). Prior to Echeverri's work, historical studies of the 1918 influenza had constituted an important subject of study in graduate theses and other academic projects of the 1980s, when History of Medicine departments in Spain were dominated by social history. Regional studies have been conducted on the Basque Country and the Balearic islands (Urquía-Echave, 1986; Lluch-Dubón, 1991; Erkoreka, 2006), while several provincial cases have been addressed by mostly unpublished theses in Salamanca (Elexpuru, 1986; Sena-Espinel, 1992; García-Faria del Corral, 1995). Most studies have explored urban settings, including Alicante (Bernabeu-Mestre, 1991), Valencia (Martínez-Pons, 1995, 1999) and Barcelona (Granero, 1984, 1985; Rodríguez-Ocaña, 1991). A most valuable contribution is by Isabel Porras (1994, 1997), who studied the case of Madrid, examining the interplay between the medical world and public opinion. Knowledgeable about the individuals and institutions driving the medical responses to this crisis, she actively continues to research this epidemic (Porras, 2008).

Despite these varying geographical scales of analysis, there remains a strong homogeneity in the descriptive historical narratives: authors study influenza victims, attempting to establish accurate mortality and morbidity numbers; their narratives move chronologically, following the timeline of the outbreaks; they

present and assess the public health measures undertaken; and their sources are identical, drawn from municipal archives, official documents and the daily press.

By stark contrast, the 1889 influenza epidemic, which constituted one outbreak within a pandemic cycle that persisted until 1894 (Teixidor, 1899, p23), has fallen into historical oblivion for two possible reasons. First, the tremendous demographic impact of the 1918 epidemic may have overshadowed other earlier influenza-related events. And second, according to scientific understandings of the day, the 1889 episode was the last of the old, atmosphere-related 'epidemic constitution' phenomena. Epidemic constitution was an explanatory concept holding that atmospheric conditions (disturbed properties of air, for example) acted upon all beings and affected their health conditions. The common features of any disease episode (known as the 'reigning malady') were understood to be the direct consequence of such atmospheric changes, although precisely what those changes were and how they worked were not understood.

The 1889 epidemic coincided with the rise of a new biomedical conceptualization of infections and contagions that became predominant at the time: Pfeiffer's bacillus, reported in 1892, was the first consensually established microbiological cause of influenza, although its role remained controversial among medical experts and did not survive as an aetiological factor during the shock of 1918.[1]

Epidemiology of the two pandemics

According to coetaneous epidemiological surveys, the epidemic of 1889–1890 erupted in Turkestan during the early summer of 1889 and travelled through Russia to reach St Petersburg by mid-November of the same year. The epidemic spread from St Petersburg in early December 1889 throughout Europe. According to newspapers, it was in Denmark on 10 December, Paris on 12 and in Madrid and Malaga on 13. The precise date of its outbreak in Barcelona is unknown, since there are no morbidity records. Local newspapers published their first stories of cases in Barcelona on 17–18 December, while medical sources later suggested that the flu broke out during the first ten days of December (Piga and Lamas, 1919, vol 1, p26). The scarce available sources reflect widespread agreement that nearly the entire population was afflicted by this influenza pandemic. As one observer put it, 'there was hardly any street, any house, any family that did not count several ill people' (Balaguer, 1890, p170). The first days of the New Year saw the highest number of cases and deaths. On 16 January, schools reopened and the city council session on the same day made no mention at all of a public health problem. The epidemic appeared to be over.

By comparison, the 1918 Barcelona epidemic took place during the second of the three waves of influenza epidemics that hit Spain between May 1918 and June 1919. Barcelona had not registered a significant number of cases during the first spring wave, unlike Madrid, which was heavily affected. It was not until mid-September that the Barcelona authorities became concerned about influenza, which had severely weakened the military garrison (Piga and Lamas, 1919, vol 2, pp53–91). And the epidemic was not officially acknowledged by the city medical officer until 9 October. The outbreak lasted until 14 November.[2]

This official 'political' chronology was contested at the time by both medical experts and the press. From early August, the local medical association issued a public statement signalling the growing incidence of influenza.[3] Press reports highlighted many cases of influenza in nearby villages by 20 September,[4] and as a result, the French Consulate began to insist that in order to obtain a visa, travellers carry a document signed by the city chief medical officer certifying a good state of public health in their home cities. From 3 October, the daily newspaper *La Vanguardia* started publishing a section entitled, 'The State of Public Health', as well as 'The reigning epidemic', a column that continued to be printed until 27 October.

In the absence of any regular epidemiological surveillance,[5] the belated official acknowledgement of the health crisis echoes local authorities' efforts not to inhibit commercial life, since commercial decline has been an unwanted consequence of contagions since the 14th century. We can assume that Barcelona officials similarly sought to avoid disrupting commerce; the city's municipal officer claimed daily that Barcelona suffered only from a 'moderate epidemic' between 9 October and 9 November, and that its end was apparent by 11 November. This latter date coincided with massive street demonstrations in support of the Allied victory against the Central Powers, but they were violently suppressed by the police. High schools reopened and the University was scheduled to resume 'in a few days'.[6]

These two epidemics had very different demographic impacts. The 1918–1919 flu epidemic produced the most severe mortality crisis of 20th-century Spain, even worse than during the Civil War in 1936–1939. Barcelona's 1918 crude death rate reached 35.53 per thousand, second only to 1886 (the last year of the cholera epidemic) in the historical records.[7] By contrast, the 1889–1890 influenza epidemic was less serious, with calculated annual death rates of 27.5–31.4 for 1889 and 28.6–33.2 for 1890 (the ranges for each year result from contradictory municipal sources).

Social and political contexts, 1889 and 1918

National and regional political and social contexts shaped both the courses of and responses to the two epidemics. The 19th century's political convulsions gave way to a calmer period by 1875 after the restoration of the Bourbon monarchy, which was supported by the two oligarchic parties, Conservative and Liberal. An

agreement between these two parties set the main parameters for the government, which at the Monarch's call was headed alternatively by the parties' respective leaders. Nevertheless, new political actors who represented growing peripheral nationalistic groups and the working classes found themselves excluded. The exclusion of these important political interests would haunt the political system in the future.

The Liberal Party under Praxedes-Mateo Sagasta was in power from November 1885 to July 1890. It produced democratic improvements, such as free association and free press, and a law of universal (male) suffrage was in the process of passing through Parliament at the time of the flu epidemic. Influenza affected numerous MPs in Madrid, although political journalists complained that some of them were hiding behind the 'reigning malady' to avoid their parliamentary duties. The three-year old King Alphonse XIII fell ill and his royal mother, who was head of State as Regent until Alphonse came of age, restricted her political activity in order to care for him.

Barcelona, the heart of the Spanish textile industry and a stronghold of industrialization, was beleaguered by increased migration, appalling housing conditions, waves of mass unemployment and explosive confrontations between workers and employers. The outbreak of influenza crowned a critical year; it followed the glories of 1888, when the city had hosted a universal exhibition from April to early December, creating thousands of jobs and spurring the development of political economic movements to address these social and economic conditions. Among the various conventions held during the exhibition, the one that founded the socialist General Workers Union (Union General de Trabajadores, UGT) had the most enduring impact. It was followed by the first national conference of the Socialist Party of the Spanish Workers (PSOE), which also took place in Barcelona.

In one sense, as Republican Democrats recognized at the time, the 1888 Exhibition symbolized an agreement between the Crown and the captains of Catalonian industry, who harboured nationalist sentiments. The exhibition was held in the outskirts of the city on land previously reserved for the military, implicitly signalling the declining political relevance of the military itself. Indeed, this exhibition reflected a new governmentality offering new opportunities for capital, both material (in the form of land development and building) and symbolic (since Catalan began to be used as a language in official forums). But the boom created by the exhibition was short-lived, and the subsequent epidemic in 1889 increased the burden of the ensuing economic crisis. Both economic hardship and the demands of the epidemic unduly strained the municipal charity organization (*beneficencia municipal*) and ultimately led to a reorganization of the city's medical services for the poor.

The decades following the 1889–1890 epidemic were ones of growing political instability. The 1898 war against the United States and the rising political power

of emerging social groups (e.g. industrial workers and professional middle classes) and ideologies (e.g. nationalism in Catalonia and Basque Country) severely weakened the older centrist agreement, and governance became particularly untenable after the murder of the Liberal Prime Minister José Canalejas in 1913. Definitive rifts splintered the dominant parties, which proved incapable of building a majority consensus around the Throne, and these political divisions worsened during World War I. Continuous political instability reigned after 1917, with some seven different Cabinets formed between 1918 and 1919. The nation, divided between pro-German and pro-Allied sentiments, suffered a rising cost of living, and various political groups sought to effect radical social change. A wave of strikes in industry and agriculture, including the first general strike, strengthened both socialist and anarchist trade unions (Ruiz, 1981; Huertas, 1994; Seco-Serrano, 1992; Romero Salvadó, 1999). Class struggle gave way to violence, making Barcelona the 'Rose of Fire' (Romero Maura, 1989).

The war in Europe had drawn a huge workforce of about half a million people from neutral Spain into France, and in the late summer of 1918, just before the armistice, the French government ordered these migrants to return home. The ensuing migration into Spain, alongside returning Portuguese soldiers and the seasonal mobility of grape-gatherers around the Northern border of the Iberian Peninsula, is considered to be one of the main causes of the influenza pandemic's second wave, which had its greatest effects in Barcelona (Echeverri, 1993, 2003).

Medical understandings of the two pandemics

Debates over the correct diagnosis of the epidemic disease were common during both episodes. In 1889, these medical discussions raised possible explanations of dengue, cholera, typhus and influenza. The simultaneous presence of a dengue fever epidemic in Asia Minor and the similarity of its symptoms to those of influenza fuelled this controversy, which peaked at the Paris Academy of Medicine in mid-December.[8] Barcelona's doctors adopted the explanation of an influenza or cold epidemic, although 'dengue' became the most popular name for the epidemic (see below). On 19 December, Dr Giné Partagás delivered a presentation in which he clarified the clinical differences of the two diseases and identified the current malady as epidemic influenza. Twenty-eight years later, the 1918 epidemic disease was described as 'plague', 'typhus' or 'influenza' until September, although by the time of the autumn wave in Barcelona, a consensus was firmly established around influenza, as evidenced by a survey in a local medical journal, *Revista Española de Medicina y Cirugía*, and in sessions held at the Barcelona Academy of Medicine and Surgery.[9] All physicians consulted except one believed that influenza was responsible; the problem was how to account for the greater number and different quality of deaths sustained, as compared with the previous great influenza episode

of 1889–1890. Doctors who had practised during both outbreaks recalled that fatal cases in the earlier occurred most commonly among the elderly and those with pre-existing respiratory or cardiac illnesses. Some suggested that the concomitant presence of a second disease increased the severity of the epidemic, while others pointed to 'microbial associations' as the lethal cause. And some placed their firm beliefs in the bacterial paradigm, *Haemophilus influenzae* (Pfeiffer's bacillus), the recognized causal germ for influenza, but it was not isolated in most extant clinical cases.

Two forensic pathologists from Madrid, Antonio Piga and Luis Lamas, wrote the most comprehensive study of the 1918–1919 epidemic in 1919, comparing it to the previous great epidemic of 1889–1890. They recalled the 1890s flu as a period of 'invaluable scientific exploits. It might be posited that the study of influenza implied checking the whole of pathology' (Piga and Lamas, 1919, p24). In other words, the time for a microbiological understanding of the pathogen of influenza had come, and nothing would ever be the same again. A closer look at the medical debates around influenza epidemics nonetheless reveals that the changes in medical understanding occurred very slowly.

Medical corporations such as academies and medical associations tried to draw lessons from their experiences of the 1890 epidemic immediately after its conclusion. The debates held in Madrid at the Academy of Medicine and Surgery and at the Royal Academy of Medicine were published in a medical journal,[10] and those celebrated by the Madrid Provincial Hospital staff were collected in a brochure (García y Mansilla, 1892). We know that similar efforts occurred in Barcelona, because some participants in the later (1919) debates recalled these publications, but I have no direct evidence of their contents. Nevertheless, it is fair to assume that in 1889–1890 medical opinions in Barcelona resembled those of medical professionals in Madrid; Catalan physicians thus favoured a 'modern' microbiological aetiology for influenza, although the epidemic's specific cause had not yet been discovered. Only two well-known physicians from the capital of the Kingdom, Dr Francos and Dr Iglesias, continued to embrace the traditional idea of a 'catarrhal epidemic constitution', while a third, Diaz de Benito, remain sceptical about the microbiological cause of influenza because of the lack of experimental evidence. But once the epidemic had ended, a Barcelona physician issued a public declaration of support for the microbiological hypothesis in a lecture at the *Ateneo* club on 29 February 1890.[11] The staff of Madrid Provincial Hospital agreed that influenza's spread and clinical features indicated an infectious disease, and that it was only a matter of time before the discovery of a causal microbe. Only then would it be feasible to study the influence of the environment on its development.

Rafael Rodríguez Méndez, professor of hygiene at the School of Medicine of Barcelona University, wrote periodical reviews about the state of knowledge in his own journal, *Gaceta Médica Catalana* (Barcelona), and these reviews were

subsequently republished in other journals, including the *Revista de Medicina y Cirugía Prácticas* (Madrid). His writings reveal that medical debate did not revolve around atmospheric conditions (or 'constitution') versus microbes. Instead, a debate ensued over the notion that bacterial agents, including vulgar symbiotic microbes already existing in the human body, were stimulated or turned pathogenic by the epidemic condition, a mysterious influenza (or influence), he wrote. Entirely opposed to this formulation were the defenders of a specific, but not yet agreed-upon pathogen.

Nevertheless, the emphasis on atmospheric conditions constituted the main feature of the conception of influenza held by many physicians and the public. On 1 January 1890, for instance, the Barcelona municipal board of health described the disease as the customary epidemic catarrh associated with winter. Precisely the same judgement was issued on 16 December 1889 by Joaquin Bonet Amigó, Professor of Obstetrics at the School of Medicine in Barcelona, in an interview in the daily newspaper *La Vanguardia*. The Socialist party depicted the increased mortality as a direct consequence of the season's 'extraordinary low temperatures'.[12] These atmospheric explanations are not entirely surprising; years later Rodríguez Méndez (1919, p306) recalled that bacteriological work did not abound in 1889–1890.

By 1918, notwithstanding the broad recognition of microbial agency, both the public and medical professional still considered environmental influences to be an important explanation for influenza. It is true that the term 'epidemic constitution' no longer appeared in the 1918–1919 literature, except to be derided as 'a construction lacking any real meaning' (Grinda, 1919, p190). Nevertheless, the outbreak was variously attributed to public works construction of Madrid's underground railway, the intensity of cannon fire on the Western front, variations in sunspots, and the poor quality of tobacco. Piga and Lamas (1919, pp73–74) reported that the 'popular classes' held these opinions, but some medical experts had proposed underground tunnelling and sunspot changes as causative factors of the great pandemic.[13] Asked in a local newspaper whether influenza was generated by cosmic conditions, a well-known meteorological expert accepted this proposition with or without the intervention of germs (Ricart, 1918).

Moreover, even clinicians accorded atmospheric conditions a decisive, albeit secondary, role in triggering the epidemic (Parada, 1919), and Barcelona officials followed their lead. On 6 October, the city council of Barcelona ordered the sealing off of all urban cesspits and prohibited the keeping of chickens and pigs within inhabited buildings as measures to prevent flu transmission. Human Influenza had been linked with animal (particularly herbivore) diseases, described as 'premonitory diseases' by the early 1860s (Fuster, 1890). The city of Barcelona's prohibition on raising animals at home applied this general, long-standing hygienic principle of avoiding putrid smells and of enforcing cleanliness in the

human environment. But this proposition was not exclusively accepted: in early October 1918, a municipal veterinary doctor published a general description of influenza, depicting it as an 'exclusive[ly] human' disease caused by the Pfeiffer bacillus (Sugrañes, 1918), and Madrid's newspapers criticized the exclusion of animals from housing on the grounds that these hygienic deficiencies played no part in the known pathogenesis of the disease (Echeverri, 1993, p149).

Barcelona's physicians expressed great confusion about the precise microbiological cause of the malady and the reasons for its lethality. On 26 October 1918, Dr Vallejo declared that 'the public has passed their panic to us' at the Royal Academy of Medicine of Barcelona.[14] Discussion on the specificity of the bacillus discovered by Richard Pfeiffer in 1892 was already an old debate by October 1918, as Rodríguez Méndez (1919) noted. Numerous opinions were expressed against this specificity, and Pfeiffer himself was not always able to isolate the bacillus during flu episodes. On 12 October, Barcelona's provincial laboratory declared that it had been unable to trace any Pfeiffer bacilli in local influenza patients so far.[15] The results of bacteriological research at the National Hygiene Institute in Madrid and in Valencia led a majority of authors in Spain to support an association of pathogens as the probable cause of influenza.[16] This was also the position of the health authorities in Barcelona, according to their warning to the population issued on 9 October.

A poll of Barcelona physicians revealed the wide range of opinions. Among defenders of a single bacterial pathogen, preferences included Pfeiffer's bacillus, *Micrococcus catarrhalis* and the French hypothesis of a filterable virus. Supporters of this latter hypothesis included practising bacteriologists Ricardo Moragas of the Holy Cross Hospital and Ramón Turró of the Municipal Bacteriological Institute. At a meeting of the Royal Academy of Medicine, the military physician López Brea proposed that Pfeiffer's bacillus be maintained as the causative agent of influenza until another specific microbe was discovered, 'lest we become prone to scientific anarchy'.[17]

Preventive measures during the two pandemics

Disease prevention in the public sphere depends on political will, exercised through institutional and legal measures, expert advice and material support. By the 1889 influenza epidemic, a health administration was under construction in Spain. The Public Health Act of 1855 was almost wholly devoted to mounting a defence against the importation of so-called 'exotic diseases' (Grabuleda, 2003; Rodríguez-Ocaña, 2006). Municipalities were responsible for their own needs; during epidemics, local health boards addressed these needs, but these boards otherwise served as consultative organisms. Provincial governors had a corresponding provincial health board to oversee and integrate local actions. However,

in accordance with the prevailing idea of the epidemic constitution, no public measures were available in 1889 to prevent influenza outbreaks anywhere, except through the promotion of personal hygiene. Thus, the only advice given by the Barcelona board of health on the first day of the New Year was to maintain 'the usual hygienic habits of the season' to avoid catching a cold. Physicians understood this inaction, and in the approving words of one contemporary, 'absolutely nothing has been tried by the authorities in order to avoid the coming of the epidemic, it would have been useless' (Balaguer, 1890, p205). Others offered timid criticisms of the wait-and-see policy of the provincial authorities, which were countered by the reminder that influenza was an epidemic but non-contagious disease. Spokesmen for workers' organizations called the health boards' advice to wear winter garments and to increase food intake a 'bitter joke'; such measures involved improving the living conditions of workers, and none were introduced.[18]

The national situation was different 28 years later during the 1918 pandemic. By then, ideas about 'infectious diseases' and 'epidemics' had been recast in microbiological terms, and Spanish society had pursued a conscious effort to develop a professional health administration. A keystone of this policy was the General Instruction on Public Health (issued in 1904), which established a permanent public health service to monitor, control and prevent infectious diseases. It created permanent health officers for making on-the-spot inspections, recycled older advisory boards, and placed executive powers under the political authority of the Ministry of Interior (the Minister for the country as a whole, the Governor for each province, and the Mayor at city level). Traditional health boards were limited to the provincial level under the management of the provincial medical officer and were obliged to create public health laboratories and vaccination institutes. These would not replace the municipal health organizations in the major cities, such as Madrid, Barcelona, Valencia and San Sebastian. Priority was given to monitoring the current health status of populations rather than border surveillance, which had been the main task of the Spanish health administration since at least the 18th century. The new medical officers of health would now be involved in the prophylaxis of all transmissible diseases, surveillance of urban sanitation, food hygiene, vaccination control, and the compilation of health statistics. While these legal provisions were sweeping, their implementation was slow. Provincial officers were not consolidated until 1925, when new regulations were issued to equip them with premises, supplies and a permanent professional task force; and municipal health officers had not been elected or lacked specific support in most cities until the 1930s (Rodríguez-Ocaña and Martínez Navarro, 2008). Nonetheless, by 1918, most provincial health officers were bureaucrats whose main tasks were to undertake health inspections of prostitutes and to act as secretaries of provincial health boards under civil governors.

Catalonia's political and public health situation was even more complex. The four Catalonian provinces had merged their provincial services into a regional administration, Mancomunitat de Catalunya, which maintained a 'technical health service' of its own, alongside the administrative offices located throughout Spain. However, the regular provincial health boards dealt with the epidemic crisis, even though they suffered from chronically low levels of state funding. The city council of Barcelona was comparatively better financed, and Barcelona's Mayor acted accordingly. The city council accepted the radical councillors' 3 October proposal to form a public health committee with full powers, leading to the creation of a municipal health commission composed of the mayor and two councillors who were also physicians.[19] After one week, this commission was merged with the provincial health board for the duration of the epidemic.[20]

In addition to this complex institutional organization of public health, authorities relied upon the Pasteurian approach to fight infectious diseases through both disinfection and isolation measures. The provincial governor led the way in Barcelona, following Home Ministry instructions restricting human gatherings, although the massive local celebrations of La Mercè (24 September) remained unaffected (Piga and Lamas, 1919, vol 1, p57). On 21 September, the provincial health board ordered the disinfection of theatres, tramways and public offices.[21] Before falling ill himself, the provincial Health Officer Dr Trallero published on 3 and 14 October recommendations to isolate individuals with bronchial pneumonia, and general hygiene regulations for rooms and dwellings.[22] On 30 September, the Mayor and the head of the Urban Hygiene Institute agreed to expand the disinfection programme if the epidemic spread further, a development that ultimately took place. The programme included the mandatory declaration of all cases of infectious disease, the prohibition of camping at railroad stations, and the isolation of sick travellers at a provisional hospital for infectious diseases in Ciudadela Park. Authorities concluded agreements on specific interventions in shops and factories, but did not make them known to the public, and they called publicly on the bishop to prevent crowding in churches.

Barcelona is situated near the French border along one of the two main railroads that link the two nations. In the early autumn of 1918, there was heavy rail traffic between Spain and France, facilitating the pandemic's spread. By mid-September, the central government had activated the six health control stations on the Catalonian side of the border, including at Port Bou, an important station that served as the main gateway to and from Spain. But the implementation of health controls was poor. On 21 September, for instance, a train with 300 passengers passed through with no application of surveillance measures (Granero, 1984). One of the Port Bou station's health officers also reported that some 40,000 workers had moved through the station in 60 days, mostly on the way home to Almeria, Murcia and Valencia (Delmás, 1919). He depicted the appalling conditions suffered by these travellers, who arrived hungry, dirty and tired after a seemingly endless journey, punctuated by many stops, with no access to beds and exposure to cold and windy conditions.

Authorities had also set up several screening and disinfection measures. Luggage was disinfected at the border health stations, and all travellers were supposed to undergo a medical examination; those with body temperatures over 37°C were sent to a nearby hospital. Upon their arrival in Barcelona, travellers were to walk under a fine shower of an antiseptic liquid, but these measures required both time and money to implement. The Port Bou station closed to prepare the infrastructure necessary to carry out the disinfection procedures, and a health station had to be constructed at Barcelona's main railway station. Passengers coming from France with fever were moved to the existing lazaretto or another provisional hospital erected on the same premises with room for up to 132 patients (Granero, 1984). Such health controls were not universally applied, however, and railway travellers from other destinations escaped altogether.[23] Moreover, these measures did not prevent the epidemic's spread. Modern analysts like Echeverri (1993, 2003) have concluded that the influenza entered Spain primarily via the railways and spread throughout the country by the annual September movement of young men starting or ending their military service at different garrisons.

The implementation of anti-crowding measures was also inconsistent. Although the bishop was asked to help prevent crowding in churches in late September, he nevertheless ordered special ceremonies to be held in all parish churches from 9 October.[24] On 12 October, massive church celebrations for the Day of the Virgin of the Column, the patron of the Guardia Civil (rural police) took place. Only on 14 October did he accept the suspension of all religious functions.[25]

Other closures followed. The provincial health board closed the University of Barcelona on 11 October and sent students home, and by 15 October, all schools had closed and a wide range of public activities were prohibited, including dances, visits to poor houses and hospitals, political meetings and motor races. But even these measures had their inconsistencies. The governor initially banned the customary visit to cemeteries on the Day of the Dead (1–2 November), but subsequently retracted the ban after protests from florists. Visitors were allowed to carry flowers to the gates of the graveyards, which were subsequently handled by inside workers.[26]

On 9 October, confronted by theoretical doubts about the causal agent of influenza and the ineffectiveness of general disinfection procedures, the city council stressed private hygiene. Municipalities throughout Spain implemented street cleansing with antiseptic liquids on a massive scale (6000 litres per day in Madrid) (Echeverri, 1993, p140), 'as if the population could be satisfied and reassured by the antiseptic odours', in the opinion of a Spanish medical commission sent on mission to France (Marañón et al, 1918). Declaring the flu to be 'the most contagious of all diseases', one that healthy people could spread and that remained unaffected by sanitary measures, the Barcelona health commission called for

increased cleanliness in dwellings and among individuals, promoted new public washing places, and advocated daily mouth-washing with a mild disinfectant. The technical health department of the *Mancomunitat* repeated this recommendation days later.[27] From 16 October, up to 4000 poor families were given a litre of bleach a day, and portable washing fountains were established in Casa Antunez, a deprived neighbourhood.[28] A new tax on tenants would finance the 1.5 million pesetas spent by the city council on health prevention, mainly for the refurbishing of disinfection centres in charge of disinfecting clothes and rooms of infected people.[29] This proposal sparked a fierce political battle. The Tenant's Union opposed it, and one city councillor demanded a tax on landlords. Three Republican counsellors abstained from voting and called for landlords to be forced to provide sanitation facilities, including water closets. Their demand was accepted, and the Mayor issued an edict on 19 October for all houses to have running water within two weeks and all apartments a privy, to be converted to a water closet before the six-month deadline (Granero, 1984, p95). Criticisms of these municipal interventions came from those who primarily believed in the effectiveness of 'the great hygiene': that is, sera and vaccines. For these critics, like the popular medical writer Alfredo Opisso, disinfection policies constituted nothing but an absurd attempt 'to close the gates of the countryside' (Opisso, 1918).

Medical care policies in 1889 and 1918

Barcelona's population gained access to medical services and various therapies through an array of public care organizations. The municipal institution offering care to the poor (*beneficencia municipal*) was responsible for the city's destitute inhabitants who had registered in a poverty census. Private charities that had provided complementary services now became essential, because municipal services were severely inadequate to cover the heavy influx of migrant workers during rapid economic change. Moreover, the relative dearth of municipal services facilitated a conscious effort to heighten the importance of Catholic institutions serving the public domain. The severe cholera outbreak of 1885–1886 overextended the meagre medical resources available in rapidly growing urban centres like Barcelona, and it led to the founding of a permanent municipal health-care scheme in 1886. When the 1889 epidemic struck, public and private organizations were thus already strained, and the heightened needs during the pandemic only worsened matters.

On 6 January 1890, on the heels of a call made by the King's mother and Cabinet to promote charities, the provincial governor called a meeting with Barcelona and provincial authorities, as well as with the region's most wealthy residents. These leaders appear to have agreed on public and private provisions to improve medical and social care for the destitute, and they announced the opening

of four provisional hospitals, only one of which was set up by 13 January. The city council hired extra medical staff for the *beneficencia municipal* to begin home medical care on 3 January; before this date, medical care could only be delivered at municipal clinics. The main local Christian charity organization, Congregación de la Caridad Cristiana, expanded its own home care programme from 5 January, increasing its expenses of soup, milk, meat, sheets and blankets, and requesting additional funding from citizens.

In the context of a major epidemic, a primary consequence of home visits was the discovery of unexpected levels of poverty and hunger in many homes. Josefa Pujol, writing her customary newspaper column for ladies on 7 January, observed that the epidemic more adversely afflicted the poor. Two days later, new accounts reported that municipal physicians had found that many households in the Atarazanas neighbourhood, suffered from 'a reign of poverty', lacking even basic foodstuffs.[30]

The home medical service continued to exist after the epidemic, and under the threat of a new cholera epidemic in 1891, it contributed to the strengthening of the municipal health service (Rodríguez-Ocaña, 1986). The reformed municipal health services comprised four sections, one devoted to medical care, a second to the health inspection of prostitutes (a task that came under provincial jurisdiction a few years later). A third section was the Institute for Urban Hygiene, responsible for health inspection and disinfection among other tasks, and the fourth section was the Bacteriological Institute, created by Jaime Ferran in 1886 (Roca, 1988). The first (health-care) section was responsible for surgeries or dispensaries, provisional hospitals and the home medical service. Recent studies on the formation of the municipal health service (Grabuleda, 2003, pp354–384) have entirely overlooked the experience of the influenza epidemic, whose 'only happy memory' was that of the home medical service (Balaguer, 1890, p208).

By the time of the great pandemic in the next century, the performance of the municipal health service was roundly criticized. A change of the service's director in mid-July 1918 had aroused opposition from *El Diluvio*, the Republican newspaper. By October of that year, *Diario de Barcelona*, a daily newspaper that usually defended government authorities, described the municipal medical services as 'deplorable'.[31] On 9 October, facing a dearth of medical personnel, the administration cancelled all leave and called back all staff professionals on duty.[32] It provisionally increased the staff with 20 new posts. Monthly reports of the home medical service show that it consulted 5 times more patients in October 1918 than in any previous month, while 20 per cent fewer people were recorded at the municipal dispensaries in October (12,749) than the monthly mean for the previous year (15,730).

Therapies could play a pivotal role in managing both individual cases and a broader health crisis. In 1889–1890 therapeutics followed the usual pattern for catarrhal respiratory diseases (diaphoretic, sedative and antitussive agents, as well

as better diet, rest and keeping warm), and it included extensive use of new chemical antipyretic remedies like antipyrine (first synthesized in 1883). Available sources do not disclose any discussion around therapy. In contrast, by 1918–1919, the higher mortality rate prompted considerable debate among Barcelona physicians, who were divided between a conservative, wait-and-see approach and a more aggressive therapeutic strategy. Supporters of the former approach criticized the enormous amount of 'imaginative (and costly) therapies dispensed' (Ribas Perdigó, 1918). One example of the latter was a proposal by Dr Freixas to inject colloidal gold and administer quinine salts, bleeding and diverse sera (Freixas Freixas, 1918, 1919). As Wilfried Witte (2003) stated in a recent paper on the response of German medicine to influenza, 'the principle of poly-pragmatism was applied: "try anything!"' Polytherapies produced a general shortage of medicaments and a complete dearth of antitussives and antipyretics, producing up to sixfold increases in prices. The Society of Pharmacists in Barcelona denounced the price spike (in which, for example, quinine derivatives prices climbed from 200–300 to 1200–1300 Ptas/Kg; codeine from 60–70 to 400–450 Ptas/100g; guaiac from 15—100 Ptas/100g).[33]

Furthermore, the microbiological rationale underlying the 1918 pandemic led to a search for sera and vaccines to stock the therapeutic arsenal against influenza (Porras, 2008). Thus, there was widespread administration of antidiphtheric serum, which had been proposed for use against Pneumonia by the French physician Charles Talamon in 1901.[34] Some physicians considered the serum suitable as a paraspecific serum to improve the general immune defences of influenza patients. The Royal Academy of Medicine of Madrid endorsed this therapy, but a Spanish Medical Commission that visited France in October 1918 found no evidence of its use there and hence ruled against its administration (Marañón et al, 1919). Jaime Ferran, a leading Spanish microbiologist, proposed normal horse serum as a paraspecific serum for influenza patients. Others searched for a vaccine using various pathogens, including 'auto-vaccines' developed from microorganisms isolated from the same patient, but without evident success.

Comparing public awareness of the two epidemics

In the 1889 epidemic, Barcelona's newspapers first used 'dengue fever' to describe the disease spreading throughout Europe, although they also mentioned influenza as a possible diagnosis. 'Dengue' thus became the common term for the disease in the first two weeks of December and persisted as a synonym for influenza, alongside the traditional Spanish *trancazo* or the French *grippe*, which in its Spanish form has now become the most common term (*gripe*).

The first reports in Madrid about the late 19th-century epidemic described the illness as an amusing diversion, as 'the disease of the moment ... a timely malady

that any person who appreciates the rules of etiquette and the duties linked to the *High Life* will rush to catch'.[35] Some well-known physicians attempted to convince the public that the disease was not severe, so long as patients sought out and strictly followed their physician's advice. On 30 December, Dr Xercavins wrote in *La Vanguardia* that recent news about the ravages and mortality of the disease in Paris and Madrid risked triggering 'a moral epidemic' that would be much worse than any infectious fever.[36] This statement – a common maxim in the medical literature on epidemics of any period! – propelled the editors to fight this 'moral and artificial' dimension of a 'natural, true and positive' epidemic.[37] In the Galenic tradition, the 'movements of the soul' were considered part of the necessary relations between the body and its broader environment; other such relations included sleep, nutrition and sexual and occupational life. These necessary relations were the first objective of medical counselling, which sought to effect a healthy equilibrium, since any excess could become pathogenic. In sociological terms, the damaged relations between the individual and broader society ('the body politic') could be manifested as a 'social disease'. Individuals' fears of disease became a public health risk as disease spread, and as a collective sensation, this fear was accompanied by feelings of unease and a lack of confidence in authorities, which became all the more dangerous in socially strained situations.

But by the New Year of 1890, views on the epidemic changed somewhat in Barcelona, as far fewer humorous observations appeared in the press. Nonetheless, composer Felip Pedrell i Sabaté's (1841–1922) private correspondence in early January 1890 reveals that educated Barcelona citizens still found dengue mostly a humorous topic. Despite having three members of his own household ill in bed, Sabaté appears to have been much more worried about the fate of his correspondent in Madrid (Gomez-Elegido Ruizolalla, 1984). Evaluations of the epidemic were not universally droll, however. On Christmas Eve, the press reported that 'the reigning malady continues to develop in family homes and some public establishments'.[38] The Charity House, the prison and the military barracks were host to such a large number of sufferers that they turned into hospitals. Many public servants stayed home sick, and there were some shortages in markets, shops and drugstores. Streets were unusually empty for Christmas time as the epidemic spread rapidly to the villages around Barcelona.[39] Elites also expressed considerable concern about the child-King's health, for he too had fallen ill with influenza. On 11 January, more than 1000 people gathered at the headquarters of the regional chief of the army and the chief of the civil administration, the governor of the province in Barcelona to call for the recovery of the King and to offer comfort to his mother. For their part, socialists considered the lethal effects of the reigning malady to be the consequence of generally poor living and working conditions for the working classes; any 'natural event, such as an epidemic, that breaks up normality' was seen to afflict the very foundations of society, producing the worst ravages among the poor.[40]

Public understanding of the 1918 epidemic stood in sharp contrast to those of 1889–1890. The 20th-century epidemic erupted in the midst of an ongoing social and political crisis, and political sympathies, particularly concerning government policies and activities, fundamentally shaped opinions about the epidemic. Madrid had already experienced the violent flu outbreak of May 1918, and by September, after the disease had spread throughout Spain during the late summer, few in Barcelona were in any mood to joke about the disease.

The Governor first issued a declaration of influenza on 20 September, offering only advice to avoid crowded places.[41] In the press, critics underscored the need to bolster disinfection equipment and to reinforce procedures to respond to the needs of the sick. In early October, the city implemented a broad plan of disinfection and isolation in railway stations, tramways, selected streets and public places. At the same time, existing scientific evidence emphasized the difficulty of containing the spread of influenza by general means, which eventually resulted in an emphasis on individual protection. New criticisms were now launched: the city had invested in now useless developments and material, but had expended no effort to pursue permanent solutions to the city's most severe public health failures, including the sufficient provisioning of piped water, the compulsory building of water closets, and the control of rising food prices and rents.[42] Speakers from the left accused the municipal government of carelessness in promoting and enforcing public health during the epidemic. And the Republic press mocked the city's efforts, deeming the city council the city's 'worst enemy' because it was unable to keep it clean.[43]

Hope in the power of modern medical science stimulated widespread demand for sera and vaccines, leading to a shortage of antidiphtheric serum for the most needy. On 23 October, the Interior Minister ordered Mayors to restrict its administration.[44] Both Liberals and Republicans had traditionally defended vaccination, as demonstrated by their support for the experimental human cholera vaccine that Ferran had tested in 1885. A vaccine produced by the Madrid municipal laboratory from pneumococci, streptococci and Gram-negative diplococci was used in 120 patients, and Republicans enthusiastically but unsuccessfully called for its administration in Barcelona (Piga and Lamas, 1919, p221). A leftist newspaper blamed 'the mayor's apathy, the governor's incompetence and the doctors' confusion'.[45]

City councillors debated the appropriate practical measures to be taken and the provision of funds. Their discussions followed broadly party lines, although certain groups were highly fragmented, such as the Republican Radical Party (RRP), the biggest minority at the time. When influenza broke out, the governing coalition of the left, formed by Radicals (including the mayor), Catalan Republicans, Liberal and other Republicans split, mirroring political cleavages in the central government in Madrid. By 23 October, the Radicals openly joined the Regionalists (moderate nationalists) to form the new de facto majority. The RRP, created in 1908, had developed as the fiercest enemy of the clergy and of nationalism; the party allied itself with the Monarchy and oligarchic capitalists, and during the Second Republic, it joined with the right-wing forces that contributed to the schism and ultimately led to war (Álvarez Junco, 1990). The RRP allied with diverse interests, and some of their representatives on the municipal council did not appreciate the shifting political alliances. Nor did they appreciate the health committee's policies, which they saw as partial. With the help of an active Republican press, namely *El Diluvio*, this faction pushed forward a fully comprehensive health plan to cope with the faulty organization of medical services and the lack of basic hygienic infrastructure. The entrance of Catalan Republican Lluis Companys into this municipal agreement paved the way for the Mayor to back a proposal to build compulsory lavatories in all houses at the owner's expense. When the municipal plan was revealed on 9 October, a Radical party spokesman advocated the use of coercion as the sole way to control the pandemic. Councillor Iglesias compared hygiene and culture, which could only be achieved *manu militari*, while councillor Vinaixa supported 'dictatorial means' when necessary. Days later, Llopis, a representative of the Liberal party, argued for a true 'sanitary dictatorship' to be imposed in order to vanquish the epidemic.[46]

The most common anti-flu measure promoted by authorities was a repeated call for people to keep calm and maintain a positive state of mind. For this reason, officials delivered news and commentaries in a moderate, relatively optimistic way. During September and the beginning of October, Governor González-Rotwes issued several notes refuting the existence of any major risk.[47] On 15 October, when the flu was almost universally present throughout Barcelona, unnamed 'individuals who hold positions in the public health domain' declared to *Diario de Barcelona* that the epidemic had diminished and was now more benign.[48] Any bad news, such as the elevated number of daily burials on 18 October, or expansion of the epidemic to a new urban district, was palliated by reports of a marked decrease in the total number of new patients. According to official information reproduced in the main newspapers of Barcelona, new patients had decreased in number since at least 13 October, and mortality had declined since 21 October.[49] As in 1890, the framing and dissemination of public information was influenced by threats of a 'moral epidemic' of fear as a contagious or psychosomatic risk.

Much of the general population explicitly resisted some of the anti-crowding measures. Despite the prohibition of football games and the cancellation of customary celebrations at cemeteries around 1 November, people defied these restrictions, and ultimately forced the government to concede to their demands that no restrictions be imposed on large traditional gatherings and celebrations, such as La Mercè in September or the Virgin of the Column in mid-October. A similar claim appeared in the official Socialist newspaper; while some socialist clubs were closed by force, 'coffee houses, theatres, casinos and churches' continued their activities unaffected by health regulations (Porras, 1992). The ban on keeping

hens, published multiple times and implemented by prosecuting citizens who refused to adhere to it, probably elicited as much popular resistance.[50] But wartime inflation had vastly increased the price of food and other supplies, and the popular classes adversely affected by this crisis were thus more likely to keep their own hens.

The most serious public problem resulting from the pandemic was the collapse of Barcelona's undertaking service. Unable to cope with the more than 4000 burials held during the first 20 days of October, coffins ran short, and hearses were always delayed, leading to several sizeable public protests and demonstrations. A strike of the anarchist Carpenter's Union made the situation worse.[51] The Red Cross and the Provincial Public Charities organizations had to cooperate with the one private funeral company that managed the service, while the leftist minority in the town council tried unsuccessfully to break that contract.

Conclusion: Looking back to see ahead

Comparing the two influenza outbreaks in Barcelona in 1889 and 1918 takes us closer to the tangled core of epidemic airborne infections. Airborne infections are impossible to avoid precisely because of their means of transmission. Human mobility and asymptomatic carriers facilitate the spread of infection, which can manifest itself in different ways, according to the particular social, political and scientific context. Both pandemics probably produced a similar number of infections, suggesting that it made no difference to transmission between no prevention at all (1889) and the disinfection and isolation measures so dubiously applied in Barcelona (1918). But the 1889 pandemic was of far shorter duration, and considerably less lethal than that of 1918. The 1918 pandemic produced considerable social disruption, and this not only depended on the pathogen's particular nature (the biological basis of the epidemic), but seems to relate directly to the simultaneous challenges to and conflicts between the existing political and scientific orders, and in relations between health authorities, practitioners and the public.

Between the late 19th and the first decades of the 20th century, health concerns gained visibility and consequently became increasingly politicized. One Professor Rodríguez Méndez (1919), who had lived through both crises, found fundamental differences in press coverage and perhaps broader social interest between the two epidemics, for in 1889, 'there was not so much writing about it' (p306), whereas in 1918 'the bells of the political press rang in excess and with harm' (p404). Such interest in the latter pandemic is not surprising, given both Spain's and Barcelona's tense and fractious political climate, where fragmenting political interests multiplied the viewpoints on health policy. Porras (1992) has found that the official journal of the Spanish Socialist Party followed events in the 1918 pandemic's second wave on a daily basis, in sharp contrast with its coverage with a single article of the 1889–1890 episode.[52]

The institutional status of public health greatly improved between 1890 and 1918, and it influenced medical experts' authority. In 1889, new biomedical explanations for disease transmission were on the rise, and there exists no evidence of competing public health strategies to control influenza; both the public and authorities agreed that prevention was impossible. But by 1918, authorities relied on an array of control efforts that aimed at either broad environmental interventions such as disinfection or individual protection. An internal conflict within biomedical circles over environmental interventions or individual protection was transformed into an open, public debate. Some members of the public accused the authorities of selecting the wrong practices to prevent influenza transmission. Others saw promise in the resolution of Barcelona's severe infrastructural problems, particularly the provision of drinking water, which authorities had apparently forgotten in their overwhelming concern for laboratory-based and environmental interventions. At the national level, the Socialist party backed a full hygienic programme, which subsequently appeared as a proposed law concerning infectious diseases (Porras, 1992).

A widespread sense of failure in controlling this great 1918 pandemic led to the goal of staffing and funding of a permanent public health service equipped with modern resources (Rodríguez-Ocaña, Martínez-Navarro, 2008). While 1889 and 1918 thus differed in how biomedical circles and the public understood the role of public health in controlling influenza transmission, both episodes generated demands to improve living standards for the working population. The amelioration of a working class standard of living remained the best prophylaxis against disease.

The most problematic intervention in the 1918–1919 influenza was the anti-crowding measures. Authorities adopted a mostly pragmatic approach, which led to a highly uneven and inequitable implementation of these measures. They closed public teaching centres but not private ones; they tolerated massive religious demonstrations but prohibited football games. This pragmatic strategy did not help to promote a general understanding of the risks of transmission, and the Socialist newspaper underscored the inherent conflicts between religious observance and scientific counsel over the prevention of the epidemic (Porras, 1992, p133).

Although the 1918 crisis sharply contrasts with the 1889 epidemic because of its high mortality, the lack of preventive measures in both pandemics put the main focus on providing medical care. The 1889–1890 pandemic witnessed new institutional strategies such as home care, which eventually became permanent. Municipal charities, always underfunded, were severely overstretched during both epidemics even though their efforts were supplemented by private charities. By 1919, it was clear that the charity system had failed to cope with popular needs, galvanizing national proposals to develop social health insurance. The deep sense

of failure following the 1918–1919 epidemic fuelled considerable medical agitation to reform health policies and public health organization in the period up to 1920 (Rodríguez-Ocaña, 2007). Although neither the modernization of the public health service nor the birth of social insurance was immediately attained, both goals entered social medicine thinking and fuelled the actions that shaped Spain's health panorama until the late 1950s (Rodríguez-Ocaña, Martínez-Navarro, 2008).

As this comparative analysis shows, major health crises can yield contradictory results. In the short term, they can exacerbate fears and lead to a loss of confidence in experts and institutions. But in the long run, however, their memory serves to keep communities alert and willing to address public health problems.

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Notes

1 Medical discussions celebrated by the Royal Academy of Medicine and the Academy of Medicine and Surgery in Madrid in February 1890 show the debate between the old (atmospheric condition, of imprecise description) and new (microbiological) conception of the disease. *Revista de Medicina y Cirugía Prácticas* (1890), vol 26, pp256–264, 309–318, 366–374, 410–411, 419–424, 476–485, 535–539, 590–595, 637–638; vol 27, pp80–91, 413–416, 474–480, 528–533.
2 Official certifications of the state of the city's health are kept in the municipal archives. IMHC, series Gobernación, folder D, 1286.
3 *Actas de la Junta de Gobierno*, Colegio Oficial de Médicos de la Provincia de Barcelona, Libro 5, acta no 392, 8 August 1918, p126.
4 *Diario de Barcelona*, 26 September 1918, p11563.
5 There were provisions to record clinical activities related to the influenza epidemic in 1918, but these were never implemented. On 9 November, the Royal Academy of Medicine and Surgery of Barcelona heard a proposal by Dr Suñé for an epidemiological inquiry in Catalonia concerning influenza, but it was never developed.
6 *La Vanguardia*, 12 November 1918, pp4–5.
7 Mortality statistics were published in 1922, as Volume 17 of the *Anuari estadistic de la Ciutat de Barcelona* (statistical municipal yearbook), including data from 1918, 1919 and 1920.

8 'Academia de Medicina de París, sesión de 17 de diciembre de 1889', *Revista de Medicina y Cirugía Prácticas*, 1890 (1), vol 26, pp91–94.
9 'Sobre la Epidemia Actual', *Revista Española de Medicina y Cirugía*, 1918, vol 1, pp185–189, 233–241; *Anales de la Real Academia de Medicina y Cirugía de Barcelona*, 26 October 1918, pp194–199, 31 October, pp200–206 and 9 November, pp207–212.
10 'Academia Médico-Quirúrgica Española. Sección de Medicina. Sesión del 6 de febrero de 1890. Estado sanitario de Madrid durante los últimos meses de Diciembre y Enero', *Revista de Medicina y Cirugía Prácticas*, 1890, vol 26, pp258–264; 'Revista española. Sociedades científicas. Real Academia de Medicina de Madrid. Sesión literaria del 15 de Febrero de 1890', *Revista de Medicina y Cirugía Prácticas*, 1890, vol 27, pp366–369.
11 'He aquí el extracto de la importante conferencia que, ... dio en el Ateneo Barcelonés el Dr Martí', *La Vanguardia*, 29 January 1890, p2.
12 'La semana burguesa', *El Socialista* (Madrid), 10 January 1890, p1.
13 Dr José Ubeda at the Spanish Hygiene Association (session April 3), *El Siglo Médico*, 1917, vol 64, p261. Dr Rigel in *El Heraldo de Madrid*, quoted by Piga and Lamas (1919, p73).
14 *Anales de la Real Academia de Medicina y Cirugía de Barcelona*, 1918, p197–99.
15 'El estado sanitario. La epidemia reinante. La naturaleza de la epidemia', *La Vanguardia*, 12 October 1918, p8.
16 'La mal llamada gripe española', *Revista Española de Medicina y Cirugía*, 1918, vol 1, pp189–192.
17 *Anales de la Real Academia de Medicina y Cirugía de Barcelona*, 1918, pp203–204.
18 See note 12.
19 Proposal on *Diario de Barcelona*, 3 October 1918, p11817 and *La Vanguardia*, 3 October, p5. Criticisms on '¡Qué dictadores sanitarios!', *El Diluvio*, 16 October, p8.
20 Archives of the City of Barcelona [IMHC], series Gobernación, folder D 436.
21 *Diario de Barcelona*, 20 September 1918, p11285.
22 *Diario de Barcelona*, 3 October 1918, p11813; *El Diluvio*, 14 October 1918, p9.
23 'El estado sanitario. La epidemia reinante. El servicio de estaciones', *La Vanguardia*, 19 October 1918, pp7–8.
24 *Diario de Barcelona*, 2 October 1918, p11778; *La Vanguardia*, 13 October 1918, p10.
25 *Diario de Barcelona*, 14 October 1918, p12273.
26 *La Vanguardia*, 19 October 1918, p7; *Diario de Barcelona*, 30 October 1918, p13046.
27 *Diario de Barcelona*, 14 October 1918, pp12275–76.
28 *Diario de Barcelona*, 18 October 1918, p12467 and 23 October, p12686; *El Diluvio*, 17 October 1918, p13; 18 October, p7 and 19 October, pp9–10.
29 'Rendición de cuentas de la comisión sanitaria, a 9 de octubre', *Diario de Barcelona*, 10 October 1918, pp12105–09; *El Diluvio*, 17 October 1918, p.13; 'La gripe', *El Diluvio*, 13 October, p.15.
30 'Páginas para las Damas', *La Vanguardia*, 7 January (afternoon edition), 1890, p1; 'Notas locales', *La Vanguardia*, 9 January (general edition), p2.

31 *El Diluvio*, 15 July, 1918, pp6–7; 16 July, p6; *Diario de Barcelona,* 15 October, 1918, pp12312–12313.
32 *Diario de Barcelona,* 9 October, 1918, p12095.
33 'La isla de los ladrones', *El Diluvio*, 26 October, 1918, p9; *Diario de Barcelona*, 25 October, 1918, p12813.
34 'Traitement de la pneumonie par le sérum antidiphtérique', *Bulletin et mémoires de la Société médicale des hôpitaux de Paris,* 1901, 3e s., vol 18, pp166–190 and *Médecine moderne (Paris)*, 1901, vol 12, pp65, 73.
35 *La Vanguardia*, 16 December 1889, (morning edition), p3. The original reads: '*la oportuna dolencia, que se apresurarán a contraer cuantas personas aprecien las reglas del buen tono y los deberes que impone la* high life'.
36 'La epidemia reinante y la opinión pública', *La Vanguardia*, 30 December 1889, main cover.
37 'Notas locales', *La Vanguardia*, 30 December 1889, p2.
38 *La Vanguardia*, 24 December 1889, (evening edition), p2.
39 *La Vanguardia*, 29 December 1889, p2.
40 See note 12.
41 *Diario de Barcelona,* 20 September 1918, p11285; *La Vanguardia*, 21 September 1918, p5.
42 *El Diluvio*, 1 October 1918, pp7–8; *Diario de Barcelona,* 9 October 1918, p12054; *El Diluvio*, 9 October 1918, pp6–7.
43 Complaints regarding the municipal mismanagement of public health are repeatedly found in the newspaper *El Diluvio*. See, for instance, 'Ornato público e incuria', 12 October, p8; 'Atrocidades sanitarias', 14 October 1918, pp8–9; 'La salud pública en el distrito VII', 17 October, p7 and 18 October, p10; 'Contra la higiene y la moral', 24 October, p6; 'La limpieza callejera', 25 October, p6.
44 *Diario de Barcelona,* 24 October 1918, p12741.
45 *El Diluvio*, 5 November 1918, p7.
46 'Informaciones de Barcelona. Ayuntamiento. La sesión. La cuestión sanitaria', *La Vanguardia*, 10 October 1918, p6, and 17 October, p8.
47 *Diario de Barcelona,* 18 September 1918, p11190; 26 September, p11549; 28 September, p11645; 2 October, pp11778, 11805; 4 October, p11894.
48 *Diario de Barcelona,* 15 October 1918, p12313.
49 *Diario de Barcelona,* 18 October 1918, p12471; 24 October, p12741; 25 October, p12874. *La Vanguardia,* 13 October 1918, p8; 16 October, p8; 18 October, p8; 19 October, p7; 21 October, p5; 22 October, p8; 23 October, p8; 25 October, p8.
50 News of confiscated animals seized by the municipal police in *La Vanguardia*, 30 October 1918, p6.
51 *La Vanguardia*, 12 October 1918, p8; 'Las pompas fúnebres', 14 October, p6, 17 October, p8; 'La epidemia reinante. Manifestaciones de protesta', 18 October, p8; 'La epidemia reinante. La conducción de cadáveres', 21 October, p5 and 'Un conflicto', p6.
52 Dr Ricardo Campos, oral communication.

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3

Prevent or Heal, Laissez-faire or Coerce? The Public Health Politics of Influenza in France, 1918–1919

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What are the fundamental lessons to be gained from the histories of public health when they are applied to pandemics in national contexts? (Porter, 1994). As a way of offering insight into this question, this chapter situates itself in recent scholarship that examines connections between science, medicine and the military (Harrison, 1996; Cooter, Harrison and Sturdy, 1999; Cooter, 2004); it provides a broad framework for exploring the relationship between knowledge about disease, public health interventions and cultural representations of infection. The 1918–1919 pandemic in France saw a shift in ways of thinking about the influence of the bacteriological laboratory and about the understanding of infectious disease as a public health problem.

What is currently at stake in mobilizing this past? These days, the Spanish influenza episode of 1918–1919 is invoked as testimony to the peril that could occur today. Yet its expression is confined most often to a topos, a stock phrase, 'The Spanish flu was more deadly than the Great War itself'. This formula, so often repeated, offers little comprehension of the phenomenon itself because of the historical incommensurability of the two events. In fact, French historiography has remained astonishingly silent about this unparalleled epidemic, expressing hardly any interest at all in the episode, although there is no doubt that it profoundly affected both France's social fabric and its culture of national hygiene. If the historical literature has been remiss in reducing this event to a parenthetical ending to the war, popular historical memory retains vivid recollections of the 'Spanish flu'. This memorial phenomenon is not without its analogies. Not only did it overlap chronologically with the war, but its memorialization has coincided with an extraordinary resurgence of interest in French society for the 'event of the Great War', a phenomenon that historians have analysed as a 'return of a repressed memory' among the third generation following the war (Audoin-Rouzeau and Becker, 2002). Numerous families have retained individual memories of this

epidemic, transmitted their stories to subsequent generations, and at times experienced a period of prolonged mourning, participating in the formation of a collective and deeply moving history from fragments of individual experience. Currently, when history and memory often conflict, it is not surprising that any reference to the great pandemic of 1918 privileges emotional recollections of this event and seeks to come to grips with the 'lived'; it appeals to personal testimony rather than making any kind of contribution to history. The historian Lucien Febvre reminds us that 'forgetting is a necessity for societies that want to live', and that counter to popular belief, history furnishes precisely 'the means of organizing the past to keep it from weighing too heavily on the shoulders of men' (Febvre, 1992). So that the burden of mass death caused by great pandemics does not crush the living, it is important to restore historicity to our analyses of this event. Thus, the Spanish influenza can instruct us about thresholds of individual and social sensitivities, about perceptions of health risk, and about the permanent recasting of notions of protection and threat between the self and the other.

The influenza pandemic in France: The construction of a public problem

Identifying the epidemic

As elsewhere in the world, France was affected in 1918–1919 by several successive pandemic waves. It was in the army that influenza first emerged – although this should not surprise us, since during wartime the health surveillance system paid careful attention to the state of health among the troops. After the first case was identified in the Third Army in Villers-sur-Coudun (near Compiègne, Oise), influenza appeared to infect several units simultaneously from 10 April 1918 (Delater, 1923). When during April multiple cases were reported in a single army barracks in Fontainebleau in the French interior, the perception of an epidemic illness took shape. Nevertheless, the first sanitary measures were not taken until 10 May. The illness appeared in many locations on the front. In the following weeks, all armies and all military regions were affected, from those in Algeria to an expedition corps of the Army of the Orient. Cases were more numerous in the army zone than in the French interior. From 20–30 June the epidemic waned rapidly. The Health Service reported an end to the epidemic phenomenon in July, although cases continued to be identified.

The second wave was occasioned by alarming rumours coming from Switzerland and Spain about epidemic pathologies with very serious complications (Renault, 1918). In France, the first manifestations were identified on 30 July in Lorraine, and in August among armies in the east and then in the centre and north. The epidemic progressed in several directions at the same time. The most

worrisome developments for military authorities were those in which transmission moved from the back lines toward the front, from military trainees to soldiers on the front, where the first foci of infection appeared during the final days of August 1918. Serious forms of bronchial pneumonia, sometimes highly acute, developed nearly 24 hours after the onset of symptoms. In September and October, the number of cases increased, as did their severity. Weekly lists from the city municipal bulletins established that mortality peaked at the end of October. From November, the virulence of the epidemic diminished, but not until January 1919 was there a lull, characterized by a return to the morbidity levels of June–July 1918. Nonetheless, there was no return to the benign character of the first wave; influenza cases continued to be very serious. During the springs of 1920, 1921 and 1922, as new recruits joined the contingent, the army registered an upsurge in influenza cases, raising debates about whether these new cases constituted new waves or a resurgence of the 1918 epidemic.

Thus, the Spanish influenza catastrophe appears from our perspectives *a posteriori* to be a well-defined crisis, concentrated within a limited period of a few months, drastic and decisive, with clear beginning and end points. But it was not perceived like this at the time; rather it was experienced as an event that made its presence felt over time, a succession of crises and moments of respite. The episodic, indeterminate nature of the pandemic was reinforced by uncertainty about the pathological phenomenon of influenza; biomedical understanding of the flu was not at the time characterized by a unified, consensus-based knowledge. In addition, a hybrid configuration of priorities guided hygienic interventions during the pandemic, in which not only medical reason, but also unstable knowledge, military logic and administrative practice were applied.

One major difficulty lay in identifying the source of the pathogen because of the explosive character of the epidemic's onset and the multiplication of 'simultaneous foci of infection', a problem that deeply troubled epidemiologists. Was this a question of disease carriers? Of a single pathogenic entity or several? In fact, the pathogenic agent was not immediately understood, because of the difficulty of unifying dispersed phenomena within a single nosology. There seemed to be no direct link between the dispersed foci of infection, which could appear as a seasonal occurrence. The multiplicity of symptoms were established most notably in the decadal reports sent to the Health Service during the course of the first wave in the spring of 1918, wherein fevers (typhoid) and dreaded epidemic illnesses (cholera, plague and typhus) were evoked. Such explanations cast doubt upon a single cause of morbidity and a single pathology.

Two points are especially worth underscoring. First, there was the problem of bronchial-pulmonary (and neurological) complications: did people die from influenza or from its complications, in particular, pneumonia? The response to this question is decisive for the statistical analysis of the illness. Military authorities frequently expressed the complaint that:

> *Too often, in effect, our influenza statistics are unduly weighted with cases that are independent of influenza, and that take note of infections that are in reality due to pneumococcus or streptococcus. Too easily incorporated under the rubric of influenza, pneumonia, broncho-pneumonia, pleuro-pneumonia, pleurisy distort our official findings with an inexact label, whereas in the statistics of the Municipal Bureaux of Health, these illnesses appear on the contrary under their real denominations. The result is that the army is unjustly accused of sustaining influenza, while influenza is declared to be absent from civil populations.* (Vincent, 1922)

This uncertainty was reinforced by the fact that in France, influenza was not on the list of notifiable diseases. In addition, the case toll among the civil population escaped medical attention, particularly in light of the brevity of the illness.

Second, the term 'influenza' (*grippe*) was also at stake. The term possessed an almost performative value: to characterize an epidemic as 'influenza' – a banal diagnosis that both patients and doctors applied to all sorts of manifestations that were neither flu-like nor epidemic – diminished the symbolic importance of widespread mortality and morbidity. Medical discourse was thus used to put the disease into perspective, insisting on calling it 'influenza' so as to weaken the impact of the disease on the populations' spirits and to reduce the threat. In Paris, the Academy of Medicine was thus able to assert in August that since the disease was only influenza, it was 'relatively less serious' (Renault, 1918).

Besides, biomedical knowledge of influenza, which came as much from the domains of bacteriology and modes of transmission as from therapy, was unstable; neither did it reflect broad scientific consensus. In addition to knowledge acquired in clinics, research laboratories sought a unified bacteriological explanation for the disease, which was expected to lead to a mastery of the disease following the application of Pasteurian precepts: study the germ, isolate it and develop a vaccine or serum. Far from achieving a consensus, the controversy on the aetiological origins of influenza erupted in 1918. Two principle theses stood in opposition. The first held that influenza was a streptococcal or pneumococcal infection of the respiratory system. According to this approach, it was a question of relating the unknown to the known, which meant the influenza epidemic according to its Italian denomination in 1889–1890. Such was the position of the Academy of Medicine in the autumn of 1918:

> *The current disease is none other than influenza, so often noted in medical annals. The term Spanish influenza, currently employed, is certainly improper if it suggests that this is a question of a new disease. The clinic will show us identical characteristics to those that had been recognized at its first appearance. The epidemic will illuminate the conditions involved in propagation, so prominently displayed during the epidemic of 1889. Bacteriology will demonstrate the intervention of cocobacillus, which Pfeiffer introduced into our knowledge in 1892.* (Netter, 1918)

In 1892 Richard Pfeiffer, a student of Robert Koch, had identified this alleged influenza bacillus in the sputum of influenza patients. The other thesis held that influenza was a highly specific, individualized disease, an entity provoked by an as yet unknown factor.

During the 1918 epidemic, in the absence of a bacteriological consensus, the controversy was fuelled by multiple experiments contradicting the very presence of Pfeiffer's bacillus. This explanation was finally disproved by the experiments of Charles Nicolle and Charles Lebailly of the Institut Pasteur in Tunis. Nicolle and Lebailly communicated to the Academy of Science their finding of an 'invisible' or 'ultra-microscopic' agent (Nicolle and Lebailly, 1918; Tognotti, 2003). Their conclusion, that of a 'filterable virus', became the dominant thesis for the aetiology of influenza in autumn 1918, relayed by the voice of the renowned French bacteriologist and immunologist, Emile Roux of the Institut Pasteur. Nevertheless, the identity of the pathogen remained an enigma.

In contrast to debates over influenza's aetiology, medical knowledge about modes of contagion further developed over the course of the epidemic and achieved a certain kind of consensus. Thus, human beings were the essential vehicle for the influenza germ, a direct and uniquely human product. Airborne contagion, through the projection of infectious dusts emitted by coughing, would almost always constitute the mode of transmission.

Influenza in wartime

Among the elements in this historical narrative of pandemic influenza, the epidemic and the war evidenced a notable interplay of dependence and causality. In addition to being a classic epidemic, pandemic influenza constituted a consequence of war and a major risk affecting the national and social collectivity, and according to the convictions of military headquarters, the health status of troops was a major strategic factor in the conflict. Its influences were amplified by the critical military events of 1918: the German offensives in the spring (along the River Marne, the German renewed threat to Paris and the farthest penetration of their military offensive in 1914), the Allied counter-offensive in autumn 1918, the arrival of an American expeditionary corps severely afflicted by influenza. Influenza thus contributed to the crisis, occurring at a decisive moment in the course of the war. It was sufficiently crucial to the development of the war that Ludendorff would later invoke the hypothesis that the German defeat could be attributed to influenza.

Also as a consequence of the war, the management of influenza took place within the military health organization, coordinated by high military command and the Under-Secretary of State of the Health Service (Rasmussen, 2007). The Under-Secretary of State, who came under the control of the Ministry of War, was in the hands of physician and politician Louis Mourier, who had succeeded

the radical reformist deputy of the Rhone, Justin Godard, in February 1918. Hence, there was no single medical institution: the acting authorities came from several ministries, which led to continual conflicts between the ministries of War and the Interior over the scope of their responsibilities and activities. Without a doubt, these incessant conflicts between political departments drove the institutional reorganization more than the prophylactic lessons of the influenza epidemic; the foremost consequence of these conflicts after the war was the creation of the unified Ministry of Hygiene, Aid and Social Pensions in 1920.

Some analysts have subsequently interpreted the weight of the war and the changing conditions that war exerted on the epidemic's management as in tension. On one hand, the war incontestably fitted into the meeting of circumstances that provoked a decline in health; conditions on the ground, declining hygienic conditions, intensified human mobility, or even the promiscuity of troops all bore witness to this decline. According to certain interpretations, influenza had acquired its extreme virulence because of the war. Some explained that these reasons were health-related, due to the 'medical privileges of the national army' (Murard and Zylberman, 1996; Zylberman, 2003), wherein medical efforts were expended on military personnel to the detriment of civil populations. Out of the 22,000 physicians in France in 1914, 80 per cent were mobilized to serve the nation at war. Their numbers would only increase during the war (Murard and Zylberman, 1996). The sanitary failure that constituted this epidemic (the inability to prevent and cure it) most violently affected deprived social classes, to the detriment of the preservation of the social collective, especially given the priority accorded to the military. Others have invoked biological explanations, contending that people were afflicted because they were weakened by four years of war. On the other hand, the 'militarization of hygiene' helped bring about an increase in resources dedicated to public health, following the conviction that good public health could protect the entire nation and that in the end victory would rest upon decisive contributions by the health services. Besides, the modes of thinking and actions engendered by war – a culture of emergency, of permanent mobilization, of optimization of human resources – were also applied to the management of the epidemic. And finally, the demographic tolls of the influenza pandemic attested to the fact that the nations most heavily affected were the non-combatant ones.

Lastly, the war provoked a close supervision of public space by a system of constraints and information control, most notably seen as censorship and propaganda and to which the term 'Spanish flu' bears witness. Although Spain was not the epidemiological origin of this influenza, its influenza outbreak in the summer of 1918 was the first to be recognized as serious, with 8 million people affected; in this neutral country, unaffected by press censorship, information about influenza circulated freely and was publicized in the media. This free circulation of information concerning influenza stood in sharp distinction to combatant countries. At the same time, the war proved favourable to the creation of a space

completely saturated with what Marc Bloch (1921) called 'false accounts' and flourishing rumours. Health information was evidently a most sensitive subject, primarily because it touched on the epidemic threat (called *Maladie 11* in military terminology). Military authority was thus caught in a dilemma: it could downplay the scope of this epidemic and contain rumours so as not to be alarmist, and not to divulge too much information to the enemy; and it needed to give the public sufficient information to ensure the adoption of its prevention policy and sanitary measures (Dauzat, 1919).

The underestimation of influenza as a public health problem

If the 1918 influenza epidemic has gained little scholarly attention in France, it is primarily due to the fact that this cataclysmic event has not found a place in the West's grand narrative of 'epidemics laid low' (Bourdelais, 2006) and their ebb in the contemporary epoch. From its first occurrence in 1918, the epidemic does not fit with a history of health services' victories over wartime epidemics, a history opening up a new era in understanding and controlling infectious disease. In effect, the rapidity of this influenza outbreak called into question the bacteriological and sanitary triumphalism which during the war had established the laboratory as the driving force at the very least in this victory over infectious disease. For the first time, pre-war statistical certainty that disease kills more than fire was reversed. On the contrary, World War I witnessed an appreciable decline on this epidemiological front. The symbol of this triumph was the spectacular success of a systematic typhoid vaccination campaign carried out among the troops from spring 1915, and which was responsible for the near-disappearance of an epidemic that had raged as recently as 1914. In addition, when influenza struck, health services went into denial, not about the disease itself, but about its link with the war and thus the military responsibility for the outbreak. If Léon Bernard, the leading figure in French health and hygiene of the interwar period, could affirm in his 1929 report to the Carnegie Foundation that during World War I, the 'threats [of the great pathological scourges] were not realized, the violence of disease was stopped, contained and stamped out' (Bernard, 1929), then he clearly excluded influenza from the larger picture. In fact, in the postwar period, the threat of influenza largely disappeared from health agendas. Influenza did not appear to loom as a most fearsome infectious disease (whereas typhus and tuberculosis did on an international scale), nor did it figure in the global history of pathology.

Underestimating the significance of influenza has also been a historiographical problem. From this perspective, the platitude 'Influenza killed in a few weeks more than the war did in four and a half years' is not a universal truth: this was certainly not the case in France nor in other combatant countries more affected

by the war, with the notable exception of the United States. The great trauma, as much as in demographic statistics as in the consequent mourning, was the war. In France, the war claimed 1.4 million dead, in addition to 4.3 million wounded, close to 8 million men mobilized. In comparison, the 240,000 deaths from Spanish influenza (based on a 3.9 per cent mortality rate) were an additional trauma, albeit acute, but they could never overshadow the massive trauma of the war. Another interpretive element which served to undermine the epidemic's historical importance is the perennial underestimation of victims on a global scale, thus diminishing the significance of this pathological event. Since the first accounting in the 1920s (Edwin Jordan's (1927) estimate of 20 million deaths long constituted the most authoritative), the numbers have continually been revised upwards, based on more rigorous approaches (Jordan, 1927; Patterson and Pyle, 1991; Johnson and Mueller, 2002). Yet this history has long been written principally from the point of view of Europeans and Americans, who turned out to be far less affected than populations in Asia.If history has proved to be reticent on this topic, it is without doubt because of the dearth of sources to keep the record. While administrative archives and medical sources are abundant, those that can round out social history are hard to find. Influenza's rapid passage and disappearance 'as it had first come' accentuated still further the difficulty of understanding this disease in the absence of communities and social identities that might have constituted themselves around influenza and left their traces. From this standpoint, influenza is not like the 'social scourges' of syphilis, tuberculosis or other chronic diseases, leaving traces that are effectively readable in the social fabric. In addition, in the case of influenza, the most important role was played by military medicine, a medicine of the masses, not of the individual.

Sanitary management of the crisis

The prophylactic credo within the framework of a bacteriological paradigm

From the middle of the 19th century, the old – indeed ancestral – problem of geographical propagation of pathogens gave rise to responses leading to first attempts at international cooperation. Organizations and international health conferences developed, inspired by terror of cholera and its paralytic economic consequences. From the 1890s, the gains made in bacteriology, which emphasized the mechanisms of infectious transmission, seemed to support the sanitary theses concerning spatial restrictions, favouring a return to early 19th-century national policies characterized by sanitary cordons and maritime quarantines. Classic epidemic management in international space consisted of closing territory and exercising control over frontiers. The Great War created a form of

'globalization' which influenced the epidemic's playing field, provoking an unprecedented mobility of troops and other persons (prisoners, refugees and displaced persons). And yet influenza subverted the notion of national frontier and sanitary cordon.

In effect, in the predominantly intellectual context of medical thinking during the first decade of the 20th century, the laboratory had to be consulted for both influenza prophylaxis and treatment. Thus on 10 August 1918, the Under-Secretary of State ordered Health Service directors in all regions to furnish bacteriological examinations 'as complete as possible for all influenza cases'.[1] These examinations would offer a framework for putting into place prophylactic measures (Hildreth, 1991).

Within this framework, what were the principal public health measures? The first great directive of 10 September 1918 ordered that epidemic influenza, as well as its bronchial-pulmonary complications, drew from the same general prophylactic measures as other contagious diseases. The catchphrase here was rapid and rigorous isolation of influenza patients, based on 'individual preservation'. One model served as a reference for this measure: measles. Nevertheless, hospital isolation quickly appeared to be insufficient, since the hospital was considered a possible 'focus of infection' according to the concept in effect since the 1880s; it was therefore necessary to create new places of isolation. Military health authorities thus stipulated that influenza be considered a 'contagious' disease, although it was not at that time, since it was not on the list of 12 contagious diseases that were legally notifiable by the 1892 law to prefectures and reinforced by the public health law of 1902. Nearly one month later, during the height of the autumn influenza wave (Circular of 3 October 1918), isolation measures were reinforced: the separation of influenza patients from healthy people no longer sufficed; it was necessary also to separate the simple influenza cases from serious and complex cases.

The second keyword was that of disinfection, collective and individual (Bezançon, 1918). It involved first of all environment – the disinfection of all premises, of laundry and of bedding, hospital precautions, even the decontamination of public places through the spraying of antiseptics in schools and theatres. Additionally, military headquarters broadly applied hygienic measures for sanitation, which they had made a priority on the battlefield. Another watchword was individual disinfection, using preventive antiseptics in the mouth, throat and nasal passages.

One problem, however, undermined these preoccupations. Although the aim was to 'isolate and neutralize the person who coughed', someone with a serious case of influenza effectively infected the 'microbial atmosphere' that enveloped him once he spoke, coughed or sneezed. Hence, 'any person breathing in this infectious atmosphere is in a comparable situation to a soldier exposed to poison gas'.

It was calculated that beyond 1m50 contagion diminished, and this measure served as the basis for spacing between beds and lines of soldiers in order to impede transmission. Airborne contagion was emphasized, most notably in the work of the biologist Auguste Trillat of Institut Pasteur. Conducting experimental research on air and the condensation of respiration, Trillat formulated the hypothesis of transmission by air as a vector of influenza, describing air as 'the agent of transport of the microbe, but also the agent of their multiplication when the air holds the necessary quantities for their alimentation' (Trillat, 1918). Wearing gauze masks was recommended, but the measure was rarely applied in France, even among health personnel, who were very critical of masks.

The third watchword sought intervention using 'favourable circumstances' that might prevent a person falling ill with influenza: the distribution of warm drinks (tea, alcohol), supplementary food (an increase in bread rations), efforts to avoid excessive cold (heating), and excessive fatigue (reduction of hard labour and long marches).

Finally, the distinction between prevention and cure was blurred. The importance of acting on the environment, the insistence on reinforcing the 'defences of the individual', the massive medical investment in the preparation of vaccines (primarily pneumococcal) all figured simultaneously in prevention and therapy. These measures effectively called into question the distinctions between prevention and cure that had been affirmed prior to the epidemic. Thus, influenza partly catalysed a long-term transformation in epidemic imagery, grounding it in the notion of invasion.

A reconfiguration of the notion of prophylaxis

In the first place, the nature of the measures adopted changed over time. Efforts thus passed from isolation, a classic measure in the face of contagion that conformed to contemporary bacteriological knowledge of influenza, to measures addressing other modalities of transmission. The notion of disinfection echoed the resurgence of theories that one might describe, perhaps a little hastily, as 'miasmatic'. The goal was to act on the environment and on locations that encouraged infection among people. 'Terrain', defined as the constitutional and environmental factors that played a role in pathological transmission, was thus reviving. These theories came principally from the sanitary tradition of hygienists, who had established correlations between variables linking the local environment and epidemic outbreaks, as Pettenkofer had done in the previous century. The notion of favourable circumstances reflected theories that had underscored the concept of 'predisposition'; it thus downplayed infection as the sole causal explanation and held that environment could influence the transmission of contagious disease.

This resurrection of the environment idea did not mean that people were simply consigned to resuscitate 19th-century theories. But there was a real revival of

elements in the older explanations applied to the new questions that this influenza pandemic raised. Most notably, such questions included influenza's exceptional capacity to spread, its contagion via the respiratory tract, and its problematic relationship with carriers of the disease, a key element in the bacteriological hypothesis that had sought to identify the origins of disease since the first decade of the 20th century. Thus, efforts to control typhoid and diphtheria had investigated suspected carriers of the disease, the segregation of whom constituted the central basis for prophylaxis. On the contrary, in the epidemiological descriptions offered of pandemic influenza, the role of healthy carriers was not central and provided no explanatory insight. The unusual character of this influenza epidemic seemed to be corroborated by the sudden and sporadic appearance of illnesses without any apparent intervention of healthy carriers, as in cases of encephalitis or cerebrospinal meningitis.

Then coercive measures from the past – such as military sanitary cordons, prohibition of human mobility, border controls – were abandoned. Both civil and military authorities in France renounced the sanitary cordon. And because the virus had already spread through France, on 12 August 1918 the High Council of Hygiene decided not to close the country's borders nor to impose quarantines, undertake disinfection (instituted for the most serious infectious diseases), require health passports or enforce surveillance on immigrants after their arrival in the country (Delater, 1923).

For French health authorities, preserving the social bond – the national bond during wartime – remained a categorical imperative. Although they lacked the tools necessary to define a prevention policy and effective therapeutic intervention, French health authorities never privileged coercive alternatives (for instance, isolating suspected cases) that had been used in Germany during anti-typhoid campaigns. Thus, military headquarters vigorously defended military leaves, even though they knew that troops on leave were a major focus for disseminating the virus and contaminating civil populations. Even at the epidemic's height, despite the Health Service's recommendation to the contrary in September 1918, these permissions were maintained.[2] The social community's support for the war, so necessary for national cohesion over its duration (what contemporaries called 'maintaining morale'), took precedence over the preservation of health, which for the military collective meant not completely sacrificing individual choice of the citizen-soldier over his own body (Smith, 1994; Harrison, 2004).

These policies were partly in response to a military problem, since at this strategic moment in operations, it was impossible to attempt to limit soldiers' mobility. On the other hand, it corresponded to a shift in the intellectual and scientific representation of contagion, as Andrew Mendelsohn (1998) has pertinently argued. This moment was witness to a transformation of the Western experience of epidemics; previously populations lived through pestilences that came from distant locations, for example, cholera, which in the 1890s had permitted

Koch to elaborate the dominant bacteriological vision of epidemic before the war. Yet now influenza was perceived as an epidemic where the threat was very close at hand and operated from within. This perception had been reinforced by the influenza virus's respiratory nature: a virus always in existence, both ubiquitous and seemingly universal. From the viewpoint of intellectual understanding of the pathology, reform of the bacteriological model manifested itself as replacing monocausation by multicausation, where environmental factors were added to that of contagion. Within the context of an influenza pandemic, 'the relationship between bacteriology and epidemiology – between the laboratory and the field, microbes and epidemics, the seed, the soil and the environment – became subjects of intense debates' (Amsterdamska, 2001). Nevertheless, it was unclear if lessons in the field of public health could be learned.

Epilogue: What lessons from influenza?

During the 1920s, health and medical administrations published their accounts of the epidemic so as to draw lessons for the next pandemic. The most ambitious reporting came from Great Britain (Ministry of Health, *Report on the Pandemic of Influenza*, 1920) and the United States, most notably from the bacteriologist Edwin Jordan of the American Medical Association and, after the influenza virus was discovered, from Burnet, Clarke and Melbourne (1942), who offered a medical study on the preceding 50 years of influenza. Following these reports, influenza became a widely-recognized symbol both of the failure of health policies and of medical impotence. Léon Bernard underscored this point in 1929 in his report dedicated to 'the defence of public health during the war':

> *The efforts to control influenza resulted in a failure in our country as it did everywhere else, and the study of the prophylactic measures implemented has been dominated by this notion of failure. The cause of such a manifest failure was our ignorance concerning this disease, an ignorance almost as fundamental as that of our ancestors who succumbed to the deadly epidemics, without ever being able resolve the puzzle.* (Bernard, 1929, p146)

The conclusions of the April 1919 report to the International Office of Public Health, derived from a questionnaire about the 1918 influenza pandemic that had been administered to all health administrators, confirmed this point:

> *Overall, the prophylactic measures taken against influenza do not seem to have exercised any notable influence over the course of the pandemic ... None of the prophylactic measures suggested or adopted inspire much confidence. Perhaps, taken as a whole, they contributed a little to diminish the violence of the epidemic and helped doctors, nurses, all health services to control it.* (Rapport Pottevin, cited in Bernard, 1929, p146)

These conclusions paradoxically encouraged a reorientation towards other health priorities. Influenza was absent from the most important epidemiological and sanitary preoccupations during the interwar period; the principal treatises and manuals effectively closed the chapter on influenza without ever evaluating new research, and the international sanitary institutions reconfigured with the League of Nations now focused on typhus, tuberculosis and the problem of malnutrition as the most pressing priorities. So, the parenthetical chapter on influenza closed again, a natural catastrophe from which no public health lesson was usefully drawn, but which nonetheless remained in the memory of its victims.

Endnotes

1 Sous-secrétariat d'Etat au Service de santé militaire aux Directeurs du Service de santé de toutes les régions, 10 August 1918. Archives du Service de santé des Armées, Val de Grâce, Paris. Carton 813.

2 Sous-secrétariat d'Etat au Service de santé militaire aux Directeurs du Service de santé de toutes les régions, 10 September 1918. Archives du Service de santé des Armées, Val de Grâce, Paris. Carton 811; Compte rendu de la réunion de la présidence du Conseil au sujet des mesures à prendre contre l'épidémie de grippe, 16 October 1918. Archives du Service de santé des Armées, Val de Grâce, Paris. Carton 813.

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Comment: Influenza Epidemics and the Politics of Historical Analogy

Patrick Zylberman

Indelible, yet not commemorated

Trying to explain why during the autumn of 2009 public opinion in most wealthy countries rejected the H1N1 flu vaccine, Dr Oshinsky, professor of history at the University of Texas, may have offered one important clue. Comparing the present day campaign with polio vaccine trials of 1954, in which American parents volunteered more than a million children to receive either an experimental vaccine or a placebo, he said: 'They also had lived through virulent epidemics. That to me is probably the biggest issue of all. [Nowadays] You're dealing with parents who've never seen a smallpox epidemic, a polio epidemic' (Klass, 2009, D5). People today have completely forgotten what epidemics were like in former days, thanks to vaccination.

Yet there is nothing new about the erasure of memories of epidemics. However terrible, the 1918–1919 influenza pandemic was quickly forgotten. But is 'forgetfulness' really the appropriate word here? According to Paul Ricœur, people obliterate fewer memories than one might imagine or fear. Traces of the past are not exactly erased; they are only unavailable, inaccessible. By contrast, almost every epidemic revives memories of past outbreaks. It bolsters our hunt for historical analogies. In 1919, two forensic doctors from Madrid tried to understand the waning pandemic by comparing it to the previous pandemic of 1889–1890 (Rodríguez-Ocaña, this volume). The hunt for analogies was even more frenetic during the swine flu scare of 1976. Between 19 January and 9 February 1976, 230 new recruits between the ages of 17 and 21 showed signs of respiratory infection on a New Jersey army base. Thirteen were admitted to hospital. On 4 February, one of the patients died from viral pneumonia. The outbreak fizzled out in February but the virus was the same A (H1N1) subtype as the Spanish influenza virus, which had not been present in humans since 1920 (Gaydos et al, 2006). The similarity of the viruses again triggered a search for historical likenesses. 'The great influenza epidemic of 1918 figured in the swine flu scare of 1976', noted the

historians of this episode, as a 'captivating analogy' (Neustadt and May, 1988, p48). Again, the same was true with the 2003 SARS (Severe Acute Respiratory Syndrome) epidemic, which, as Esteban Rodríguez-Ocaña writes, 'provoked a concomitant interest in the history of influenza'. The 2009 influenza pandemic will set into motion an identical mechanism. Soon after the first cases were detected in France (29 April), and in keeping with the pandemic plan, the Minister of Interior took control. At one cabinet meeting, the compulsory vaccination of every person over three years of age and the requisitioning of physicians and nurses were discussed. It was thought that the situation might become catastrophic: the 1918 flu was on everyone's mind (Zylberman, 2009a). Only a few years earlier in 2005, when anxiety about avian flu had reached its peak, the new WHO coordinator for influenza did not hesitate to predict between 2 and 150 million deaths should an avian flu pandemic descend upon humanity. A few months before that WHO itself offered its figure of choice: 50 million deaths 'as in 1918' (Nau, 2006)! 'As in 1918' came to be the tune, the strains, and the logo of the entire period. Past experience of epidemics has been preserved in the collective memory, silently consigned to a sort of 'oblivion playing the role of a latent reserve' (Ricoeur, 2000, p541), from which present-day experience, rightly or wrongly, draws.

Was the influenza pandemic of 1918 forgotten? Probably not. But it is true that it was never commemorated. Indeed, neither physicians nor politicians had any accomplishments to celebrate. Putting an end to the 'mentality of forgetting' (Crosby, 1976; Witte, 2003, p57), which had so far been the signature of the historiography of influenza epidemics, 'Asian' flu (1957), the second pandemic of the 20th century, aroused a deep anxiety about the recurrence of a 1918-type disaster and aroused the interest of historians of influenza (Phillips and Killingray, 2003, p15).

There is nothing like the definitive forgetfulness of modern influenza epidemics. People usually forget very logically and very naturally past flu pandemics during interpandemic periods. But they don't need professional historians to remind them to consider ancient flu outbreaks when a new one afflicts them. It takes a new epidemic – not a new history book – to reawaken memories of past epidemics sleeping in the collective, family and individual memory.

Learned memory and folk memory

Searching for past analogies is usually one of the major concerns of historians. It is also a matter of concern to the individual and collective sense of epidemic risk. Denying risk very often takes advantage of historical comparison: such was the case in Germany at the end of May 1918, when the disease was deemed similar to the one in 1889 and thus declared a minor disease (Witte, 2003, p49). Worst-case

scenarios are also frequently based on analogies: it should suffice here to cite yet again the series avian flu-SARS-1918 influenza pandemic. Why this thirst for historical comparison?

Data seem to invite comparison. Epidemiologists repeatedly use what has been called 'incorporated comparison' (McMichael, quoted in Olstein, 2008, p29): instead of juxtaposing data to be compared, the analogy is drawn between intrinsically connected data, for instance, two epidemics featuring two viruses 'antigenically related' (Dr D. J. Sencer, Director of the Centers for Disease Control (CDC), quoted in Neustadt and Fineberg, 1983, p19). In 1976, the virus resembled the 1918 virus (H1N1) that killed more than 500,000 Americans, while in 2009, influenza morbidity and mortality struck those age groups where victims had been most numerous in 1918–1919. Besides learned 'memory', folk memory also plays an important part (Neustadt and May, 1988, p56). In fact, political casuistry (subjective probability and memory) would increasingly get the better of technical casuistry (objective probability and history).

Current sources tend to convey a conflicting picture of learned opinion at the time of the 1976 swine flu scare. According to Richard Krause, then Director of the US National Institute for Allergies and Infectious Diseases (NIAID), in February 1976 experts from the CDC, NIAID and Merck agreed that there was a risk of a pandemic 'perhaps similar to the pandemic of 1918'. There was considerable alarm (Krause, 2006, p41). Nevertheless, in his memorandum to the White House, the director of the CDC, Dr David J. Sencer 'specifically underemphasized the specter of the 1918 pandemic' (Sencer and Millar, 2006, p30). At the same time, he underscored a 'strong possibility' of a pandemic virally related to 1918 (Neustadt and Fineberg, 1983, p19). In contrast, Dr Walter Dowdle, then chief of the virology section at the CDC when the A/New Jersey/1976 subtype was isolated, claimed that on 10 March 1976, 'the Army provided data to the US Advisory Committee on Immunization Practices that confirmed person-to-person transmission of swine influenza virus. The single swine influenza death loomed large, although most cases were mild. No one at the advisory committee meeting equated the disease potential of this [1976] virus with 1918' (Dowdle, 2006, p35).

At the time, debate centred around the measures that the country should take in the absence of tangible signs of an imminent epidemic. Experts had difficulty in quantifying a vague possibility. The press and Congress toyed with the image of the Spanish flu and its horrors like a poisonous prophecy. Dr Theodore Cooper, Assistant Secretary for Health and a cardiologist, linked the 1976 swine flu and 1918 in a note addressed to the White House. Basing himself on a fashionable theory, he wrote that severe influenza epidemics occur approximately every ten years. Cooper's father, himself a doctor, had told him about certain painful reminiscences of 1918, such as soldiers burying flu victims en masse in Pennsylvania where he grew up. What might possibly happen suddenly became a real threat

based on past events, which he remembered vividly. True-to-life, memories were regarded as a sound basis for predicting the future. Calculating probabilities was never part of the decision to launch a preventive mass vaccination campaign in 1976. 'Expertise counts for a lot', wrote the two historians of swine flu, 'but only by way of informing subjective judgement'. In their view, the subjective probability (the image of 1918) would 'in any case' have won the day (Neustadt and Fineberg, 1983, p88). In this game played by learned and folk memory, historical comparison ('as in 1918') appears more as a kind of seductive or intimidating trick than as a way of hunting down a useful analogy.

The history of influenza takes an external route

We are not dealing here with social history. Too often social history satisfies itself by framing epidemic infectious diseases against the backdrop of an ethnography of social and cultural practices (Halévi, 2007, p72). Instead, we need comprehensive historical enquiries about the governance of infectious diseases (among the few examples, see Baldwin, 1999). A few years ago the disciplines of virology and molecular biology revealed important historical information (see, among other examples, Oxford et al, 2002; Taubenberger and Morens, 2006; Morens and Taubenberger, 2009). Concomitantly the boundaries of historical influenza epidemic studies have expanded. The first ever conference on the 1918–1919 flu pandemic, held in Cape Town in September 1998 (Phillips and Killingray, 2003, p2), compared the internal, traditional route to influenza epidemic history, with the external, problem-solving, pragmatic approach mainly oriented toward contemporary history.[1]

External history is never shy of revisiting classics. Because 'new microbes and mutant germs imperil health and the survival of human species, ad infinitum', according to the epidemiologist D. A. Henderson, the history of epidemics forms a seamless and endless line, past, present and future. Conversely, many infections are evitable ones, as virologist Stephen Morse reminds us. He considered 'traditional' public health measures to be helpful if applied in a coherent and universal way (Morse, 1993, p20), in the way that quarantine would demonstrate itself to be efficient some years later during the SARS epidemic. Everything repeats itself, despite the fact that changes are incessant, Henderson insisted. 'Some questions that we ask ourselves today have been raised at least once.' The return of problems allows us to return to old ideas. Not knowing what new measures to take when confronted by the originality of unexpected situations, we draw on these old ideas, or on what Paul Valéry (1960, p917) called our 'imaginary memories'. In a clear illustration of this characteristic reaction, the US Assistant Secretary for Health sent President Gerald Ford a copy of Alfred Crosby's *Epidemic and Peace, 1918* early in the swine flu scare of 1976. Crosby's book was one of the first books, if

not *the* first, to describe the Spanish influenza as an historical issue, and it was published in 1976, just at the time when the first swine flu cases occurred.

Looking back for analogies, external history based on the theory of emergent viruses thus provided new templates and concepts. Not by accident, the historicization of epidemics is coterminous with the notion of emergent disease. In an age of uncertainty, we cling to anything that can provide comfort and show us the way forward. And why should we not cling to historical precedent (MacMillan, 2009, p15)?

Making good use of historical comparison

Who controls analogies? According to the historians of the 1976 swine flu scare, the experts were in full control of the analogies. Dr David Sencer, the head of the CDC, organized a group bonded by deference. Attached to the CDC, the Advisory Committee on Immunization Practices was described as 'a clubby group and deferential' to its chair, Sencer himself. Argument was banned, and no dissenters could gain access to President Ford. Unanimity made the conclusions of the experts a *sine qua non* for Ford. Yet the media, Congress and medical opinion also competed to control the historical analogies. They found themselves in conflict with government experts. Such developments may explain why, far from shedding light on the present, historical comparison can sometimes be deceptive. In the management of the 2009 flu pandemic, any analogy with 1918 has been especially misleading. In July 2009, Britain's Chief Medical Officer, Sir Liam Donaldson, published a worst-case scenario suggesting the United Kingdom would suffer 65,000 deaths. This prediction was revised downwards twice, first in September (19,000), then in October (1,000). As the 2009 pandemic has progressed, however, it may turn out to be the weakest in history, at least for now (Laurance, 2009).[2] With respect to the politics of epidemics, historical comparison should be analysed in the same way that Ricœur scrutinized the uses and abuses of memory and oblivion.

In order to correct mistaken hypotheses and perceptions, historical analogy should question implicit presumptions that lay people (and therefore politicians) tend to understand as facts. One must question whether the chosen analogy is a well-grounded one. Henri Bergson has very clearly shown why this questioning remains such an arduous task, when he observes,

> *While an event can always be explained, after the fact, by such and such a precedent ... how not to see that, under similar circumstances, other antecedents differently selected would have explained a wholly different event just as easily – nay, that the same antecedents, provided they had been differently arranged, differently distributed, and differently regarded by a retrospective attention, would have explained a new development just as handily?* (Bergson, 1959, p1343)

In conclusion, historical comparison is one strategic variable in the process of public health decision making. But historical analogy has value only if it helps us to disentangle quickly likenesses from differences, and in so doing, to do away with false analogies and to make sure we do not take likenesses for likelihoods (Neustadt and May, 1988, p56). Historical comparison is interesting and useful in that it compels us to emerge from ourselves and to identify the days of old for what they are: a world alien from our own in many ways (Veyne, 1976, p13). 2009 is not 1918 (Zylberman, 2009b, p15).

Notes

1 This conference had been inspired by the work of K. David Patterson (1986).
2 If confirmed, this trend would corroborate the hypothesis of a global downward trend in flu mortality, recently argued in Doshi, 2008.

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Comment: Influenza and Historians: A Difficult Past

Ilana Löwy

New visibility of an old pandemic

The 1918–1919 influenza pandemic (as well as earlier outbreaks of this disease, especially in 1889–1890) was simultaneously a highly visible and a partially hidden event. It was difficult to hide the full hospitals and nearly paralysed economies, mounting piles of cadavers and coffin shortages. Yet these relatively brief epidemics of an acute illness did not favour the development of disease-centred identities: the effects of the 1918 pandemic blended with other war-related disasters; the global number of the dead was very high, but most sick people recovered, and high mortality in 'peripheral' countries such as India was not immediately visible in the West. Despite numerous articles in professional journals and the general press – important direct and indirect political consequences of the 'Spanish flu' – it became a forgotten pandemic, or as Anne Rasmussen aptly puts it, an event that was invested in strongly by memory, but weakly by history. The oft-repeated statement, 'the Spanish Flu killed more people than World War I', provided a glib and superficial conclusion that masked the absence of serious scholarship. But this is no longer true. Over the last 20 years, there has been a growing interest in past influenza pandemics, and particularly that of 1918, among virologists, molecular biologists, epidemiologists and demographers, as well as historians.

Scientists literally resuscitated the virus. Studies of viral fragments discovered in the frozen bodies of influenza's victims and laboratory experiments with reconstructed viruses have produced several intriguing but inconclusive hypotheses about the reasons for the 1918–1919 pandemic's exceptional virulence. At the same time, historians have uncovered previously unknown sources, bringing to life many aspects of this pandemic. Anne Rasmussen's and Esteban Rodríguez-Ocaña's chapters are important contributions to a rapidly growing body of historical scholarship on influenza. My comment here will examine three questions: debates over the aetiology of the 1918 influenza pandemic; public health measures;

and therapies. It will focus on the difficulties of dealing with a complex story that offers neither uplifting conclusions nor clear-cut resolution.

Aetiology

The scientists' failure to identify the aetiological agent of influenza was a global phenomenon. It was also a long-lasting one. Some experts maintained in 1918 that influenza was induced by a bacterium, *Haemophilus influenzae* (Pfeiffer's bacillus), which had been identified in 1890; others claimed that the disease was produced by an unknown filterable virus (on the status of bacteriological knowledge, see Amsterdamska, 1987; Mendelsohn, 1996; Mendelsohn, 2001). The repeated failure to recover Pfeiffer's bacillus from all influenza cases strengthened the viral hypothesis, first proposed in a coherent form by Pasteur Institute researchers, Charles Nicolle, Charles Lebailly and René Dujarric de la Rivière (Dujarric de la Rivière, 1918; Nicolle and Lebailly,1918; see also Tognotti, 2003). Although many specialists were persuaded by Nicolle's, Lebailly's and Dujarric de la Rivière's experiments, others remained sceptical until the isolation of the influenza virus in the early 1930s.[1] Numerous French doctors, Rasmussen explains, continued to believe that influenza was induced by Pfeiffer's bacillus, pneumococcus, streptococcus or some combination of these bacteria. Moreover, the description of putative aetiological agents of this disease did not answer the practitioners' primary concern: the reason for deaths among their patients, especially young and healthy ones. It remained unclear why some people developed severe, untreatable neurological and bronchial-pneumonia complications, or what could be done to prevent such dramatic sequellae.

In 1889, Rodríguez-Ocaña shows, Spanish doctors assimilated influenza with dengue fever, mostly on the basis of its symptoms, but also on the basis of the belief of shared microbial origins. They did not abandon, however, their earlier explanatory framework of a seasonal illness, 'winter catarrh'. In 1918, despite widespread acceptance of bacteriological/virological theories, doctors continued to invoke numerous environmental variables to explain the advent of the epidemic, from sunspots and the intensity of cannon fire on the Western Front, to the construction of the Madrid underground and poor quality tobacco. Such explanations, as well as specific atmospheric conditions, were seen to have an important, although secondary role in triggering influenza epidemics. The principal cause, physicians agreed, was an infectious agent, either Pfeiffer's bacillus or the 'filterable virus' advocated by French specialists. The hypothetical agent remained elusive, and in Spain, debates on the exact nature of the infectious agent had no practical value.

Public health measures

There was, however, general agreement that influenza was a highly contagious, airborne infection, difficult to control using ordinary public health measures. The fluctuating virulence of epidemic waves, the high incidence rate, and the relatively low proportion of deadly cases (with the exception of especially deadly outbreaks, like those during autumn 1918), exacerbated the difficulties of implementing public health measures, while sanitary authorities usually failed to organize an efficient response to emergency. For example, the British public health response was surprisingly understated, offering very few centralized public health measures. The closure of public spaces occurred only rarely, and the primary topic of public health debate was implementing the appropriate ventilation of cinemas. Moreover, central provisions for emergency care of the sick and burial of the dead were often vastly insufficient, and main relief came from responses usually initiated by lay people (Tomkins, 1992).

Problems in Spain and France resembled those in the UK. During the 1889–1890 epidemic, Rodríguez-Ocaña explains, Barcelona's sanitary authorities did not attempt any collective action, limiting their interventions to the promotion of personal hygiene. In 1918, however, with the general acceptance of the notion that influenza was produced by an infectious agent(s), sanitarians relied on measures such as the surveillance of urban sanitation, food hygiene, street disinfection, border surveillance, isolation of the sick, anti-crowding measures, and the collection of accurate statistics on the epidemic's progress. The implementation of these measures was, however, slow and inefficient, and many doctors doubted their efficacy, recommending instead individual protection measures: personal hygiene, antiseptic mouthwash and a positive attitude. In addition, people strongly resisted interdictions of such gatherings as football games or religious ceremonies and ultimately forced the government to rescind these interdictions. The Barcelona sanitary authorities not only failed to stop the epidemics, but were unable to provide such basic services as burying the dead. The conviction that the municipality of Barcelona was unable to cope with a sanitary crisis promoted the development of more efficient organization of public health in the interwar period.

French sanitary responses were also diverse and inefficient. They included short-term closure of some public gathering places, fumigation and advice concerning individual protection with such substances as menthol, eucalyptus, hydrogen peroxide or phenol (Hildreth, 1991). As Rasmussen argues, however, the French response to the influenza epidemic was above all strongly influenced by the fact that the country was at war. The army played a central role in the implementation of public health measures, or rather in the lack of such measures. Influenza – unlike typhus or tuberculosis – was not perceived as an immediate danger for the military. Moreover, attracting attention to a disease that was

simultaneously banal, deadly and poorly understood could detract from army hygienists' pride in their successes in controlling other transmissible diseases such as typhoid fever, dysentery or typhus. Interventions of the military and civilian sanitary authorities focused mainly on individual protection: promoting disinfectants, isolating the sick, and undertaking actions (distributing food, blankets and hot drinks) to prevent exhaustion, which could increase people's susceptibility to infection. In France, too, the failure of public health measures to halt the epidemics led to the recognition that existing sanitary policies were insufficient and to calls for reform.

Therapy

In the absence of a specific therapy for influenza, doctors tried nearly every available treatment, both traditional and 'scientific'. French doctors recommended antipyretic compounds, disinfectants and fortifying substances such as aspirin, quinine, opium camphor, iodine, turpentine, eucalyptus and blood serum, cold baths and mild laxatives. They also employed sera and vaccines for other diseases, such as diphtheria or pneumonia, but used them as non-specific, symptomatic treatments. French physicians, Anne Rasmussen explains, attempted to halt the spread of epidemics by hospitalizing the sick, especially those who coughed or had 'serious cases', since influenza was identified early on as an airborne infection. Some specialists also promoted the use of gauze masks, but the latter measure was rarely implemented (for additional descriptions of anti-influenza therapies, see Hildreth, 1991; Smith, 1995; Loeb, 2005). Spanish doctors similarly believed in trying all available therapies, including antitussive and antipyretic drugs, sedatives, colloidal gold, quinine and guaiacum. They also strongly relied on the new 'scientific' therapies, antisera and vaccines, employing these preparations to boost the human organism's general immunity. Such remedies, Rodríguez-Ocaña states, included anti-diphtheric serum, vaccines against different pathogens and mixtures of pathogens, 'auto-vaccines' prepared from the patient's own bacteria, and normal horse serum (on the use of such non-specific vaccines and sera, see Löwy (2005)).

In hindsight, we know that none of these medications could work beyond offering purely symptomatic relief. The only therapeutic measure that seemed to affect survival was bed rest and good quality nursing. The medical profession failed, however, to notice that all these treatments were useless. Most professionals continued to believe in the efficacy of their interventions, and they did not change their minds once the epidemic was over. This is not surprising. While the global death toll of the Spanish flu pandemic was very high, only a small proportion of the sick – less than 5 per cent, and in some localities, less than 2 per cent – actually died. Hence, the vast majority of patients of each doctor would have survived the epidemic; doctors may have attributed their patients' good fortune to the efficacy of their cures.

Tangled histories

Leopold von Ranke (1795–1886), often presented as the 'father' of modern historiography, is famous for his proposition that the historian's primary aim was to show 'what really happened' ('*wie es eigentlich gewesen*').[2] This proposal has usually been interpreted as a recommendation that historians pay close attention to all available archive materials, to search creatively for new sources, and to strive to approximate as closely as possible an accurate reconstruction of past events (Ginzburg, 1991). The 'greatest pandemic since the Black Death' was surprisingly invisible for scientists and historians for over half a century. This invisibility may have been linked to the difficulties of producing a 'constructive' narrative showing how scientists, clinicians and public health experts gradually increased their knowledge and capacities to intervene efficiently in epidemics. Improving such interventions is possible even when one cannot identify the agent responsible for an epidemic outbreak. Cholera epidemics in Europe and North America, for instance, were successfully contained before the isolation of *Vibrio cholera*; each new cholera wave provided an opportunity to test sanitary measures and to learn from experience (Rosenberg, 1962; Hamlin, 2009). Nevertheless, similar improvements did not occur during successive waves of influenza, probably because the 1918–1919 pandemic was a unique event, so different from the milder 1889–1891 pandemic and smaller outbreaks in the early 20th century. Moreover, we are probably not immune to subsequent influenza epidemics. Despite impressive progress in our understanding of influenza's aetiology and epidemiology, many experts believe that the emergence of a highly lethal strain will again produce a high death toll, especially in developing countries.

Another obstacle for studying the history of the 1918–1919 pandemic was the dissonance between this story and the progressive narrative of triumph of bacteriology and hygiene. Attempts to control, prevent and cure influenza highlight the sharp contrast between the promise of the 'bacteriological revolution' and the reality of the uncontrollable spread of a lethal disease. Their history provides a picture of professional powerlessness, incompetence and confusion, coupled with high levels of confidence in the efficacy of the proposed preventive and therapeutic means. The ideology of scientific medicine has helped to mask the severity of a pandemic. A poem, written in 1913 by the French physiologist Charles Richet to glorify Pasteur, boldly proclaimed a watershed in the ways that doctors addressed infectious diseases, a final victory in the war against pathogenic microorganisms (Richet, 1914). The 1918 influenza pandemic flew in the face of this optimistic affirmation, but it did not serve to discredit faith in the progress of

science. During the epidemic and its immediate aftermath, doctors and public health experts continued to adhere to their older optimistic understandings of bacteriology and virology.

The reaction to the massive loss of life induced by 'Spanish flu' stands in contrast to responses to the mortality of World War I. The war shattered faith in the progress of humanity, leading to waves of deep pessimism, far-reaching political, economic, philosophical and artistic changes (Griffin, 2007). The influenza pandemic did produce important shifts in scientific knowledge and public policies, but these shifts were gradual and incremental. There was no immediate, radical change in the practices of clinicians, researchers and public health experts, or in the public image of these professions. Medical elites, general practitioners, public health experts and politicians maintained a positive attitude, avoided self-criticism and self-recrimination, and reconstructed retrospectively their views of the epidemic, carefully editing the more embarrassing bits. If one accepts the view that the deep crisis of values in the aftermath of World War I favoured the political instability that led to World War II, one may similarly argue that health professionals' reluctance to recognize the extent of their failure to contend with the influenza pandemic may have been a positive development: it prevented a massive collapse of confidence in the medical profession. On the other hand, this attitude may have slowed advances in evaluating the efficacy of therapies and public health measures. It may have also hampered historical research on this pandemic.

From the current perspective, one can understand better professionals' reluctance to acknowledge the extent of their ignorance and to meditate on the dangers of applying chaotically every available preventive and therapeutic approach. One can also better appreciate the difficulties of historians, disarmed by the scope of this event and its emotional burden, and baffled by disparities between narratives that emerge from different sources. These difficulties have lessened recently. We probably will never be able to know precisely 'what really happened' during the 'Spanish flu' pandemic, but thanks to the accumulation of superb historical scholarship, this pandemic is no longer hidden from history. Dense and fine grained studies, such as those of Rasmussen and Rodríguez -Ocaña, restore for us the scientific, cultural and emotional depth of the 1918–1919 influenza pandemic, and they greatly increase our understanding of the ways in which people have perceived sanitary dangers, coped with their burdens, and processed their memory.

Notes

1 When Alexander Fleming observed in the late 1920s the antibacterial properties of the mould penicillium, he hoped to be able to use this mould to facilitate the laboratory culture of *Hemophilus influenza*, in his view the causal agent of influenza (Fleming, 1929).

2 This expression, from Ranke's first book, published in 1824, *The History of Latin and Teutonic People from 1494 to 1514*, is alternatively translated as 'to show what essentially happened'.

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Part 2

Epidemiology, Virology and 20th-century Epidemics

4

Are Influenzas in Southern China Byproducts of the Region's Globalizing Historical Present?

Robert G. Wallace, Luke Bergmann, Lenny Hogerwerf and Marius Gilbert

Introduction

Transnational influenza

The emergence of pandemic swine flu H1N1 in Mexico in 2009 surprised scientists and public health officials alike. Over the past decade many had trained their eyes on influenzas circulating in East Asia instead, specifically in southern China. The latter region is currently ground zero for a variety of influenza subtypes circulating across livestock and waterfowl. Among them, influenza A (H5N1), the bird flu virus that until this year served as influenza's poster child, first emerged as a highly pathogenic recombinant in the southern Chinese province of Guangdong in 1996. In the decade that followed, H5N1 spread across Eurasia, into Africa, and south to Indonesia, infecting millions of birds and, as of April 2010, 493 humans (World Health Organization, 2010).

In other ways, however, the 2009 pandemic offered support for an emerging hypothesis that new agricultural practices have expanded ecological niches for livestock influenzas worldwide, from which a variety of human infections have arisen (Shortridge, 2003; FAO, 2004; US Council for Agriculture, Science and Technology, 2005; Greger, 2006). There now circulates a veritable zoo of influenza subtypes, in addition to the new H1N1, that have proven themselves capable of infecting humans: H1N2, H5N1, H7N1, H7N3, H7N7, H9N2, in all likelihood H5N2, and perhaps some of the H6 series (Puzelli et al, 2005; World Health Organization, 2005; Myers et al, 2006; Ogata et al, 2008).

Since 1918 livestock pigs have hosted their own versions of seasonal H1N1. From 1930–1998 the pig version evolved only slightly (CDC, 2009; Garten et al, 2009). But in the 1990s, the virus was subjected to a series of reassortment events, wherein different genetic segments are traded with those of other influenzas. An

aggressive swine H1N1 emerged in 1998 in the United States with internal genes of a human H3N2 virus and an avian influenza. The virus subsequently spread across pig populations, but with limited transfer to humans, usually in farm workers (Shinde et al, 2009).

In early 2009 a previously undescribed influenza, what we now know as swine flu H1N1 (2009), emerged in humans in central Mexico and spread around the world. Three of the new virus's segments appeared to be from the seasonal swine influenza (HA, NP, NS), three from the North American H3N2 swine recombinant just described (PB2, PB1, PA), and two from a Eurasian swine recombinant (NA, M) (Garten et al, 2009). Each of the new H1N1's genetic segments is most closely related to those of influenzas circulating among swine (Smith et al, 2009).

How did influenza genomic segments from pig strains in one part of the world combine with those from another distant part? No migratory waterfowl can be offered as an intermediate host by which viruses are transported long distances, as in the case of avian influenzas. By the time of swine flu H1N1 (2009)'s emergence, only hog populations appear implicated. As hog transport is facilitated by human handlers alone, there can be no mistake that human agency has played a defining role in the spread of swine flu's source strains, although the details remain to be investigated.

The most parsimonious explanation for the pandemic strain's origins is that it emerged in the area in which the first human cases were reported (Gibbs et al, 2009; Wallace, 2009a). A more complicated possibility, with the first human infections estimated months before the first recognized outbreak in Veracruz, is that the strain emerged in China, where all three of the influenzas that would form sfH1N1 (2009) have been found (Smith et al, 2009). For several of the strain's genes, samples from Hong Kong appear basal to the pandemic strain's clade. In this scenario, infected humans would have transported the virus from China to Mexico. Smith et al conclude, however, that the long phylogenetic branch lengths leading to the sfH1N1 clade indicate a dearth of sampling. In other words, the Hong Kong samples do not resolve where exactly the virus emerged as a human-specific strain.

The mode by which swine influenzas are spread, if not all their specific pathways, is, however, broadly understood. Live hogs are usually trucked, from farm to farm or farm to processor. But with the globalization of the livestock filiere or food supply chain (Otte et al, 2007; Wallace, 2009b), the distances over which food animal populations are transported have increased to continental and even intercontinental scales. Baltussen et al (2009) report 22 million piglets and slaughter pigs were shipped across Europe (Figure 4.1). Indeed, the agro-economic pressures placed on the geographic extent of livestock transport are only increasing. Hogs are now routinely flown by cargo plane half-way around the world (Rollason, 2009).

Source: Baltussen et al (2009). Reproduced with permission

Figure 4.1 (a) Most important transport routes for live piglets and slaughter pigs within Europe (in million live heads)

Source: Boris Minkevich, *Winnipeg Free Press*. Reproduced with permission

Figure 4.1 (b) Containers holding pigs bound from Winnipeg, Canada to Germany are loaded onto a Boeing 777 cargo jet

The livestock revolution

The surge in livestock miles is synchronous with the global spread of a corporate model of vertically integrated husbandry associated with farm consolidation and abrupt increases in heads per farm (Wallace, 2009b).

Until the end of World War II poultry farming worldwide was largely a backyard operation. Boyd and Watts (1997) show that as of 1929, 300 million chickens were widely dispersed across the United States at an average flock size of 70 birds. The production filiere was comprised of local hatcheries that sold eggs to backyard poultry producers and independent farmers, who in turn contracted independent truckers to bring live poultry to city markets. After the war, Tyson, Holly Farms and Perdue, among other companies, vertically integrated the broiler filiere, buying up other local producers and putting all nodes of production under each company's roof (Manning and Baines, 2004; Striffler, 2005). By 1992, US poultry production was largely concentrated in a few states in the South and in parts of a few other states elsewhere, now hosting a total of 6 billion broilers, at an average flock size of 30,000 birds.

This 'livestock revolution' was so successful that it produced more chickens than American families typically ate. Using food science and marketing the poultry industry repackaged chicken in an array of new products, including chicken nuggets, strips of chicken for salads, and cat food. Multiple market shares were developed large enough to absorb the value-added production domestically and abroad. The US was for many years the world's leading poultry exporter.

The pressure on the industry was also relieved by geographic expansion. American companies initiated joint ventures in other countries. World poultry production would spread from the global industrial core to an archipelago of industrializing nations, especially in Asia. The development appears a variant of David Harvey's (1982/2006) spatial fix, in which overaccumulated capital can be relieved by finding alternate localities in which to reinvest. At the same time, local producers began their own bouts of integration and consolidation. In the 1970s Asia-based companies such as Charoen Pokphand (CP) set up vertical filieres in Thailand and, soon after, elsewhere in the region. Indeed, CP was the very first foreign company allowed to set up production in Guangdong under Deng Xiaoping's economic reforms. As a result, the poultry industry has undergone a historical shift in its quantity, intensity and geographical context.

In 1970, global poultry meat production totalled about 15 million tons (Windhorst, 2007). By 2005, 81 million tons were produced. Not only did production levels rise by a factor of five, but the proportions and quantities of poultry traded over long distances, as we have noted, also increased dramatically. Exports increased from 3.5 per cent of production in 1970 to 12 per cent by 2005, differentiating poultry-importing and poultry-exporting nations. Egg production has also increased severalfold. Global egg production increased from less than 20 million tons in 1970 to almost 60 million in 2005. Developing countries produced less than 25 per cent of global egg output in 1970 but almost 70 per cent by 2005. China alone increased its share from 7 per cent of world production in 1970 to 41 per cent in 2005.

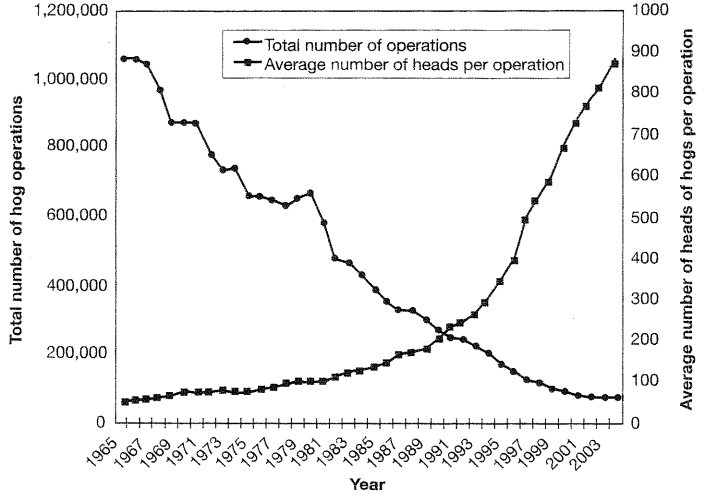
China, the focus of this chapter, has hosted a veritable explosion in annual chickens and ducks produced (Gilbert et al, in press). Increases in poultry have also occurred throughout Southeast Asia, though not nearly as much as in China. National statistics suggest that while the human population less than doubled between the end of the 1960s and 2005, the pig population underwent a nearly 100-fold increase and the poultry population grew 1000-fold (Wang et al, 2008), a growth path that tests our capacity for superlatives.

The means by which the geographic expansion has been undertaken are of critical epidemiological importance. By way of structural adjustment programmes and neoliberal free trade agreements, agribusinesses are moving company operations to the global South to take advantage of cheap labour, cheap land, weak regulation and domestic production hobbled in favour of heavily subsidized agro-exporting (Manning and Baines, 2004; McMichael, 2006). But companies are also engaging in sophisticated corporate strategy (Burch, 2005). Agribusinesses are spreading their production line across much of the world. The CP Group, for

one, the world's fourth largest poultry exporter as of 2003 (Chanyapate and Delforge, 2004), has poultry facilities in Turkey, China, Malaysia, Indonesia and the USA. CP has feed operations across India, China, Indonesia and Vietnam. It also owns a number of fast-food chain restaurants throughout Southeast Asia.

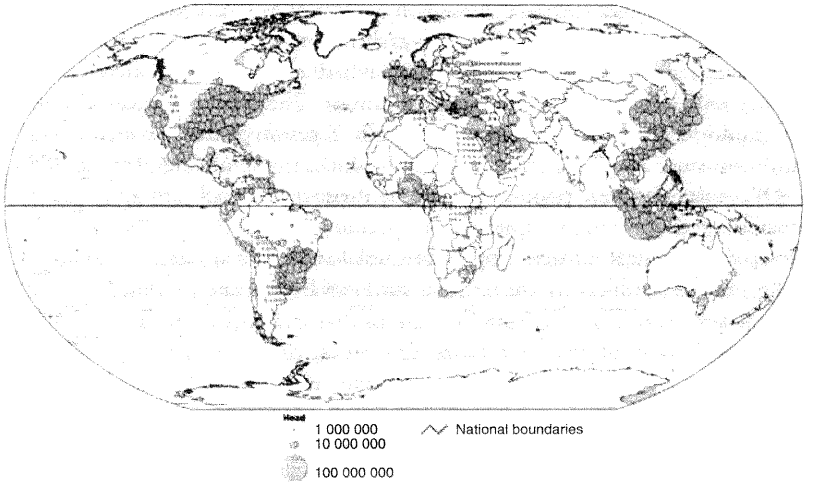
A supply chain arrayed across multiple countries allows some companies the means by which to compensate for interruptions in business, including those of their own making (Sanders, 1999; Manning et al, 2007). The CP Group operates joint-venture poultry facilities across China, producing 600 million of China's 2.2 billion chickens sold annually (Burch, 2005). When an outbreak of bird flu occurred in a farm operated by the CP Group in Heilongjiang Province, Japan banned poultry from China. CP factories in Thailand filled the market gap by increasing exports to Japan.

Consolidation and globalization in the hog industry have followed similar trajectories in the West, taking off later, especially during the 1990s (Figure 4.2). As a result, the globe is now circled by veritable cities of industrial poultry and pigs, largely concentrated in China, the USA and Western Europe, but expanding elsewhere (Figure 4.3). The implications for influenza are fundamental. Global agribusiness appears to be a key player in the emergence and spread of new influenzas. No smallholder has the industrial capacity necessary to export live livestock of any consequence across countries, nor access to international markets locally that emergent influenzas require in order to spread through the global filiere.



Source: Myers et al (2006). Reproduced with permission

Figure 4.2 US hog operations and average number of hog heads per operation, 1965–2005



Note: *Only subnational areas where industrial production is dominant were considered. Data were aggregated over a global grid of 250 x 250km. Only industrial populations greater than 1 million head are represented here

Source: Steinfeld et al (2006). Reproduced with permission

Figure 4.3 Distribution of industrially produced a) poultry and b) pig populations estimated from the differences between local total populations and locally estimated land-based system-held population

Confined livestock and influenza's evolution

Evidence is accumulating that the increases in the average size of industrial livestock populations and the extent of their transport also affect influenza's evolution.

Wild waterfowl have been implicated as a standing reservoir of source strains for livestock influenza as well as a vector for specific migration events between livestock populations (Cecchi et al, 2008; Gilbert et al, 2008; Ward et al, 2009). But waterfowl have been largely indemnified from direct involvement in highly pathogenic influenza evolution. Capua and Alexander (2004), reviewing recent avian influenza outbreaks worldwide, found no endemic highly pathogenic strains in wild bird populations. Instead, multiple low pathogenic influenza subtypes in such populations developed greater virulence only once they entered populations of domestic birds.

Duan et al (2007) identified low pathogenic relatives of highly pathogenic H5N1 in migratory birds, in lineages dating as far back as the 1970s. None of the recently emergent low pathogenic H5 relatives became established in aquatic or

terrestrial poultry. In contrast, the origins of recent H5 virulence appear characteristic of domestic poultry alone. Vijaykrishna et al (2008) meanwhile showed the source 1996 Guangdong strain of highly pathogenic H5N1 entered regional poultry with all eight genomic segments intact. The subsequent diversification into multiple genotypes, including the deadly Z genotype that has seeded H5N1 outbreaks since 2003, occurred in domestic ducks in China mid-1999 to 2000.

Of course, domestic populations can be divided into backyard and industrial. Smallholdings have been implicated in specific outbreaks (Sims et al, 2005), but the epidemiological burdens appear greatest for industrial farms. Graham et al (2008) found significantly greater odds for H5N1 outbreaks in Thailand in 2004 in large-scale commercial poultry operations than in backyard flocks. The pattern is repeated across influenza serotypes (Otte et al, 2007). In British Columbia in 2004, 5 per cent of the province's large farms hosted highly pathogenic H7N3 infections, while 2 per cent of its small farms hosted outbreaks. In The Netherlands in 2003, 17 per cent of industrial farms hosted H7N7 outbreaks, whereas only 0.1 per cent of backyard farms suffered infections.

A converging line of research is beginning to describe the mechanisms by which confined animal feedlot operations (CAFO) associated with intensive husbandry select for and spread virulent strains:

- Confined livestock are characterized by little or declining genetic diversity, offering fewer immune firebreaks against outbreaks (Garret and Cox, 2008; Megens, et al, 2008).
- Immune systems can be depressed under commercial densities and housing conditions, increasing transmission and pathogen load (Caroprese et al, 2009).
- Greater population densities can facilitate the transmission of livestock pathogens (Vermeulen, 2004).
- Increases in transmission rates reduce the evolutionary costs of pathogen virulence (Ito et al, 2001; Dieckmann et al, 2002).
- A high turnover rate – the duration from birth to slaughter has been reduced to 40 days in chickens (Striffler, 2005) – may select for more virulent strains that must reach their transmission threshold before their hosts are sacrificed (Shim and Galvani, 2009; Wallace, 2009b).
- By increasing the throughput speed, and reducing the age of food animals at slaughter, the livestock industry may also be selecting for strains able to transmit in the face of younger, more robust immune systems.
- Violations in biosecurity and biocontainment are routine. Graham et al (2008) describe spread off-site via farm workers, livestock transport, animal waste and environmental contamination. The widespread engagement of smallholder contractors for raising juvenile livestock means violation in biosecurity is built into the industrial model (Wallace, 2009b).

- Subnational regions hosting farms for one type of livestock often host other types too, permitting greater reassortment of influenza's genomic segments across host species (Otte et al, 2007; Wallace, 2009b).
- In shipping livestock across greater geographic extents, as described above, previously isolated influenzas can overlap and trade genomic segments (Wallace, 2009c).
- Geographically expanding, intensive agriculture destroys wetlands on which many waterfowl typically stopover during migration. Waterfowl migrate instead to where the food is now located (Jeffries et al, 2004; Van Eerden et al, 2005), including the very farms that replaced their traditional habitats. The resulting agro-ecologies expand the epidemiological interfaces shared by wild birds and livestock, increasing opportunities for reassortment and host switching (Woolhouse and Gowtage-Sequeria, 2005).

The resulting increases in the virus's standing genetic diversity – by accumulating point mutations and repeated transcontinental reassortment – act as the fuel for influenza's natural selection, including selection for greater transmissibility and virulence in humans.

History matters

Such a theory of industrial influenzas appears riven by a logical fallacy, however. On the surface, the working hypothesis, relating CAFOs to accelerated influenza evolution, seems to offer an example of the error of converse accident, in which circumstances coincidental to one pandemic are mistaken for the cause of all pandemics. If post-war confined animal feedlot operations select for virulent influenzas, how can we explain the 1918 pandemic, which killed 50–100 million people worldwide, or any other previous pandemic for that matter? As no such industry existed in 1918, a cause other than livestock intensification must account for influenza's recurrence.

The rebuttal, however, relies on a narrow reading of evolutionary theory that downplays context and history. The 1918 comparison presumes repeated events are determined by the same underlying causes. In other words, it imposes a categorical algorithm upon a contingent history, where the latter resists such easy abstraction. The reading often lays the recurrence of pandemics at the feet of a number of generative molecular mechanisms. A repeated series of reassortment events or functionally equivalent amino acid replacements associated with a host switch to humans is, in this view, intermittently selected for (e.g. Horimoto and Kawaoka, 2005; Taubenberger et al, 2005; Tamuri et al, 2009). Such molecular mechanisms do indeed have a place, one to which we will return at the end of the chapter, but the characterization on its own misses a critical point.

The counter-explanation mischaracterizes natural selection. Selection, including for repeated host switches, is indeed algorithmic: (i) phenotypic variants are proposed by chance, (ii) those unable to respond to their environments are disposed of, (iii) repeat. But the concrete virological results here are dependent on an era-specific mélange of passing socio-ecological juxtapositions; and the mix of previously selected adaptations extant influenzas express leading into a pandemic (Gould, 2002; Wallace, 2009d). From pandemic to pandemic, then, we need to ask how the host populations entrained in the new influenza's emergence were ecologically organized with respect to one another. In other words, history and context matter, as much for pathogens as the humans they infect. At the risk of reifying arbitrary blocks of time, pathogens have their own origins, diasporic migrations, classical eras, Dark Ages and Industrial Revolutions. As human pathogens evolve and spread in a world of our own making, these analogous eras are often coupled with our own.

It is in this framework – the historicity that bounds biological life's trajectories – that we hypothesize here an explanation of why southern China has acted over the past few decades as a major geographic source for a wide variety of influenzas. In addition, we address what in the light of our introduction appears a contradiction: why southern China acts as such a source of influenzas even as multinational agribusiness, spreading worldwide, apparently acts as a driving force in the evolution and spread of modern pathogenic influenzas.

The explanations are largely grounded in two concepts: Harvey's (1982/2006) notion of an 'active moment' in a spatial configuration and Louis Althusser's (1965/2009) characterization of the 'historical present'. What we find in southern China today is neither effortlessly remade independent of history nor enslaved to a static past. The region has neither been disconnected from the rest of the world nor had its specificities erased by a wave of recent generic globalization. The socio-ecological environment in which influenzas are evolving there is the complex and layered product of past and present, of global and local. The causes of emerging influenzas in southern China today are threads which may bind many places, peoples and times together, though never evenly, and in a place-specific way.

In this chapter we will describe the evidence that modern southern China has acted as a primary source for influenzas, with particular emphasis on the coastal province of Guangdong. We will discuss new research addressing the combination of agro-ecological characteristics that better promote influenza persistence in this and similar regions, in contrast to areas elsewhere in the world. We will address how such combinations emerged in this case, reviewing the history of southern Chinese agro-ecology both pre-1980 and after economic liberalization. We conclude with an epistemological note, in which we articulate what the historical present tells us about the nature – and study – of the evolution of human pathogens.

We believe the programme outlined here is mission critical. Researchers and health officials alike must begin to unravel the threads that tie together influenza's agro-ecologies across geographic scale and disciplinary domain before better addressing the repeated emergence of near-pandemic recombinants in southern China, the most successful of which express a trifecta of virulence, xenospecificity and environmental persistence.

Influenza in southern China

A primary source

For decades a variety of influenza subtypes have been discovered emanating from southern China (Chang, 1969; Shortridge and Stuart-Harris, 1982; Cheung et al, 2007; Xu et al, 2007). In the early 1980s, with livestock intensification in its early stages there (as described below), University of Hong Kong microbiologist Kennedy Shortridge (1982) identified 46 of the 108 different possible combinations of hemagglutinin and neuraminidase subtypes circulating worldwide at that time in a single Hong Kong poultry factory.

Shortridge offered a number of reasons why he thought southern China has served, and will continue to serve, as ground zero for influenza pandemics:

- Southern China hosts mass production of ducks on innumerable ponds, facilitating faecal–oral transmission of multiple influenza subtypes.
- The greater mix of influenza serotypes in southern China increases the possibility that the correct combination of gene segments would arise by genetic reassortment, selecting for a newly emergent human strain.
- Influenza circulates year-round there, surviving the interepidemic period by transmitting among waterfowl by the faecal–oral mode of infection.
- The proximity of human habitation and a proliferation of live bird markets provide an ideal interface across which a human-specific strain may emerge.

The conditions Shortridge outlined nearly 30 years ago have since only intensified with China's liberalizing economy. Millions of people have moved from inland rural regions into Guangdong and other coastal provinces over the past decade, a part of one of the greatest migration events in human history (Fan, 2005). The population shift was accompanied by an attendant transformation in the landscape, pressuring wetlands and juxtaposing the urban and the rural. Shenzhen, for example, one of Guangdong's Special Economic Zones for open trade, grew from a small city of 337,000 in 1979 to a metropolis of 8.5 million by 2006. Concomitant changes in agricultural technology and ownership structure have put

hundreds of millions more animals into production (Luo et al, 2003; Burch, 2005; Sun et al, 2007).

A growing number of studies have tracked the resulting sero-epidemiology across southern China's production filiere. Lu et al (2008) showed that Guangdong hosted a variety of influenzas. Seasonal influenzas H1N1 and H3N2 comprised most of the 1214 human cases discovered, but antibodies for H5N1 (2.5 per cent) and H9N2 (4.9 per cent) were also found among all tested, with a significantly greater prevalence of H9N2 antibodies (9.5 per cent) in those occupationally exposed to birds. Wang et al (2009) meanwhile detected very few cases of H5 among 2191 Guangzhou workers occupationally exposed to birds, in all likelihood because of the vaccination campaigns in poultry against H5. H9, on the other hand, appeared widespread across the commodity chain, especially among poultry market retailers (15.5 per cent), wholesalers (6.6 per cent), and workers in large-scale poultry-breeding enterprises (5.6 per cent).

Even regional efforts to control influenza have been shown to diversify the virus. In 2006 virologist Guan Yi and his colleagues at the University of Hong Kong identified the previously uncharacterized Fujian-like H5N1 lineage (Smith et al, 2006). The team ascribed the emergence of the strain as a viral evolutionary reaction to governmental campaigns to vaccinate poultry. As in the case of other influenza serotypes (Suarez et al, 2006; Escorcia et al, 2008), the virus appeared to evolve from underneath the pressure of vaccine coverage.

As Mike Davis (2005, p63) summarizes it, by the time of onset of pathogenic H5N1 in 1997, only the latest pathogen to emerge under the region's socio-ecological conditions:

> *Several subtypes of influenza were travelling on the path toward pandemic potential. The industrialization of south China, perhaps, had altered crucial parameters in the already very complex ecological system, exponentially expanding the surface area of contact between avian and nonavian influenzas. As the rate of interspecies transmission of influenza accelerated, so too did the evolution of protopandemic strains.*

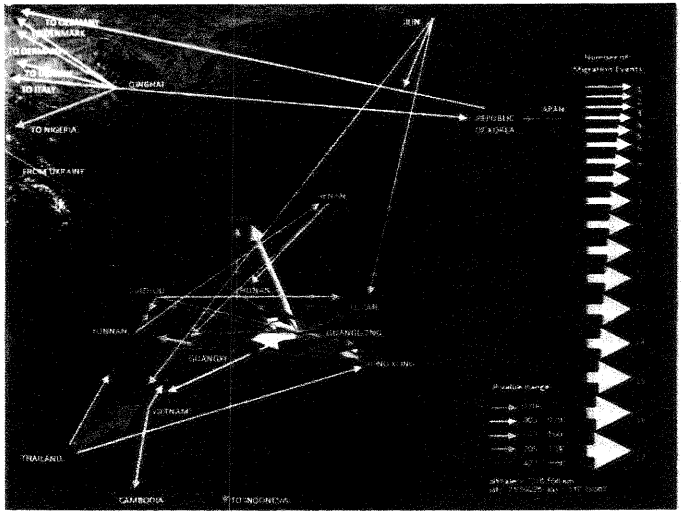
What were these crucial parameters? And how did these protopandemic strains converge on the region in the first place?

Regional phylogeography

The hemagglutinin protein of pathogenic H5N1 was first identified by Chinese scientists from a 1996 outbreak on a goose farm in Guangdong (Tang et al, 1998). News reports during the initial H5N1 outbreak in Hong Kong detailed local health officials' decision to ban poultry imports from Guangdong, from where several batches of infected chickens originated (Ng, 1997). Phylogeographic analyses of the virus's genetic code have pointed to Guangdong's role in the

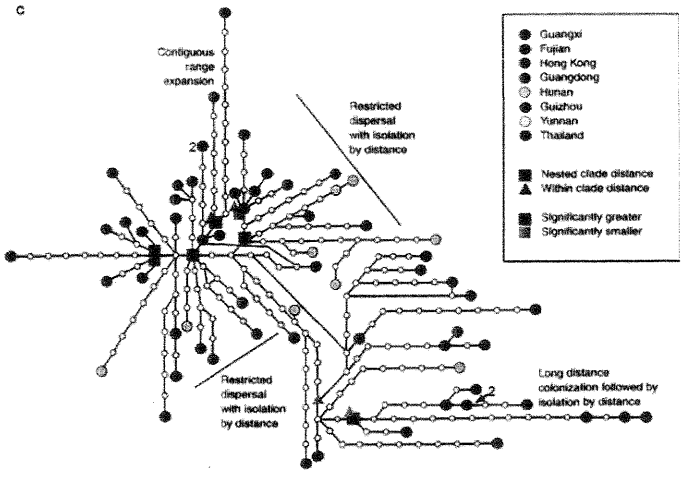
emergence of the first and subsequent strains of pathogenic H5N1 (Wallace et al, 2007; Lemey et al, 2009). Scientists from Guangdong's own South China Agricultural University contributed to a 2005 report showing that a new H5N1 genotype arose in western Guangdong in 2003–2004 (Wan et al, 2005).

Subsequent work has complicated the picture. With additional H5N1 samples from around southern China, Wang et al (2008) showed virus from the first outbreaks in Thailand, Vietnam and Malaysia appeared most related to isolates from Yunnan, another southern Chinese province. Indonesia's outbreaks were likely seeded by strains first isolated from Hunan Province. These are important results, showing the complexity of influenza's phylogeographic landscape, which appears shaped by continuous and overlapping bouts of restricted dispersal, long-distance colonization, and contiguous range expansion across the region (Wallace and Fitch, 2008) (see Figure 4.4).



Note: See www.earthscan.co.uk for a colour version of this figure.
*Inferred by parsimony through a maximum likelihood phylogeny for 1235 hemagglutinin nucleotide sequences sampled across 28 Eurasian and African localities 1996–2007 ($3 \leq n \leq 166$ isolates per locality). Orange vectors are statistically significant ($a = .05$) under an upper-tail Monte Carlo test of 999 trials and a sparse false discovery rate (sFDR) correction. Non-significant vectors are colour-coded by Monte Carlo P value: the brighter the yellow, the greater the support. Quintiles are defined by breaks in ranked P values of more than .01, except within the final quintile. The map is based on satellite photos made available in World Wind 1.4.
Source: Hogerwerf et al (2009). Reproduced with permission

Figure 4.4 (a) Map of HPAI H5N1 regional migration events across East Asia



Note: Rectangle represents the hypothesized ancestral genotype. All genotypes, except two, are represented by a single isolate. The exceptions are represented by two isolates ('2'). Squares represent significant nested clade distances and triangles significant within clade distances as determined by nested clade analysis. Black shapes represent nodes at which subclades express significantly greater distances than expected by chance begin and extend to the tips of the branch. Grey shapes represent the starting node of a subclade of lesser distance than expected by chance. Two subclades showed relationships consistent with restricted dispersal and evolutionary isolation by distance, one with long-distance colonization followed by isolation by distance, and one with contiguous range expansion.
Source: Wallace and Fitch (2008). Reproduced with permission

Figure 4.4 (b) Statistical parsimony haplotype network for 67 samples of a single clade 2.3 H5N1 strain circulating in southern China 2005–2006

At the same time the results need not refute what may be Guangdong's role as geographical keystone. Even if a number of H5N1 strains emerged elsewhere in the region, Guangdong's socio-economic centrality may have acted as an epidemiological attractant, drawing in novel poultry trade-borne strains from around southern China before dispersing them again back out across China and beyond.

Mukhtar et al (2007) meanwhile traced the origins of the genomic segments from the original 1996 outbreak in Guangdong. The internal proteins (encoding for proteins other than surface proteins hemagglutinin and neuraminidase) appeared phylogenetically closest to those of H3N8 and H7N1 isolates sampled from Nanchang in nearby Jiangxi Province. The 1996 hemagglutinin and neuraminidase appeared closest to those of H5N3 and H1N1 isolates from Japan. In the months before the outbreak in Hong Kong several of the proteins were again

replaced by way of reassortment, this time via strains of H9N2 and H6N1 (Guan et al, 1999; Hoffmann et al, 2000). H5N1 strains in the years that followed the Hong Kong outbreak emerged by additional bouts of reassortment (Li et al, 2004).

The specific sociogeographic mechanisms by which the various segments first converged (and were repeatedly shuffled) in Guangdong remain to be better outlined. The results so far do indicate that the spatial expanse over which reassortants originate may be greater than Kennedy Shortridge, or anyone else, previously imagined. Guangdong and the rest of southern China may represent a locus wherein circulating influenzas are reassembled into regional epidemic and even pandemic potential. But genomic origins tell us little about how these complements lead to viruses that *locally evolved* their virulence and xenospecificity, other than showing the genetic variation upon which the viruses drew.

A more functional approach to southern China's agro-epidemiological context, then, appears necessary. If successful, this approach would better illuminate the conditions that selected for such deadly and easily spread pathogens: not only H5N1, but a diverse viral portfolio, including Influenza A (H9N2) (Liu et al, 2003), H6N1 (Cheung et al, 2007), H3N2 (Russell et al, 2008), and SARS (Poon et al, 2004). What exactly are the 'crucial parameters' Davis presumes shaped the area's disease ecosystem? What changes in southern China's agro-ecology led to regular influenza outbreaks, emanating out to the rest of China and the world? How did such changes come about?

Why do multiple influenzas persist in southern China?

Agro-ecological niches

Influenza's xenospecific epidemiology is characterized by a fundamental contradiction. On the one hand, the virus is highly infectious, spans a short generation time, and tends toward boom-and-bust population dynamics (quickly burning through its supply of susceptible hosts) (Villareal et al, 2000). At the same time, several deadly influenza subtypes circulate long-term uninterrupted. The H5N1 epizootic, now in its 12th year and counting, remains the longest recorded highly pathogenic influenza outbreak in poultry.

A number of explanations have been offered for highly pathogenic avian influenza (HPAI) H5N1. First, the virus rotates across multiple host types (Olsen et al, 2006; Barrett et al, 2008; Wallace and Fitch, 2008), providing alternate hosts when a first host species' population becomes too small to maintain local transmission. Second, H5N1 experiences shifts in life history across host types, including a reduced virulence (and increased persistence) in duck reservoirs (Keawcharoen et al, 2008). Third, a virulent strain can be an evolutionary stable strategy in

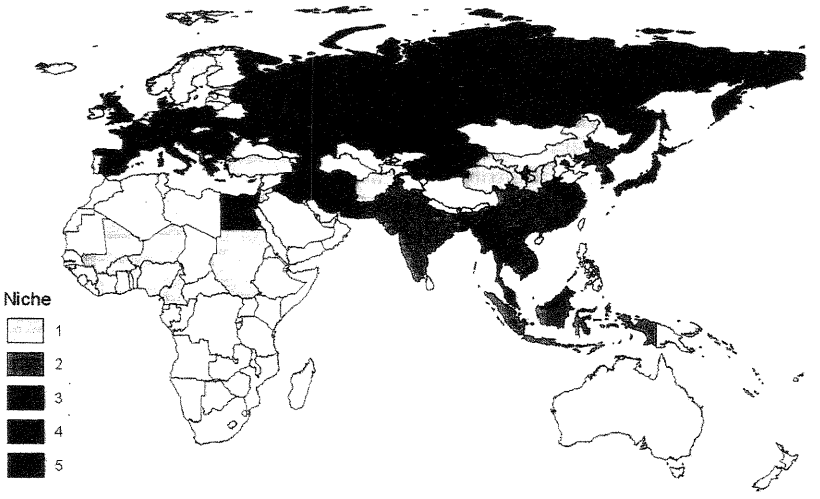
situations where an ample supply of susceptibles is available, especially if such populations are distributed over wide geographical areas, as is the case with HPAI H5N1. Fourth, persistence in the physical environment may contribute to sapronotic transmission, particularly from waterways to aquatic birds (Brown et al, 2007).

New work by Hogerwerf et al (submitted) suggests that some agro-ecologies permit influenza outbreaks to persist longer than others, perhaps by better integrating the aforementioned mechanisms. To identify such environments, the team focused on HPAI H5N1. H5N1's extensive geographic spread over the past decade represents a natural experiment, albeit an unfortunate one. Multiple exposures across multiple countries permit statistically testable contrasts that the new swine flu H1N1, for instance, cannot presently offer: we can track fast-evolving H5N1 as it repeatedly spreads over three continents, contacting an increasing variety of human–animal environments, including locale-specific combinations of prevalent host types, modes of farming and animal health measures.

By a principal components analysis and multivariate clustering of a set of 15 agricultural, environmental, climatic and socio-economic factors, Hogerwerf et al identified six variables that together discriminated the areas with human cases and persistent outbreaks: agricultural population density, duck density, duck by chicken density, chicken production output/input ratio, the product of both agricultural population density and chicken output/input ratio, and purchasing power per capita. The analysis identified five agro-ecological clusters, or niches, that vary by degrees of H5N1 persistence and human spillover (Figure 4.5).

At the global level, the niches are clearly structured by geography, with the most H5N1-vulnerable niches (2 and 3) arrayed across South and East Asia, including along the Chinese lowlands and coastline into the river basins of Indochina and, further south, Indonesia. The southern Chinese province of Guangdong, identified as a phylogeographic source (Wallace et al, 2007), marks the spatial medoid of niche 3, the most vulnerable niche, and is characterized by large densities of domestic duck and agricultural populations, shown previously to be associated with persistent outbreaks (Gilbert et al, 2008). At the same time, other regions in niche 3 are scattered across H5N1's range. Egypt and wetland areas in northern Nigeria support agro-ecologies similar to those that allow H5N1 to persist so well in southern China. The niches' geographic distribution, then, may offer another mechanism by which HPAI H5N1 persists. In acting as something of a western hub for persistence, Egypt may assist in seeding repeated outbreaks in sub-Saharan Africa.

Vulnerable niche 3, with the most persistent outbreaks and the greatest number of human cases of H5N1 per capita, largely includes countries or provinces with intermediate levels of poultry productivity and low-to-medium purchasing power per capita (e.g. Thailand, Egypt, Guangdong and Fujian provinces). Many of these regions are in punctuated transitions into industrial economies and



Note: The niches were identified by a clustering analysis of study localities across a bivariate space defined by the first two principal components for this combination of agro-ecological variables. Niches 2 and 3 showed significantly greater HPAI H5N1 outbreak persistence and human case load.

Source: Hogerwerf et al (2009). Reproduced with permission

Figure 4.5 Map of five agro-ecological niches defined by different combinations of agricultural population density, duck density, output/input chicken and purchasing power per capita

presently comprise geographic mosaics of old and new modes of livestock production. The pluriformity may offer influenzas the array of micro-niches needed to (i) evolutionarily radiate across host types and (ii) persist in the face of losing access to any one of several local host species (by migration, vaccination, culling or immune response).

So it seems, then, that the significance of the shifts for influenza evolution in the global geography of poultry sector output, with which this chapter began, might exceed the impact arising from the mere spatial shuffling of such industrial production alone. It remains to be seen to what extent the shifting agro-ecological context in which industrial poultry production is enmeshed has non-linear and synergistic effects, thereby potentially increasing any evolutionary risks associated with intensified production alone. For example, does the niche modelling described above support the possibility that the spatial juxtaposition of highly capitalized agribusiness production alongside any number of smallholding or integrated farming techniques – in the dynamic, heterogeneous, peri-urban,

agro-ecological mosaics found in the semiperiphery of the capitalist world economy – produce environments more conducive to influenza persistence or evolution than either smallholding or industrial production alone? It is a topic to which we will return.

The niche results also beg the question why countries within each agro-ecological niche are for the most part geographically contiguous. While shared enviro-climatic conditions may contribute to the spatial autocorrelation in niche geography, the geographic diffusion of agricultural innovations may account for the spatial structure. Prevalent modes of regional agriculture have deep historical roots, which have influenced subsequent developments. In China, rice cultivation marked the transition between Mesolithic foragers and the surplus food-producing economies of the Neolithic (Zong et al, 2007). Domestic ducks were being used in the rice paddies for pest control around 500 years ago. Poultry intensification was introduced at scale during the economic liberalization of the past 30 years (Wallace, 2009a; Gilbert et al, in press). The H5N1 duck-rice-poultry niche in Asia resulted from a series of changes in agricultural practice – ancient (rice), late imperial (ducks) and present-day (poultry intensification) – melding in the historical present in such a way as to apparently support the evolution of multiple influenzas.

Influenza's spatiotemporal dynamics are complicated and limited to no single province or country (Figure 4.4). A broader investigation of how historical and geographical processes shaped agro-ecological niches at larger – and smaller – scales, including their interactions, remains open to additional research. A more detailed understanding of the history of Guangdong's socio-ecological geography is, however, an important first step in understanding influenza's larger historical presence in southern China. It is impossible to investigate how contemporary Guangdong may influence influenza's present evolution without understanding the socio-ecology of contemporary Guangdong, a regional keystone. In turn, crucial socio-ecological aspects of contemporary Guangdong are unintelligible without reference to factors with histories, some contingent and some path-dependent. To understand the present dynamics of the agro-ecological landscape mosaic in southern China, it is necessary to understand the contextual drivers of these landscapes' histories, as well as their extra-local interconnections.

Pre-1980 agro-ecology

A historical geography of agro-ecological features that have shaped 'deep-time' influenza evolution in southern China may be difficult to establish, given the epistemological challenges of confronting the breadth, complexity and shifts in society over the course of the region's long history. Furthermore, we have framed influenza evolution in terms of distinct eras, in which different synergies of place and practice are thought relevant. The degrees to which the practices described here are relevant to the historical development of influenzas must remain at this point speculative, as this represents a projection back in time based on knowledge framed by the narratives of present-day dynamics. Actual history, as we learn more, may not cooperate with such a facile heuristic.

That said, all is not lost. To begin, general contours of certain fundamental agro-ecological practices in China can be described. While various forms of slash-and-burn agriculture can be dated to 12,000 years BP (Peng, 2000), the origins of southern China's characteristic rice agriculture began at least 9000 years ago, followed by generally northern millet agriculture at least 8000 years ago (Li et al, 2007). Albeit much later, efforts to alter the hydrological landscape, often for irrigation, became of central importance to agricultural society. The ingenious Dujiangyan project taming the Min River (a tributary of the Yangtze in Sichuan province) has been in operation for more than 2200 years. Systematic land reclamation and irrigation began in the same era, greatly expanding rice paddies and other cultivation (Heilig, 1997), transforming agro-ecological landscapes, and finding echoes with many projects of the socialist state in the 20th century (Stone, 1988). Some such activities may have had the additional side effect of bringing migratory bird habitat closer to agricultural activities, with obvious implications for influenza's host range.

The history of animal husbandry in China is also quite lengthy. Whether of pigs or poultry, husbandry there has often been quite effectively integrated, not merely juxtaposed, with other elements in local agro-ecological systems. The domestication of ducks has been dated to at least 3–5000 years ago (Simoons,1991; Cherry and Morris, 2008), with funerary art dating from the Eastern Han Dynasty (25–220 CE) depicting agricultural scenes with rice fields and ducks and fish in a pond (Cai et al, 1995). Already, by about 500 years ago, in the mid Ming dynasty (according to Huo Dao, who lived 1487–1540), ducks were very popular for pest control in the rice paddies of the Pearl River Delta (Peng, 1994). From various points in the Ming and Qing dynasties, ducks were also promoted for the control of locusts in Fujian and northern China, with pest control by chickens recorded significantly earlier (Peng, 1983; Peng, 1994). Rice–duck systems, in which herds of ducks, whether backyard or more nomadic, are allowed to graze fields after the harvest, have long been used (Tai and Tai, 1999).

Simoons (1991) reviews a number of foreign accounts that indicate early duck husbandry bore the markings of high-order poultry intensification. One 16th-century account:

> *described a sophisticated system of Chinese duck husbandry, with thousands of ducks kept in cages on boats at night. In the morning the ducks were permitted to leave, entering the water by means of bamboo bridges, feeding in paddies during the daylight hours, and returning when their owners, as evening approached, signalled them to return.*

Contemporary practices bear similarities. An international team of influenza disease experts recently witnessed a similar permeability, wherein domestic ducks intermixed with wild birds on the ducks' daily commute into Lake Poyang in Jiangxi Province (Wallace, 2009a).

Simoons summarizes a late-19th-century account that included hatcheries which:

> *sold the young ducklings to duck merchants who raised them in enclosures. When sufficiently grown, such ducks were sold by the merchants to itinerant duck vendors who transported them by water, as many as two thousand to a boat. While he kept the ducks, a vendor permitted them to feed twice a day along the river or in nearby fields, thereby saving the cost of feed... Though the itinerant sold ducks retail in communities along the way, most found provision dealers who specialized in salting and drying them.*

By the time of early 20th-century agricultural surveys, ducks and chickens were found in much greater densities in rice-growing regions, especially in double rice cropping regions (Simoons, 1991). Although literature suggests some pre-20th-century commercial raising of Aylesbury ducks outside London, it would appear that ducks were domesticated much later in Europe and never reached the socio-ecological integration long prevalent in East Asia (Cherry and Morris, 2008).

Integrated farming practices, ecologically interwoven, have a rich history in China. The origins of rice-fish farming extend back at least 1700 years (Guo, 2001) and records from over 2000 years ago describe aquatic plant-fish systems (Yang et al, 2001). Whereas various livestock-crop systems are widespread and relatively well-known, livestock-carp systems are a somewhat more unique contribution, less widely understood today but dating in China at least back to the Ming dynasty. Livestock-carp systems did reach Malaysia by the end of the 19th century, perhaps via Chinese diasporas, and had reached many other Southeast-Asian countries before World War II, though various integrated fish systems were long practised by various ethnic groups in Southeast Asia (Csavas, 1992). Similarly, by about 400 years ago, fruit tree-fish and mulberry-silkworm-fish dike-pond integrated systems (discussed below) are documented (Yang et al, 2001). Finally, various injunctions against the killing of various types of agriculturally beneficial wild birds reach back several thousands of years as well (Peng, 1989).

Our concern here is primarily with those dynamics that have brought humans, birds domestic and wild, and pigs into close association, beginning with Guangdong. We first focus, then, on those processes that have intersected in the Pearl River Delta, at the core of the province, and around which contemporary centres of industrial production and population such as Guangzhou, Shenzhen and Hong Kong, each under different conditions, were built. Much of the Delta itself has emerged within the past 2000 years, some causes of which are anthropogenic, from conscious acts of reclamation to increased siltation from deforestation upstream (Lo, 1996; Weng, 2000).

Beginning perhaps in the Song Dynasty (960–1279 CE), delta wetlands were increasingly converted to ponds divided by soil piled onto dikes, forming the first iterations of what would be known as the dike–pond system (Marks, 1998). Fish were raised in the ponds, then fruit trees and various crops were planted on the banks, with chickens and ducks potentially integrated (Peng, 2000). By the latter half of the 16th century, in the mid Ming dynasty, however, instead of fruit trees, mulberries were increasingly planted on the banks in order to feed silkworms, helping close a rather efficient nutrient cycle between banks and ponds (Zhong, 1990). Guangdong was a key point for foreign trade and a long-distance international market for silk was explicitly driving the development of local land-use and the rise of the dike–pond system.

By 1581 the mulberry dike-pond system occupied about 30 per cent of certain key counties in the delta (Marks, 1998). By the early 20th century almost all land in a number of parts of the larger area had been converted to this silk-producing system.

The presence of mulberries within an integrated cycle did not necessarily mean that there was no space devoted to other relevant agricultural activities on the dikes around the ponds, however (Chan, 1996). Watson (1994) provides evidence of the presence of domestic ducks within the mulberry–fish dike–pond systems in the 1860s.

Yet whatever the socio-ecological virtues of dike-pond arrangements, in no sense were they simply 'sustainable' systems of locally closed loops (Marks, 1998). The system was open and at the centre of many flows, sustained by products exported internationally and by substantial food and potentially other inputs imported interregionally (Csavas, 1992; Marks, 1998). By the middle of the 18th century, Marks argues that the Delta plus a vast hinterland stretching into neighbouring provinces had been functionally integrated within a single differentiated agro-ecosystem. The whole landscape of the region would then also have been more directly coupled to the dynamics of an emerging global political economy, influenced by either the expansion of world silk markets or by the emerging crises of capitalism in distant lands.

Within this larger interconnected region, but further away from major population centres and their resources than the dike-pond regions, other agro-ecosystems were prevalent. For example, Peng (1994) narrates the rise and decline of the *zheng gao* system, a variant of paddy-rice intercropping requiring less labour and resources to expand output in those parts of the Delta peripheral to the growth seen at the cores where the export economy was flourishing. Extensive use was made of ducks, as well, to eat crab pests in the paddies and to recycle grain waste in the fields after the harvest. The system grew alongside the dike-pond systems from the Ming to the Qing until state initiative in water-management projects to raise yields eliminated it in the early years of the socialist period in the 1950s.

Much of the 20th century was a time of particular flux for the agro-ecological landscapes of the Pearl River Delta. The mulberry version of the dike-pond system, facing a number of questions about its ongoing socio-economic viability, collapsed in the wake of the Great Depression (Watson, 1984). A greater diversity of plantings was then experimented with on the dikes, including sugarcane and fruit. More generally, war against Japan and civil conflict brought great disorder. During the chaotic times of the 1930s, early agricultural survey work indicated that around 97 per cent of calories in China were being provided by plant-based foods (Lohmar and Gale, 2008), indicating an extremely limited scope for poultry production at the time.

After the 1949 victory of the Revolution, the Maoist period brought a number of agrarian reforms, including changes in cropping systems, in land-tenure, in labour conditions, in social relations and in extra-regional economic linkages. Development was aimed, in theory, at avoiding polarization and dependence on the export markets of the global core, and instead creating spatially and socially even production focused on a national economic space. The Pearl River Delta's previous international trade linkages and associated flows of commodities and money were thus radically reshaped. Agricultural development alongside a doubling in population required a focus on increasing grain production in order to meet the basic caloric needs of the people, a task which met with several excruciating setbacks and which was only secured in the 1980s after the maturation of the fertilizer industries in which heavy investments were made in the 1970s.

In the Pearl River Delta, beyond the replacement of the *zheng gao* cropping system and the previous decimation of the silk–mulberry economy, integrated farming wavered greatly. For example, rice–fish farming was promoted early in the socialist period, perhaps with 700,000ha nationally by the late 1950s, but disruptions, whether political, policy or pesticide in origin, resulted in a sharp decline during the 1960s and 1970s (Guo, 2001). In Guangdong, rice–fish acreage declined from around 40,000ha to a mere 320ha by the beginning of the Cultural Revolution in 1966.

By the middle and late 1970s, interest in ecologically integrated farming was on the rise again, with communes establishing farms and conducting research on optimizing combinations of rice, silkworms, chickens, ducks, fish and/or pigs (Hu and Yang, 1984; Chen, 1989; Jiang, 1989; Yang and Hu, 1989). However, at the same time that some communes were experimenting with ecological integration, others were leading the way in researching and implementing industrial poultry intensification (Chen, 1989). At the dawn of the economic reforms in 1980, a USDA researcher reported gaps in the systems which monitored and ensured livestock health, including a paucity of diagnostic virology at facilities, but also commented favourably on a ubiquitous high level of human care provided to animals, suspecting that it had been helping to 'decrease mortality and morbidity among livestock and poultry in China' (Hyde, 1980).

Economic liberalization

In the late 1970s, with the rehabilitation of Deng Xiaoping, China began to move away from a cultural revolution policy of self-sufficiency, in which regions were expected to produce most foods and goods for their own uses. In its place the central government began an experiment centred upon a reengagement with international trade in Special Economic Zones set up in parts of Guangdong (near Hong Kong), Fujian (across from Taiwan), and later the whole of what would become Hainan Province. In 1984, 14 coastal cities – including Guangzhou and Zhanjiang in Guangdong – were opened up as well, though not to the extent of the economic zones (Tseng and Zebregs, 2003).

Measured by many of the macroeconomic indicators favoured by establishment economists, the policy was a success. Between 1978 and 1993 China's trade–GNP ratio grew from 9.7 per cent to 38.2 per cent (Perkins, 1997). Much of this growth stemmed from manufactured goods produced by foreign-funded joint ventures, and township and village enterprises (TVE) allowed greater autonomy from central control. Starting in 1979, foreign direct investment (FDI) increased from zero to US$45 billion by the late 1990s, with China the second greatest recipient after the US. Sixty per cent of the FDI was directed to cheap-labour manufacturing. Given the extent of China's smallholder farming, little FDI was initially directed to agriculture (Rozelle et al, 1999).

That soon changed. Through the 1990s poultry production grew at a remarkable 7 per cent per year (Hertel et al, 2000). Production for domestic consumption and investments was not confined to chickens, given the longstanding interest in the consumption of duck and goose. Yet processed poultry exports grew from US$6 million in 1992 to US$774 million by 1996 (Carter and Li, 1999). China's Interim Provisions on Guiding Foreign Investment Direction, revised in 1997, aim to encourage FDI across a greater expanse of the country and in specific industries, agriculture included (Tseng and Zebregs, 2003). The government's 2005 five-year plan set sights on modernizing agriculture nationwide (Tan and Khor, 2006). Since China joined the World Trade Organization in 2002, with greater obligations to liberalize trade and investment, agricultural FDI has doubled (Whalley and Xin, 2006). It appears opportunities for additional agricultural FDI are still available and open to a wider array of sources of investment. By the late 1990s Hong Kong and Taiwan's contribution to China's FDI had declined to 50 per cent of the total, marking the introduction of European, Japanese and American investment.

In something of a bellwether, in August 2008, days before the Beijing Olympics, US private equity investment firm Goldman Sachs bought ten poultry farms in Hunan and Fujian for US$300 million (Yeung, 2008). The outright ownership appears a step beyond the joint ventures in which the firm had until then participated. Goldman Sachs already holds a minority stake in Hong Kong-listed China

Yurun Food Group, a mainland meat products manufacturer, and 60 per cent of Shanghai-listed Shuanghui Investment and Development, another meat packer. Goldman Sachs's new purchase, further up the filiere, signalled a shift in the global financial environment. The firm adeptly moved out of high-risk US mortgages and, during a global food crisis, into the brave new world of offshore farming in China.

Transformative changes introduced by the reforms may be far from over, however. In October 2008 China's leadership took a step towards formalizing such privatization (Wong, 2008). Under the rubric of land reform and doubling rural income, peasants are to be allowed to engage in unrestricted trade as well as to buy and sell land-use contracts. These contracts are also to be extended from a ceiling of 30 years to 70. Contracting permits the government to retain land sovereignty as a political emblem. However, if such policies are extended and expanded, precipitously or after lengthy periods of local experimentation, the effect could be unpredictably transformative for rural society. For poultry production more specifically, companies both domestic and foreign are likely to be the sole entities with the reserves on hand to enter such contracts, potentially leading to streamlined, vertically-integrated systems, although contracting with farmers remains popular today.

Experimental reforms in the political economic realm often have unintended consequences and positive feedback which requires repeated policy interventions (Hart-Landsberg and Burkett, 2005). In introducing a movement toward land privatization in Chinese rural society, whatever the supposed short-term benefits, China's small farms may find themselves open to a great land rush, resulting, intended or not, in an 'accumulation by dispossession' managed by a communist party (Harvey, 2006). The agro-ecological environments in which influenzas are presently evolving would themselves again shift in ways that one can only imagine.

Guangdong, as throughout the region's history, remains at the cutting edge of these economic shifts. It hosted the central government's first efforts at internationalizing the rural economy (Zweig, 1991; Johnson, 1992; Xueqiang et al, 1995). Starting in 1978, Guangdong agricultural production was redirected from domestic grain to Hong Kong's market. Hong Kong businesses invested in equipment in return for new output in vegetables, fruit, fish, flowers, poultry and pigs. In something of a reprisal of its historical role, Hong Kong ('the front of the store') also offered Guangdong ('the back of the store') marketing services and access to the international market (Sit, 2004; Heartfield, 2005). In a few short years Guangdong's economy again became entwined with and dependent upon Hong Kong's economic fortunes, and vice versa. As of the 1997 H5N1 outbreak in Hong Kong, investment in China comprised four-fifths of Hong Kong's FDI outflow (Heartfield, 2005). Much of Hong Kong-funded production is now conducted in Guangdong, with Hong Kong's industrial base increasingly hollowed out as a result.

Eighty-five per cent of the agricultural FDI brought into China during the 1990s was funnelled into Guangdong and several other coastal provinces (Rozelle et al, 1999). Guangdong was allowed to invest more in its transportation infrastructure, in part as an invitation for further investment. Many of the province's companies were allowed to claim 100 per cent duty drawbacks. Guangdong also developed trading arrangements with many of the 51 million Chinese overseas (Gu et al, 2001; Heartfield, 2005). In aggregate, diasporic communities control large percentages of regional market capital, including in Indonesia, Thailand, Vietnam, the Philippines, Malaysia and Singapore. At the time of the first H5N1 outbreaks, overseas Chinese collectively comprised the group with the greatest investment in mainland China (Haley et al, 1998).

As a result of the area-specific liberalization, Guangdong accounted for 42 per cent of China's total 1997 exports and generated China's largest provincial GDP (Lin, 2000; Gu et al, 2001). Of the coastal provinces, Guangdong hosted the greatest concentration of joint-venture export-oriented firms, with the lowest domestic costs for each net dollar of export income (Perkins, 1997). Guangdong's three free economic zones (Shenzhen, Shantou and Zhuhai) boasted an export-to-GDP ratio of 67 per cent, compared to a national average of 17 per cent.

Economic liberalization, particularly its changes in ownership structure and its geographic integration within and beyond southern China, has had a fundamental effect on regional husbandry. By 1997, and the first H5N1 outbreak in Hong Kong, Guangdong, home then to 700 million chickens, was one of China's top three provinces in poultry production (Organisation for Economic Co-operation and Development, 1998). Fourteen per cent of China's farms with 10,000 or more broilers were located in Guangdong (Simpson et al, 1999). Some of Guangdong's poultry operations were by that point technically modernized for breeding, raising, slaughtering and processing birds, and vertically integrated with feed mills and processing plants. Agricultural FDI helped import grandparent genetic stock, support domestic breeding and update nutrition feed milling/mixing (Rozelle et al, 1999). The majority of breeds used in industrial production are now imported, bred for profit and high rates of capital turnover (Wang, 2006). At times, production has been somewhat constrained by access to interprovincial grain and the domestic market's preference for native poultry breeds less efficient at converting feed. Of obvious relevance, production also suffered from less-than-adequate animal health practices.

Presently, expansion is robust and so-called 'high quality' chickens, longstanding domestic breeds or hybrids, are increasingly being produced, despite their higher costs and longer turnover times. Guangdong is producing approximately one billion of these high-quality broilers a year (Yang and Zheng, 2008). Guangdong is now the second-largest provincial poultry meat producer overall according to the 2005 *China Agricultural Development Report* (Poon, 2006).

Guangdong's ascension was not without its detractors, a dynamic with potential epidemiological consequences. Among them, landlocked provinces chafed at the liberalization the central government proffered coastal provinces alone (Zweig, 1991). With so much domestic currency on hand, the coastal provinces could outcompete inland provinces for livestock and grain produced by the inland's own TVEs. The coastal provinces were able to cycle their competitive advantage by turning cheap grain into more profitable poultry or simply re-exporting the inland goods, accumulating yet greater financial reserves. At one point rivalries became so intense that Hunan and Guangxi, bordering more prosperous coastal provinces, imposed trade barriers on interprovincial trade.

The central government's efforts to negotiate interprovincial rivalries included spreading liberalization inland (Tan and Khor, 2006). Provinces other than Guangdong and Fujian were also becoming entrained into market agriculture, albeit in something of a reprise of pre-Revolution dynamics, at a magnitude still outpaced in certain sectors by their coastal counterparts. Industrial poultry's expansion – through reexporting and inland development – increases the geographic scope for the emergence of market-oriented influenzas and may explain the roles Yunnan and Hunan appear to have played in serving up H5N1 abroad.

The landscape mosaic

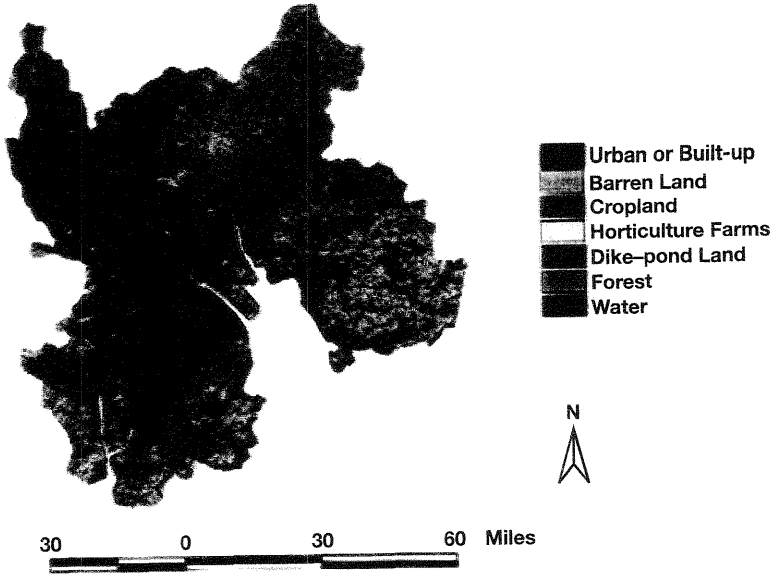
China is a diverse territory, and the numerous forms of ownership, organization and production that have co-existed in the Chinese poultry sector make it no exception to the larger rule. Foreign investment and intensive production have not eliminated all backyard producers. Equally, not all small-scale producers are operating independently. Instead, thick webs of contractual obligations interweave a diverse ecology of economic actors, and are likely to continue to do so for some time (Poon, 2006). By some metrics, the world's largest duck producer, a firm based in Henan, presently has a relationship with a large UK agribusiness and several hundred local contract farmers (Yan, 2004). The largest chicken producer in Guangdong in the early 2000s, Guangdong Wen Foodstuff Group, drew revenues of 1.6 billion RMB in 2000, employed about 4400 employees in the central company and 12,000 contracting household farmers, and maintained a close relationship with South China Agricultural University (Luo et al, 2003). As of the 1990s, local feed mills were operated publicly, by village cooperatives, by joint ventures and by private capital (Crook et al, 1999).

Such developments in the poultry industry, many of them in the greater region around Guangdong's Pearl River Delta, are not occurring in isolation, but in a period of extremely rapid urbanization, suburbanization, inward migration, industrial expansion, interregional integration and economic differentiation, and export-led growth. The greater delta's agro-ecological landscape mosaic was built, and is being built, on the historical dynamical patterns described above. At the same time,

the development represents a historically unprecedented density and juxtaposition of activities, with potentially fundamental consequences for influenza evolution.

We begin examining landscape dynamics in the core of the larger delta region, with the caveat that future research should explore the hinterlands, whose rapid development are linked to the core, as well as related systems in nearby provinces. Figure 4.6 shows maps from two studies of land use in the Pearl River Delta, approximately 10 and 20 years after the start of economic liberalization, respectively. Figure 4.6a shows that in 1989 huge swathes of land were still cropland, cities were relatively compact (Guangzhou, to the upper left, is spatially the most prominent), and the dike-pond land was relatively isolated from concentrated populations. By contrast, in 1997 urbanization is vastly greater, spreading out not only from a number of centres (prominently, Shenzhen in the southeast), but also creating a number of suburban filaments stretching through the countryside (Figure 4.6b).

Studies have indicated that much land-use change in the Pearl River Delta is fragmenting and is directly related to FDI (Seto and Fragkias, 2005). The question remains, however, as to the exact relationship livestock industry investments may have with such patterns. Landscape ecological metrics also suggest significant increases in developed land 'edge density' over this time period, on the fringes of



Note: See www.earthscan.co.uk for a colour version of this figure.
Source: Weng (2002). Reproduced with permission

Figure 4.6 Land use and cover in the Pearl River Delta, (a) 1989 and (b) 1997

the major cities in the Pearl River Delta (Seto and Fragkias, 2005). Cropland in the later time period is almost absent, having been replaced by horticulture, development and ponds.

The story of the growth of aquaculture is also apparent in the maps. As aquaculture's economic returns were perhaps two to three times those of cropland in the time between these two maps (Wu et al, 2009), it is not unexpected that much land would be converted, often by village cooperatives (Johnson and Woon, 1997). Much of what is described as 'dike–pond' land in these maps may actually reflect a greater emphasis on 'pond' than previously, as the land is converted into aquaculture (Liu et al, 2008). However, some observers still suggest that aquacultural ponds are also likely to be used for the production of waterfowl (Yang and Zheng, 2008). As ponds have spread out from the traditional core of the dike–pond region in the west section of the area, the amount of built-up land spread across the pond regions appears to have increased greatly, potentially bringing increased populations – and population densities – of humans and aquatic habitat into proximity.

New layers of export-driven landscape are being superimposed upon those of previous eras. However, as the Delta's export-driven economy develops, diversifies industrially, moves toward more costly technologies, and further urbanizes, there is pressure to move livestock industries farther away from valuable urban land (Chen, 2007). Other large producers have long been located in smaller urbanized areas in the peripheries of these larger interurban systems. There appear to be certain similarities between the resulting landscapes and the growing suburbanizing patchworks in semiperipheral newly industrializing states of Southeast Asia called *desakotas* ('city villages') or *Zwischenstadt* ('in-between cities') (Johnson and Woon, 1997; Davis, 2006). Many share the same agro-ecological combinations described in the section on modelling niches above. Are such economically and agriculturally diverse landscapes local instantiations of the national-scale niches found associated with epidemiological vulnerability? Additional research is clearly needed.

The sum effect for the Pearl Delta, and further afield across southern China, may include the possibility that poultry intensification and the pressures placed on agro-ecological wetlands have squeezed a diversifying array of influenza serotypes circulating year-round through something of a virulence ratchet. The resulting viral crop – for 1997, H5N1 by molecular happenstance – can be subsequently exported out by an international trade facilitated by Hong Kong and diasporic capital.

Conclusions

Agro-ecology and pathogen path-dependency

A growing literature addresses the ways pathogen life histories evolve in response to the environments in which pathogens are embedded (Wallace, 2004; Ebert and Bull, 2008). Deforestation or changes in agricultural practice, for instance, may open up new opportunities for pathogens able to evolve the requisite phenotypes needed to spread into new populations and localities (Wolfe et al, 2005; Pearce-Duvet, 2006; Woolhouse and Anita, 2008). Changes in socio-ecological configuration, whether in typical home ranges or in newly invaded territory, may promote, for example, new bouts of host switching (Woolhouse and Gowtage-Sequeria, 2005). Some such changes may accrue only over hundreds of years.

For most of its history the cholera bacterium made its living eating plankton in the Ganges delta (Johnson, 2006). Only once humanity became urbanized and later woven together by 19th-century transport was cholera able to make its way across the world's cities. There, the bacterium was able to transform from a marginal human pathogen into a roaring epidemiological success when municipalities began drawing drinking water from where they dumped their sewage. In short, the evolutionary environment in which cholera is evolving has shifted radically. Cholera is, in turn, itself no longer the same. Human practices have also shifted in various ways, including the establishment of modern public health, in part themselves a reaction to cholera epidemics. Cholera and society are thus each today not what they were yesterday, but at the same time thoroughly depend on what they were yesterday.

A similar transition characterizes influenza. For eons the virus rotated among waterfowl populations that summered on the Arctic Circle (Olson et al, 2006). Influenza expanded into humans once humanity turned to farming and its population densities and geographic connections, and those of its livestock, grew enough to support the boom-and-bust dynamics of such an acute infection (McKeown, 1988). Since World War II, however, influenza may be entering a new global context and so a new phase. In influenza's 'industrial revolution' billions of livestock in monoculture are now pressed up against each other, an effort for which humanity has employed itself as a major contractor.

That today's livestock feedlots do not explain the 1918 or any other previous influenza pandemic does not mean they are innocent of the current batch of influenzas. To say otherwise would be arguing along the lines that oil cannot act as a cause for today's wars because the Romans never fought for it. That is to say, we acknowledge our own historical trajectories. We should, then, be able to acknowledge those of our pathogens as well. The opportunities and constraints to which they are exposed shift in time. At the same time, the events and circumstances any single influenza strain confronts are in large part dependent on those they followed.

Historicity in and of itself is not enough, however. The past is something much more than prelude (deterministic, contingent or otherwise). The agro-ecological conditions found in southern China today arise from an amalgam of historical innovations and circumstances, some of which are still in operation in one form or another today. Intensive duck farming relies in part on agro-ecosystems dating

back at least 500 years. In some areas, the more traditional techniques of duck husbandry remain in practice. The elements of eras past and present interact to such an extent that they are effectively contemporaneous, in what Althusser (1965/2009) defined as the 'historical present'.

Our review of the sweep of southern China's historical present vis-à-vis its agro-ecology can perhaps be thought of as at best concise. We have, however, been able to show here that livestock populations and their socio-ecological positionalities with respect to humans have been, and continue to be, dynamic and far from provincially bounded in their causes. In other words, southern China's role as a primary influenza epicentre is far from inherent, instead arising from a contingent confluence of factors in a Harveyesque (1982/2006) 'active moment' in spatial configuration. At the same time, our knowledge of the exact distributions and intensities of interrelationships of ducks, poultry, pigs and humans within the larger Pearl River Delta over time, as well as the exact relationships among the local and transregional processes responsible for landscape composition and change, remains limited.

What are the exact locations and practices of intensive livestock operations across the region? What is their proximity to smallholders practising duck-fish aquaculture? Is the effect of present-day industrial siting of significance? If polyculture, intensified poultry production, wild birds and high-density human settlements exist within the fragmented landscape mosaic characterizing a system far-from-equilibrium, are there synergies for influenza evolution today that were not present in the less spatially heterogeneous rural systems still prevalent 30 years ago? Is there a connection with the growing suburbanizing patchworks in semiperipheral newly industrializing states of Southeast Asia?

Efforts at putting numbers on the relations between the historical environments and the evolution of influenzas are correspondingly more challenging – of another order of complexity altogether. Are these mixed landscapes what produce the aggregate averages of the most epidemiologically vulnerable agro-ecological niches? Are such economically and agriculturally diverse landscapes instantiations of the national-scale niches found to be associated with the emergence and persistence of this era's novel influenzas? Are some molecular phenotypes repeatedly selected by specific micro-niches?

Our review here does seem to indicate that the whole of the landscape's historical moments have shaped, and continue to shape, the region's post-1980 socio-ecology. By small-area niche modelling, phylogeography and sero-epidemiology, the effects of the more recent changes on the development of influenza are now beginning to come into better focus. But what now of the compound effects of history's long trajectory? Does the historical present, with its long reach back in time, facilitate influenza evolution in ways outside those expected from prevalent models of evolution? In short, does the virus use a synchronous history to its advantage? And can such adaptations be observed in the virus's very genome?

Influenza evolution and the historical present

New pandemic influenzas may retain the capacity to evolve molecular phenotypes of bygone eras. To address whether exposure to previous H1N1 strains, back to the 1918–1919 pandemic, protected humans from the worst of new influenza swine flu H1N1 (2009), Itoh et al (2009) exposed the new H1N1 to influenza antibodies circulating in humans of different age groups. Only patients born before 1920 expressed the antibodies that could neutralize the new virus. The new H1N1 appears to be expressing epitopes similar to those of the 1918 H1N1, antibody targets to which very few humans can presently immunologically respond.

The result raises two important implications. First, seasonal H1N1 influenzas may be in fundamental ways different from their 1918 ancestors. Second, swine flu H1N1 (2009) may have been able to revisit molecular solutions from another pandemic strain expressed 90 years ago. Although influenzas – with life cycles of only a few days – evolve from infection to infection, the molecular constraints upon, and opportunities for, influenza evolution here may extend back nearly a hundred years, influenza's equivalent of a geological eon.

Influenza's phylogeny is riddled with such parallelisms, arising when independent lineages evolve similar adaptations above and beyond chance alone (Wallace et al, 2007). The parallelisms may accrue from more than mutational dumb luck, although the numbers involved in influenza infections could very well permit such raw selection in principle.

We offer here that, in drawing upon the structural constraints that shaped previously evolved responses, the genome engages in a type of cognition (Gilbert, 2003; Wallace et al, 2009). At the risk of anthropomorphizing, a cognitive virus can choose, depending on its context, among a variety of genomic responses. But unlike the molecular work described in a section above, in which viral evolution is thought to algorithmically converge on the same or similar combinations of amino-acid replacements via random mutation, we hypothesize that the convergences are context- and path-dependent. In other words, the effects of an agro-ecological historical present on the evolution of livestock pathogens may be fundamental. The very real presence of an agriculture's past, albeit transmogrified by waves of cultural reappropriation and reemphasis, may offer pathogens a hook on which to draw upon their own histories.

How so? We hypothesize a variant of Conrad Waddington's (1942, 1953; Hall, 2001) 'genetic assimilation'. In Waddington's assimilation, an organism's contingent response to the environment is canalized into the genome across generations and so remains expressed even as the environment changes. In our version, the canalized response *hides* when environments change but remains potentiate even generations later, as an open-ended polymorphism.

By what mechanism would such polymorphism be tapped? The genetic variation within any local population may be greater than what organisms actually express in the field (Gibson and Dworkin, 2004). A local environment may select for characteristics consonant with the expression of only a limited genetic combination from a greater cryptic reservoir. Once the environment changes, however, that reservoir can be drawn upon. In effect, the hidden potentiality may act as a kind of genetic archive from which to reconstruct relevant adaptations or converge on related ones once they are again needed. A viral adaptation in the archive associated with a host switch routinely undertaken for hundreds of years – say, duck to human – may be revisited if only by way of the architectural constraints canalized on the genome and on emergent biochemistry (Wallace et al, 2007). The constraints are embodied by stereochemical relationships among amino-acid residues, path-dependent epigenetic and biochemical pathways across loci, and a related compensatory evolution, wherein changes in one amino acid select for changes in another (e.g. Rimmelzwaan et al, 2005).

Whenever the pathogen is confronted with elements of the new agro-ecology that reappear from previous eras, the constraints together channel viral expression to the right amino-acid combination. That's the 'historical' in the historical present. At the same time, the molecular solutions may be arrived at by way of a novel evolutionary trajectory. The trajectory through the combinations of possible phenotypic expression may depend on the current mix of agro-ecological actors and opportunities. The successful virus must step through a unique combination of changes to 'solve' the new matrix of agro-ecological relationships as they are presented across the landscape. That's the 'present' in the historical present.

We have here, then, something very different from the algorithmic approaches to influenza's molecular parallelisms described earlier. The virus evolves by more than just mutation-selection to immunological or prophylactic environments 'from below' in the immediate time interval (Gilbert, 2003). We hypothesize the virus also expresses a genomic cognition that permits a choice in emergently archived host- and niche-specific characteristics asked of it 'from above'. The cognition may help explain influenza's capacity to succeed in agro-ecological niches defined by shifting geographic mosaics of old and new forms of farming.

Although the mechanisms for such a molecular cognition require further elucidation, including its capacity in the face of environmental fluctuation (Ancel, 1999), it appears influenza can straddle past and present. The duck-human interface Kennedy Shortridge proposes as the means by which influenzas have long seeded human outbreaks across southern China appears to have undergone a fundamental shift once intensively farmed livestock were added. Virulent influenzas selected in such intensive operations may be able to avoid the extirpation expected from burning so fast through host populations by switching to free-range ducks that, under one system or another, have been feeding in local waterways and on

waste grain for hundreds of years. It would appear that, across this landscape, everything old for influenza is new again.

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5

Past Influenza Epidemics and Implications for Contemporary Influenza Research

Sylvie van der Werf

Influenza has probably been with us for a very long time. Some descriptions in antiquity resemble influenza epidemics; the 'Cough of Perinthus', described by Hippocrates in Book IV of his *Epidemics*, has been thought by historians to resemble influenza symptoms (Hippocrates [Farr], 1780; Martin and Martin-Granel, 2006). In this paper, I explore the implications of past influenza epidemics on contemporary research, focusing mainly on the virological aspects.

Two types of epidemics actually occur with influenza: the seasonal, yearly epidemics, which are due to two types of influenza viruses, type A and type B viruses. Currently, among type A viruses two subtypes (H1N1 and H3N2) are responsible for the yearly epidemics. Influenza H3N2 viruses usually give rise to more severe epidemics, whereas type B viruses are generally responsible for milder epidemics. However, we should not forget that those yearly epidemics constitute an important burden both in terms of morbidity and mortality with attack rates of 10–20 per cent of the population leading to an estimated 300,000–500,000 deaths worldwide annually (Simonson, et al, 1997; Simonson et al, 1998; Thomson et al, 2003; World Health Organization, 2008). Occasionally, and this happens only when a new type A influenza virus is introduced in the human population, we experience pandemics; this has probably occurred many times over the past centuries, extending back to antiquity. An example of such a pandemic was the deadly 1918 Spanish flu pandemic, now estimated to have been responsible for some 20–40 million deaths worldwide (Johnson and Mueller, 2002). Not only was it severe, producing very high mortality rates, but the so-called Spanish flu pandemic had some unusual traits, especially in terms of the age distribution of the most severe cases. The 1918 pandemic afflicted not only the very young and the elderly, as in other influenza pandemics, but also young adults.

We know today that the 1918 pandemic resulted from the introduction in the human population of H1N1 influenza viruses (Laidlaw, 1935; Zimmer and Burke, 2009). The Asian influenza pandemic in 1957 was due to the introduction

of H2N2 viruses, which actually replaced the H1N1 viruses (Zimmer and Burke, 2009). In 1968, H3N2 replaced the H2N2 viruses and were responsible for the Hong Kong influenza pandemic. In 1977, the H1N1 virus that had circulated in the early 1950s caused the so-called Russian influenza epidemic or pandemic, which was much less severe than other pandemics because many people had already encountered this virus earlier in life and had protective antibodies (Dowdle, 1999).

Recall that at the time of the Spanish influenza pandemic, viruses were unknown; René Dujarric de la Rivière of the Pasteur Institute recognized that influenza was due to a filterable agent, and this was probably a virus (Dujarric de la Rivière, 1918). The first influenza virus was isolated from swine in 1931 by Richard Shope and the first human viruses were isolated by Andrewes, Laidlaw and Smith in 1933 (Shope, 1931; Smith, Andrewes and Laidlaw, 1933). It was not until this time that we had in hand the actual agent responsible for the yearly influenza epidemics.

We have seen no introduction of a new virus subtype since 1977, and the novel H1N1 influenza pandemic of 2009 is the first pandemic that we have experienced since 1968. But beginning in 1997 with the avian flu outbreak in Hong Kong, caused by the highly pathogenic H5N1 virus, it has been recognized that Avian influenza viruses can be transmitted from poultry to humans and be responsible for human infections. In late 2003, new outbreaks of highly pathogenic H5N1 viruses occurred in Southeast Asia. The viruses subsequently spread to other parts of Asia, Europe and Africa, being responsible for 467 cases of infection in humans, 282 of which were fatal (World Health Organization, 2009). Other outbreaks in poultry involving other influenza subtypes have been responsible for cases of human infections: in 2003 the chicken flu outbreak linked to H7N7 viruses in The Netherlands resulted in 83 human cases (Koopmans et al, 2004), and in 2007 an outbreak in poultry on a small farm in the United Kingdom was linked to human cases of avian flu, which were due to H7N2 viruses (Eurosurveillance Editorial Office, 2007).

Where do new influenza A virus subtypes come from? It is now well established that the reservoir for all influenza viruses is aquatic birds. These aquatic fowl contain the genetic diversity of all known influenza viruses, namely, all the different influenza viruses that can be distinguished on the basis of their two surface glycoproteins: hemagglutinin (HA) and neuraminidase (NA). Sixteen species of hemagglutinin and nine species of neuraminidase are known today, lending their letters (H and N) and numbers to the current nomenclature of influenza subtypes. It is from this aquatic avian reservoir that new influenza virus subtypes can be transmitted to domestic poultry, as well as to various mammalian species. Eventually, those new influenza subtype viruses can establish themselves in a new host.

What are the mechanisms allowing this transmission and ultimately establishment in a new host? What would lead to such events in human beings and thus

result in pandemics? It has been found that the viruses responsible for the 1957 and 1968 pandemics were actually what we call 'reassortants', in between an avian virus and a human virus. In a co-infection event, different viral segments from an avian virus and a human virus were exchanged, resulting in a virus that acquired, as in the 1957 virus (H2N2), three gene segments from an avian virus, two of which correspond to the surface glycoproteins, which are actually the targets of the antibody response. A third segment PB1 encoding the viral polymerase also originated from an avian virus. The other segments derived from a human virus, which probably made the new virus quite well adapted to replicate and establish itself in humans. Similar reassortment events produced the 1968 pandemic virus (H3N2). Essentially, these viruses were new in terms of immunity in human populations, differing from the H1N1 viruses that had been introduced during the 1918 pandemic.

It has been postulated that pigs could be an intermediate host and serve as a mixing vessel, because pigs can be infected quite efficiently with both avian and human viruses, whereas humans are not usually efficiently infected directly by avian viruses. Pigs also harbour both types of receptors on their respiratory tract epithelium – those that are preferentially used by the avian viruses and those that are preferentially used by human viruses. Previously, it was thought that it was absolutely necessary to have this kind of mixing event in pigs to catalyse a pandemic, but researchers studying 2009 A(H1N1) speculate that the virus may have had a different intermediate host (Cohen, 2009).

It has been, of course, much more difficult to establish the characteristics of the 1918 virus, since at that time, the cause – the influenza virus – was unknown. Jeffrey Taubenberger and Ann Reid, virologists at the Armed Forces Institute of Pathology, first determined the sequence of the 1918 virus from pulmonary tissue biopsies of World War I soldiers who died of influenza and whose tissue samples were preserved in paraffin. The identification was later confirmed using virus isolated from a 1918 flu victim buried in the Alaskan permafrost (Taubenberger et al, 1997). Sequencing of the virus's entire genome has been achieved from several viruses dating from this event. In addition, by employing reverse genetics methodologies, the actual live H1N1 virus from 1918 could be reconstituted. The phylogenetic analyses of the genome of those viruses and of their properties have confirmed that an H1N1 virus was responsible for the 1918 pandemic, and that, most likely, the virus was not a reassortant. Unlike the viruses producing the 1957 and 1968 pandemics, the 1918 virus was probably transmitted wholly from birds, possibly through an intermediate host. The intermediate host was probably a mammalian species, but that is unknown at this time.

In the case of the 2009 A(H1N1) virus, analysis of the sequence showed that it derived its segments from various lineages of viruses circulating in pigs, although all the gene segments, whether from swine, human or avian viruses, ultimately have an avian origin (Garten et al, 2009).

The notion that direct or indirect transmission in total of an avian virus to humans is possible was reinforced by the various episodes mentioned above of human infection by fully avian viruses and the more recent outbreaks of H5N1 since 1997, H7N7 in 2003, and H7N2 in 2007. For all of these episodes, there has been either very limited or no human-to-human transmission, showing that those viruses have never adapted fully and have never established a chain of human-to-human transmission required for the onset of a pandemic.

The questions now are: what does it take for an avian virus from the aquatic reservoir to establish into an intermediate host, to transmit eventually to human beings, to adapt to human beings, and then to establish a human-to-human chain of transmission? First of all, it is important to understand better the circulation of influenza viruses in birds; to establish the dynamics of circulation of those influenza viruses in relation to the dynamics of the different bird populations; to understand how a virus continuously evolves genetically during that circulation; and to evaluate the contribution of the environment. Virologists and ornithologists have been working collaboratively in France's Camargue and Dombes wetlands, and their research has underscored the importance of environment. Such investigations may also provide greater insight into the potential role of wild migratory birds in the dissemination of influenza viruses (Lebarbenchon et al, 2007a; Lebarbenchon et al, 2007b; Roche et al, 2009).

Current research has focused careful attention on the highly pathogenic H5N1 viruses, the so-called avian flu that circulated in Southeast Asia and spread to Europe, the Middle East and Africa in 2005–2006. An analysis of the genetic evolution of the H5N1 viruses over time, beginning with the virus's progenitors responsible for the 1997 Hong Kong bird flu episode, has shown that not only variation by accumulation of mutations but also by a number of genetic reassortment events is ongoing continuously. For the H5N1 viruses that are responsible for human cases, this has resulted in the emergence of a particular genotype, the genotype Z, which became dominant at a certain point; all human cases are due to viruses that belong to this genotype. This does not mean that the viruses belonging to this genotype are unique: they are actually very diverse, continue to evolve, and can be subdivided in different clades and subclades that are genetically and antigenically different. Such insights are important for potential vaccine developments (Li et al, 2004; Peiris et al, 2007; World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization/H5N1 Evolution Working Group, 2008; Buchy et al, 2009; World Health Organization/World Organisation for Animal Health/Food and Agriculture Organization/H5N1 Evolution Working Group, 2009).

In addition to tracking the circulation of influenza viruses in birds and tracking highly pathogenic H5N1 viruses that pose a threat, we would like to be able to follow the potential emergence of determinants that are important for the virulence of those viruses and for adaptation and capacity to transmit to humans. We

know that this process is complex, that is, polygenic; some determinants have been identified on the surface of glycoproteins, others on the polymerase complex, and still others on the non-structural proteins that are only expressed in the infected cell (Hatta and Kawaoka, 2002).

For instance, the PB1F2 protein and the NS1 protein from the 1918 virus have been studied and shown to be responsible, or at least in part responsible, for the virus's high virulence, by modifying the normal interplay of the host response to the viral infection. Determinants harboured by the hemagglutinin and the neuraminidase are probably the best known in terms of host-specificity. The hemagglutinin clearly carries the major responsibility for determining virulence in domestic poultry. It has been shown that the presence of a so-called multibasic cleavage site, which allows the hemagglutinin to be cleaved inside the cell and not to depend on the presence of extracellular protease, correlates with the ability of the virus to replicate not only in the respiratory tract and in the gastro-intestinal tract (as with all pathogenic viruses), but also to replicate in multiple organs (Steinhauer, 1999). This is why it is highly pathogenic.

This trait is not, however, strictly correlated with the ability to infect humans nor with high virulence. The 1918 virus, for instance, did not possess this sort of multibasic cleavage site. Hence, other determinants are likely to be important as well. A major determinant of host-specificity is the specificity of the hemagglutinin for its receptor, for the binding that is required for the virus to enter the cells where it replicates. Human viruses will use sialic acids that are linked by an alpha-2,6 linkage; the avian viruses preferentially use sialic acids that are linked by an alpha-2,3 linkage (Ito et al, 1998; Ito et al, 2000; Wan and Perez, 2006). Notably, those hosts believed to be potential intermediate hosts between aquatic birds and human beings actually do possess both types of sialic acids. In human beings, it is also important to note that the human receptor, the alpha-2,6 receptor, is actually distributed throughout the respiratory tract epithelium, whereas alpha-2,3 receptors are only found in the lower respiratory tract (Shinya et al, 2006; Van Riel, 2006). Replication in the case of the human infections by the H5N1 viruses is mainly restricted to the lower respiratory tract, so there is some correlation there. But this change of receptor specificity is clearly not sufficient to allow the establishment of human-to-human transmission. We know that the 1918 virus had acquired specificity for the alpha-2,6-linked sialic acid – the human-like receptor – and the exact amino-acid changes that are responsible for this change in specificity have been identified.

Important determinants of adaptation and virulence are also located on the polymerase complex (Naffakh et al, 2008). These could be identified by constructing reassortant viruses between the 1918 virus and the classic seasonal, fully human-adapted H1N1 virus. This has allowed scientists to show that virulence determinants are located on the hemagglutinin (H) but also on the polymerase complex (Tumpey et al, 2005). Similar work done by analysing virulence for mice

of reassortants between a low-pathogenic chicken H5N1 isolate and highly pathogenic H5N1 virus isolate from a human case showed that for those H5N1 viruses only the polymerase complex is required for virulence (Salomon et al, 2006).

Within this polymerase complex, one protein and specifically one residue have been found to be particularly important. It is residue 627 of PB2, usually a glutamate in the case of the avian viruses and a lysine in the case of the human viruses. For the 1918 virus, it was a lysine residue (Taubenberger et al, 2005). The lysine is also found in the majority of human isolates in cases of infection by the highly pathogenic H5N1 viruses (Chen et al, 2005; Liu et al, 2005; Smith et al, 2006). However, there is no strict correlation between the severity of the symptoms and the presence of this specific amino-acid change.

Intensive research has been carried out on this particular residue (627 of PB2), demonstrating that it is an important determinant that permits the avian virus's derived polymerase complex to function in mammalian cells. It has been shown that this particular residue also determines the ability of the avian polymerase complex to function at low temperatures, primarily at 33°C (Massin et al, 2001). Yoshi Kawaoka's group has taken this observation one step further, showing that this residue is not only important for the ability of the avian polymerase complex to function at low temperatures, but also to replicate in the upper respiratory tract of mice (Hatta et al, 2007). This action may be related to the ability of an avian virus infecting human beings to replicate in the upper respiratory tract of humans and eventually to be transmitted from person to person.

All these observations call for research to understand better the molecular mechanisms of interaction of the polymerase complex within the mammalian cell and to identify the cellular interactors. This kind of research is currently ongoing in Nadia Naffakh's group in my own laboratory, in collaboration with other units at the Pasteur Institute (Labadie et al, 2007; Rameix-Welti et al, 2009).

The exact determinants of transmission remain ill-defined, and more research needs to be done in that area. In addition, given the significant morbidity and mortality burden that could result from the initiation of a pandemic, effective control measures need to be put in place and need to be evaluated, for instance, by using epidemiological modelling. Control measures would have to include vaccines based on standard inactivated vaccines, produced by a process similar to that of the current seasonal vaccines, but also include the development of various alternative approaches based on either subunit vaccines or recombinant viral factors. Highly active vaccine development research on alternative approaches is currently under way.

The aims of such vaccine research are to increase the immunogenicity of vaccines, for in the event of such a pandemic, all populations would be entirely immunologically naïve, and thus would require vaccination against the new virus. Among several possible approaches, we seek to determine the extent to which the

second glycoprotein – the neuraminidase in addition to the hemagglutinin – could contribute to increased immunogenicity and more protective immunity. In the event of a pandemic, extended immunogenicity, and possibly single-dose approaches, will be needed. The potential for cross-protection constitutes a very important issue, given the very rapid genetic and antigenic evolution of the influenza viruses in general. Progress recently has been made by making use of potent adjuvants, which offer potential for increased immunogenicity and cross-protection (Leroux-Roels et al, 2007); such adjuvanted vaccines have been recently authorized for pre-pandemic and for pandemic use (European Medicines Agency, 2008; European Medicines Agency, 2009).

In the event of a pandemic, we also have another control method – antivirals, of which there currently exist two available classes. The amantadine or rimanatidine class, blocking one step of the virus's entry into the cell, may turn out to be of little use because we have already identified potential natural resistance of seasonal and H5N1 viruses towards these antiviral drugs. The other class of antivirals is the neuraminidase inhibitors (NAIs), which block the release of the virus and prevent the virus's ability to spread from cell to cell. There are two compounds available today: the oseltamivir (Tamiflu®) and zanamivir (Relenza®). They are active and, until recently, all seasonal influenza viruses and H5N1 viruses were sensitive to these compounds. Patients' resistance to the NAIs has been observed upon treatment both in seasonal flu and H5N1 infections. However, in the case of H5N1 or H1N1 viruses resistant to oseltamivir, the viruses remain sensitive to zanamivir.

Natural genetic variation can have an important impact on sensitivity. We have shown, for instance, that due to natural genetic variation there could be an increased sensitivity to oseltamivir of clade 1 H5N1 viruses. More recently, McKimm-Breschkin in Australia has shown that clade-2 H5N1 viruses demonstrate a decreased sensitivity (McKimm-Breschkin et al, 2007). Similarly, a decreased sensitivity has also been observed in viruses isolated in Egypt (Rameix-Welti et al, 2006).

Recent events have also taught us much about influenza viruses. In January 2008, the emergence of H1N1 viruses naturally resistant to oseltamivir was observed, and these have been found to circulate widely (Rameix-Welti et al, 2008; Meijer et al, 2009). Such observations indicate that genetic variation may also confer unusual fitness on viruses that have the resistance mutation, and that such an event could very possibly occur for a pandemic virus as well. We therefore need new antivirals and an evaluation of combined therapies.

Clearly, we must live with influenza viruses. We know that they can be transmitted to various domestic poultry, but also to other domestic animals in contact with human beings. Two main mechanisms of adaptation have been recognized through analysis of pandemic viruses: the first is an adaptation through successive mutations, perhaps through some other intermediate mammalian host, as in the

1918 virus; and the second is the mechanism at work in 1957 and 1968 – the reassortment between an avian virus and a human virus, which could occur in pigs, but might also occur with a seasonal virus in human beings.

Important questions therefore remain. What other intermediate hosts could be important in the path to adaptation of an avian virus to human populations? What range of pandemic virus subtypes could establish in human beings? We only know about H3N2, H2N2 and H1N1 viruses that have circulated in human beings so far, but we do not know whether an H5 or an H9 or an H6 could adapt to human beings. There remains much to learn about the actual basis for virulence in human beings and the mechanisms underlying efficient human-to-human transmission.

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6

Influenza and the Remaking of Epidemiology, 1918–1960

John M. Eyler

In the spring of 1938 both Thomas Francis, Jr, then at the Laboratories of the International Health Division of the Rockefeller Foundation, and John Paul from Yale University's Department of Internal Medicine called for a new approach to epidemiology, which they called 'clinical epidemiology'. To issue their call they both chose important venues. Francis chose his DeLamar Lecture at the Johns Hopkins School of Hygiene and Public Health (Francis, 1938, p77; Francis, 1939, p915; Francis, 1953, p377). Paul included his call in his Presidential Address to the American Society for Clinical Investigation (Paul, 1938, p539). Francis's definition was more concise. Clinical epidemiology, he wrote, was the 'epidemiology in which the unit for study is broken down from the herd to actual observation and investigation of each individual in the herd by carrying the laboratory to the patient' (Francis, 1938, p77). Francis's and Paul's visions of clinical epidemiology were remarkably similar, although the experiences that had brought them to issue their manifestos were quite different. John Paul had been investigating outbreaks of polio and rheumatic fever. Francis, on the other hand, was America's leading student of the human influenza virus. This chapter explores the changing shape of influenza research reflected in Francis's call for a new type of epidemiology. It will emphasize the work of Francis and other American researchers.

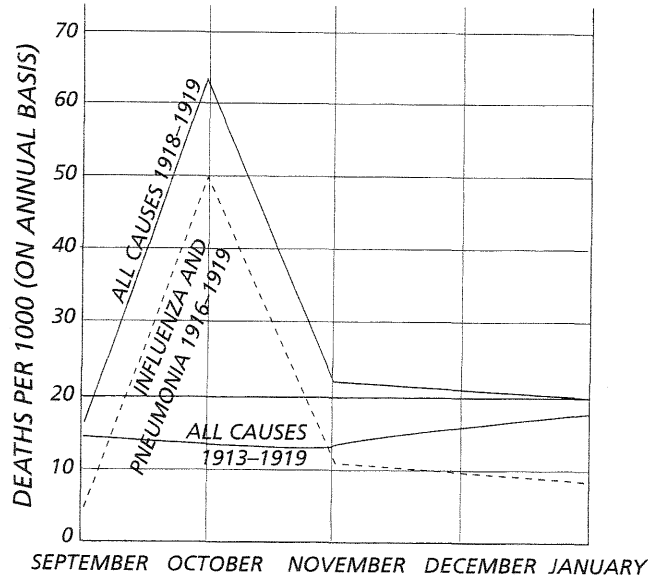
Strictly speaking, Francis at the time was an outsider, a trained laboratory scientist, not a traditionally trained or experienced epidemiologist. Both the tools he would use and the scale of his studies were new to the epidemiology of this disease. To appreciate the nature of the change Francis was calling for, we need first to notice how epidemiologists had studied influenza in the past, particularly during the pandemic of 1918–1919. The great pandemic spawned a host of epidemiological studies in America. Because the months of this outbreak were very trying times for American health authorities, it comes as little surprise that these studies varied enormously in scale and quality. Many were little more than descriptive reports of the outbreak. Most of them, like the best-known epidemiological

studies of the 19th century, were statistical analyses of mass mortality data. All studies of the 1918–1919 influenza struggled with uncertainties of diagnosis. The best of them grouped influenza and pneumonia deaths together for analysis. Insofar as they offered analysis of the data they provided, these earlier epidemiological studies of influenza sought to demonstrate how the risks of disease and death were distributed in the population and what environmental factors might help account for that distribution. Also, as Francis's definition suggests, the studies of the 1918–1919 influenza epidemic focused on the herd, not on the individual. An important measure of an investigation's significance was the size of the population studied – the larger the population base, the more reliable the results were thought to be. The study that W. H. Frost compiled from Public Health Service surveys in ten US cities and a collection of small towns and rural areas in Maryland reflects this view, when it ends with the warning that even so large a survey was too small to offer an accurate picture of the epidemic (Frost, 1920, p597).

One of the most substantial studies undertaken in the immediate aftermath of the pandemic was the analysis of the outbreak in Connecticut by C.-E. A. Winslow and J. F. Rogers of the Department of Public Health of Yale University School of Medicine (Winslow and Rogers, 1920). Their analysis was based on vital statistics collected by the state health department. Winslow and Rogers sought to demonstrate the severity of the outbreak by calculating excess mortality rates. They calculated weekly mortality rates for influenza and pneumonia and for all causes during the weeks and months of the outbreak and illustrated the outbreak's magnitude by comparing these mortality rates during the epidemic to comparable average figures for the years immediately preceding the outbreak. See Figure 6.1.

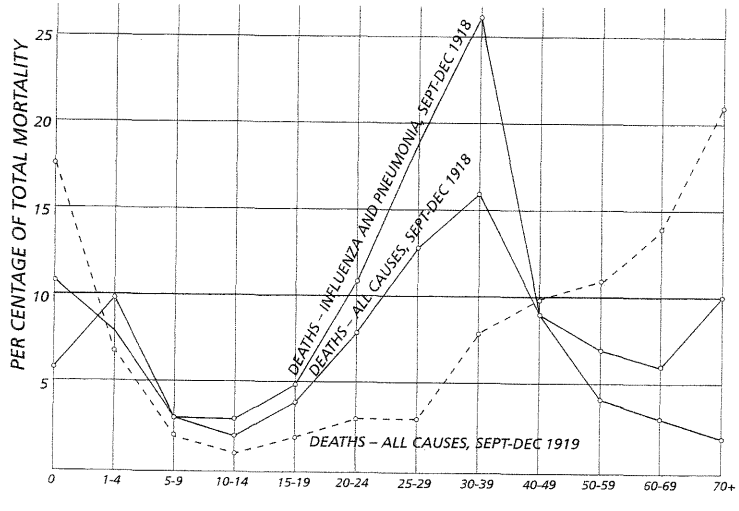
They next studied the geography of the epidemic by calculating mortality rates for individual towns and cities, as well as the outbreak's midpoint in each county, i.e. the date on which half the deaths occurred. A comparison of such place-specific mortality rates suggested that the disease was highly contagious, had a very short incubation period, and was probably spread person-to-person at close range. Large cities and industrial towns had the highest rates. Rural areas and towns furthest from the railroad had the lowest rates. The mortality rates and the midpoint dates suggested that the severity of the disease moderated somewhat as the outbreak moved north and west across the state from its initial focus in the state around New London.

Winslow and Rogers then turned to a demographic analysis. They calculated age- and sex-specific rates of deaths from influenza and pneumonia from September to December 1918, rates of deaths from all causes in those same months, and rates of death from all causes during 1917. This outbreak seemed to be unique in putting at highest risk of death those younger than age five and those between the ages of 20 and 40. See Figure 6.2.



Source: Winslow and Rogers (1920). Reproduced with permission

Figure 6.1 Monthly death rates in the state of Connecticut

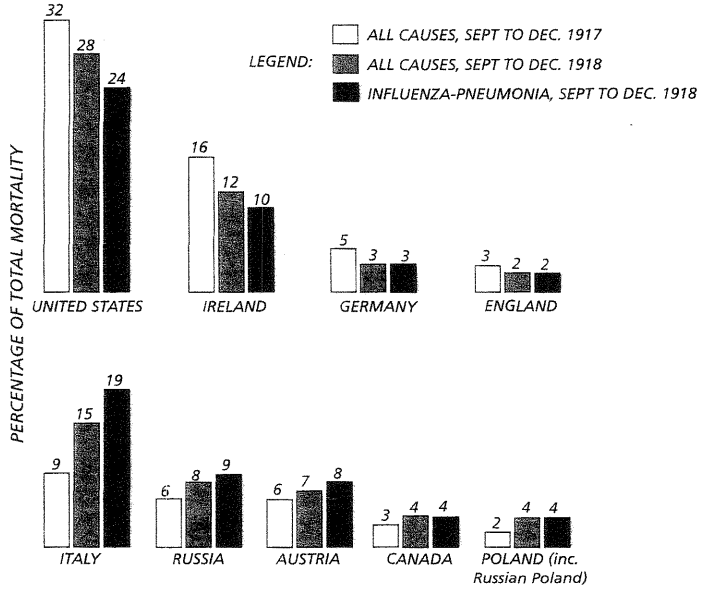


Source: Winslow and Rogers (1920). Reproduced with permission

Figure 6.2 Age distribution of deaths from the influenza epidemic compared with normal

Winslow and Rogers conceded, however, that using mortality data alone, they were unable to determine whether this peculiar pattern of mortality was due to high rates or morbidity or to high case fatality rates at those ages (Winslow and Rogers, 1920, p196). Males had higher rates than females. This difference, these researchers suggested, might be due to either greater exposure of men, or a tendency among men to 'keep up and about when ill' (Winslow and Rogers, 1920, p196). They turned next to what they called 'race' ('ethnicity' we might say), by which they meant nation of mother's birth. Certain ethnic groups (Irish, English and Germans) had lower mortality from influenza and pneumonia during the epidemic, while other groups, notably Russians, Austrians, Polish and Italians, had much higher rates. See Figure 6.3.

These researchers believed that these results reflected not innate differences in resistance or susceptibility but rather differences in the age-structure of these population groups. The groups with the highest rates were more recent immigrants with the highest concentration of members at the ages facing the greatest risk of death. They also suggested, but did not attempt to investigate, that the differences also resulted from socio-economic factors, including differences in housing. We will have a bit more to say about this study shortly, but it should be apparent from this review that it offered a thorough and careful analysis of mortality data



Source: Winslow and Rogers (1920). Reproduced with permission

Figure 6.3 Distribution of deaths in Connecticut by mother nativity

and of the demographic and geographical factors deemed relevant to the outbreak. By the standards of its day, it was a very competent study. However, given the data at their disposal and the understanding of influenza at the time, there were many aspects of this outbreak that these researchers could not explain.

A very different approach was taken by Raymond Pearl, Professor of Biometry and Vital Statistics at the Johns Hopkins University in a long article published in *Public Health Reports* (Pearl, 1919). Pearl was highly critical, even contemptuous, of the mathematical innocence of contemporary epidemiologists, and he sought clarity in a higher order of mathematical analysis. If Francis is correct that past epidemiologists had focused on the herd and not on the individual, Pearl's study would serve as one of Francis's best examples. Pearl's study is primarily an analysis of mortality curves for the populations of large cities. For this study, Pearl analysed the crude mortality curves for 39 American cities before and during the pandemic. See Figure 6.4.

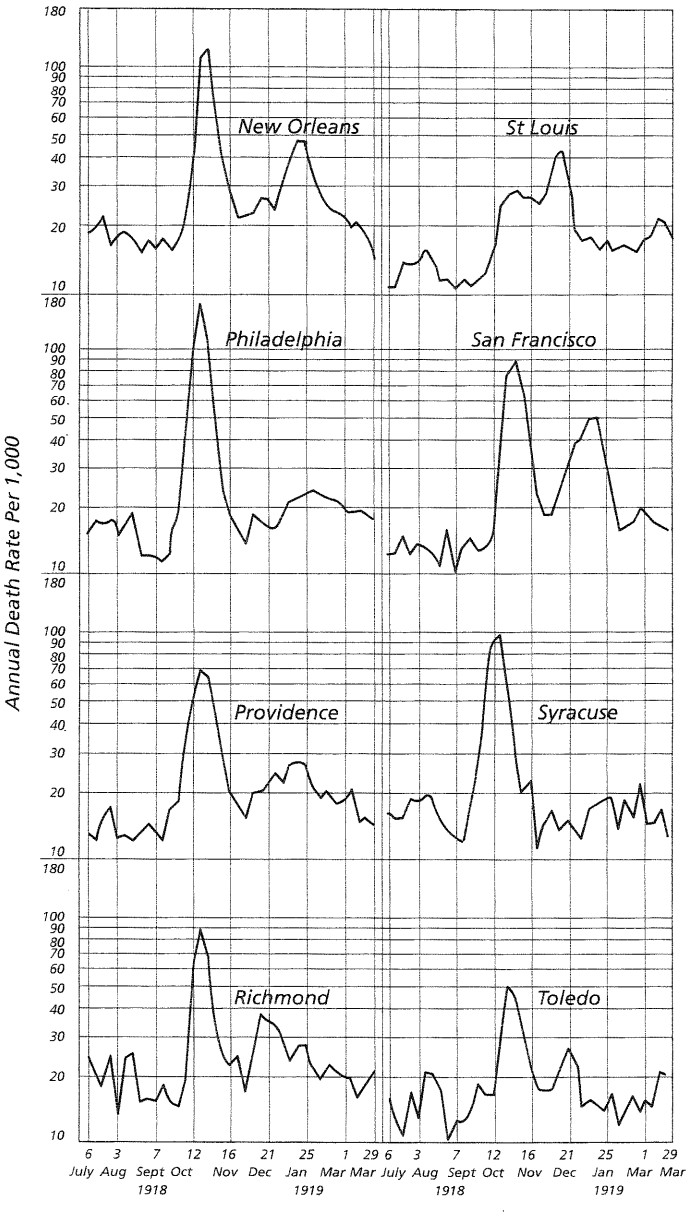
He calculated several mathematical expressions, indices of epidemicity he called them, to analyse these curves. His favourite was the Peak-Time ratio which measures explosiveness:

$$I = P - M'/T' \quad (1)$$

where P is the peak weekly mortality
M' is the mean weekly mortality from 6 July 1918 until the beginning of the local outbreak
T' is the time of the upward slope of the curve

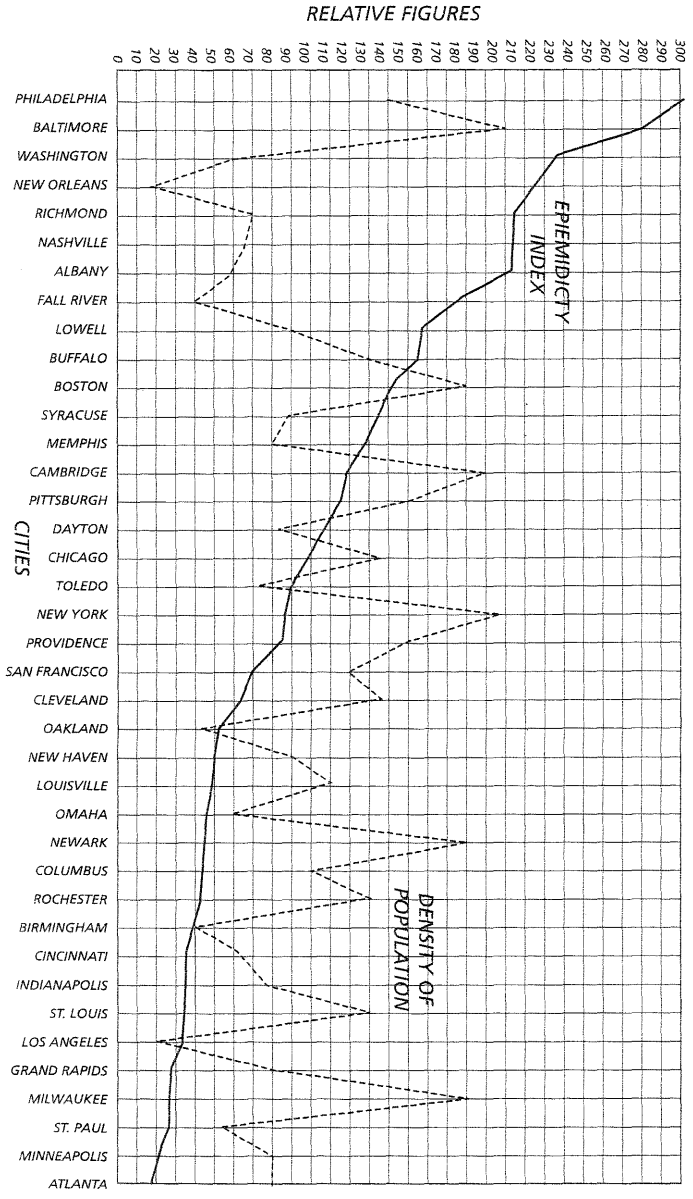
He found no correlation between the explosiveness of the outbreak or its severity and any social or demographic factor that he considered. See Figure 6.5 for the role of population density. Pearl calculated the correlation between the explosiveness of the outbreak and population density to be $r = +0.092 \pm 0.107$. The strongest correlation he found was between the explosiveness of the outbreak and the city's crude mortality rate before the epidemic. The coefficient of correlation in this case was 0.661 ± 0.061. There were also fairly strong correlations between explosiveness and mortality from pulmonary tuberculosis, heart disease and Bright's disease (Pearl, 1919, p1782).

For all its statistical sophistication, Pearl's study did little to penetrate the mysteries of the great influenza pandemic. Using mathematically simpler modes of analysis, Winslow and Rogers were able to confirm some of Pearl's major findings and tellingly criticize others. The Yale researchers suggested that Pearl's conclusion that human crowding was not a factor in this outbreak was unjustified, because all his data came from very large cities in which there was ample opportunity for human-to-human transmission. The inclusion of data for small towns, villages and rural areas, such as they had for Connecticut, showed that population density was probably a factor in the transmission of the disease (Winslow and



Source: Pearl (1919). Public domain

Figure 6.4 Annual death rates by weeks per 1000 population for eight cities



Source: Pearl (1919). Public domain

Figure 6.5 Diagram showing lack of correlation between variation between epidemicity index and density of population

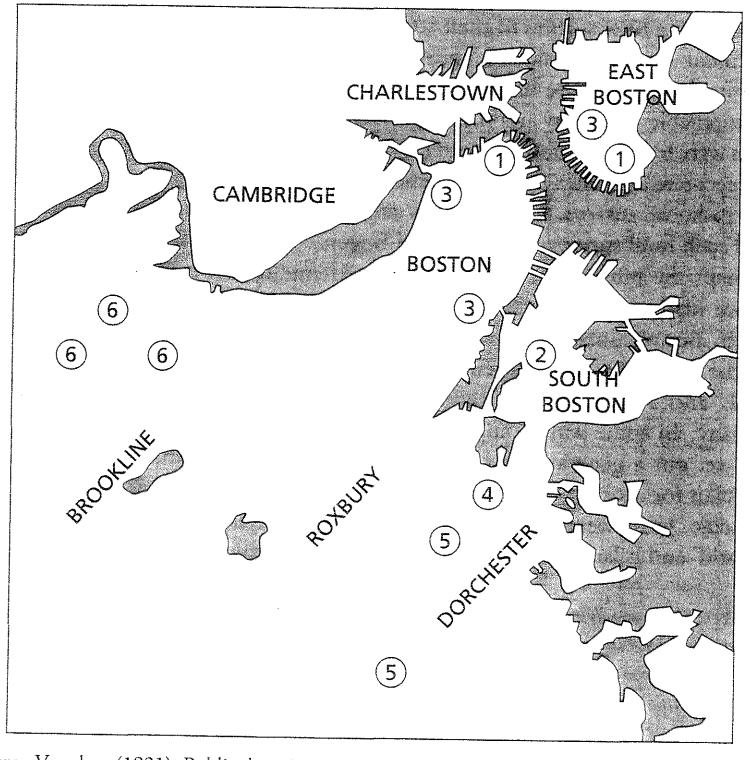
Rogers, 1920, pp202, 204). They also pointed out that one could not ignore the possible role played by differences in the age structure of the populations studied. In addition they questioned the way Pearl had analysed the role played by distance from the primary focus of the pandemic in the United States and the explosiveness of an outbreak. For this calculation, Pearl had assumed a single focus, Boston, and simply used the linear distance from each of his 39 cities to Boston. But Winslow and Rogers insisted that there is no reason to assume just one focus, nor is distance as the crow flies a good proxy for the routes of transmission (Winslow and Rogers, 1920, pp205–206).

Winslow and Rogers were clearly more conscious of the biological and medical complexities of disease outbreaks. They recognized, for example, that working from mortality data alone was a serious handicap. Accurate information of cases would be a great help in understanding the pandemic. It could help, for example, to clarify the highly unusual age distribution of deaths from influenza and pneumonia. Connecticut had made influenza a reportable disease on 18 September 1918, and in a brief section of their study, Winslow and Rogers used state health department records to calculate morbidity and case fatality rates. They warned, however, that the disease had been seriously underreported, and that these rates were unreliable (Winslow and Rogers, 1920, pp190–191). Most of their generalizations were based therefore on patterns of deaths from influenza and pneumonia. More accurate estimates of the incidence of influenza could only be obtained by house-to-house surveys, and Winslow and Rogers cited case fatality rates from several such local surveys (Winslow and Rogers, 1920, pp190–191).

Perhaps the most interesting study of epidemic influenza in these years, and one that made a serious attempt to analyse morbidity, is Warren T. Vaughan's study in Boston during the outbreak of 1920 (Vaughan, 1921). Vaughan was from the Department of Preventive Medicine and Hygiene of Harvard Medical School, and his study was sponsored by the Metropolitan Life Insurance Company. In some ways Vaughan anticipated the goals that Francis and Paul would set out a generation later. We are indebted, Vaughan explained, to the statistician for most of what we know about the epidemiology of influenza. The statistician 'has a wealth of information of a general nature … from all parts of the world' and is 'armed with fascinating mathematical instruments':

> *Like an aviator flying over enemy territory he acquires a breadth of vision and a general perspective which is to a great extent denied to those remaining on the ground. But also like the aviator, from the very fact of his high position he loses the ability to recognize detail. An Army depending entirely upon its aeroplane reconnaissance would find itself helpless in combating the enemy. The aeroplane is useful, yes, it could not be dispensed with, but never an opportunity is lost for scouting parties to explore the enemy front lines.* (Vaughan, 1921, pp175–176)

Vaughan conceived of his study as one of those scouting parties, as a way to improve on the large statistical studies by collecting more complete and more accurate information on a small sample of people. More specifically, he moved his focus from the herd to, if not the individual, the family unit. Using trained social workers who spoke the language of the families studied, an Italian-American community physician and recently graduated Harvard MD, he mounted an intense local study using six carefully chosen districts in Boston comprising about 10,000 people. As he identified them, one was an Italian neighbourhood, one was Irish, another Jewish, the fourth was a middle-class, ethnically mixed neighbourhood, and the last two were a moderately well-to-do Jewish neighbourhood and a well-to-do neighbourhood of old American families (Vaughan, 1921, pp129, 133). See Figure 6.6. During the 1920 influenza epidemic, his assistants contacted every household in their districts and recorded information on each family's size, housing and apparent standard of living and a health history of every family



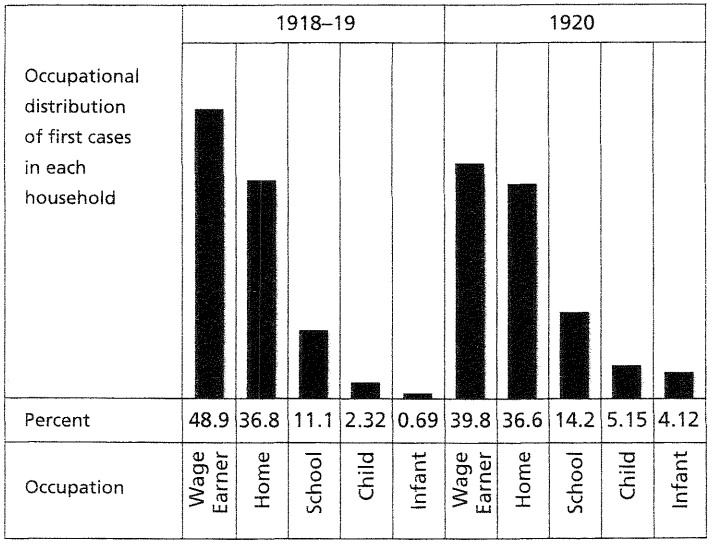
Source: Vaughan (1921). Public domain

Figure 6.6 Map of greater Boston showing the distribution of the districts covered by Vaughan's house census

member during both the 1918–1919 and the 1920 influenza epidemics. Family members were asked specific questions about symptoms, the severity of their attacks, whether a doctor had been called, and whether they had stayed in bed for more than one day during their illnesses. From these returns, Vaughan made all the retrospective diagnoses.

Vaughan was able to confirm and modify some results of recent analyses of mortality data. His results showed that larger, poorer, more crowded families did in fact experience more cases of influenza, but he conceded that it was difficult to disaggregate poverty, family size and domestic crowding. In one attempt to do so he classified cases by their degree of intimacy to a previous case in the family. Those sharing the same bed with an influenza case were more likely to contract influenza that those who shared the same bedroom or the same dwelling. He could also test several theories about how influenza spread. He found, for example, that schoolchildren did not play the critical role in disease transmission that some observers had suggested. In those six Boston districts the first case in a household was usually the wage earner. See Figure 6.7.

From our perspective the most interesting result was Vaughan's realization that what made the 1918–1919 epidemic in Boston so serious was not the deadliness of an attack. According to Vaughan's figures, the average case fatality rate for influenza was only 2.5 per cent. What accounts for the outbreak's terror was the enormously high morbidity rate, which stood at 20 per cent of the entire



Source: Vaughan (1921). Public domain

Figure 6.7 Table showing occupational distribution of cases in each household

population. Influenza was clearly highly contagious and capable of spreading with great speed. But for that reason, it was remarkable how many people escaped the disease. Vaughan concluded that 70 per cent of those living in his six districts escaped influenza in both outbreaks and that even during the 1918–1919 epidemic 55 per cent of those sharing the same bed with an influenza case escaped the disease. In a suggestion that most of Vaughan's readers probably missed and whose significance he may not have fully understood himself, Vaughan argued that the key to understanding the epidemiology of influenza lay in understanding herd immunity. If measles conveyed no lasting immunity, its outbreaks in large towns would resemble the great influenza pandemic (Vaughan, 1921, pp209–210, 230–231).

This was a rare insight which would not be confirmed for almost two decades. During and for a decade following the great influenza pandemic researchers could describe influenza outbreaks in great detail but do very little to explain the disease's nature or behaviour. Two examples will suffice. In both we can see in retrospect how fuller knowledge of agent and host response were lacking. During the winter of 1918–1919, Milton Rosenau directed an experimental study of influenza at the quarantine station in Boston harbour that was jointly sponsored by the United States Public Health Service and the Navy (Rosenau, 1919; Rosenau et al, 1921). In this study, 100 volunteers whose health histories indicated that they had not previously contracted influenza were experimentally inoculated. At first cultures of the Pfeiffer's bacillus, *Hemophilus influenzae*, the presumed cause of influenza when the pandemic began, were sprayed first into the volunteers' noses and then into their throats and eyes as well. When those inoculations failed to produce illness, the volunteers were inoculated first by spray and then by sterile swab with a mixture of organisms taken from the nose and throats of patients in the influenza wards of Boston. Some volunteers were injected with blood from influenza patients. Finally, 13 of the volunteers were taken into the influenza wards and exposed to ten influenza patients each. They were asked to shake hands with these patients, to talk with them at close range, and to allow the patients to cough directly into their faces. None of the volunteers in this study contracted influenza by any of these means. While Rosenau hypothesized that it was possible that his volunteers may not have been susceptible to influenza, he ended his article with a masterpiece of understatement. 'We entered the outbreak with a notion that we knew the cause of the disease, and were quite sure we knew how it was transmitted from person to person. Perhaps, if we have learned anything, it is that we are not quite sure what we know about this disease' (Rosenau, 1919, p313).

That the next decade did little to dispel the uncertainties and confusion is perhaps best illustrated by the massive 500-page review of influenza literature published by Edwin O. Jordan, Professor of Hygiene and Bacteriology at the University of Chicago in 1927 (Jordan, 1927). This was a definitive review dealing with every conceivable biological and medical aspect of the disease, but definitive

answers to fundamental features of the disease were in short supply. The cause of influenza was unknown and its pathology indefinite, Jordan told his readers, so the disease could only be identified by its epidemiology, its patterns of occurrence. It was uncertain whether an attack of this disease conferred immunity to future attacks, and if it did how long that immunity lasted. Major pandemics were an important feature of influenza, but it was not known why they occurred when they did or why they attacked some places and left others untouched. In fact it was even uncertain whether the disease that occurred in small outbreaks and sporadic cases almost every winter was the same disease that caused the major pandemics (Jordan, 1927, pp47–55, 58–60). Jordan continued the practice of distinguishing between 'influenza', the disease of routine winter occurrence, and 'epidemic influenza', the condition that most concerned medical and public health authorities. There are suggestions in Jordan's review that changing virulence might be an important factor in influenza and that scientists were beginning to suspect that the cause might be a filter-passing microorganism such as the one suspected of causing the common cold, but these were only possibilities for which there was no direct evidence.

Four years later, new and vitally important evidence began to appear. In 1931 Richard Shope at the Rockefeller Institute's Department of Animal Pathology in Princeton isolated a virus from hogs suffering from Swine Influenza and identified it as a causal agent (Shope, 1931). Two years later a team of researchers at the National Institute for Medical Research at Mill Hill near London isolated a virus from human influenza patients (Smith et al, 1933). This result was confirmed a few months later by Thomas Francis at the laboratories of the International Health Board, when he isolated a virus from material sent to him from the throats of patients suffering from influenza in Puerto Rico and Philadelphia (Francis, 1934). Francis was at the time primarily a laboratory scientist who would play an important role in developing the laboratory methods of working with flu viruses.

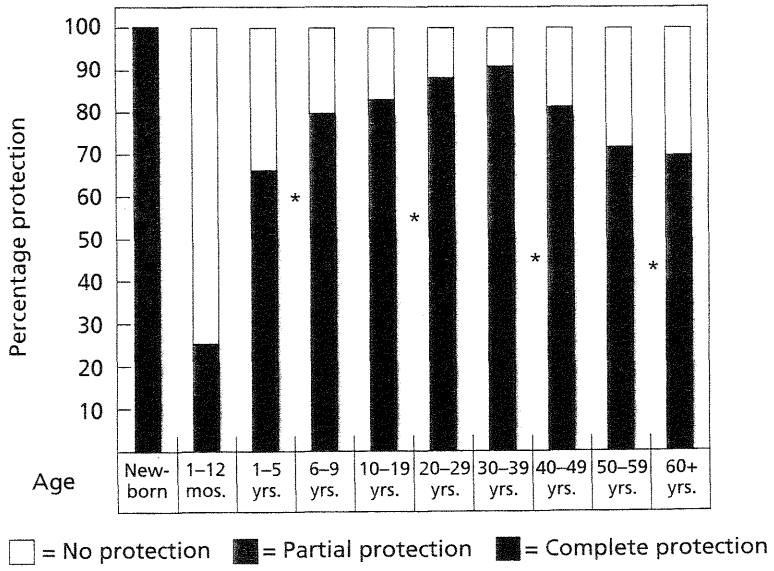
One might expect that the discovery of an agent for influenza and the development of laboratory methods of working with it would answer most of those fundamental questions that Jordan had to leave unanswered. By the second half of the 1930s influenza had a known cause, but much of its behaviour was still unexplained. As it would prove, to answer those unanswered questions and even to understand the nature of the new viral agent, researchers would have to develop methods to study the human immune response to the influenza virus. The laboratory would have to go to the patient.

To understand what is involved in using this approach, it is important to recognize that the laboratory methods in use in the 1930s provided no direct knowledge of the influenza virus. This new agent, after all, could not be seen with available microscopes or manipulated by the established means used with bacteria. All experimental knowledge of the virus had to be inferred by the response of laboratory animals to inoculation. Influenza viruses were initially isolated by nasal

inoculation into ferrets. If an inoculated ferret became sick and characteristic lesions developed in its lungs, other ferrets could be infected by the inoculation of lung material from the sick ferret that had first been ground, suspended and passed through a bacterial filter. In these years the virus was cultivated exclusively by serial inoculations in animals, initially only in ferrets, later through mice. The chains of successive animal passages could be very long indeed. By 1940 the virus strain that Thomas Francis had isolated in 1934, the PR8 virus, the one the laboratories of the International Health Board used most often for its influenza research, had been through 330 consecutive passages in mice (Horsfall et al, 1941, p336). Animal inoculation also provided the means to measure antibody titer against the flu virus. In the neutralization or mouse protection test the serum to be tested was diluted in series and groups of mice inoculated with each dilution mixed with a lethal dose of the virus. The antibody titer was taken as the inverse of the dilution which protected half the inoculated mice in one of those groups (Francis et al, 1937b, pp1142–1143; Siegel et al, 1942, pp59–60). These were slow, labour-intensive and expensive methods, but they provided the first definitive information on the agent of influenza.

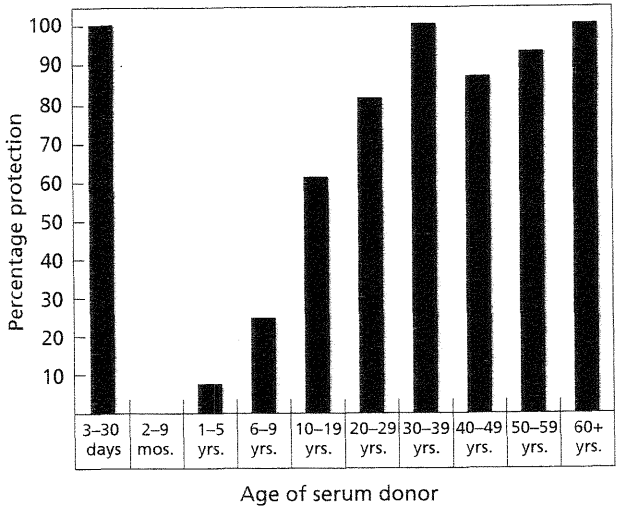
Francis wasted little time in using them to expand what was known about influenza and its epidemiology. In 1935, the year after isolating the PR8 virus, he first took his laboratory methods into the field. In the spring of that year, Francis and Richard Shope, the two Americans who first isolated influenza viruses, initiated a small research project that resulted in three consecutive articles in the *Journal of Experimental Medicine* (Francis and Mcgill, 1936; Francis and Shope, 1936; Shope, 1936). They first conducted cross-neutralization studies of the four known strains of human influenza virus (WS, Phila, PR8 and Alaska) and the swine influenza virus, S-15. They concluded that the human influenza viruses then cultivated in laboratories were antigenically identical, but that while the human and swine virus shared some antigenic properties, they were distinct (Francis and Shope, 1936, pp652–653). They next turned their focus to the human host, proposing to explain basic questions about epidemiology of influenza by studying the distribution of influenza antibodies in the human population (Francis and Mcgill, 1936, p664). The scale of the study was modest. They collected clinical histories and serum samples from 136 hospital patients in Philadelphia, Baltimore and New York, and from staff members of the Rockefeller Institute. Shope conducted the tests for antibodies against the swine influenza virus, S-15. Francis tested the samples for antibodies against the PR8 virus. They found that antibody levels against both PR8 and S-15 were widely distributed in their sample population but that that distribution differed a great deal according to age. See Figures 6.8 and 6.9.

Newborns had very high antibody levels against both viruses, but in young children, those levels fell dramatically and then increased with age to a peak in early middle age. When combined with clinical histories of influenza, this



Source: Francis and Shope (1936). Reproduced with permission

Figure 6.8 Percentage protection noted according to age



Source: Francis and Shope (1936). Reproduced with permission

Figure 6.9 Percentage of persons of various ages whose sera neutralize the virus of swine influenza. Sera giving both complete and incomplete protection are included

distribution of antibodies was highly suggestive. It also seemed that almost all adults, even those who had no clinical history of influenza, had been exposed to both viruses. Mild cases and subclinical infections were clearly common. The distribution of antibodies against swine flu was particularly interesting, since that virus had never been isolated from humans. Shope concluded that the distribution of antibodies against S-15 gave credence to the theory that the swine flu virus had been the cause of the pandemic of 1918–1919 and that humans occasionally continued to encounter that virus (Shope, 1936, pp682–683). The most difficult result to interpret was the prevalence of antibody levels adequate only to partly protect experimental animals (Francis and Mcgill, 1936, pp664–665). Did these levels indicate a poor immune response to recent infection or dwindling immunity to infections more distant in time? The age distribution of partly protecting antibody levels was consistent with either interpretation.

In a review article in the *American Journal of Public Health* in 1937, Francis tried to synthesize the results of this study with the current body of knowledge of influenza (Francis, 1937). One of the most puzzling aspects of the epidemiology of influenza he found was in the fact that an attack of influenza seemed to offer little immunity. Clinical histories indicated that many individuals had been infected more than once, sometimes in two successive years. Francis considered four possible explanations:

1. The agent responsible for influenza has low antigenic properties.
2. Many different strains exist and cross-immunity does not obtain.
3. Immunity develops following the disease but persists only a short time.
4. A fourth phrase has recently been gaining in prevalence, a pretty phrase but one for which little evidence exists: 'general immunity without mucous membrane immunity'.

(Francis, 1937, p213)

At the time Francis dismissed possibilities 2 and 4. After all, the cross-neutralization studies he and Shope had just completed suggested that all human influenza viruses were antigenically identical. He focused instead on possibilities 1 and 3, the quality of immunity and its waning. Recently generated laboratory evidence suggested that animal inoculation with influenza virus resulted in robust immunity that persisted for several months. The persistence of immunity in humans, however, was unclear. It seemed that it lasted at least one year following an attack. On the other hand there seemed good reason to think that it did diminish with time. In their recent study, Francis and Shope had found that the serum of 87 per cent of those who had had influenza between 1933 and 1935 completely neutralized the PR8 virus, while only 50 per cent of the sera of those who had last experienced influenza in 1918–1919 would do so. In this review Francis raised two other problems: the relationship between human and swine influenza and the relationship between influenza and diseases that resembled it (Francis, 1937, pp216–233). The former issue he left to Shope. The latter, as we will see, he would return to three years later, with striking results.

This study with Shope in 1935 seems to be the origin of Francis's idea of clinical epidemiology. As we can clearly see, he had changed the focus of epidemiological investigation from the herd to the individual and had done so by taking the laboratory to the individual. He clearly found the approach promising and pushed its utility further. The 1935 survey we have just considered was undertaken between outbreaks. For that reason it could say little about the immediate antibody response to infection. The next year he and his laboratory undertook the same sort of survey during an outbreak. During the winter of 1936–1937 he collected both throat washings and serum from 120 patients diagnosed with influenza and from 48 contacts who had no clinical history of the disease (Francis et al, 1937a; Francis et al, 1937b). He succeeded fairly consistently in isolating the virus by inoculation into both ferrets and mice. He also showed that serum of mice inoculated with this newly isolated virus neutralized the PR8 virus but not the swine flu virus (Francis et al, 1937a, p567). The virus in this outbreak, in other words, was a human influenza virus that seemed immunologically identical to the one that had circulated in 1933–1934. In order to study the antibody response in humans he succeeded in obtaining a serum sample in the acute phase of the disease, during the first three days, and another in convalescence, three or four weeks later. He measured the antibody titer using both the mouse protection test and a recently introduced complement fixation test. The results seemed to bear out his expectations.

In most cases the individual from whom he could isolate the virus showed a significant increase in antibody titer, typically by a factor of ten. In other cases he had been unable to isolate a virus, but a similar rise in antibody titer had occurred. Such an antibody response, he believed, was diagnostic of the disease. Cases where he could neither isolate the virus nor detect a rise in antibodies, he decided, were not influenza (Francis et al, 1937a, pp1148–1149). In other words, Francis seemed to believe that he had found tools that would not only make clinical diagnosis more accurate but which would also answer some of the basic questions about the epidemiology of influenza, questions that had plagued Jordan in the late 1920s: what was influenza; was it one disease or several; did an attack convey immunity; how long did that immunity last?

While the results of this small study seemed to put the study of epidemic influenza on a firmer footing, they also raised some troubling questions, questions that would soon force Francis to rethink some of his conclusions. The human immune response to influenza infection seemed to be highly individual. In general, people with low initial titer usually had the greatest increase in antibodies during their illness, but this was not always the case. For another, the relationship between illness and antibody levels was not at all precise.

Antibody levels rose during the epidemic even among those who were not sick. Here was additional evidence that during an outbreak there might be many sub-clinical infections. Furthermore, there was no precise relationship between antibody titer and immunity to influenza. In general people with low titer were more likely to become sick, but some people with very high titer contracted the flu. There seemed, in short, no identified titer that guaranteed protection.

Francis had made an earlier excursion into the field to study an outbreak, but this time he had been disappointed in the results, and he did not publish them, at least initially. It would be the beginning of some of his most important work. He had flown to San Joaquin County, California, in February and March of 1936 to investigate an influenza outbreak. The disease clearly seemed to be influenza. It had all the clinical and epidemiological features health officials looked for. As he was to do in New York several months later, Francis made throat washings during the acute phase and drew blood from patients during the acute and convalescent phases. He shipped these specimens by air express back to his laboratory in New York for testing. This time, however, he could neither isolate a flu virus nor detect its presence from a rise in influenza antibodies to either the PR8 or S-15 viruses. Puzzled, he stored the serum for future reference, and, in a short section of the review article he published in the spring of 1937 labelled 'Relation to other Respiratory Diseases of Similar Character', he reflected on this episode (Francis, 1937, pp220–223). He did not simply dismiss the results as proof of misdiagnosis on a large scale. The clinical and epidemiological picture was simply too convincing. It was possible that the cause of the outbreak was an influenza virus but one of very low virulence or that his specimen had been damaged in shipment. He doubted that either was the case. The most likely explanation was that the outbreak in California was caused by a different virus. He continued:

> *If this be the case, it is evident that the term 'influenza' embraces more than a single aetiological entity and that continued efforts must be made to isolate the aetiologic agents and to differentiate such clinically similar but aetiologically different diseases.* (Francis, 1937, p223)

Experience over the next three years confirmed that this speculation was correct. Several other researchers encountered outbreaks that seemed to be influenza on clinical and epidemiological grounds but which they could not confirm by laboratory means. Faced with this occasional experience the laboratories of the International Health Division and the National Institute for Medical Research reached an agreement on an international nomenclature and a research challenge, which they published in *The Lancet* in early October 1940 (Horsfall et al, 1940). They decided to label as 'Influenza A' the disease caused by the currently known human influenza viruses. They labelled 'Clinical Influenza' any 'aetiologically indefinite symptom complex' resembling influenza.

> *If and when hitherto undescribed viruses are isolated from this group and are shown to be of aetiological significance other specific diseases in the group could be labelled influenza B, C, etc., as they are found to be caused by the as yet hypothetical agents influenza B virus, etc.* (Horsfall et al, 1940, p414)

The very next month Francis, who by this time had moved to New York University, announced that he had isolated one of those anticipated agents, and he labelled it 'influenza B' (Francis, 1940). In short, he had shown that with an agent distinct from influenza A, which he had isolated from patients who seemed to be suffering from influenza, he could satisfy all the criteria that the British team in 1933 and he in 1934 had used to identify the first human influenza viruses. That he succeeded this time, when he and other researchers had failed in earlier attempts, is probably due to the fact that the results he obtained were now recognized possibilities, so he persisted. It was a narrow thread of evidence. He was investigating another of those flu-like outbreaks. This one was in a convalescent home for children with rheumatic fever. He took throat washings and drew blood from four patients. He could detect no rise in antibodies to the PR8 virus in the sera of these patients, and at first the results of animal inoculation with the throat washings also seemed negative. All the mice and two of the three ferrets he had inoculated remained healthy and had no lesions in their lungs. But one of the three ferrets, the one inoculated from a patient named Lee, began to show signs of illness on the fifth day. Its temperature fell. It stopped eating, remained quiet and had some trouble breathing. When Francis dissected the animal on the sixth day he found only a slight bluish tinge in the lower lobe of the lung. From that lung tissue he made 13 serial passages of filtered lung tissue in ferrets. He also inoculated a series of mice. He found fairly consistent results – an elevation in temperature and the formation of mild lesions in the lungs. In mice the symptoms and the lesions became more pronounced with successive passages. He showed that immune serum against several poorly defined mouse viruses did not neutralize this Lee virus (Francis, 1940, pp405–406). So his results were probably not an artefact of laboratory contamination. He found that the convalescent serum from the children at the home neutralized the Lee virus but not PR8, indicating that this new virus was the cause of the outbreak. He also found that the serum from the sole convalescent ferret in the Lee series failed to neutralize PR8. Furthermore, PR8 immune serum, even hyperimmune serum produced by repeated inoculations with the PR8 virus failed to neutralize even small amounts of the Lee virus. This virus was clearly antigenically distinct from influenza A virus, yet it produced a disease indistinguishable from influenza A.

Francis did not stop there. He showed that the stored serum from that mysterious outbreak in California in early 1936 also neutralized the Lee virus, and so did the sera from patients at Duke University Hospital and from patients in an outbreak in the West Indies who seemed to be suffering from influenza but whose

sera did not neutralize PR8 (Francis, 1940, p407). The Lee virus was not only distinct: it was capable of producing outbreaks of influenza. The outbreaks of 1936 and 1940 were due, he concluded, to the Lee virus, influenza B. Those of 1936–1937 and 1938–1939 were due to influenza A. So, judged on aetiological grounds, it seemed that influenza was not one entity after all, but two.

It is obvious by now what Francis had in mind by the approach he called 'clinical epidemiology' and why he was so optimistic about its utility. In a short time he had used his laboratory methods with a small number of individuals to throw a great deal of light on those chronic problems of influenza epidemiology. But over the next few years that clarity began to cloud. Notice that in his studies Francis had used the PR8 virus he maintained in his laboratory to test for the presence of antibodies against human influenza virus. He and the world's other influenza researchers were convinced that all human influenza A viruses were antigenically identical. But by the late 1930s cross-neutralization and cross-immunity studies were showing slight antigenic differences among strains. Experience over the next few years proved that those differences were indicative of a much greater potential for variation than researchers could possibly have imagined.

During World War II Francis led the Influenza Commission of the Army Epidemiological Board in a crash programme to develop an influenza vaccine (Eyler, 2006, pp225–237). By the fall of 1942 his laboratory had developed a polyvalent vaccine containing formaline-inactivated PR8, Lee and a recently isolated influenza A virus called Weiss. A clinical trial was planned but failed, because there was no outbreak of influenza at the three test sites (Francis, 1945, pp2–5). The following year the Commission successfully conducted a large scale, randomized, placebo-controlled vaccine trial involving 12,500 students at universities and professional schools spanning the nation from California to New York. The results were conclusive. The vaccine was highly effective in preventing influenza A (Commission on Influenza, 1944; Special Issue on Influenza, 1945). In the aggregate the vaccine reduced the incidence rate from 7.1 per cent to 2.2 per cent. In most sites the reduction was even greater. In 1945 the Army used this vaccine to vaccinate all US soldiers. In the outbreak of influenza B that year the vaccine proved even more effective than it had been against influenza A in 1943. In the Army unit at the University of Michigan it reduced the incidence of influenza B from 9.9 per cent among the unvaccinated to 1.1 per cent among the vaccinated. At Yale the incidence rates fell from 12.5 per cent to 0.5 per cent (Study Committee on Influenza Vaccination, 1947, p1109).

Given these results, confidence was running high when the same vaccine was used again in the armed forces and among civilians during the flu season of 1947. There was a substantial outbreak that year, but this year the vaccine offered no protection whatsoever (Loosli et al, 1948; Mellanby et al, 1948; Siegel et al, 1948; van Ravenswaay, 1948). Investigations soon showed that the vaccine still raised antibody titers against its constituent viruses. It was also true that the serum of

convalescents from the 1947 influenza showed a slight rise in antibody titer to the PR8 virus, but they showed a much greater increase in antibodies to a virus strain that had been isolated during the outbreak, FM-1. Most significant, however, was the fact that none of the sera stored from previous influenza outbreaks contained antibodies against FM-1. It seemed that FM-1 was a new virus or at least one that had never been detected. The failure of the Army's influenza vaccine in 1947 forced influenza researchers to reevaluate the growing evidence of differences among strains. By the late 1940s systematic cross-immunity and cross-neutralization tests among strains and their antisera showed marked differences, especially among older and newer strains. The influenza viruses isolated during or after 1947 were markedly different from those isolated before 1947. Also, researchers observed that they were no longer isolating older strains from patients. WS and PR8 existed only in laboratories (Andrewes, 1954, p15). It was uncertain whether these older strains had gone extinct or whether they continued to exist undetected somewhere in nature.

The meaning of such antigenic variation became one of the most pressing issues in influenza epidemiology, and, as I have argued elsewhere, after 1947 a major divide opened among influenza researchers (Eyler, 2006, pp429–437). British and Australian researchers, most prominently C. H. Andrewes and Frank MacFarlane Burnet, argued that the influenza virus was capable of endless and unpredictable evolutionary change. According to Macfarlane Burnet, 'it appears that influenza A virus survives by constantly building serological novelty on to its past antigenic structure' (Burnet, 1951, pp170–171). Most American researchers, probably because they were committed to the development of a vaccine that could be used for extended periods, argued that this antigenic change was finite and limited. Figure 6.10 is Francis's model of this antigenic variation. There were, he argued, a finite and small number of antigenic components in the influenza virus. Their relative proportions might vary from year to year, but their identities remained unchanged, and they might all be included in the ideal, universal vaccine (Francis, 1954, pp137–138; Francis, 1955, pp535–536). His protégée, Jonas Salk, used a different model to arrive at a similar conclusion. He also believed that there was a finite number of influenza A antigens. These antigens might cycle in prominence as antibodies against them rose and fell in the population, but it would be possible to discover all such antigens and incorporate them into a vaccine that would offer universal protection (Salk, 1952).

The experience of the Asian influenza pandemic of 1957 turned the tide in this debate. The complement fixation test suggested that the virus causing this outbreak was the influenza A virus, but the hemagglutination-inhabition test could detect no similarity to any known influenza A virus (Robinson, 1961, p105). The appearance of this great pandemic would later be understood as the result of an antigenic shift, the first that researchers had observed, from the H1N1 influenza A viruses researchers had been studying to an H2N2 influenza A virus.

The magnitude of the change was unanticipated, and it dampened, if not extinguished, hope that there would be a simple means of preventing influenza outbreaks. It was clear by 1960 that the influenza A virus was capable of continuous and enormous antigenic change and that it was this change that had made the epidemiology of this common disease so difficult to understand. The techniques of investigation that Thomas Francis, Jr had labelled in the mid-1930s 'clinical epidemiology' and had so productively employed were important factors in the unravelling of this epidemiological mystery. He may have placed unwarranted faith in the development of a universal vaccine and in so doing had been encouraged to minimize the influenza virus's capacity for variation. He also may have underestimated the importance of studying the herd as well as the individual. However, his suggestion that the laboratory should be taken to the patient and his demonstration of the utility of serological studies to epidemiology were invaluable. By the time Francis retired most of those basic questions about the epidemiology of influenza that Edwin Jordan had had to leave unanswered in 1927 could now be explained by antigenic variation and its consequences.

Conclusion

I have tried to argue in this paper that in the 1930s what Thomas Francis called 'clinical epidemiology' was both a novel and a highly productive approach to the epidemiology of influenza. Among other things this case study demonstrates the value of interdisciplinary communication in the biomedical sciences. Following the isolation of the viral agent of influenza and the development of several rudimentary tools for isolating that virus and measuring antibody titre against it, Francis and his colleagues initiated studies that differed radically from the influenza epidemiology research of the past. They focused on human antibodies, not on reported deaths or illnesses. Hence they might include those who had been neither sick nor who had died. They might take place between as well as during outbreaks. They did not depend on highly developed statistical tools. Finally, while the value or reliability of the epidemiological studies undertaken in 1918–1919 was thought to depend on sample size, the studies of Francis and colleagues sometimes produced highly significant results from very small-scale studies. While Francis brought new laboratory tools to the epidemiology of influenza, he was highly dependent on the fund of knowledge about the disease that previous epidemiologists had compiled, and, as his more reflective writing illustrates, he framed his research in response to that knowledge.

Revolutions seem to face three fates: they may fail and leave little trace, they may succeed and become the dominate type, or they may be incorporated into the mainstream and leave a mark that is sometimes hard to identify in retrospect. 'Clinical epidemiology' in the sense that Francis used it, not in the sense that it is sometimes used in the 21st century, would seem to be an example of the third fate. Serological studies of human populations are now accepted tools of infectious disease epidemiology. While there was some precedent for work of this sort before Francis took the laboratory to the patient, because the problems of explaining the behaviour of influenza and of working with its agent were so great in the 1930s, his studies had particular salience in gaining recognition for this important approach.

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7

Hong Kong Flu (1968) Revisited 40 Years Later

Claude Hannoun with Susan Craddock

The Hong Kong pandemic was the third of the 20th century. The Spanish influenza in 1918–1919 was a world catastrophe with at least 20 million deaths. In the following years, the virus remained active and caused a number of annual episodes, though it was never as virulent as during the first two waves ending in 1919. Its composition is known today as A(H1N1), but inside this group, many variants appeared, the result of a continuous antigenic drift. For instance a significant seasonal outbreak occurred in 1948 with a variant called A' (A prime). A few years later, in 1957 a new virus appeared which was completely different from all the viruses [that had] so far been isolated as A or A'. It was understood later that its formula was A(H2N2). This virus caused a sudden and important pandemic with two to three million deaths, as well as a number of more minor episodes during the following years.

The Hong Kong pandemic

By the 1960s, much progress had already been made in what was known about the influenza virus, including how it spread and how it mutated. However, in 1968, there was some surprise to see another pandemic invade the world. During the winter 1967–1968, there was a 'normal' seasonal epidemic of flu due, like that of ten years before, to the H2N2 virus. But suddenly in July 1968 a new virus was isolated in Hong Kong which could not be typed within known human viruses. The virus was quickly recognized as showing antigenic differences from those isolated during the preceding years but it was not clear if it was a completely new virus or not. It was commonly designated as A2 Hong Kong and this ambiguous designation was used until 1973. This was not just a matter of vocabulary, but a more important concern, since it was not possible to decide on vaccine composition without a clear understanding of the nature of the surface proteins of the new agent.

The virus emerged officially in Hong Kong ('Hong Kong flu') though there are indications that the virus had already been present in other regions of continental China a few months before. A 1969 overview of the flu in Hong Kong by W. K. Chang, the Senior Medical Officer of the Hong Kong Government Virus Unit, indicated for example that travellers to the neighbouring Chinese province reported incidences of influenza-like infections prior to the outbreak in Hong Kong, even though no official word of an outbreak came from mainland Chinese authorities (Chang, 1969, p349). Similarly, *The Times* of London reported a widespread outbreak of acute respiratory disease in south-eastern China on 12 July 1968 – the first signal of a possible new influenza outbreak, according to two members of the World Health Organization's Virus Unit (Cockburn, et al, 1969, p345). As these two reports confirm, a new virus cannot be detected easily and rapidly if it emerges in a remote country where facilities for specialized medical and diagnostic care are not available.

The virus's appearance in Hong Kong might have been due to the many boats and trains going to and fro between China and Hong Kong carrying supplies and passengers, but it was, and is, also an 'effective place for virus exchange' given its busy port and tourist trade (Chang, 1969, p349). However it got there, in Hong Kong, the outbreak was spectacular. At least 500,000 cases were reported in a few weeks in July 1968, with the peak occurring in the week of 27 July. All age groups were affected, indicating that the new virus did not find any immune barrier or memory. The symptoms, however, were mild and no excess deaths were reported during the duration of the epidemic (Chang, 1969, p351).

From Hong Kong the virus spread very rapidly eastwards, westwards and southwards, affecting Singapore, the Philippines, Thailand, Taiwan and Vietnam by August; and Australia, Iran and India by September (Cockburn, Delon, and Ferreira, 1969, p346). The virus was introduced in Thailand first among US military personnel at the Korat Royal Thai Air Force Base in late July, most probably from pilots returning from other parts of Asia where influenza was already present (Buescher et al, 1969; Suvongse, 1969). Soon after its appearance on the military base, the virus spread to Bangkok and other parts of the country, reaching epidemic peak in October (Suvongse, 1969). Clinical symptoms were generally mild and affected all age groups (Suvongse, 1969). In India it appears that influenza first arrived in Madras in September 1968, spreading quickly to cities in the rest of the subcontinent and into rural areas more slowly (Veeraraghavan, 1969). As in Thailand, the epidemic peaked by November in India, but children were more affected than adults (Veeraraghavan, 1969). Though cases were reported in Japan in August and September, influenza did not develop into a more generalized epidemic until mid-October for reasons unclear to health authorities (Fukumi, 1969, p353).

The virus reached the US very shortly after it had started in Hong Kong. On 2 September 1968 the virus was isolated from a Marine Corps in Atlanta, Georgia,

who had shared a bunker on his last night in Vietnam with a friend who had just returned from Hong Kong (Sharrar, 1969, p361). The epidemic invaded the entire country very suddenly, appearing at a West Coast Marine Corps Drill Instructors' School within the same week as the Atlanta case, and even spreading to Hawaii and Alaska by mid-September as a result of military personnel returning from Southeast Asia, according to contemporary reports (Sharrar, 1969). The outbreak did not affect civilians, however, until mid-October when it appeared in the California town of Needles. By mid-November the virus had spread across the country to the East Coast, and by December every state was affected. Most striking were the high illness and death rates in the United States following the introduction of the virus on the West Coast, about which more will be said below.

At the same time, the activity of the new virus was moderate in the UK. In a few other countries in Europe, there were only sporadic cases. At the end of the winter 1968–1969, there was moderate activity of the virus in virtually every country in Europe, but by April, it disappeared completely, as seasonal flu epidemics do. In France mortality was of about 36,000 deaths in two months and all ages were concerned, although morbidity was slightly higher in children and the elderly. Social consequences were very dramatic because absenteeism rates were very high during a very short period. Everyone who lived through that outbreak remembers that the offices looked empty since 25 per cent of staff were affected at the same time. The situation was very impressive for a few weeks. However, if the total duration of the epidemic at country level was about six weeks, local effects were much shorter. The peak of the outbreak in a given city, Paris, for instance, lasted about two weeks and the wave moved to other regions. There were problems of information circulation, of resource distribution, and there were especially problems in the hospitals. The wards were completely overburdened, especially intensive emergency care facilities, and there were even problems in taking care of the corpses of dead patients.

Poland was the hardest hit of any European country, reporting 3–4 million cases of potential influenza, but in all European countries the epidemics were mild and very little excess mortality was reported (Cockburn et al, 1969). However, a few months later the next year, in November–December 1969, the virus reappeared in Europe producing a second epidemic wave that was sudden and strong; and the epidemic was rather severe, like it had been the year before in the US. It is worth contrasting the different effects of the two waves of epidemic in the US, England and France. In the US, 70 per cent of the cases occurred during the first wave, from November 1968 to March 1969, and 30 per cent during the second wave in December 1969. In England, the proportions were around 30 per cent in January–March 1969 and 70 per cent the following winter. In France, it was about 10 per cent in March–April 1968 and 90 per cent in December 1969–January 1970.

In September 1969, there was a meeting called by WHO in Geneva to evaluate the consequences of this outbreak and it was concluded that there had been a strong outbreak in the USA but a much milder one in the rest of the world. Altogether, the 1968–1969 pandemic was less intense than the two first of the 20th century. Worldwide mortality was evaluated at around 1.5 million deaths.

In the papers emerging from this conference, three points are worth mentioning. The first was that the spread of the epidemic was irregular on both macro and more regional geographic scales. From Hong Kong to Japan and from Japan to the West Coast of the USA, the spread of influenza was very fast. However, transmission of the virus to much of the rest of the world was slower. Some countries, including Kenya, Brazil, Sri Lanka (then Ceylon) and Indonesia were not affected at all during the first wave of the epidemic in 1968, only in 1969. Similarly in the southern hemisphere the virus generally did not appear until well into 1969. South Africa reported cases by mid-March, but Argentina, Chile, New Zealand and Uruguay reported cases starting in mid-May of 1969 (Cockburn et al, 1969). Within particular countries or subnational regions, irregularities were also noted. In Japan, for example, there was no explanation that public health officials could offer for why it took until mid-January 1969 for a generalized epidemic of influenza to take root, even though numerous and repeated introductions of the virus had been occurring since August (Cockburn et al, 1969).

A second question was why the effect of the virus varied in different places in terms of severity of symptoms and mortality rates. As mentioned above, the epidemic was generally mild across the globe with few exceptions, the primary one being the USA. Not only was the epidemic extensive across the country, but in every administrative reporting area the increased number of deaths from pneumonia-influenza was significant, equalling the mortality rates during the generally more severe 1957–58 epidemic (Cockburn et al, 1969). As noted by Cockburn and his colleagues, the unique behaviour of the virus in the US was 'one of the most striking features of the epidemiological behaviour of the Hong Kong strain. Such differences have rarely been reported in the past' (Cockburn et al, 1969, p347).

One comparative case study made between the outbreak of influenza on the Korat Air Force Base in Thailand and in the Panama Canal Zone raised similar questions about differential behaviour of the virus. Though these regions share hot and humid climates, the virus spread slowly on the military base in Thailand, 13 per cent of men were infected but only 8 per cent showed any symptoms, and only 1.5 per cent were infected at any one time over the three months that influenza remained in the area. But in the Panama Canal Zone, which experienced influenza only a little later, clinical case rates reached 50 per cent, non-symptomatic infection was only present in 5 per cent, but the epidemic only lasted six weeks (Buescher et al, 1969).

Two hypotheses were offered at the 1969 WHO meeting to explain these differences. One was that there might have been two variants of the virus rather than one. The epidemic in the USA, then, could within this scenario have been caused by a more virulent variant of influenza A spreading from East Asia, while the UK and much of Europe was 'seeded' by a milder variant during the first wave of epidemic, but then hit by the more virulent variant in the second wave (Andrewes, 1969). The second hypothesis focused on differential risk in populations as determined by build-up of antibodies from previous circulations of A2 virus. As suggested by one conference participant, a second 'lineage' of A2 that had characteristics of the main A2 viruses but also some suggestions of the Hong Kong mutations circulated only in Australia and New Zealand in 1960. By the time the Hong Kong virus hit, the populations of this region had enough experience with these 'bridging antigens' to ensure that symptoms remained mild (St Groth, 1969).

Finally surveillance systems were not yet very trustworthy, despite advances driven by the previous influenza epidemics. First, only case notification was used along with data of virus isolations which were not representative of virus circulation. As Cockburn and his colleagues suggest (Cockburn et al, 1969, p348), in contrast to the precise information about the virus itself, the quantity and quality of epidemiological information was much more variable. One main problem was in the comparability of information. There was no standardization of reporting, and the differences in health-care systems, availability and quality of laboratories and diagnostic tools, and methods of reporting meant that each country not only reported cases in a different format but that discrepancies in accuracy of incidence were evident. Of the information available, very little was categorized according to age or sex, and complications were not always characterized (Langmuir and Housworth, 1969). In addition to isolating the virus, countries also relied variably on a number of other signs of increased influenza activity, such as absence from work, school closures, visits to emergency rooms, and hospital stays for respiratory indications. Though reflecting the likely presence of influenza in a region, these factors hardly represent accurate measures of the true incidence of influenza (Langmuir and Housworth, 1969).

Mortality was also used with a number of hypotheses to reflect an epidemic situation. Yet here, too, problems arose. One of these was the variability in the way countries designated deaths as influenza-related. As Langmuir and Housworth suggest in their overview of surveillance during the 1968–1969 epidemic, the number of 'excess deaths' has been an important indicator of the severity of influenza epidemics since William Farr introduced the concept in the 1848 epidemic in London (Langmuir and Housworth, 1969, p394). Yet some countries measure excess deaths as those resulting from pneumonia alone, while others report excess deaths from all respiratory diseases. Langmuir and Housworth found the latter to be the most accurate reflection of influenza impact (Langmuir and Housworth, 1969). Another problem not solved by the move to a more encompassing mode of reporting is that excess deaths in 1969 also did not reflect which deaths were those of otherwise healthy individuals, and which deaths were those of individuals with other health risks or health complications. Again as Langmuir and Housworth (1969) point out, the inability to differentiate mortality rates based on age, sex, healthy or high-risk individuals doubtless affected the ability to get vaccines to those populations most in need of them.

As a personal side note, in 1968 an International Congress of Tropical Medicine took place which was the occasion of a very nice experiment of nature. The International Congress of Tropical Medicine in Teheran started in September, just at the beginning of the spread of the new virus. I was attending the meeting to present data on West Nile infections in France. Participants came from all over the world, including Asia. On the first day, cases of influenza obliged several colleagues to stay in bed. The outbreak rapidly spread to many other participants, including myself. A questionnaire sent to the 1036 registered scientists a few months later received 844 answers: 372 mentioned influenza-like illness (44 per cent of responders or 36 per cent of the total number of subjects exposed). Clinical symptoms were quite trivial: fever, malaise, sore throat, cephalea, anorexia. Only specific remark: signs lasted longer in subjects over 54 years. There were no severe cases.

There was no influenza in Teheran before the Congress, and the disease was quite probably introduced by one of the travellers. Eight showed signs before/or on the first day on the meeting (7 September); they came from Macao, Malaya, Singapore and Taipei (this last subject had been in contact with sick persons coming from Hong Kong).

At the end of the meeting, 50 participants left Teheran when they were still symptomatic or before the fourth day of the disease, so were probably contagious. In 18 cases, there were secondary cases around these patients after they returned to their country, occurring in the US, Thailand, Belgium, Liberia, Senegal, Pakistan, UK and Kuwait. This observation shows how the virus was carried over borders and oceans by infected or contagious travellers.

The Hong Kong virus

An immediate identification of the new virus was not easy since there were discrepancies between the results of different tests: there were some analogies with the previous agent but also differences. It is of course easy today to understand the structure of the Hong Kong virus, but it was more difficult at the time and it took a few years to understand what we know today. This virus had some elements in common with the former H2N2 virus (1957–1968) and it was at first taken for a minor variant. It was designated for a long time as A2 Hong Kong, which is quite

misleading. It resulted in fact from the reassortment of human H2N2 with an avian virus already known as A/Ukraine/Duck/63 (H3N2). Only the hemagglutinin and one of the internal genes came from the avian virus, the six other segments of the genome being similar to those of the human H2N2 virus. This virus persists even now and has been responsible since 1970 for seasonal flu epidemics.

Sero-archaeological studies have demonstrated that the majority of the very elderly had H3 antibodies before they were exposed to the A(H3N2) pandemic virus (Dowdle et al, 1969; Marine and Workman, 1969). These antibodies were remnants of the immune response to exposure to H3N2 viruses that circulated before 1891. Thus the 1968 pandemic virus apparently contained an H3 antigen 'recycled' after 77 years of absence. Marine and Workman hypothesized that the pre-existing anti-H3 antibodies were the result of 'original antigenic sin' (Davenport et al, 1953) – childhood exposure to H3 antigens – and that these antibodies might have protected the elderly during the 1968 A(H3N2) pandemic (Marine and Workman, 1969).

Vaccines

When it started, there were no defensive tools available to intervene in the transmission of the Hong Kong flu virus, or to mitigate symptoms in individuals. There were no antivirals and the vaccine that was used did not work well because it was made with the A(H2N2). A study was conducted to evaluate the efficacy of the vaccines over a long period of time from 1956 to 1977, according to the fit between vaccine and epidemic strains, reflecting the effects of antigenic drift of the hemagglutinin. It showed that when the epidemic is due to a virus similar or identical to the vaccine strain, there are fairly good results: 85 per cent, 72 per cent or 95 per cent efficacy, which are all within the normal range of protective capacity for vaccines. Sometimes there is a poorer fit: England 1972 was different enough from Hong Kong 1968 to reduce the [overall] efficacy of the vaccine to a lower value. Then in 1968 the vaccine used in the US contained Ann Arbor 67, an H2 virus. But the population was exposed to an H3 virus and thus there was a low level of protection, 35 per cent. This is particularly poor, but not completely useless: and from a virological standpoint, it was an interesting indication since it meant that this H2N2 vaccine was not completely inefficient. In addition, a study of US national mortality data confirmed that people over the age of 77 were, in fact, protected from influenza-related mortality during the 1968 pandemic (Simonsen et al, 2003), compared to surrounding severe non-pandemic seasons.

Due to a prompt reaction, vaccine was produced immediately in the US and the first million doses were released in November 1968, just at the time of the first cases. The bulk of the production arrived a little late, but a number of high-risk subjects were, however, be vaccinated on time. Producing the vaccine in six months was already an exceptional achievement. Unfortunately, discussions were still pending in Europe about the real constitution of the pandemic virus and no vaccine was available even in January 1970, 18 months after the emergence of H3N2. Experts and authorities were still in discussion about the question: was this a new virus or not? In focusing their attention on this problem, ultimately the action was not quick enough.

Comparisons

It is interesting to compare the situation in 1968 to what could be observed today if we suppose similar levels of morbidity and mortality. Although we have today more tools to combat influenza including antivirals, vaccines if available, and antibiotics to treat super infections, there are reasons why a situation with the same level of intensity has the potential to result in worse consequences because of the changes that have been observed in ways of life. In fact the spread of H1N1 in spring 2009 and again in autumn 2009 provides a good example. Air traffic is much faster now, and significantly more people are flying to more and more distant parts of the globe than in 1968. Human concentrations in urban areas are increasing, along with the risks of spread. In efforts to curb transmission and mitigate overcrowding at medical facilities, public health authorities are urging individuals to stay home from work or keep their children home from school at the first signs of possible influenza infection. Though possibly effective as interventions, they also increase absenteeism at work and school as even some who do not have influenza stay home. Distributors of vaccines are now using systems of 'just-in-time' (in French *flux-tendu*), which means that only two days' supplies are stored. Despite careful regional and national planning, hospitals and other medical facilities face the possibility of overcrowding as few can easily accommodate excessive numbers of patients. The problem of a necessary separation between those suspected of having influenza and other patients because of the risks of local contagion is difficult to solve without additional structures, yet temporary structures such as tents are not feasible in colder climates. The availability of intensive care facilities dedicated to influenza patients has to be considered, taking into account other ongoing needs.

On the positive side, we have now a very efficient international network of surveillance; we have a coordinated network of laboratories which can rapidly evaluate and identify the virus, and WHO is at the centre of this system. Compared to 1968, the genotype of viruses can be determined much more quickly, not only because of improved surveillance but because of advances in genetic sequencing. The circulation of information also has been much improved. However, it is also very clear that in many parts of the world, information is missing or withheld. In China, for example, technological surveillance capacity has improved markedly in major urban areas, and after the SARS epidemic Chinese officials have been more

forthcoming in reporting outbreaks to the WHO. Yet because China is such a big country, even with 10 or 20 good laboratories cannot cover the whole country. If a new virus were to emerge in rural China, who knows how long it would take to reach Beijing or Hong Kong or Shanghai? And not only there: none of Africa is well covered in terms of surveillance capacity, so while it is not very likely that the virus could emerge there, it is one region among others that requires assistance in closing case reporting and information gaps.

There are two concepts now for vaccines in the case of a pandemic. The *pandemic* vaccine is made with the virus of the pandemic; so by definition it cannot be developed before the virus emerges and has already indicated potential for widespread transmission. The vaccine also needs six to seven months of preparation at a minimum; the H1N1 virus proved to be much more slow-growing in the typical egg medium used for vaccine production, so supplies were late and took several more weeks than originally predicted for general distribution. The *pre-pandemic* vaccine on the other hand is made according to predictions about the virus that is expected to emerge, so it is a bet: if it turns out to be the correctly predicted type of virus, then the vaccines made from it will be effective. If not, it must be discarded as useless. It is, in fact, a very difficult dilemma.

Conclusions

One can draw a few important conclusions from these observations.

1. Pandemic spread can exhibit very different speeds, from very rapid (1957) to relatively slow (1968) and, in the latter case, there is more time to develop plans, to organize the distribution of antivirals and to produce vaccines. This means that if a new pandemic started in Asia, there would be a few months for Europe, the USA and most of the rest of the world to prepare for the pandemic.
2. The use of antivirals can be very useful for the rapid containment of a pandemic and for the treatment of severe cases in high-risk patients. During the first wave, it is the only effective mode of protection and treatment.
3. It is essential to identify as soon as possible the emergence of a new virus and to confirm its originality in order to make the crucial decision of launching a campaign of vaccine production and vaccination. Each additional week or month of delay jeopardizes the availability of a proper vaccine. This applies to the identification of a new virus through surveillance networks and to the decision about the originality of the virus at the Reference Center.
4. It is clear from the recent episodes that not all pandemics emerge after an epizootic in domestic animals.

The first draft of this chapter (April 2009) discussed the A(H5N1) avian flu as the best candidate for a new pandemic. At the time of finalizing this chapter, A(H5N1) is only second behind the new Mexican hybrid strain of porcine origin A(H1N1). At this time, the latter is highly transmissible but not as pathogenic as many previous pandemics. Nevertheless, as with so many previous pandemics including the 1968 outbreak, it has proved unpredictable despite improved scientific and technological capabilities.

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Comment: Influenza Histories and the Coexistence of Old and New

Frédéric Keck

Why write a history of influenza? One could simply answer that lessons must be drawn from the past in order to improve current systems of surveillance. But Chapter 4 allows us to propose another hypothesis:

Influenza's xenospecific epidemiology, Wallace and his colleagues argue, 'is characterized by a fundamental contradiction. On the one hand, the virus is highly infectious, spans a short generation time, tends toward boom-and-bust population dynamics... At the same time, several deadly influenza subtypes circulate long-term uninterrupted.'

The influenza virus appears at the same time very old and always new. As Van der Werf reminds us in Chapter 5, 'Influenza has probably been with us for a very, very long time' so that 'we have to live with influenza viruses'. Yet we tend to forget the lessons of past flu pandemics, as Eyler argues for the 1918 Spanish flu pandemic and Hannoun for the 1968 Hong Kong flu. The 2009 H1N1 pandemic clearly seems to reverse this contradiction: we constantly compare it to pandemics of the past, yet the behaviour of the H1N1 virus is entirely new. So how is this contradiction between a short-term outbreak and a long-term evolution borne out for 20th-century influenza history?

Epidemiology seems to resolve the contradiction, as it transcends a series of tragic narratives and traces the curve of an epidemic that can be compared to other epidemics. But epidemiology in itself is not a history of influenza; as Eyler shows, the flu caused a major change in the practice of epidemiology, and that development in itself calls for historical analysis. Eyler recalls the role of a group of American researchers around Thomas Francis at the Rockefeller Institute, who founded what they called 'clinical epidemiology'. After the 1918 influenza outbreak, they defined an 'excess rate' of mortality, distributed in groups defined by race, class and sex. They wanted to go beyond the immediate panic of a 'herd' seized by the epidemic, in order to define statistically families, and even individuals, at risk. With that purpose in mind, they reproduced the epidemic in experimental studies, linking studies in the field with studies in the laboratory. Eyler

recalls that the cause of the 1918 influenza pandemic at the time was unknown; the influenza virus was identified through filtration only in the 1930s, but the virus itself was not visible before the invention of electronic microscopy. Therefore, the behaviour of the virus had to be studied through the inoculation of ferrets, which like human beings are susceptible to the virus. Finally, epidemiologists could investigate antibody titers in human populations, wherein immunity functioned as a memory of the disease. In reading this detailed history of the epidemiology of the 1918 pandemic, we can see that epidemiologists had to develop alliances with virologists and immunologists to transcend statistical distributions and to link them to local, and even molecular, levels of determination.

Yet epidemiological knowledge seemed to be inefficient in predicting new flu outbreaks. The flu virus seems to display an intrinsic variability that defies historical knowledge. Eyler recalls Francis's investigation of a 1936 influenza outbreak in California that proved to be less virulent than the 1918 pandemic, and ultimately led to the distinction between Influenza A and Influenza B, often presented as a difference between pandemic influenzas and seasonal ones. How is it possible that the same virus can cause huge outbreaks with millions of deaths among apparently healthy people and smaller outbreaks that kill only the most fragile people? This question is not only theoretical but also practical, and it has for a long time been a problem for the production of vaccines. Vaccination implies that the virus strain is clearly identified so that an attenuated strain can induce an immune response in the patient. But as Eyler recalls, the vaccination campaigns during World War II failed because the virus had changed. The question that remained for virologists was thus: how to explain this intrinsic variability of the virus?

The work of Frank MacFarlane Burnet, trained in the British school of virology and founder of the Australian school of immunology, provided an evolutionary explanation of the influenza virus's intrinsic variability (Burnet, 1953; Sexton, 1991). Burnet discovered the process of hemagglutination, permitting the study of the virus's antigenic properties and their reproduction through the inoculation of eggs. The 1957 flu pandemic confirmed his analysis: it was caused by an Influenza A that had changed its pattern, thus leading to the classification of flu viruses according to their hemagglutination properties (H1N1, H2N2). The discovery of the structure of DNA by Watson and Crick enabled an explanation of this transformation by constant mutations in the replication of the virus, characterized by a single strand of DNA – even though the complete sequence of the 1918 flu virus was not available before the work of Taubenberger and his team in 1997. The 'revolution' that Francis had introduced with his 'clinical epidemiology' had come to an end, says Eyler, and a new revolution was on the verge, drawing another link between the lab and the field. With Burnet, the field is not only a social aggregate of individuals, who could be replaced by ferrets in the lab, and through which the virus is transmitted in a series: it becomes a complex ecosystem of animal species, a constantly evolving reservoir from which new viruses emerge.

Indeed, opening up the space of transmission allows us to explain the virus's mutation rate by its capacity to transgress the barriers between species.

As Hannoun argues, the 1968 Hong Kong flu pandemic, caused by a new Influenza A virus called H3N2, was a surprise because the 1957 pandemic had occurred only recently. This virus introduced a new piece of information: that influenza pandemics were emerging from southern China. It remains unclear from where the 1918 pandemic emerged, as the data on the occurrences of the disease are not reliable enough. By contrast, the 1957 pandemic was declared in Singapore before spreading to the rest of the world. As Hannoun recalls, 'in Hong Kong, the outbreak was spectacular. At least 500,000 cases were reported in a few weeks in July 1968, with the peak of the outbreak occurring in the week of 27 July. All age groups were affected, indicating that the new virus did not find any immune barrier or memory', and 'from Hong Kong, the virus spread very rapidly eastwards, westwards and southwards', with two waves in winter 1968–1969 and winter 1969–1970, causing altogether 1.5 million deaths worldwide. Probably because of the British colonial health system reforms after a massive wave of immigration from China and natural catastrophes that had precipitated hundreds of deaths, Hong Kong was able to gather high quality epidemiological data and served as a sentinel, capable of issuing early warnings about pandemic emergence.

Following Hannoun, we may also conclude that this pandemic also offered the WHO a prominent role in influenza surveillance; the 1969 WHO meeting in Geneva facilitated the study of the disease's intriguing variability throughout the world. Classical epidemiology, with its distribution of excess rates in social groups, was applied to the whole planet, but ultimately failed because of one formidable obstacle:

> *the comparability of information. There was no standardization of reporting, and the differences in health-care systems, availability and quality of laboratories and diagnostic tools, and methods of reporting meant that every country not only reported cases in different formats but that discrepancies in accuracy of incidence were evident'.*

Moreover, vaccine production in Europe, in contrast to the USA, was not sufficiently rapid to meet the pressing needs of the pandemic because of disagreements about the virus strain. The rest of the world, however, remained without any vaccine at all. The global political response to the pandemic was insufficiently effective and coordinated, even though the event formulated the need for such a response, probably for the first time.

If classical epidemiological tools could not adequately outline a picture of the last pandemic's human distribution, the revolution introduced by Burnet and his team could lead to another solution: prediction of the next pandemic at the animal level, using what is often called in the nuclear industry strategies of 'preparedness'. To implement this strategy, two major discoveries have been

necessary: the first by Robert Webster of St Jude Children's Research Hospital in Memphis (Tennessee, USA), that waterfowl constitute the chief reservoir for mutations of the influenza virus; and the second by Kennedy Shortridge of Hong Kong University that southern China is an 'epicentre' for influenza pandemics, because its complex ecology mixes ducks, pigs and humans in rice ponds, facilitating the emergence of new flu viruses. Van der Werf tells us that the 1957 and 1968 pandemic viruses were 'reassortants', 'subtypes between an avian virus and a human virus'. Pigs appear to function as 'mixing vessels' in which reassortants are produced, because they 'harbour both types of receptors: the ones that are preferentially used by the avian viruses and the ones that are preferentially used by human viruses'. These insights offer a hypothesis concerning the pathogenicity of pandemic influenza virus, which had remained unexplained after the genetic research of Taubenberger and his team. Multi-cleavage sites or sialic acid receptors may explain why some influenza viruses are able to cross frontiers between species and cause efficient human-to-human transmission. Hence, a new relationship between the field and the laboratory has developed: in the laboratory, interspecies transmission is mimicked following mutations or inhibitions of the virus's components, and new forms of vaccination have been created to target different strains of the virus and thus to offer cross-protection. Antiviral drugs are also now produced to target the entry or the emergence of the virus and help to slow the infection.

These scientific discoveries following the 1968 Hong Kong flu pandemic, however, cannot explain the mobilization of research around the H5N1 virus, which emerged in Hong Kong in 1997, jumping directly from birds to human beings without reassortment in pigs, and killing some 70 per cent of those infected. It is possible to argue that the identification of this new influenza virus was the consequence of surveillance work led by Shortridge and Webster at the animal level. However, Shortridge and Webster's research cannot account for the intense mobilization against H5N1 at the global level, which gave Hong Kong the role of sentinel for future pandemics. In this volume, Wallace and his colleagues refer to 'two events of geopolitical significance': the handover of Hong Kong to the People's Republic of China, and the financial crisis beginning with the devaluation of the Thai currency. These two events transformed relations between Asia and the rest of the world, so that Asia not only constituted a site where international crises started, but also one which mobilized the power to regulate them in the first place. Wallace and his co-authors reveal that this situation is characterized by a new dependence between the rest of the world and Asia; the transformation of Chinese agriculture made it one of the biggest producers of poultry and pigs in the world, followed by Thailand. Shortridge's hypothesis concerning southern China as the epicentre of influenza pandemics takes a new turn when considered in light of a geopolitical analysis of economic transformations. According to Wallace his co-authors, foreign direct investment (FDI) has

revolutionized traditional agriculture, creating confined animal feedlot operations (CAFO) and producing new evolutionary niches for flu viruses. We can embrace Shortridge's analysis of traditional agriculture as the site for emerging new viruses because of the mixing of three species, and yet still agree with Wallace's argument that intensive husbandry has favoured the spread of the virus due to the lack of genetic diversity among poultry. If agribusiness cannot explain the emergence of the 1918 influenza virus, it nonetheless accounts for the transformations of influenza viruses at the end of the 20th century.

Wallace's narrative provokes a further question about the transformed relations between public health and communication. H5N1 has become such a dreaded virus throughout the world, despite its limited number of human victims (approximately 260), primarily because each viral outbreak within animals has given rise to an important media campaign. Unlike previous epidemics of human influenza, the 1997 outbreak did not develop into a huge pandemic, followed by a return to ordinary flu transmission. Rather, it constituted the beginning of a series of outbreaks, in which the H5N1 virus reappeared regularly in south Asia, and then in Europe and Africa. Two singular events gave a new meaning to the recommended biosecurity measures to prevent transmission from animals to humans: the 9/11 terrorist attacks in New York followed by threats of bioterrorism, and the SARS episode in Hong Kong, followed by a new communications policy in China that was increasingly orientated towards a more transparent system of surveillance. If Wallace's hypothesis integrates animal breeders and veterinarians in the global history of influenza, then a study of the 'outbreak narratives' helps us to understand the implication of media and governments in global mobilization against flu pandemics.

Wallace and his colleagues' final hypothesis is worth meditating on. They argue that influenza viruses possess a sort of cognition that allows them to 'choose' the best strategy to evolve in a given environment, rather than to mutate randomly. Mutations of the influenza virus are 'context- and path-dependent'; they incorporate previous combinations to produce a new one. Thus, the current H1N1 pandemic is not only a return to 1918, but also adds a globalized swine industry to human populations' memory of the H1N1 virus. This hypothesis suggests a history of influenza that neither repeats the same patterns nor produces a constant emergence of novel forms. Rather, past and present influenza evokes what Althusser called 'the historical present', a set of multiple determinations intertwined in an apparently contradictory way, producing new situations whose understanding requires an attitude of active engagement. If flu viruses are simultaneously very old and very new, it is because they depend on an evolutionary reservoir of animal species, as Burnet's epistemological revolution showed. Each outbreak casts in a singular way all actors who represent this animal reservoir in often contradictory ways: breeders, veterinarians, virologists, immunologists, epidemiologists, physicians, journalists, governments and patients. These actors produce a form of

distributed cognition that, following the strategies of the virus, configures in new ways the constantly evolving history of influenza.

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Part 3

Governmental and Non-governmental Institutions and the Politics of Epidemic Management

8

Mobility Restrictions, Isolation and Quarantine: Historical Perspectives on Contemporary Debates

Tamara Giles-Vernick, Susan Craddock and Jennifer Gunn

This chapter provides a comparative historical analysis of containment measures in one African colonial context, Zimbabwe, and a rural western setting, the Upper Midwest of the USA during the 1918 influenza pandemic. While it argues that diverse factors (economic, racial, logistic) shaped the imposition of and responses to these measures, it also shows how authorities offered epidemiological certainty in the face of contradictory medical understandings and popular fears. A pandemic is a singular event, the convergence of specific virological, political, social, economic and ecological networks. The complex interactions between pathogens, people and their environments are historically specific. The point of pandemic histories is not to evaluate the success or failure of a particular intervention, but rather to identify the multiple complexities that inhere in every juncture of decision making, implementation, public response and outcome of containment measures. Our two case studies illustrate the pragmatic value, function and limits of certainty.

Public health authorities, policymakers, ethicists and health-care providers have long debated whether public health measures that curtail individual freedoms such as quarantine, isolation and mobility restriction are warranted during pandemics, and if so, their forms and durations (Markel, 1997; Craddock, 2000; Barbera et al, 2001, p2712; Gostin, 2006, p1700; Bensimon and Upshur, 2007; Fairchild et al, 2007; WHO, 2007). Although the terms 'quarantine' and 'isolation' are often used interchangeably, quarantine is the isolation of healthy individuals or populations who have been exposed to a pathogen, whereas isolation segregates people already sick with a contagious disease. Mobility restrictions, sometimes referred to as 'social distancing' measures, typically seek to keep people in or out of specific geographic sites, boundaries or national and regional borders (Barbera et al, 2001, p2712; WHO Writing Group, 2006). Epidemiologically, as Lawrence Gostin (2006, p2700) notes, the effectiveness of these three measures depends upon a number of factors, including the stage of the pandemic, the mode

and efficiency of transmission, incubation period and serial interval (the mean interval between the onset of illness between two successive individuals).

Yet as some health policy analysts and numerous historians of medicine have noted, these measures cannot be evaluated exclusively in epidemiological terms (Markel, 1997; Bensimon and Upshur, 2007, pS44; Fairchild et al, 2007). Other considerations invariably shape decisions to implement restrictive public health measures, their modes of implementation and their negotiation during pandemic. Most frequently, debates centre on ethical or economic issues, including whether the potential efficacy of restrictive public health measures warrants intrusion on personal freedoms or the curtailment of regional or national economic activities (WHO 2007, pp9–11). How different actors understand transmission, the various lenses through which they interpret susceptibility, the logistics of enforcing large-scale quarantines, public demands to see rapid government response and the particular dimensions of local or regional conflicts play into the application of and responses to these containment measures.

The debates around the measures implemented during the novel H1N1 pandemic of 2009 illustrate this point well. Hinchliffe and Bingham (2008, pp1535, 1542), among others, have deployed the term 'biosecuring' to refer to 'attempts to manage the movement of ... diseases' and to the always 'unfinished business of making safe'. In the spring of 2009, for example, the US sought to secure the health of its population by advising against nonessential travel to Mexico, even though the World Health Organization (WHO) insisted that restricting movement would not mitigate transmission (quoted in Gostin, 2009, p2377). There seems to be little agreement on the efficacy of these restrictions because they are difficult to apply fully, although they can slow transmission and reduce mortality (Stern et al, 2009). In April 2009, for instance, many of Mexico City's schools and businesses were closed, but public transportation remained functional, sending some city residents fleeing to other parts of the country – and potentially carrying influenza with them (Partlow and Booth, 2009). In early July, Thailand closed over 1000 schools and requested internet café owners to shut down for 15 days, not long after Britain abandoned school closures altogether, contending that it did not have sufficient resources to sustain these measures (Percy, 2009). In all of these cases, state health authorities invoked the defence of public health as a justification for their containment measures, but clearly, political and social justifications figured into their decisions as well.

While the term 'biosecuring' has emerged recently in the context of contemporary technologies and mobilities, it is also a useful concept for studying past pandemics. Our case studies demonstrate that at the moment of pandemic emergencies, the political and social rationales are frequently elided. In such situations, epidemiological claims to authority, to truth – often despite the careful efforts of epidemiologists to delineate ambiguities and limitations – can acquire a certainty that trump any other considerations (Schnirring, 2009). The simplification and mapping of certainty onto the 'dynamism and looseness of a disease network, its adaptabilities and accommodations', argue Hinchliffe and Bingham (2008, p1547), display 'a logic of control and instrumentalism, one that underestimates the nonhuman [e.g. virus] and thereby fails to adjust to the indeterminate characteristics of networks'. More pragmatically, this mapping of certainty onto deeply unpredictable, often unknown circulations of viruses and people enables authorities not only to do *something* and to present the appearance of active intervention in emergencies, but to assign blame – to wayward fleeing African mineworkers, mobile soldiers and their families or parents who send sick children to school.

Two rural settings: Colonial Zimbabwe and the Upper Midwestern US

We have chosen colonial Zimbabwe and the Upper Midwestern US because they highlight the importance of rural areas, so frequently overlooked in the development of pandemic preparedness plans and underserved by public health or medical infrastructures. Rural areas constitute excellent sites in which to examine the circulations of people, pathogens, authority and resources, but also the negotiation of social distancing measures.

The British South Africa Company (BSAC), a concessionary company controlled by British and South African capitalists, launched its military domination over the area that became known as Southern Rhodesia in 1890. Gaining control through writ from the British government, 'dubious' treaties and military conquest, the BSAC imposed its authority over Ndebele and Shona populations (two predominant ethnic groups), as well as immigrant populations from southern Africa in the late 19th century (Summers, 1994, pp19–20). But by 1918, the BSAC had significant rivals in the colony's white settler populations who were accumulating political power and exercising increasing control over the Zimbabwean colonial state. Just five years after the pandemic, settlers had acquired self-rule. They were also economically active, engaged in both mining and commercial farming (Summers, 1994, p169; Andersson, 2002). Even as the BSAC sought to coordinate its response to the pandemic emergency in 1918, this centralized, quasi-state institution was being forced to contend with political and economic competition.

The colonial health infrastructure reflected some of these tensions. Colonial Zimbabwe possessed a very small colonial medical service that operated primarily in town centres, with racially segregated facilities for European and African populations. In rural areas, the administration had to rely on private organizations and entities such as missionaries and mining companies to distribute medical care (Simmons, 2009, pp31–32). The British involvement in World War I depleted

trained medical personnel in rural and urban areas, and the colony was dependent on South Africa for certain medical supplies and services.

Yet colonial Zimbabwe was not solely an isolated rural expanse. It possessed important urban centres, and workers were also concentrated in closed mining compounds, sites of industrial production, white settlers' farms and areas functioning as labour reserves for industrial and agricultural producers (Phiminster, 1974, pp84–86; Simmons, 2009, p40). Extended family compounds in the rural reserves could contain numerous residents.[1] Some rural areas were linked to urban centres by the railroads or by passable roads, but others suffered considerable isolation, accessible only by oxen, mule, bicycle or foot. Schools, tax collection centres and regional pass offices, which served as centralized clearing houses for African labour, also brought together population concentrations. And finally, colonial Zimbabwe was a site of high labour mobility: migrant workers from Malawi (Nyasaland), Mozambique and colonial Zambia (Northern Rhodesia) moved into the colony to search for work, while other labourers moved out of Zimbabwe into South Africa to gain higher wages.

The upper Midwestern US, including the states of Wisconsin, Minnesota, Iowa, South Dakota, North Dakota and Nebraska, displayed both similarities with and differences from colonial Zimbabwe. The populations here, too, were multi-ethnic, including several different Native American peoples and northern and central European immigrants. During the 1910s, this region was largely rural, dominated by an array of economic arrangements from extractive industries like logging and mining to ranching and family farming. There were a few large population centres, including Minneapolis, Duluth and Milwaukee, where milling, other industrial processing of agricultural products and shipping took place. In the countryside, roads were often unpaved and impassable in certain seasons; railroads, inter-urban rail lines and horse-drawn sleds and cutters in winter were the primary means of connecting rural people and products with larger towns and cities.

The medical and public health infrastructure was more developed in the urban Midwest, but both urban and rural regions relied on a mix of public and private provisioning of medical services. Doctors and small, physician-owned cottage hospitals were concentrated in small towns throughout the region. Attempts to develop public hospitals in rural counties often met opposition from local physicians and taxpayers, slowing the expansion of access to hospital care.

Moreover, at the time of the 1918 pandemic, fewer than 109 out of more than 2500 rural counties or districts in the US had a formal public health infrastructure (Lumsden, 1928, p872). Rural towns and villages had part-time health officers, physicians or laypersons responsible for addressing communicable diseases and sanitary nuisances, but they relied on distant state departments of health for bacteriological laboratory services, vaccines and sanitary engineering. Private organizations supplemented the state health departments' meagre services

with maternal and child health care, public health nursing and hygiene education.[2] As in colonial Zimbabwe, during World War I recruitment of physicians and nurses for military service further depleted the rural medical workforce.

Although African and American rural settings differed, there were some important similarities. Both were underserved by medicine and public health, but at least some areas had important transport connections to urban centres, geographically mobile populations and sporadic points of population concentration. Hence the assumption that rural areas were uniformly healthier than cities because of low population density and isolation from contaminated, urban industrial environments was not always the case. Second, the dearth of medical and public health infrastructure necessitated that states rely heavily on federal agencies and private organizations to provide these services (Lumsden, 1928, p872). To the extent that they were able to do so, the Red Cross, private doctors, medical missionaries and others supplied essential public health as well as medical needs. The regions' multi-ethnic populations did not share the same understandings of disease transmission, prevention or care; their diverse ideas influenced the reception of state efforts to distribute medicine or prescribe preventative measures.[3]

Colonial Zimbabwe and selective limits on mobility

The first signs of influenza appeared in colonial Zimbabwe around 9 October 1918. Authorities responded with containment measures that should be familiar to readers now: they closed schools, churches, places of entertainment and other sites of aggregation in urban areas, and simultaneously opened emergency hospitals and soup kitchens, and ordered medicines and vaccines. The administration also instructed native commissioners to advise Africans in the rural reserves to stay in their compounds and restrict 'intercourse with other natives' to stem the spread of influenza.[4] They further prohibited colonial subjects from visiting urban areas and from migrating to neighbouring Nyasaland, and instructed mine companies and other employers to restrict movement of Africans from infected areas back to reserves, where their families resided. For Africans already in the reserves, official instructions were to stay away from their crowded compounds and remain in open areas to the extent possible[5] (see also Heaton and Falola, 2006, p210).

Strict quarantine was rarely attempted, although two geographically isolated German mines in Belingwe and in the Filabani district did impose quarantines that successfully kept influenza at bay.[6] Instead, mobility restriction focused on rail travel. By 12 October, only three days after influenza's first appearance in the colony, the administration prohibited train travel for Africans, and then extended this prohibition to all people of colour. White populations, however, retained the right to train travel (Phiminster, 1973, p143). The administration imposed some mobility restrictions on the white population, but they reserved the most stringent measures for African colonial subjects. This disparity reflected a widespread

racial ideology that Africans were more susceptible to influenza, and that the disease became more virulent as it passed through them.[7] Banning railroad travel for all people of colour had a two-fold purpose: to slow the spread of influenza and to protect white passengers from exposure to African-borne 'virulent' influenza. Racialized mobility restrictions, however, permitted movement of equally infectious white populations, almost certainly undermining the epidemiological efficacy of these containment efforts.

Restrictions on mobility were defended on epidemiological grounds, even if they were flawed by contemporary thinking about differential virulence and vulnerability. But they dovetailed with other political and economic interests as well, which in the long run contributed to popular resistance to public health mandates. For example, mine owners who already faced serious labour shortages were eager to retain workers in place to keep mines operating. They consequently enforced containment measures, but influenza nonetheless spread widely among African and white workers, while African workers proceeded to desert mines in relatively large numbers. For the mining industry, the result was interrupted or reduced output (Phiminster, 1973, p143).

It is also evident that many African colonial subjects throughout the continent did not heed recommendations of colonial medical and administrative authorities (Ohadike, 1981; Phillips, 1987; Musambachime, 1993; Heaton and Falola 2006, p210; Simmons, 2009). African understandings of influenza, its causes and appropriate treatments differed from those of Western medical authorities, whose own ideas were fragmented. Some African colonial subjects interpreted influenza as a new illness, introduced by Europeans or by the war effort. Finally, many perceived colonial medical and public health measures against the pandemic as ineffective.

In colonial Zimbabwe, this scepticism translated into a refusal by some to abandon their family compounds and to move into the bush or open areas.[8] We can only speculate about the reasons for this reluctance, since available archives do not reveal such perspectives. Inability to move sick family members, as well as the difficulties of living in open country with neither sun protection nor facilities for sleeping and cooking may have figured in rural Africans' decisions.[9]

Prohibitions on leaving mining compounds were similarly disregarded. Severe food shortages, deplorable housing and unsanitary conditions added to the perceived and very real chances of viral transmission, leading to workers fleeing 'in large numbers' when the illness appeared (Phiminster, 1973, pp144–145).[10] That logic proved wise: death rates for mineworkers far exceeded those of either African colonial subjects on reserves or European populations. The medical director of the colony estimated mine mortality rates from influenza and pneumonia were 91.74 per 1000 workers, compared to 9.3 per 1000 Europeans and 25.4 per 1000 Africans on reserves.[11] While their flight liberated workers from a clearly unhealthy environment, it also helped to spread influenza to the reserves.[12] The colonial

administration struggled vainly to stem workers' flight from the mines, sending out patrols to capture absconders and offering food and medicine to lure them back to their places of employment, but evidence suggests that such efforts were unsuccessful throughout the pandemic.[13]

Isolation of the sick was another measure implemented for both Europeans and Africans in colonial Zimbabwe. Racially segregated emergency hospitals and lazarettos in urban centres were opened almost immediately after the onset of influenza, a traditional tactic to separate the sick from those still uninfected. Given the paucity of medical providers, centralizing care maximized the efficient delivery of medical services even as it almost certainly increased mortality. Of the 1053 Africans treated for influenza in the Salisbury lazaretto between 21 October and 5 November 1918, 151 died (14 per cent); on a single day, 24 October, some 106 out of 691 patients perished, prompting many patients to flee.[14] This last statistic exemplifies one of the enduring complaints about lazarettos across time and epidemics: they become places to die rather than to recover. Not only were medical personnel in short supply because of the war or because many of them succumbed to flu, but conditions in African hospitals were poor, with overcrowding a major problem.[15]

In addition to social attitudes and competing economic agendas shaping the formulation and efficacy of containment strategies, the contradictory logistics of tracking and treating influenza in rural areas ultimately undermined the effectiveness of many interventions.[16] Europeans moved relatively freely, and Africans could be moved for the continuity of colonizers' economic or political activities. As Terrence Ranger has noted, the pass office, which regulated all movement of African men over 14 years old for travel and work, itself became a sort of disease vector through the congregation of men waiting for passes and travel to work sites. Although pass offices in Salisbury, Gwelo and Umtali were closed relatively soon after the outbreak, it appears likely that rural men gathered and waited near the offices until they reopened (Ranger, 1988, p173).[17] Colonial administrators sent messengers to communicate the mobility restrictions and social distancing measures to rural chiefs and headmen, but the messengers themselves fell ill. Administrators were thus forced to suspend this effort, but probably not before the messengers had contributed to spreading infection. Africans were also still assembled at central points to pay their taxes and, ironically, for missionaries and members of the administration, to inspect them for influenza or to vaccinate them. One missionary, for example, confirmed prohibitions on inter-village communication and visiting among Africans, while in the next sentence he reported his successful assemblage of regional chiefs to inform them of influenza measures, a move that undoubtedly raised the risks of influenza transmission to other reserves.[18]

This brief history of pandemic influenza in colonial Zimbabwe reveals, on one hand, inconsistency, unpredictability and resistance to restrictions and

simultaneously a hope – projected as certainty – that containment measures could be effective. Medical personnel were acutely aware of what they did not know about influenza at the time and what they could not control. In confessions reminiscent of those recently uttered among public health experts about the novel H1N1 pandemic, medical and administrative officers during the 1918 pandemic confessed to being unable to 'speak with any degree of certainty' about the numbers of people or compounds struck by influenza, about morbidity or mortality rates or why certain regions or family compounds were more afflicted than others.[19] One administrator visiting rural family compounds in the Gutu District confessed to difficulties in simply recognizing when the 'Vera' influenza epidemic had first struck:

> *Vera seemed to take a long time in coming and one was almost led to believe that we were going to escape. Then we seemed to have an epidemic of Dysentery, an epidemic of sore eyes and generally there were very many more applications for medicine for chest troubles and headaches than usual. One now believes that those were different forms of Vera. After that Vera came in unmistakable forms and one kraal after the other went down...*[20]

A. M. Fleming, the colony's medical director, observed in the midst of the epidemic, 'The public must be made to understand that the spread of this disease has been found humanly impossible to control', and his claims were echoed by missionaries and administrators dispensing assistance to African villages.[21] Following the pandemic, Fleming claimed even more emphatically: 'It must be admitted as a regrettable fact that the recent epidemic of influenza has defeated the combined efforts of the whole civilised world to control it.'[22]

Despite this apparent truth, some administrators evinced remarkable certainty in the efficacy of the containment measures imposed. Only eight days after confessing that he knew little about influenza morbidity or mortality, the acting assistant native commissioner of Gokwe pronounced:

> *I am of the opinion ... that a large percentage of the kraals will escape altogether, as a result of the restrictions placed on natives travelling and visiting and the very satisfactory attitude adopted by them in following this advice. The fact that kraals are for the most part widely scattered will, in itself, act as a good check.*[23]

Others were equally convinced of the mobility restrictions' effectiveness, while some acknowledged the 'very difficult' nature of this measure and expressed 'hope' that 'the "isolation" advice ...[that] patrols are carrying may prevent the spread'.[24] In cases where African colonial subjects suffered high morbidity and mortality, officials argued, it was because they failed to follow colonial containment measures.[25] Influenza morbidity and mortality, then, resulted not from the virulence of the pathogen or from the administration's incomplete 'biosecuring' of colonial Zimbabwe's rural regions from infection; rather, the victims themselves were to blame for biosecurity failure. Both claims of uncertainty and certainty accomplished a particular kind of political work, providing cover for public health officials who were roundly criticized during and after the pandemic for not doing enough to reduce transmission, relieve the suffering of those who fell sick, or alleviate the economic burdens of the emergency on mine owners and on municipalities.[26] As the second pandemic wave was waning, Chief Native Commissioner Herbert Taylor vehemently denied complaints by the Chamber of Mines that administrative efforts had failed to curtail influenza's spread. He insisted, 'There is no doubt that the early steps taken to restrict the movement of natives and the advice given to adopt open air life were most efficacious in curtailing the ravages of the disease.'[27]

Containment in the Upper Midwestern USA

In the upper Midwestern USA, where the pandemic had erupted in mid-September 1918, limitations on population mobility played out somewhat differently (Jordan, 1953, p410). Midwestern states responded with several containment measures. Statewide ordinances in principle quarantined towns, but left it to the towns to apply the measures. An army training corps camp in Fort Crook, Nebraska and Iowa State University similarly prohibited residents from leaving or visitors from entering a restricted area.[28] State agencies and municipalities also forbade public gatherings at dance halls, billiard parlours, swimming pools and movie theatres, and closed schools.[29] As in the case of colonial Zimbabwe, these containment measures could be justified on epidemiological grounds and might have mitigated transmission. But the specific ways that these measures were created and applied selectively also dovetailed with military, economic and political priorities, which over the long run, undermined their potential efficacy.

Quarantines, for instance, were for the most part unsuccessful, with the notable exception of small isolated communities and the US Army Balloon School in Fort Crook (Markel et al, 2006). At this military training camp, strict quarantine had kept infection at bay, and very few cases of influenza developed. But in late October 1918 military commanders began to argue about when to lift the quarantine, in part because the quarantine appears to have been unpopular among bored military trainees. The camp also had relied on local (civilian) community members to furnish services and supplies necessary to its functioning. By restricting access to many of those civilians who provided essential services, the Fort Crook camp found itself short of crucial supplies, including warm clothing. Pressure to lift the quarantine then mounted. One surgeon raised concerns that commonly trouble health authorities about quarantines; he warned that the camp's trainees were probably immunologically naïve, and that releasing the sequestered men into the community or bringing in new trainees could simply

provide 'fresh fuel for the epidemic'.[30] In the end the senior commander at Fort Omaha lifted the quarantine after another week, permitting entertainment and civilian employee access, but continuing to segregate all new arrivals for six days.[31]

Town quarantines, however, were undercut by two problems. First, towns enforced quarantine only *after* the local outbreak of influenza; second, those people wealthy enough to own or have access to private vehicles could move freely to do business or seek entertainment in towns where quarantine had not yet been imposed – precisely what contemporary citizens of Mexico City did in spring 2009, when they sought to escape the shuttered city. When the town of Virginia, Minnesota, enforced prohibitions on public gatherings, residents headed for the nearby town of Eveleth for their entertainment. Although Eveleth had not yet suffered any cases of influenza, its local Board of Health decided to close cinemas and ban public meetings to prevent visitors from introducing the virus into the town. Visitors, unaware of these measures, came to Eveleth only to discover that the cinemas had been shut down. They then gathered in the billiard halls and 'soft drink' parlours, which were not covered by the Board of Health's closure order.[32]

Mobility restrictions also proved less efficacious because of the contradictory demands of limiting mobility and of moving troops, their families and medical personnel in wartime. Railroads continued to operate during the pandemic emergency, for they were deemed essential for economic, military and later medical needs, transporting agricultural products, military personnel and medical personnel throughout the nation. But the railroads also undermined the efficacy of other mobility restrictions, serving as a vector for spreading influenza throughout the Midwest, continuing operations even with masses of sick employees. The operations manager of the Great Northern Railroad, for instance, reported that St Cloud, Minnesota – a town through which the railroad passed – had more than 2800 cases of influenza out of a population of fewer than 15,000.[33] Almost 900 railroad employees on the lines east of Williston, North Dakota were sick with influenza on a single day.[34]

In an unsuccessful measure to limit public exposure to traffic from influenza-ridden military camps, the Secretary of the Minnesota State Board of Health sought to restrict unnecessary train travel for soldiers. But the military refused to accede to these restrictions, arguing that it made no sense to do so. As W. P. Chamberlain, an army medical officer insisted:

> *it does not appear to this office desirable to attempt to limit the movements of the authorized [military] escorts for the dead [to the homes of their families] … or the casual soldier on leave, in view of the fact that hundreds of thousands of civilians who have been equally exposed to the infection are freely travelling about the country.* (quoted in Jordan, 1953, p412)

Moreover, civilians, such as contractors and parents rushing to the bedsides of their stricken sons, also had access to military camps, and thus could potentially introduce influenza infection among military personnel.[35]

But it was not just the economic or military priorities that created inconsistencies in the formulation and application of mobility restrictions. In the state of Minnesota, the overlapping of authority also undermined the epidemiological efficacy of these strategies. The state Commission of Public Safety (CPS), created during World War I, had acquired extraordinary wartime powers that superseded those of the State Department of Health and other agencies. One of its powers was to coordinate all wartime emergency response among state agencies and private organizations, and it appears that the commission initially perceived the pandemic emergency as falling under this authority. But when rural communities requested medical assistance to cope with the epidemic, the CPS often added considerable delays in responding to the local needs by deferring responsibility for response to other agencies. The Middle River Village Council, for instance, had asked the Great Northern Railroad (GNRR) to facilitate the transport of a doctor to care for Middle River flu victims, whose only access to medical care was 22 miles away on impassable winter roads.[36] The Council's request worked its way through the railroad hierarchy, where it was denied, and so the council appealed to the CPS for help. Instead of acting upon the query, the CPS delegated the decision to the State Board of Health, which allowed it to languish for another four days before a health official took up the matter with the GNRR.[37] Evidently, the presence of a centralizing authority with the power to manage the public health, legal and logistic considerations of the pandemic was no guarantee of efficient or effective action.

It is clear from these examples that uncertainty permeated authorities' understanding of influenza itself and human responses to it, the efficacy of diverse containment measures and the exercise of police powers by an intricate tangle of municipal, state and military authorities and private interests. Quarantine on the Nebraska army training base, for instance, elicited considerable questions about the nature of influenza and the development of human immunities.[38] Late in the pandemic, public health officials expressed doubt that isolation and quarantine could be effective and enforceable measures.[39] Town quarantines, such as one in Deer River, Minnesota, provoked uncertainties among town officials and within the ranks of the state Commission of Public Safety about the town clerk's power to exclude itinerant pedlars or other incomers.[40]

Debates about school closures among state and local officials and parents of schoolchildren illustrate most clearly the fundamental unpredictability of a public health measure's influence on pathogen, human behaviour and environment interactions. Then – as now – it remains unclear whether school closures decreased influenza mortality or slowed influenza's spread (Cauchemez et al, 2009, pp473–76; see also Effler et al, 2010). School officials in 1918 expressed considerable

uncertainty about whether closures could counter the increased risks of 'children... wander[ing] the streets' or even remaining 'in unsanitary and unventilated homes'.[41] Midwestern public health authorities placed their confidence in the protective capability of the school nurse and early diagnosis, despite the apparent contradiction with their own policies banning public gatherings and evidence that in many places, the school nurse or doctor had gone off to war. Like mineworkers in colonial Zimbabwe, Midwestern American parents acted on their own certainty about influenza transmission: they kept their children home and urged districts to close the schools. Eventually, school officials and public health authorities in many communities acceded to public pressure and closed schools entirely.[42]

Hence, while historical actors in the upper Midwest confronted the influenza pandemic's unpredictability by placing their faith in specific measures as epidemiologically sound, they did so for different reasons than in colonial Zimbabwe. Midwestern American parents had had considerable experience with a polio epidemic in 1916 and frequent smallpox outbreaks, and they expressed a confidence from practical experience that the same strategies of social distancing could protect their children from infection. Although this assumption was misplaced, since influenza was more easily and rapidly transmitted than either polio or smallpox, it nevertheless offers insight into how ordinary people's recollections and first-hand experience of other infectious diseases shaped their demands for certain kinds of prophylactic measures.

For their part, public officials projected an appearance of epidemiological certainty that belied the recognized limits of knowledge about influenza and the efficacy of traditional interventions. Over the objections of several health officials, the Minnesota State Board of Health decided in 1919 that influenza would subsequently require individual case reporting and quarantine. Board members, like other health officials around the US, were aware that diagnosis, reporting and quarantine of influenza cases could be very difficult, but nonetheless argued that 'the quarantine has been shown to be a very necessary thing'.[43] As the Board of Health president observed candidly:

> *We thought we ought to have some regulations that can be enforced. We do not think that they will control an epidemic of influenza but we have regulations and we can enforce them ... I think the important thing is that should we have an epidemic and the public comes in and asks what we have done we can tell them that we have passed certain regulations.*[44]

In other words, public health officials had to show that they were doing *something*, even if they had private doubts that their interventions would accomplish anything. This pressure to do something speaks to a concern that health authorities and political officials have manifested in multiple health emergencies: the need to demonstrate their effectiveness to their constituents and to inspire public confidence. There is also a specific historical dimension to the State Board of Health's decision. The public health infrastructure in the upper Midwest was highly underdeveloped in 1919. Implementing regulations (even ineffective ones) might help to convince the American public that active public health interventions, delivered by established public health departments, were worthy of public investment.

Conclusion

What can this investigation of past quarantine, isolation and mobility restrictions tell us about efforts to curtail future pathogenic transmissions? Our goal has not been to be prescriptive about necessary elements for success or failure of social distancing measures during a pandemic. These recognized and long-standing measures have, in particular circumstances, mitigated transmission. Our historical case studies do, however, underscore Gostin's statement regarding the convergence of factors informing every public health decision: that is, containment measures and other interventions can be imposed for compelling epidemiological reasons, but political, social and economic priorities also shape their configuration, imposition and negotiation. In some cases, these priorities can undermine the measures' efficacy and even contribute to the spread of disease. The lesson here is not in the details, which will always be specific to time and place. Instead, the lesson underscores the need for public health officials to recognize that steps taken to prevent or reduce pathogenic transmission are informed as much by geopolitics, public expectations, corporate pressures and social perceptions of differential vulnerability as they are informed by biomedical understandings of viral behaviour.

This chapter has focused on rural areas not only because they have received inadequate attention in past pandemics, but also because they continue to pose particular challenges for present and future pandemic planning. Rural regions in the Upper Midwestern US and colonial Zimbabwe tended to be poorer, often making their inhabitants more vulnerable to disease because they were less able to afford nourishing food and tended to engage in more physically taxing occupations (farming and mining, for instance). The countryside also had meagre medical and public health infrastructures, which meant that people had less access to preventive and palliative care during the crisis. Rural areas were not identical, of course; the upper Midwestern US, for example, had some public health nurses and Red Cross-organized community responses to influenza that almost certainly improved morbidity and mortality rates, a factor that colonial Zimbabwe lacked. Currently, rural areas are equally differentiated, yet there are commonalities cutting across many geographical regions. Many parts of the world, for example, now face a trend towards concentration of medical services in urban areas,

resulting in the closure of rural clinics and a reduction of health-care personnel. In Zimbabwe, the ratio of health care personnel in population is very low, with only 2 physicians per 10,000 population (World Health Organization, 2004). Given this skeletal infrastructure, disseminating preventative resources such as vaccines and providing health care for the sick under epidemic conditions may be impossible. Simultaneously, many rural populations are already immune-compromised by high rates of infectious and chronic diseases and dietary deficiencies, making them more vulnerable to an epidemic.

Our historical analysis also highlights the inherent tensions existing between viral behaviour, epidemiological and virological understandings of that behaviour, authorities' obligation to respond to epidemics, and public expectations. A pandemic is a highly dynamic event; the virus itself can change over time and operates within mobile human bodies that can behave in unpredictable ways. Controlling viral transmission under such volatile circumstances can be exceedingly difficult. But a sceptical, fearful public expects authorities to implement policies that can mitigate the pandemic and for their part, officials feel obliged to respond to these public expressions. Our historical investigation reveals that authorities may intervene for a range of reasons. Solid epidemiological and virological evidence can certainly constitute grounds for action, but in 1918 there was much that authorities did not know or understand. In the face of such uncertainties, public officials marshalled interventions to accomplish specific aims: to blame particular social groups for the failure of containment measures; to promote the perception that officials were doing something to protect the public health and avert catastrophic mortality; to be pragmatic and apply past methods to new and unpredictable events; and to educate the public about the merits of investing in public health. More generally, they may attempt to respond to overt economic, social or political pressures, to placate a doubtful and frightened public, or even to demonstrate that they are doing something even when they recognize that little can be done.

In responding to any pandemic, one way past the tensions is to recognize Hinchliffe and Bingham's contention that biosecuring will always be incomplete. Bringing this concept to bear on our historical case studies provides tools to enable a more critical evaluation of containment measures made during the course of a pandemic. Not all measures are equally valid, or equally appropriate. But deploying analytical concepts of complexity and biosecurity within a comparative historical analysis of pandemics can better equip public health officials to evaluate the social, political and economic context in which they impose containment measures – and to avoid misguided and unfortunate decisions.

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Notes

1 Estimates in available documents from 1918 revealed compounds as small as 12 persons and moderately sized compounds of 45 persons. T. C. Zunckel, Acting Assistant Native Commissioner to Native Commissioner, Gwelo-Sebungwe (22 November 1918), No. K. 765/204/18, Zimbabwe National Archives [hereafter ZNA] File3/12/30/1; H. M. Meade, Ag. Compound Inspector, 'Report on Special Duties Performed by Compound Inspector, Gwelo, in connection with combating [sic] Influenza Epidemic, Continued', p7 (26 November 1918), ZNA File A3/12/30/1.

2 Such organizations include anti-tuberculosis associations, women's clubs, local civic groups, philanthropic foundations and industrial employers.

3 See 'Influenza Epidemiology Memorandum by Chief Native Commissioner on Chamber of Mines' (23 December 1918), p1, ZNA File A8/3/8/vol.1.

4 'Influenza Epidemiology Memorandum by Chief Native Commissioner on Chamber of Mines' (23 December 1918), p1, ZNA File A8/3/8/vol.1.

5 (Sgd) S. E. Buckley of the Balla-Batonga Mission of the Primitive Methodist Church, Kanchindu, to the Native Commissioner, Belingwe, December 5th, 191[8], p3, ZNA File A3/12/30/3–5; Native Commissioner's Office, 'Spanish Influenza' (22 November 1918), ZNA A3/T2/30/1.

6 J. Morton, Rhodesia Chamber of Mines, Bulawayo, to His Honour the Administrator, Salisbury (23 December 1918), p31, ZNA File T2/29/29/1–2.

7 Public Health Department, Southern Rhodesia, 'Memorandum for the Prevention of Epidemic Influenza' (n.d.), p4, ZNA File A8/4/5–7.

8 (Sgd) S. E. Buckley of the Balla-Batonga Mission of the Primitive Methodist Church, Kanchindu, to the Native Commissioner, Belingwe, December 5th, 191[8], p3, ZNA File A3/12/30/3–5; Native Commissioner's Office, 'Spanish Influenza' (22 November 1918), ZNA A3/T2/30/1.

9 Simmons does, however, cite the well-known missionary, Robert Moffat, who had observed in the mid-19th century smallpox epidemics in Matabeleland that 'the king would leave his kraal and live at one of his outposts to avoid contagion. When individuals became sick, they were removed to the woods where a relative took care of them.' (Simmons, 2009, p31).

10 H. N. Meade, Acting Compound Inspector, 'Review of compound inspectors' Reports for October, 1918' (10 December 1918), ZNA File A8/3/8/vol.1.

11 A. M. Fleming, Medical Director, 'Report on the outbreak of epidemic influenza in Southern Rhodesia in 1918' (1 May 1919), pp4–6, ZNA File A8/4/5–7.

12 J. W. Posselt, Ag. Native Commissioner (3 December 1918), ZNA File A3/T2/30/1; Sgd. With. Skold, Church of the Swedish Mission to the Native Commissioner, Belingwe (3 December 1918), ZNA File A3/T2/30/1. Phiminster has noted, however, one Native Commissioner contended that worker dispersal outside of mines actually lowered mortality. (Phiminster, 1973, p147).
13 'Spanish Influenza Epidemic' (n.d.), ZNA File A3/T2/30/1.
14 Robert Gordon to the Mayor of Salisbury (2 November 1918), ZNA File A3/T2/30/1; W. W. Jenkins, 'Salisbury Lazaret – Spanish Influenza Epidemic' (6 November 1918), ZNA Files A3/T2/30/1. Simmons' mortality estimates in Bulawayo hospitals are similar: among 1067 Africans treated, 160 died. Another hospital treated 240 Europeans but lost 34 to influenza (Simmons, 2009, pp29–32).
15 J. S. Harris, 'Report on Vera Epidemic in the Lomagundi District' (n.d.), ZNA File A3/T2/30/1.
16 'It must be clearly realised that the disease is to all intents and purposes unpreventable by quarantine restrictions, except of such a nature as to be prohibitive to the commerce of this country', in Public Health Department, Southern Rhodesia, 'Memorandum for the Prevention of Epidemic Influenza Issued by the Public Health Department, Southern Rhodesia', p1, ZNA File A8/4/5–7.
17 'Spanish Influenza Epidemic' (n.d.) ZNA File A3/T2/30/1.
18 S. G. Buckley, 'Report on the Spanish Influenza Epidemic in the Zambesi Valley, November 1918–January 14th, 1919' (14 January 1919), p1, ZNA File A3/T2/30/1. See also A. Campbell, Native Commissioner, Belingwe to the Superintendent of Natives, Bulawayo (15 December 1918), ZNA File A3/T2/30/1.
19 T. C. Zunckel, Acting Assistant Native Commissioner, Native Commissioner's Office, 'Spanish Influenza' (22 November 1918), ZNA File A3/T2/30/1; J. S. Harris, 'Report on Vera epidemic in the Lomagundi District' (n.d.), ZNA File A3/T2/30/1; N. Jnodu Plessis to the Native Commissioner, Belingwe (4 December 1918), ZNA File A3/T2/30/1; Native Commissioner's Office Gutu to the Superintendent of Natives (13 November 1918), ZNA File A3/T2/30/1; Native Commissioner Gokwe, 'Spanish Influenza' (4 December 1918), ZNA File A3/T2/30/1.
20 (Sgd) G. S. Murray (31 December 1918), ZNA File A3/T2/30/1.
21 A. M. Fleming, Medical Director to the Secretary, Department of the Administrator (21 November 1918), ZNA T2/29/29/1–2; Sgd. With. Skold, Church of Sweden Mission to the Native Commissioner, Belingwe (3 December 1918), ZNA File A3/T2/30/1.
22 A. M. Fleming, Medical Director, 'Report on the outbreak of epidemic influenza in Southern Rhodesia in 1918' (19 May 1919) ZNA File A8/4/5–7.
23 T. C. Zunckel, Ag. A. N. C. (30 November 1918), ZNA File A3/T2/30/1.
24 S. G. Buckley to the Native Commissioner Gokwe (Ref. No. K/765/204/18) (5 December 1918), ZNA File A3/T2/30/1; Archie A. Campbell, Native Commissioner, Belingwe, to the Superintendent of Natives, Bulawayo (24 November 1918), ZNA File A3/T2/30/1. H. S. Keigwin, 'Spanish Influenza, Lomagundi' (17 December 1918), ZNA File A3/T2/30/1.
25 S. G. Buckley to the Native Commissioner Gokwe (Ref. No. K/765/204/18) (5 December 1918), ZNA File A3/T2/30/1; Archie A. Campbell, Native Commissioner, Belingwe, to the Superintendent of Natives, Bulawayo (24 November 1918), ZNA File A3/T2/30/1. H. S. Keigwin, 'Spanish Influenza, Lomagundi' (17 December 1918), ZNA File A3/T2/30/1.
26 J. D. Morton, Secretary, Rhodesia Chamber of Mines to His Honour the Administrator, Salisbury (23 December 1918), ZNA File T2/29/29/1–2; (Sgd) F. D. Morton to the Secretary, Department of Administrator, Salisbury (18 November 1918), ZNA File T2/29/29/1–2.
27 Herbert J. Taylor, 'Influenza Epidemic – Memorandum by Chief Native Commissioner on Chamber of Mines, Letter of 23rd December, 1918' (n.d.), ZNA File T2/29/29/1–2.
28 'Influenza Ban is on at Duluth', *The Daily Virginian* (12 October 1918); 'New Quarantine Regulations from Headquarters', *Iowa State Student* (11 October 1918), p1; Post Surgeon [John L. Travis] to Commanding Officer, Ft. Omaha, 'Lifting Quarantine'. RG18 Records of the Army Air Forces, US Army Balloon School, Fort Crook, NE B.1 Correspondence, September 1918–January 1919, f. Correspondence, 301–400, October–November 1918. National Archives and Records Administration Central Plains, Kansas City, MO.
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9

Flu Epidemics, Knowledge Sharing and Intellectual Property

Maurice Cassier

The threat of an H5N1 influenza pandemic from 2005 to 2007 and the spread of the H1N1 pandemic in 2009 have contributed to the construction of a new field of debate concerning intellectual property and access to treatment. Discussions about influenza epidemics are now part of a new biopolicy that emerged in the late 1990s; this biopolicy emerged within the dual framework of health policies that sought to combat the AIDS epidemic (Moatti et al, 2003; Cassier and Correa, 2009) and of conflicts over the appropriation of biological resources (Bellivier and Noiville, 2009). This biopolicy, aimed at safeguarding patients and populations and at affirming their 'right to heath' (see the Brazilian constitution of 1988) and 'right to life' (Foucault, 1976), is promoted by an alliance of certain activist states, such as Brazil, in the health field. The alliance also includes NGOs engaged in campaigns for access to treatment and generics laboratories such as the Far-Manguinhos Federal Laboratory in Brazil and the Cipla laboratory in India. The conflict over patents and breast cancer genes in North America and Europe between 1995 and 2008 also illustrates this biopolicy concerning access to treatment (Cassier, 2002).

Since 2005, an interesting aspect of the avian flu threat is that it has amalgamated several debates concerning the ownership and accessibility of science, life forms and drugs. Four events have transpired: first, in the autumn of 2005, there was a clash over Roche's patented molecule, Tamiflu, and the generic copies that the Indian laboratory Cipla wanted to produce. Second, tensions surfaced over the restrictions imposed on the rapid circulation of virus sequencing data between laboratories, resulting in August 2006 in the creation of an international consortium for 'data sharing'. Third, a conflict broke out in 2007 between Indonesia and the World Health Organization (WHO) Surveillance Network over whether sovereign states should withhold virus strains that were identified and isolated in their territories. Finally, debates erupted over the proliferation of the sequences of the H5N1 virus and their impact on the development and accessibility of health technologies – a proliferation that worried the WHO to the point where it

commissioned a report on this issue in November 2007 (World Intellectual Property Organization (WIPO), 2007). Moreover, there is an abundance of reports on intellectual property and avian flu (Yeh, 2005; Hammond, 2007).

The threat of a flu pandemic in autumn 2005 and the spread of the H1N1 flu epidemic in 2009 has intensified these debates over intellectual property and access to treatment. Influenza pandemics provoke great concern because they can spread suddenly and rapidly, afflicting rich and poor countries alike throughout the world, and the virus's circulation and variations must be monitored in real time to develop new vaccines. The urgency of the situation also demands the rapid availability of antiviral drugs to be administered from the first symptoms (Ferguson et al, 2005). Concerns about intellectual property and access to treatment have not always been of central importance. In the 1960s, Louis Galambos and Jane Eliott Sewell, investigating Merck's research on influenza, describe a relatively open, cooperative system of knowledge exchange in the characterization of new type B viral strains and vaccine development (Galambos and Sewell, 1995). The authors observed:

> *Although less severe than type A influenza, the new strains of type B stirred up a great deal of cooperative effort in several corners of the virology network. Scientists and production workers throughout the industry, universities and various government agencies in the USA and abroad worked to produce a vaccine of a new composition.* (Galambos and Sewell, 1995)

Nor was intellectual property or access to treatment of concern in the 1970s Swine Flu Affair, described and analysed in the Neustadt and Fineberg Report (1978). The question of industrial secrecy in vaccine preparation technologies was noted by the authors of the report when it hindered their inquiry:

> *Other manufacturing impediments slowed some production labs, how much is hard to tell. Each company vaccine is somewhat different from the others. Their products must meet the same FDA standards, but their processes are private. Taken as a whole, we know that their production rates fell below Sencer's (hence Cooper's) early expectations. Just how much and why is obscured by the privacy.* (Neustadt and Fineberg, 1978, p42)

The impact of this secrecy on the circulation of technologies between firm, and the rapidity of the scaling up of vaccine production, are not identified by the authors as problems. That controversy centred on a question of responsibility and guarantees that firms sought from the state to cover risks concerning vaccines. A cooperative and open system of knowledge sharing in the past contrasts sharply with today's more proprietary atmosphere, saturated with patents and material transfer agreements.

This sudden proliferation of debates about intellectual property and avian flu may be a result of the new context created by the AIDS epidemic, which put drug

patents and generics at the centre of public and political discourse in the early 2000s. Two high-profile disputes about drug patents and generics erupted at that time, as well as one international declaration: in May 2000, a complaint lodged by the United States at the WTO against Brazil for threatening to suspend patents if the patented invention was not produced locally within three years; in March 2001, a lawsuit filed by 39 international pharmaceutical firms against the South African government for its new law on medication; and the Doha Declaration of November 2001 on intellectual property and public health.

Generally, these debates are seen to participate in the emergence of a new governance of the health and drug economy, involving the pharmaceutical and scientific laboratories of the North, the generic drug-producing laboratories of the South, countries claiming sovereign rights over their biological resources, and NGOs campaigning for access to treatment (Nau, 2005). For example, the AIDS patient organization Act Up has joined an NGO in Burkina Faso to demand access to Tamiflu generics. The French trade union, the CFDT, has denounced the asymmetry between industrialized countries and poor countries regarding access to antivirals.[1] The Indian generics laboratory Cipla has intervened in both industrial and public domains to defend the possibility of producing generics of flu antivirals.

These controversies over the appropriation of virus strains, genetic sequences and antiviral drugs and vaccines have been accompanied by various proposals and plans concerning intellectual property and the circulation of knowledge and biological entities. For example, inspired by the open-source model, the GISAID consortium has defined a licence for access to genetic data, so as to avoid any restrictions on the circulation of data (Anon., 2006). The WHO report on patents on the H5N1 virus has proposed the creation of patent pools to avoid situations of lock-in of the technologies needed to develop vaccines. Patent pooling enables any potential inventor to gain access to all useful technologies in the development of a new vaccine (WIPO, 2007). The WHO is seeking to develop solutions that can reconcile virus-sharing with benefit-sharing for equitable access to vaccines (WHO, 2008). Exploring in detail diverse aspects of these controversies, this chapter argues that the threat of an avian flu pandemic has been a laboratory for designing and testing new solutions to conflicts over intellectual property rights and the rights of access to treatment. Defining models of circulation and appropriation of knowledge and technologies pertaining to flu remains a critically important aspect of health policies during pandemics.

Patents and generics: The Tamiflu patent controversy (October 2005–October 2009)

In the autumn of 2005, after the WHO recommended stockpiling antiviral medicines in all countries (WHO, 2005), debate focused on Roche's legal monopoly

on Tamiflu[2] and on the production of generic drugs, especially in India, Thailand and Taiwan. While the Indian laboratory Cipla announced that it had synthesized the molecule in vitro and would manufacture it, Roche reasserted its legal and technological monopoly over Tamiflu. The battle over the rights to Tamiflu thus erupted on several fronts: production capacities and the available supply of drugs in case of a pandemic; the complexity of the manufacturing technology required to produce Tamiflu; the accessibility of the raw materials needed to produce the drug; and finally, the respect for property rights and for patients' right to live.

The confrontation first surfaced with India's new intellectual property law, which recognized patents on pharmaceutical products from 2005 only. At the end of 2005, Cipla announced that copying Tamiflu was entirely legal, since no patent on the molecule had yet been issued in India. According to the company's managing director, Yusuf K. Hamied, 'Since the currently available drugs to treat avian flu have not been granted patents in India, nobody can stop any generic manufacturer from producing it in the country'.[3] The generic drug laboratory therefore used the absence of an Indian patent to practise reverse engineering and to launch its industrial production of the drug. Hamied continued, 'So legally as of today I can produce the drug in India. Until the patent is granted...'[4] Roche reacted immediately, pointing out that a patent application had already been filed in India.[5] Cipla and Ranbaxy responded by requesting a non-exclusive licence from Roche, but to no avail. In February 2006, the Drug Controller General authorized Cipla to commercialize a generic version of Tamiflu, thus confirming the legality of generic drug production. 'Roche', the authority maintained, 'does not have a product patent in India and the international patent is not enough according to Indian patent laws. The companies can manufacture generic versions of the drug medicine by filing a licensing application with the government'.[6]

In May 2006, while the Gilead patent application was still pending, Cipla and another generics laboratory, Meditab Specialities, filed a complaint against the Tamiflu patent with the New Delhi Patent Office. The complaint insisted that there existed a 'prior art' on the molecule before the patent application. The General Controller of Patents in Delhi approved this opposition and dismissed the patent application.[7] The Indian generics firms were thus engaged on three fronts: on the technological front, by conducting reverse engineering on Tamiflu; on the commercial front, by demanding authorization to commercialize in India; and on the legal front, by opposing Roche's patent application on Tamiflu in India and calling for its rejection.

Roche's legal monopoly was simultaneously strongly challenged because the company lacked the industrial capacity to meet global demand during a pandemic. In the autumn of 2005, the UN Secretary General suggested that the Tamiflu patent should reflect greater flexibility during the context of a pandemic threat. One American Democratic Senator, Charles Schumer, wrote to Roche asking the

firm 'to compromise on its patent rights for the sake of public health'.[8] States and international non-governmental organizations (NGOs) campaigning for greater access to medicines recommended the production of generic drugs. In situations where necessary, a compulsory licence would allow the drug's production without the patent owner's authorization (Nau, 2005). At the time, the Indian government approached generic drug firms to explore the possibility of producing generics 'essentially for stockpiling' under necessary circumstances with the patent owner's authorization.[9]

After insisting that it be Tamiflu's sole producer,[10] Roche envisaged granting licences on its patent to a network of manufacturers of its choosing,[11] but it refused any proposals of compulsory licensing and generic drug production. In early 2006, the firm revealed the scope and organization of its global network of licensees, which would include several of Roche's sites and more than 15 external contractors located in nine different countries around the world.[12]

Roche thus extended the capacity to produce the drug, while retaining control over production standards and maintaining intact its ownership of the remedy. Its control over the network was based on property rights and justified by the licensees' quality standards and industrial capacity. This organization of production made it possible to increase the production of Tamiflu while limiting the emergence of generics. In December 2005, in the context of its dual with Cipla, Roche granted a licence to an Indian producer, Hetero Drugs. To reduce the price of the drug and increase its accessibility, Gilead, the owner of the patent, announced that it would not demand the same royalties on Tamiflu that it required from its sublicensees.

NGOs, economists and jurists nevertheless criticized Roche's sublicensing policy on several grounds. The Third World Network, for instance, disclosed that these sub-licensing agreements contained restrictive clauses that would prevent widespread circulation of generic drugs. They would allow production solely for domestic use and for government stockpiling, but allowed Roche to maintain its control over the most lucrative markets. Moreover, the agreements would only permit the highly limited transfer of manufacturing technology.[13]

The Third World Network recommended an alternative solution to the problem of drug access: compulsory licences that allowed for the development of a generic drug supply for countries' domestic needs and for export in circumstances where importing countries also possessed a compulsory import licence. Economist and jurist Carlos Correa advocated a similar solution, in which Roche's patent rights would be suspended in the event of a pandemic threat. 'What will happen if there is a human flu pandemic?' he queried. 'The rational response would be to produce and provide the drug – if proven effective – independently of the patent situation' (Correa, 2006). Both the Doha Declaration of November 2005 and Article 31 of the Trade Related Intellectual Property Agreements (TRIPS) had codified this solution of lifting exclusive patent rights during a health emergency.

Opponents of the compulsory licence, however, insisted that this solution would discourage new pharmaceutical research. As Alec Van Gelder, a researcher specializing in technology issues at the International Policy Network in London, observed, '[I]f governments break the patent on Tamiflu, no pharmaceutical company is going to want to develop a new antiviral for fear that their expensively developed innovative medicine will simply be stolen without adequate compensation for the tens or hundreds of millions of dollars invested' (Van Gelder, 2005). The Indian generic drug producer Cipla responded with a public campaign, posing the question, 'What interest is there in developing drugs which can save lives if the patients can't obtain them?'

Roche not only defended its monopoly by seeking to protect its property rights, but shifted the terms of public debate, observing that the major barrier to expanded Tamiflu production was not patent rights at all, but technological capacity. According to one Roche manager, 'For us, the problem is not the patent but the capacity for Tamiflu production. We have ten years' experience and we would like to be consulted as this is a long, complex process'.[14]

Yet this barrier was not as insurmountable as Roche had claimed. Since the 1970s, generics laboratories had built up sound technological experience that permitted them to copy molecules as complex as ARVs. Recognizing the complexity of duplicating Tamiflu, Cipla highlighted its symmetrical experience in copying other complex molecules. As Yusuf Hamied acknowledged, 'It's not an easy synthesis, but our company is used to manufacturing difficult things... One of the steps in zidovudine for example uses sodium azide, and that's the step that Roche said was dangerous and hazardous. We've been doing it for the last 14 years. It's all chemistry'.[15] Cipla could reuse a synthetic technology to produce zidovudine for Tamiflu's manufacture, and in the autumn of 2005, the company announced that it had successfully developed a generic that was a significantly less expensive version of Tamiflu. It added, 'Once the lab work is done, things don't take too long. We are in the process of scaling-up and commercializing. That should be completed next month.' The following February (2006), Cipla delivered its first 100,000 dose batch of Tamiflu. At least one other laboratory followed suit, with the October 2005 announcement by a Taiwanese laboratory that it had also mastered Tamiflu production technology.[16]

Roche tried to win another argument about barriers to generic production: the bottleneck in the procurement of the raw material for Tamiflu manufacture. The crucial material was shikimic acid, found in star aniseed, a plant which grows only in certain parts of China (Van Gelder, 2005). In October 2005 the threat of an avian influenza pandemic caused the price of this material to skyrocket from US$40 to $1000 per kilogram. This situation revived interest in alternative production technologies. At first Roche approached Michigan State University, which had patented a technology to obtain shikimic acid from recombinant bacteria (patent filed with the USPTO in 1999). The inventor of this synthetic

method, Professor John Frost, believed that shikimic acid was not an obstacle (Enserink, 2006). Roche exploited the fermentation technology and paid royalties to Michigan State University. Then, in February 2006, a group of researchers from Tokyo University patented an artificial synthetic method that seemed more productive. Roche entered into negotiations with the Japanese university to acquire the new technology.

To overcome problems pertaining to the price and procurement of shikimic acid, the generics laboratories also had the possibility of using an alternative raw material. Ranbaxy,[17] for instance, used a different intermediate, quinic acid, to manufacture the Tamiflu molecule. It claimed that it had negotiated procurement contracts for adequate supplies of this ingredient and of shikimic acid.

Cipla asked Roche to divulge its process for humanitarian reasons. Hamied opined:

> *My suggestion is that if Roche wants to make a humanitarian gesture, let it publish its manufacturing process openly. Whoever uses Roche's process should pay it a 4 per cent royalty on net sales. Countries have to put pressure on them. The Tamiflu issue shows that the destiny of a country or of the world cannot rest in the hands of one company or one inventor.*[18]

This controversy developing around the production of Tamiflu generics was part of the emergence of a new pharmaceutical economy, one that implicated several actors who sometimes worked in concert: global South generics labs that could learn and reproduce complex molecules, governments, international institutions and NGOs defending universal access to treatments. The vanguard of the old economy, proprietary laboratories, sought to navigate the new one by seeking to protect their exclusive rights and responding to pressures for wider access to drugs. The spectre of debates over access to antiretroviral drugs in the AIDS epidemic was clear to all participants. The UN Secretary General, for instance, explicitly indicated of the Tamiflu generic drug debates, 'I wouldn't want to hear the kind of debate we got into when it came to the HIV anti-retrovirals'.[19] NGOs such as Médecins Sans Frontiers (MSF) and Act Up, which had campaigned for broad access to treatment in the AIDS epidemic, perceived a direct linkage between the AIDS and potential avian flu epidemics when it advocated the production of Tamiflu generics. A joint petition by Act Up and a Burkina Faso network for access to essential drugs read in part, 'For the African countries, which have been unable to stockpile Tamiflu, which can already see migrating birds arriving from contaminated regions of the world, and which have the highest HIV-prevalence rates, there is no more time to lose: Roche must immediately authorize and facilitate the unconditional launching of a generic production of Tamiflu' (Nau, 2005). Older alliances that had solidified in the AIDS epidemic were mobilized with the threat of an avian flu pandemic. The Indian generic drug laboratory

Cipla and MSF had been key partners in the campaign for generic ARVs, and they collaborated to launch the campaign for Tamiflu generics.

Proposals to apply compulsory licensing on Tamiflu came not only from these alliances, but from states themselves. In November 2005, a report prepared for the US Congress envisaged the same solution on the grounds that:

> *Voluntary licenses between Roche and generic drug manufacturers could help to increase production of Tamiflu to satisfy global demand. Compulsory licenses are also a possibility if Roche's sublicensing efforts fail to adequately expand production, or if poorer countries determine they cannot afford Roche's licensing fees.* (Yeh, 2005)

An international consortium for the sharing of genetic data (August 2006–)

Debates on the appropriation of knowledge and technologies also appeared far upstream from the drug economy; this time, they erupted in the economy of science, among laboratories engaged in deciphering the H5NI virus genome. Academic scientists undertook to reopen science as soon as they encountered restrictions in the circulation of data.

Nature's (Anon., 2006) publication of the 'Global Initiative on Sharing Avian Flu Data' (GISAID) embraced a similar objective to that of the Human Genome Project consortium: to expand the public domain of science, since the threat of a flu pandemic and the concomitant need to accelerate genetic research reinforced the exigencies of freely circulating data. According to the GISAID, 'The current level of collection and sharing of data is inadequate, however, given the magnitude of the threat. We propose to expand and complement existing efforts with the creation of a global consortium' (Bogner et al, 2006). The pooling of a large collection of virus strains and the rapid circulation of genetic and clinical data were essential to both research on the H5N1 virus's genetic evolution and the timely development of prophylactic treatments. The GISAID consortium's rhetoric explicitly linked data access to the interests of public health: 'Timely development of vaccines, diagnostics and therapeutics depends on the availability of information. Such information is important for global health security' (GISAID, 2008).

The first aim of this 'world' consortium was to broaden access to sequencing data that until then had circulated within the WHO Surveillance Network, but was criticized by some researchers and biotechnology firms as too limited and compartmentalized. In March 2006, for instance, the biotechnology firm Recombinomics complained of excessively restricted access to this WHO database, which was 'limited to 15 laboratories'.[20] At roughly the same time, an Italian virologist, Ilaria Capua, decided to put data into the GenBank public database,

rather than publishing them on the WHO Influenza Sequence Database site. The virologist's initiative gathered momentum, and several countries and international agencies began sharing their avian influenza virus data more freely. On 22 August 2006, the FAO network on avian influenza (OFFLU) reiterated its objectives of exchanging scientific data and biological material, including virus strains from various countries. That same day, researchers from the US Centers for Disease Control (CDC) entered into Genbank data on some 650 flu virus genes. Just 2 days later, 70 researchers, 6 of whom were Nobel Prize laureates, published a letter in *Nature* announcing the creation of the GISAID consortium.

The GISEAD consortium was formed to promote the principles of data sharing, teamwork and collaborative publication. The signatories of the founding letter justified their actions by invoking rules previously established by the International HAPMAP consortium,[21] which they described as 'a project to map, and make freely available, data on DNA sequence variations in the human genome' (Bogner et al, 2006). Data had to be put into the public domain at latest six months after validation – an interval that would be reduced as the consortium became more experienced. Any registered user could gain access to the consortium's data, but only if that user agreed:

> *to share and to credit the use of others' data, to analyze findings jointly, publish results collaboratively, and not to assert intellectual property rights against each other over technology derived from the data. Such common access will allow the technology to be used both for research and rapid development of products such as diagnostic, antiviral drugs and vaccines.* (Bogner et al, 2006)

These regulations have tended not only to place genetic data in the public domain, but also to put research tools into a sort of technology pool accessible to all consortium members. Research tools derived from the database could be covered by patents, but these would not apply to members of the consortium. The owners of such property rights could, however, exploit them outside the circle of the consortium's authorized users. The consortium itself had no patents.

The consortium effectively came into existence in early 2008, and an access licence to its database has been available since May of that year. This licence first defines the databases containing the virus sequences, their annotations, health security information pertaining to the use of these data, and the regulatory authorizations of vaccines and therapies derived from the consortium's data. It then specifies the scope of users' rights and the nature of their obligations. All the data collected by GISAID are accessible to the community of authorized users and contributors. Licensees are 'granted a non-exclusive, worldwide, royalty-free, non-transferable and revocable license to access and use the GISAID Epiflu Database'; they can use, amend and distribute these data, including for commercial use. In return, they agree to grant GISAID 'a non-exclusive, worldwide,

royalty-free, transferable and irrevocable license to collect, store, reproduce, access, modify, display, and distribute and otherwise use the data submitted by You' (the provider). The data supplier has to agree to the sequences that it contributes to the consortium being placed in the public domain: 'You acknowledge that such sequences shall be freely accessible through said publicly funded database.' 'Authorized Users' are both data suppliers and users who are signatories of the access licence. On the subject of intellectual property, GISAID users agree not to exercise rights that may restrict the use of the data by other authorized GISAID users. Any data that they have contributed can be used by other authorized users to develop vaccines, diagnoses or drugs. Although an authorized user is free to impose restrictions on non-members for the use of data that it has put into GISAID, it may not prevent them from joining GISAID and thus becoming authorized users (GISAID, 2008).

To what extent is this sharing of data compatible with patents on viruses and on their gene sequences? The access licence published by the consortium in May 2008 does not proscribe them; it nevertheless specifies that signatories of the licence shall not exercise rights that limit the access and use rights of other users, who have the right to use data provided by any supplier, including for the development of vaccines, diagnostics and drugs. It is therefore not authorized to exercise an exclusive property right on data contributed to the consortium, against another user who has signed the access licence. Moreover, the consortium's code of conduct stipulates that 'all participants in GISAID accordingly agree to respect proprietary rights but voluntarily set them aside for others who have agreed to share them in the same way. We view this equitable sharing as an important safeguard for global public health' (GISAID, 2008). The consortium's position seems to be extremely unfavourable to virus patenting. According to GISAID:

> *influenza viruses have not been subject to intellectual property rights historically. This tradition has been important because the required changes in influenza viruses contained in human influenza virus vaccines to match those viruses circulating currently in the field must occur at a speed far in excess of the legal process associated with the attainment of commercial protection.* (GISAID, 2008)

Apart from the difficulty of patenting eminently variable objects, a convention does exist in the biomedical community on the non-patentability of viruses, because it remains in the interests of the broader public health: 'In order to allow rapid development of products such as vaccines and other interventions on an equitable basis by all countries and other interested parties, the convention has been for human health professionals to share virus specimens and data openly without creating barriers of exclusivity such as the filing of patents' (GISAID, 2008). But even prior to the consortium's creation, from 2004, patents on sequences of the H5N1 virus proliferated. The WHO consequently

commissioned a report which recommended, inter alia, the creation of patent pools to avoid situations of lock-in (WIPO, 2007).

Finally, one GISAID consortium objective was to encourage cooperation between industrialized countries and developing countries disproportionately affected by avian flu. Among its intentions were 'to draw international attention to the necessity to increase funding and technical assistance for affected countries, and to set up surveillance programmes' (Pearson, 2006). Indonesian, Chinese, Vietnamese and Thai scientists were signatories of the GISAID agreement,[22] and the Indonesian government originally supported efforts to pool data and biological material. But in late 2006 a crisis erupted when the Indonesian government withheld virus strains isolated on its territory from the WHO Global Influenza Surveillance Network. Indonesia nevertheless agreed to participate in the new international GISAID consortium.[23] With the GISAID database it was possible to identify the contributors and users of virus strains: public laboratories, pharmaceutical firms and universities. GISAID also included a licence requiring the users of viral strains to request the supplier's authorization before filing a patent on a vaccine. The consortium furthermore urged scientists to collaborate with national laboratories that provided information on the virus.

The GISAID EPIFLU database, hosted by the Swiss Institute of Bioinformatics, a private firm, was launched in May 2008, simultaneously with the disclosure of the access licence to the consortium's data. It became a reference research tool for the scientific community and WHO.[24] In April 2009 the sequencing data of the H1N1 virus were entered into the GISAID and WHO databases. But in July 2009, just as swine flu was spreading, disagreement broke out between GISAID and the Swiss bioinformatics firm, SIB, which GISAID accused of misappropriation.[25] While the database remained accessible for users on the private firm's website, it was no longer available on the consortium's site. In August 2009, GISAID sued SIB in the US and Geneva to reopen its Internet link. The consortium eventually shifted its database to the Max Planck Institute for Informatics (Butler, 2009).

Virus sharing and benefit sharing: The clash with Indonesia (2006–2007)

Research on the H5N1 virus opened a third front in the intellectual property field: states' sovereignty on viral strains isolated on their territories, and equitable agreements of the 'virus against treatment' type, for the benefit of countries that provided strains. At the beginning of 2006, Indonesia decided to suspend the payment of virus strains isolated within its territory. The Indonesian government, subsequently joined by Thailand, justified its action on two grounds: first, strains freely provided to the WHO Surveillance Network by Southeast Asian countries

had been patented by research centres affiliated with the WHO network without the consent of the countries of origin; and second, the vaccines and antiviral medications remained inaccessible to countries of the South, even though they had been developed from virus strains isolated in poor countries, for instance, from Vietnam. A Thai government representative, Suwit Wibulpolprasert, maintained that virus sharing needed to be premised on full and equal access to vaccines and treatments. 'We are not opposing the sharing of information and viruses', this official asserted, 'but on the condition that every country has the equal opportunity to get access to vaccine and antivirals if a pandemic occurs.'[26]

This decision to suspend contributions of virus strains to the WHO Surveillance Network was strongly criticized by the US Secretary of Health and Human Services who denounced any measure to retain viruses, and by the scientists attached to the international system of sharing virus strains. For about 50 years, one journalist noted, 'the system has operated on goodwill with its costs borne by the WHO membership and no compensation offered for viral contributions' (McKenna, 2007a). Claiming ownership of virus strains would effectively slow down the process of vaccine development and would raise the price of vaccines, lamented biologist Doris Bucher of the New York Medical College (McKenna, 2007a). Indonesia was accused of ruining the system of free sharing of data (McKenna, 2007a). Some worried that 'countries might claim their H5N1 samples are protected under intellectual property laws, which could hamper the monitoring of genetic mutations, the development of therapeutic products, and scientific work on a host of other pathogens', thus damaging both public health and science (Anonymous, 2007).

In view of Indonesia's claims of inequity, some WHO experts recognized the need to change the terms of the exchange, 'to balance the sharing of viruses through global surveillance and ... to make the access to vaccines and those sorts of technology broadly available' (McKenna, 2007b). In early 2007, the WHO General Assembly began discussing these concerns. But by May of that year, tensions heightened when more than 20 countries threatened to withhold virus strains isolated within their territories on the grounds that the 1992 Rio Convention on Biological Diversity had given states the rights to genetic resources in their territories. These countries called for the renegotiation of the virus-sharing system, in which their contribution of viruses to the WHO network would receive compensation through a significant increase in research investments in developing countries, and a guarantee of 'fair and equitable vaccine distribution'. Indonesia advocated for the right of countries of origin to decide if their virus strains could be given to pharmaceutical companies, and many of its counterparts in the global South petitioned to develop their own manufacturing capacity of vaccines. In February 2007, the WHO reported that negotiations with the Indonesian Health Ministry involved developing a local capacity to produce vaccines.

Faced with the threat of effective mutiny, the WHO took two measures that acknowledged but did not entirely concede to these countries' grievances. First, it announced a more transparent monitoring of viruses through the WHO Global Influenza Surveillance Network. The WHO resolution in May 2007 specified that vaccine manufacturers would have free and total access to viruses during a public health crisis; Indonesia, on the contrary, had sought for the WHO to provide virus samples to vaccine manufacturers only with the consent of the country from which they originated (McKenna, 2007b).

Second, it established an international stock of vaccines for the H5N1 virus or any other pandemic virus and adopted rules for the equitable distribution of these vaccines during a pandemic; but it did not permit, as some countries of the global South had proposed, the development of individual country vaccine stockpiles and their own manufacturing capacity.

Indonesia had indeed been jockeying to acquire vaccine production technology, something that the WHO had months earlier explicitly recommended (WHO, 2007). Indonesia ultimately developed a partnership with the vaccine producer Baxter International, offering its virus samples in exchange for vaccine development technologies. This partnership agreement was non-exclusive, and thus did not prohibit Indonesia from sharing its virus samples with other parties. Egypt subsequently petitioned the WHO to guarantee the transfer of vaccine technologies to developing countries.

This episode with Indonesia and other countries of the global South propelled to the fore questions about technology sharing and equal access to treatment, by revealing profound asymmetries in a system of sharing biological materials, particularly when capacities for vaccine research and production are unevenly distributed and when legal monopolies on medical products and technologies are derived from these biological materials. The system is rife with contradiction: Virus strains are freely donated and circulated, and they exist as public goods, while at the same time, certain agents (pharmaceutical companies, for instance) retain exclusive rights on the medical technologies based on these freely circulating virus strains (Chan and de Wildt, 2007). Various institutions and networks have sought to address these disparities. In August 2007, for instance, the WHO published a declaration on 'the sharing of flu viruses and access to vaccines, and other advantages' (World Health Organization, Department of Immunizations, Vaccines, and Biologicals, 2007), and it spearheaded discussions to devise the means for sharing benefits, in which participants articulated principles of pooling strains and sequencing data and generated initiatives for sharing technologies and medical products. The GISAID consortium also attempted to tackle these questions by prescribing shared access to inventions derived from the data that it collected and produced (members of the consortium may not assert intellectual property (IP) rights against one another). But these measures alone were insufficient to guarantee technology transfer and the equal accessibility of the most recent products.

Moreover, exclusive property rights continued to proliferate on the vaccine preparation technologies, and the WHO was finally compelled to respond in late 2007.

Proliferation of patents, patent pooling and compulsory licences

Over the course of 2007, several reports evaluated the scope of intellectual property on the H5N1 virus and vaccine preparation technologies and assessed the impact of these patents and Material Transfer Agreements on the development and availability of vaccines. The Third World Network (Hammond, 2007) and the WHO (WIPO, 2007) drew up these reports in which they both developed proposals to organize the collective management of property rights or to use the flexible provisions of the TRIPS agreements on intellectual property to advocate compulsory licences in case of a health emergency.

These reports noted a steep increase in the number of patents filed in 2006 and 2007, a trend consistent with the steady increases in influenza vaccine patents from the 1990s. But in the case of avian flu, this pattern was even more dramatic: in the first nine months alone of 2007, some 35 per cent of all patents were related to the H5N1 virus (Hammond, 2007; WIPO, 2007). These patents covered the genetic sequences of the virus, the key technologies of vaccine production (reverse genetics, adjuvants and cell culture technology).

While in general, a patent on a gene sequence confers property rights on all the uses of that sequence, the patents on influenza virus gene sequences present particular problems because of the wide variability of viral strains. Patent authors nevertheless seek to circumvent this problem by claiming rights to a particular sequence and any other sequence that is 95 per cent similar to it. They can also lay claim to numerous variations of the same gene. The gene patents that they acquire often have a very broad scope, covering the genes and their variants, the proteins encoded by these genes, their antibodies and the uses of the genes and proteins in vaccines. Several of the existing patents cover avian influenza gene sequences from strains isolated in Indonesia, Vietnam, China and Thailand. For example, the US firm Protelix owns a patent that covers HA and NA genes derived from Indonesian and Thai strains, as well as a method to obtain variants used in vaccines.[27] Such patents covering many variants will probably block or hinder the development of a vaccine that impinges upon the patent.

MedImmune's patents cover a new technology for altering viruses to obtain vaccine viruses. Whereas older techniques to reassemble viruses were not patented, reverse genetics technology to produce influenza viruses from gene sequences is patented, as one November 2007 WHO report observed (WHO, 2007). Vaccine manufacturers could find themselves dependent on this patent covering a key technology. In the case of reverse genetics, according to one *Nature* article,

'companies that make ... [a] vaccine would have to pay royalties to the patent holders. Companies are reluctant to do this, but scientists working in the field say that industry is trying to hammer out this issue' (Check, 2005, p405). MedImmune announced in the event of a pandemic emergency, it would authorize the free use of the technology, but only during the research and development phase, and thereafter would charge once the commercial production of vaccines commenced. But if a company asserts its rights to royalties once the vaccines are commercialized, how would it be possible to assert equal access to vaccines and to protect the broader public health? The Third World Network notes that the US government *can* legally compel a firm to grant open or free licences in the event of a pandemic if it financed the firm's research; under the 'march-in rights' class of the Bayh Dole Act, a US government funding agency can disregard a patent under certain circumstances (Halperin, 2001).[28]

To address the dispersal of property rights and lock-in situations, which impede the use of key technologies or material, the WHO has recommended several types of measures. Its 2007 report (WIPO, 2007) suggested ensuring wide access to new medical technologies through the structuring of 'patent pools' or the 'strategic use' of patents held by public institutions or public/private partnerships.

Several complexities make such changes politically challenging to effect: the difficulties of creating patent pools in the biotechnology sector; the heterogeneity of actors, firms, universities and government agencies; and the wide dispersal of property rights. But a public agency or government could credibly initiate these changes. Although one expert commissioned by the WHO did not envisage such a role for the WHO, this international health organization could well play a central political role in the collective management of property rights to ensure the development and widespread accessibility of vaccines.

Several countries have proposed a system of compulsory licenses in the event of a pandemic crisis. Thailand, noting that in 2006 and 2007, it and Brazil used compulsory licensing to manufacture generic drugs for HIV/AIDS and for cardiovascular diseases, emphasized that these licences would be especially justifiable during a pandemic emergency (Khor,2007). India has gone even further, requesting that during health emergencies countries be authorized to produce vaccines, irrespective of the patent owners. In such a system of automatic compulsory licences, countries could legally produce vaccines without any restrictions at all (Khor, 2007).

Conclusion

The threatened avian influenza pandemic has been a laboratory for developing new ideas about intellectual property as it is applied to science, life forms and drugs. It has precipitated debates over intellectual property rights on viral strains,

vaccines, antivirals and genetic data, but at the initiative of public authorities, it has simultaneously created new claims and proposals for the collective management of IP rights. Such management schemes have sought to work within flexible provisions in IP rights to produce generic drugs, to hasten the development of accessible medical technologies, or to make new rules between those countries that donate viral strains and those that produce vaccines for sharing more equitably the benefits of these new medical technologies.

Debates over intellectual property in the context of a menacing avian flu pandemic helped to facilitate the establishment of a new biopharmaceuticals economy populated not only by traditional actors (the WHO and pharmaceutical laboratories), but also new ones, including NGOs, countries of the global South, scientific consortiums and biotechnology firms. To be sure, this new biopharmaceutical regime not only characterizes the world of influenza research and medical technology development; it developed during the AIDS epidemic, and more generally flourished in the changing legal contexts of IP rights on drugs and life forms since the 1980s. But the threat of an avian influenza pandemic revived and updated it.

The spread of the H1NI flu pandemic in 2009 has raised questions about intellectual property and technology transfer that had earlier appeared between 2005 and 2007. Debate reverted to issues of unequal access to antivirals and vaccines in developing countries and the poorest countries. Discussions about antivirals focused on the role that generic drugs should play in combating the pandemic. The Indian generics producer Cipla and NGOs put pressure on the WHO to recommend the use of generics (Médecins Sans Frontières, 2009). The Third World Network criticized the WHO's antiviral reserve, arguing that the WHO was attempting to curry favour with pharmaceutical companies from which it sought donations to its stock of antivirals. MSF criticized the restrictive terms of the voluntary licences granted by Roche in India and China, which stipulated that generics produced in this framework could be sold only to the local government to address a ' risk of a pandemic'. Instead, the NGO recommended compulsory licences. Roche replied that Tamiflu could be reproduced freely in several countries of Southeast Asia where it was not patented (Thailand, the Philippines and Indonesia). In light of the extreme concentration of vaccine production in countries of the North, MSF called for an active transfer of production technologies to developing countries. In July 2009 at a conference of the WIPO (World Intellectual Property Organization), the WHO Director Margaret Chan navigated her way very carefully through the minefield of intellectual property and public health. Even as the flu pandemic was spreading, she refrained from mentioning the use of generics for antivirals, as did an earlier WHO report (2009). Chan also explicitly rejected the argument that intellectual property restricted vaccine availability. 'This shortage of vaccine supply', she asserted, 'faced with a universal need, is the result of a limited world production capacity. Basically, it is not the result of problems of intellectual property' (Chan, 2009). On the question of increasing the world's vaccine production capacity, the WHO pointed out that it had helped six producers in developing countries to acquire the technology (WHO, 2009). Médecins Sans Frontières again emphasized the link between the question of vaccine technology transfer and that of intellectual property, and urged the WHO to intervene in this respect: 'The WHO should give more support to the laboratories in developing countries that are ready to produce the vaccine, including by reviewing and proposing new ways of overcoming obstacles pertaining to IP and technological know-how' (Fournier, 2009). These discussions illustrate the new configuration of players in the struggle against flu epidemics: both traditional players such as the WHO and producers of vaccines and antiviral drugs in the North and new ones – generics laboratories of the global South, international NGOs and IP organizations (WIPO).

Notes

1 'This raises the question of the patent and this antiviral's patent rights. Are we going to agree to leave people to die because a firm has the exclusive right to a drug and blocks the production of generics?' CFDT, October 2005.
2 More precisely, the Tamiflu patent is the property of a US biopharmaceutical laboratory Gilead, which sold the rights on the molecule to Roche in 1996. In June 2005 Gilead tried to breach the licence contract with Roche, which it accused of not being engaged enough in the molecule's commercialization.
3 Yusuf K. Hamied, Managing Director (2005) *Business Standard*, 9 December.
4 'The Indian pharmaceutical company Cipla is first in line to make generic Tamiflu, but India's officials gesture despair at flu threat', *Global Forum for Health Research*, 21 October 2005.
5 *Indian Express*, 26 October 2005.
6 'No Roche patent here, India Inc can produce bird flu drug', *Indian Express*, 26 October 2005.
7 Decision dated 23 March 2009, Patent Office of Delhi.
8 'Indian industry pushing for compulsory licences for Tamiflu', *Intellectual Property Watch*, 25 October 2005.
9 'Indian industry pushing for compulsory licences for Tamiflu', *Intellectual Property Watch*, 25 October 2005.
10 D. G. McNeil (2005) 'Indian company to make generic version of flu drug Tamiflu', *New York Times*, www.nytimes.com/2005/10/14/health/14virus.html, 14 October.
11 Roche, Basel, 16 March 2006, Media release.
12 Roche, Basel, 16 March 2006, Media release.
13 The Swiss giant retorted that it had granted other companies rights on some of the ten stages of the Tamiflu production process, but that it was not prepared to give up its patent nor grant the entire manufacturing process to a third party (*La Tribune*, 12 October 2005).

14 'Countries seek to bypass Tamiflu patent', *Swissinfo*, 26 October 2006.
15 Yusuf K Hamied, *Global Forum for Health Research*, 21 October 2005.
16 Taiwan Info, site of the Ministry of Information, Republic of China.
17 'Thus, in the autumn of 2005, Ranbaxy, one of India's main generics firms, developed a production line for a generic Tamiflu'. *Financial Express*, 2 December 2005.
18 Yusuf K. Hamied, 'We will oppose the patent for Tamiflu', *Business World*, 20 October 2005.
19 *San Francisco Chronicle*, 13 October 2005.
20 'Recombinomics identifies American Sequences in the H5N1 Virus', *PR Newswire*, March 2006.
21 The HapMap – Haplotypes Map – is a catalogue of common genetic variants that occur in human beings. The HapMap consortium groups together the world's main centres of genome research: the US, the UK, Canada, Japan and China. Its policy for data dissemination is inspired by open source licences and is opposed to any patent that could limit free access to data produced by the consortium: 'The participants in the Project believe that patents should not be issued for a SNP or haplotype for which a "specific utility" – as defined in patent law – has not been generated. However, if a specific utility can be demonstrated for a SNP or haplotype, any group, whether associated with the Project or not, should be able to apply for a patent, as long as this action does not prevent others from obtaining access to data from the Project', International HapMap Project, Data Release Policy.
22 'Recombinomics identifies American sequences in the H5N1 virus', PR Newswire, March 2006.
23 Signatories, as of 23 August 2006, corrected 17 October 2006, GISAID Platform.
24 'Indonesia agrees to hand bird flu information to new online database' (Associated Press, 16 May 2008) and 'Indonesia's Minister of Health Announces the Launch of GISAID Database', Indonesia, 28 March 2007, GISAID Platform.
25 Max Planck Institute for Informatics, 'The Recent Outbreak of the Novel H1N1 Influenza: MPII Provides the Portal for Accessing the Relevant Viral Sequence Data', 28 April 2009.
26 'GISAID Launches Second Influenza Database', GISAID Foundation, 14 September 2009.
27 PCT Application WO2007051036, 3 May 2007.
28 The march-in-rights provision was included in the Bayh Dole Act to protect the public against unreasonable use of patented inventions stemming from state-funded research. It provided for suspension of a patent licence if the licensee 'has failed to make the product available to the public on reasonable terms' or if 'action is necessary to alleviate health or safety needs which are not reasonably satisfied by the current manufacturer' 18 USC Section 203(1)(b).2.

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10

Biosecurity in the Time of Avian Influenza, Vietnam

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In April 2009, Hanoi's World Health Organization (WHO) spokesperson congratulated Vietnamese authorities on their formidable mobilization against the new H1N1 epidemic, observing that, 'Given previous experiences dealing with both avian influenza and SARS, Vietnam already has many surveillance and early detection mechanisms in place'.[1] Vietnam had announced its H1N1 control measures immediately after the WHO raised its pandemic alert level; it instituted the surveillance of travellers disembarking in its international airports, the isolation of sick individuals, the notification of hospitals and laboratories to be on alert, and the creation of a hotline offering information about the new virus.

In line with the authorities, the Vietnamese press acted as if a new crisis were looming large and evoked the history of 20th-century influenza epidemics. While initially the Vietnamese government evinced uncertainty about banning pork imports, authorities subsequently opted not to provoke panic as they had in early 2004 during the avian influenza epidemic. Instead, they requested the media to inform the public about simple safety measures to take, such as cooking pork meat well. They also sought to reassure consumers that local and imported pork was subject to strict controls and thus safe to consume.[2] Moreover, they reported a short-term decline in pork consumption and in overall meat purchases, and the amplification of urban consumers' movement from traditional markets to supermarkets.[3]

In the H1N1 epidemic management, the Vietnamese authorities put into practice the four 'critical functions' of 'global health governance' identified by Nick Bingham and Steve Hinchliffe (2008): surveillance, protection, response (e.g. regulation of the movement of both goods and people), and public communication. In their study of Egypt's control strategy of avian influenza (AI), the authors suggested that biosecurity, a commonplace term now used by policymakers, is a 'world-making problematization'. This security regime has three major characteristics:

> *First, it concerns itself with regulating circulations, so that 'good things' (e.g. trade) or people (e.g. tourists) can continue or be encouraged to move while 'bad' things (e.g. viruses) or people (e.g. terrorists) are stopped or at least slowed down. Second, it proceeds by paying close attention to the material specificities of particular environments insofar as those specificities (from the global distribution of poultry farming to the network of international travel) represent opportunities or obstacles to the management of the aforementioned circulations. Finally, the biosecurity that we are describing here intervenes not by attempting to totally refashion the spaces in which we operate (imagining, for example, that it might be possible to completely eradicate certain sorts of diseases from the world), but instead by modulating or adjusting existing conditions such that the best possible conditions are in place for ensuring the future maximization of positive circulating elements (being well prepared for what the WHO describes as the 'inevitable' influenza pandemic) (Bingham and Hinchliffe, 2008).*

In this chapter, we suggest that Vietnam's strategy of AI control is embedded in global influenza governance, as defined by the three major international agencies: the WHO, the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE). After briefly describing the Vietnamese context, we shall discuss three issues. First, we will focus on the written media (*public communication*) and argue that the press, due to the central role it played within the biosecurity apparatus, has gained some autonomy concerning health issues. Second, we will deal with the restructuring of the farming system and of the distribution of poultry goods in line with the rationale of *surveillance* and *response*. Third, we will trace the history of poultry vaccination (*protection*).

Background

The *Đổi mới* (renovation) era, which began in 1986, initiated market-oriented reforms of a once state-controlled economy. In setting up a privately owned enterprise sector while retaining Communist Party rule, Vietnam followed the Chinese model. This private sector has been developed through the entry of foreign capital into state companies and the encouragement of domestic initiatives. Vietnam's entry into the World Trade Organization (WTO) in 2006 was the culmination of this process.

The reforms also profoundly affected Vietnam's health-care system. At first, the government reduced resource allocations to the medical service and then in 1987, partially privatized state-run health services and facilities, subsequently introducing user fees in the public sector (1989) and establishing mandatory health insurance for workers (1991) (Nguyen and Popkin, 2003). These liberalization policies were clearly double-edged, resulting in sharp overall declines in poverty and in morbidity from certain diseases like malaria and tuberculosis, but

also bringing about increased economic inequalities and health disparities between socio-economic groups and regions (Nguyen and Popkin, 2003; Fritzen, 2007).

One obvious consequence of such policies has been the shrinking of the state's direct hold over conduct within the privatized fields, and, thus, its greater need to lean on persuasion and to rely on the media to cultivate obedience. But authoritarian orders do not always persuade populations. Thus, despite the fact that the press continues to be supervised by the Party, it has gained some power and some freedom to manoeuvre within the sectors that are no longer under the state's tight control. This is especially true of the health sector, a fortiori in time of epidemic[4] (Figuié et al, 2008). Hence, one byproduct of the *Đổi mới* policies, particularly with the advent of avian influenza, has been that the state has somewhat loosened its grip over the media.

In the absence of government action early in the avian influenza epidemic, the press succeeded in carving out a somewhat autonomous role within the field of biopower. As we shall see, the press was a major actor in determining the timing of the disclosure of the epidemic's presence in Vietnam, which had until then been a state secret. The press was a driving force of government-issued information and an active partner in the production of norms, practices of surveillance and self-regulation.

An important evidentiary source for this study is the Vietnamese press. Among news sources in Vietnam, television commands the lion's share of audiences. Nevertheless, print journalists remain major actors in the country's media life. Over 600 print news publications constitute the press. The Vietnam News Agency (VNA), an official government organ from which the media generally draw for information, also edits several newspapers, among which are the *Vietnam News* and *Le Courrier du Vietnam*.

This chapter examines articles on avian influenza published on the websites of these newspapers and of other national newspapers between January 2004 and August 2009, such as *Tuổi Trẻ* (Young People) and *Thanh Niên* (The Youth). The latter are two highly popular newspapers edited by the Communist Youth Association.[5] In the course of several research trips to Vietnam, we also consulted other newspapers, including *Người Lao Động* (The Worker), *SàiGòn Giải Phóng* (Saigon Liberation), *Saigon Tiếp Thị* (Saigon Market) and *Pháp Luật Thành Phố Hồ Chí-Minh* (Ho Chi Minh City Law).[6]

The first AI outbreak began in mid-2003, but was officially declared in January 2004. This first outbreak was followed by additional waves.[7] Until October of that year, 111 AI human cases were registered, 56 of whom died.[8] The Vietnamese government took several major measures: the mass culling of poultry in areas stricken with AI; a ban on keeping, selling and eating chicken in big cities at particular times and locations; a ban on live poultry in cities and towns; strict regulation of poultry processing, conditioning, transportation and slaughtering; and,

since 2005, mass poultry vaccination campaigns (Guénel and Klingberg, forthcoming; Vu, 2009).

Communication during the epidemic

On 9 January 2004, the newspaper *Tuổi Trẻ* declared, 'Huge Numbers of Dead Chickens in the Mekong Delta: What Do MARD [Ministry of Agriculture and Rural Development] Leaders Say?' This headline was not only alarming to readers, but it heralded a substantial transformation in relations between the print media and the Vietnamese state. *Tuổi Trẻ* journalists had attempted to garner information on what seemed to be obvious signs of an avian epidemic from the Deputy Minister of the MARD the previous day, but without success. Indeed, the paper disclosed the government's efforts to cover up the epidemic:

> *On 8 January 2004, our reporters were present at the office of the MARD Deputy Minister Bui Ba Bông, the chair of the Committee for Avian Influenza Disease Control and Prevention (NSCAI), asking to interview him about the measures taken. Mr Bông was sitting in the back office ... and refused our request. We asked some questions as he was getting to his feet and turning toward the door.*
>
> *'Sir, what will the MARD do to address the massive deaths of chickens over the past several days?'*
>
> *'No, I will not answer. Journalists should go and ask these questions of the veterinary services.'*
>
> *'Sir, you are in charge of farming. Why won't you inform the public what has been happening to poultry?'*
>
> *'I will ask the Veterinary Service to organize a press conference and to invite all of the newspapers.'*
>
> *'Sir, if a farmer asked you to say one sentence about what the MARD would do concerning this poultry hecatomb?'*
>
> *'Enough is enough'.*[9]

The newspaper, however, did not relent, and on 10 January, it succeeded in obtaining some answers from the same Deputy Minister Bui Ba Bông, who was also asked to account for the government's delayed reaction to the epidemic.[10] The published article's title quoted his partial admission to the government's embarrassment over its handling of the epidemic: 'Public Opinion Saying That Government Was Slow To React Is Partly Correct'. In response to journalists' aggressive questions, the Deputy Minister tried awkwardly to explain the government's cover-up of the epidemic since August 2003, when tests had confirmed that avian influenza had precipitated massive avian deaths in June of that year. He claimed that information about a new disease would only be legally disclosed if the government had failed to control it.

In compelling this admission, the *Tuổi Trẻ* achieved what many newspapers seek: to force the state to admit to what it has sought to conceal. Its accomplishment was an impressive one, inducing the Vietnamese government to concede that an avian influenza outbreak was under way. Avian influenza thus offered the press an opportunity to demonstrate its usefulness and to mobilize its power[11] (Bingham and Hinchliffe, 2008). Although the press continued to criticize various targets throughout the epidemic, to our knowledge, there have been no other cases of such brilliant journalistic performance concerning AI.[12]

After this official declaration of an avian influenza epidemic, the print press coverage was both copious and alarmist. During the first half of February, the *Tuổi Trẻ* was replete with fearful reports about the epidemic's spread throughout the country and the world, appalling accounts of rivers as huge drifting cemeteries for fowl, official statements about the impending dangers of avian influenza, warning against poultry consumption. It had gone so far as to devote a special daily column to avian influenza. In its 6 February issue, an article detailed the hecatomb in the Mekong delta provinces, noting, 'Watercourses are polluted by chicken carcasses. People are lining up to kill off their chicken, duck, quail... They rapidly throw the animals into the rivers, tributaries, ponds, and lakes.' The article continued by describing desolate scenes in which foul-smelling bird carcasses floated into irrigated paddy fields and rivers that supplied drinking water.

During this period, the press also signalled the threat of meat shortages and the increasing importance of commercial livestock suppliers in reversing these shortfalls. One 12 February article in the *Vietnam News* reported, for instance, that:

> *With the end of the bird flu epidemic nowhere in sight, food companies have been instructed to stock food and livestock to head off any possible shortage, a trade ministry official said. The official, who wished to remain unnamed, said that with the avian influenza situation remaining complicated, meeting demand for meat in the next few months is a priority.*[13]

But by March 2004, the alarmist tenor of print media reporting had changed somewhat. In addition to fewer frightening descriptions of dead fowl, the press printed more reassuring predictions of the epidemic's control. A 3 March *Vietnam News* story, for instance, proclaimed 'Bird flu outbreak partially contained', and quoted the spokesperson for the National Steering Board for Avian Influenza Control, Bui Quang Anh, who stated, 'We are preparing to declare the country free of the outbreak.' The story also noted that the People's Committee in Ho Chi Minh-city announced chicken sales would resume on 5 March.[14]

Other optimistic declarations quickly followed this pronouncement. On 4 March, a *Vietnam News* story reported the Prime Minister Phan Van Khai announcing that 'bird flu had been contained', although he warned of 'a risk the disease could reemerge and urged agencies to sustain their preventive measures'.[15]

The same story noted that the Animal Health Department expected the country to be influenza-free by the end of March. On 10 March, health officials observed that no new avian influenza cases had been detected in chickens for over a week, and a Ministry of Health official declared that Vietnam would be considered AI-free as no new cases were discovered during 20 days.[16] And nine days later, *Vietnam News* announced that, 'HCM City declares end to flu, resumes poultry trade.'[17]

Contrary to the official Vietnamese News Agency, *Tuổi Trẻ* was much less complacent about the AI government declarations. Although constrained from launching a direct attack on Vietnamese authorities, the paper opted instead to voice criticisms by quoting one WHO representative in Asia, who cautioned that the dangers of avian influenza still existed throughout the continent.[18]

With almost every new AI outbreak, a pattern of journalistic reporting emerged in which newspapers would initially publish alarming announcements of new cases and then follow with declarations celebrating the Vietnamese control strategy; however, over the years, the pattern became less pronounced. On the one hand, reports over time became less alarming and dramatic, since epidemic management became a routine, and AI human cases were isolated and small in number. All these factors thus reflected a reduced threat of a human pandemic, at least in the near future. On the other hand, illusions about a rapid victory had already been shattered in the course of the year 2004. By October, media reports had grown so subdued about the prospects of immediate eradication that they and their government sources openly acknowledged the very high risk of recurrence. The MARD Minister Lê Huy Ngo candidly admitted that although bird flu was diminishing, it had not disappeared altogether.[19] During the fifth AI wave in late March 2007, for instance, after a veterinary department official stated that no new cases had been declared in the past 22 days, the VNA dispatch headlines referred to a Deputy Minister of MARD's humble statement, declaring, 'It is not yet possible to declare the end of avian flu.'[20]

In order to reassure the Vietnamese public that they had adopted the most effective and appropriate control strategy, the authorities and newspapers worked in concert and increasingly resorted to quoting foreign sources, who described Vietnam's epidemic management in laudatory terms. Official modesty contrasted with international experts' fulsome praise of the Vietnamese avian flu strategy. The VNA prominently quoted James Adams, vice-president of the World Bank in the Asian Pacific, who observed that Vietnam had developed 'the model of ... struggle [against avian influenza]' now applied in some 30 countries, and that this model was 'worthy of being reproduced'.[21] Numerous articles in other newspapers documented government control measures, their implementation, and at times their mismanagement or corruption in this process.

As we have shown, the print media pushed the state to ease its close watch over journalistic expression. But the Vietnamese state also had a vested interest in slackening its control over the press. With their lively and engaging writing, journalists were far better at communicating government messages than state officials. Moreover, with only a few exceptions, the central government welcomed the print media's aspersions on local authorities, technicians or employees. The papers reported almost every new outbreak as the result of local officials' failure to observe preventive measures, conveniently enabling national authorities to sidestep any blame. And finally, permitting some press freedoms has allowed the state to burnish its image as a resolute modernizer (Guénel and Klingberg, forthcoming).

For its part, the press used these new freedoms to champion government epidemic control strategies, with long-term consequences for Vietnamese society and economy. To be sure, Vietnamese newspapers audaciously confronted high government officials for their secrecy and contradictory efforts, and they sympathized with small peasants wronged by local authorities and even national policies. But they have simultaneously supported government control strategies that 'modernized', 'restructured' or 'rationalized'. Given the fact that during the AI crisis the media had acquired a certain degree of autonomy, we suggest that this support should not be read as mere press compliance with government priorities. Rather, as the following section will show, a consensus developed between the Vietnamese government, the press and international health and agriculture institutions around the promotion of industrial farming, processing and distribution. This consensus espoused specific interest groups pushing their own agenda: agribusiness and supermarket corporations.

Producing and marketing in time of epidemic

When first confronted with the epidemic, the Vietnamese government had no relevant model of successful avian influenza control to follow. Several years earlier in 1997, Hong Kong, the international financial centre of just over 1000 square kilometres, had undertaken a simple, radical and astonishingly effective measure to stop avian influenza transmission: it culled all chickens.[22] But the Hong Kong model, however tempting, was impossible to impose on a country like Vietnam, whose area is over 300 times that of Hong Kong.

We argue that since Vietnam has scrupulously followed the recommendations of international agencies, its AI control strategy was promoted as a model by the latter. In this section, we detail the conception and policy of the FAO, WHO and the OIE concerning AI surveillance, how it was implemented by the Vietnamese government, and its socio-economic repercussions.

The three major international organizations (WHO, FAO and OIE) strengthened their coordination and attempted to build a new world order with a global health governance, whose most important task is surveillance. The very nature of

avian influenza makes its control an insuperable undertaking. Migratory bird populations can be infected with AI, and they can potentially transmit it to domesticated fowl. Although there appears to be considerable dispute about whether migratory fowl present a real danger to domesticated poultry, both the FAO and WHO have actively promoted the notion that migratory birds transmit H5N1, infecting fowl along their routes. While a 2006 *Lancet* editorial (entitled 'Avian influenza goes global, but don't blame the birds') conceded that migratory birds had probably introduced the virus to Europe, it also observed that:

> *despite extensive testing of wild birds for the disease, scientists have only rarely identified live birds carrying bird flu in a highly pathogenic form, suggesting these birds are not efficient vectors of the virus. Furthermore, the geographic spread of the disease does not correlate with migratory routes and seasons. The pattern of outbreaks follows major roads and rail routes, not flyways.*[23]

Following the same surveillance rationale, the international agencies had a marked preference for large-scale poultry farms. The WHO identified backyard poultry farms as sources of human infection.[24] Small-scale animal husbandry is the common mode of farming in Southeast Asia and in Vietnam. Monitoring a few large poultry farms may have appeared far more manageable than inspecting many small ones. It is noteworthy that prior to the epidemic, family farms constituted 65 per cent of Vietnam's national poultry production (Delquigny et al, 2004). The FAO, which had previously encouraged small-scale domestic poultry farming, embraced WHO's recommendations. As FAO Assistant-Director General Louise Fresco declared, 'There are countries which are quite overwhelmed by what is happening, a case in point being Indonesia where we have probably 1 billion backyard chickens... The real work has to be done in the backyards in Indonesia, in the waterways of the Mekong Valley.'[25]

The major problem with favouring commercial poultry production was available evidence – published by the FAO itself – that chickens in large-scale commercial facilities had a *higher* risk of avian influenza infection than those on backyard farms (Otte et al, 2006). The AI aetiology is the object of various narratives, one of them suggesting that 'the international movements of birds and products from factories that have made the chicken the most mobile birds on the planet are deeply implicated in the disease network' (Bingham and Hinchliffe, 2008).

The public health policy promoting factory farms clearly dovetailed with the interests of commercial producers and processors. The Southeast Asian director for the USA Poultry and Egg Export Council remarked, 'We cannot control migratory birds but we can surely work hard to close down as many backyard farms as possible' (GRAIN, 2006) – a move that would strengthen the position of large-scale poultry farms.

Vietnam's AI control policy carefully aligned itself with the international agencies' strategy, particularly with respect to restructuring the poultry breeding sector. The government, particularly the MARD, recognized in the beginning that culling poultry reflected a certain arbitrariness, since small farms were relatively safe, as indicated by an early *Thanh Niên* news report that no avian influenza cases had been detected on a family farm. State officials realized, moreover, that mass culling would destroy an important source of income for peasants. But following the initial outbreak, the government proceeded by designating particular regions of the country as specialized areas of production,[26] and shortly thereafter, by encouraging restructuring of breeding farms for industrial-scale poultry production.[27] The results would be devastating to small-scale farmers; even the FAO, which had supported these measures, acknowledged that a million small-scale poultry farmers would lose a significant source of income (McLeod et al, 2005).

Less than a month after the official declaration of the epidemic, the *Vietnam News* noted that Hanoi had adjusted its earlier culling policy, by 'spar[ing]... the lives of healthy poultry living less than 3km from areas infected with avian flu' because 'the old policy of destroying all birds within 3km of an outbreak was causing many farmers to suffer heavy losses'. Indeed, the Minister of Agriculture observed that 'birds on many farms close to infected areas stayed healthy because farmers adopted careful methods of isolation...' As the chair of the National Steering Committee to control avian flu noted, 'The policy to slaughter all poultry [within a 3km radius of an outbreak], as was being done, was not practical *because most of the birds are raised on small farms*' (our emphasis).[28]

Nevertheless, Vietnamese authorities continued to encourage factory farming to the detriment of backyard peasants. And as early as March 2004, commercial poultry processors anticipated that new regulations to curb the epidemic offered a valuable opportunity. The Deputy Director of the Agricultural Engineering Mechanics and Post-Harvest Technology Institute suggested that, '[p]rocessing enterprises should grasp the chance to modernise their production lines...'[29]

The result of culling, of a ban on urban live poultry markets (where backyard-raised poultry were sold), of reorganized slaughter houses and large-scale processing was a step towards the wholesale commercialization of poultry production and marketing. In 2006, the *Thanh Niên* stressed government changes in poultry marketing, indicating that it had:

> *propose[d] ... to alter the way that chicken, a major food, changes hands. It is phasing out the markets where consumers choose live birds and have them slaughtered, and substituting birds killed in a modern slaughterhouse and sold shrink-wrapped and chilled in supermarkets.*[30]

A 2006 study conducted in Ho Chi Minh City (the country's largest food market) after the avian influenza epidemic interviewed some 704 consumers and found a decrease in poultry consumption, as well as less poultry sold in market stalls and more poultry appearing on supermarket shelves[31] (Phan Thi Giac Tam and Reardon, 2007).

One mid-2009 article in the *Vietnam News* recounted Vietnam's inexorable movement toward supermarkets. The author, relying on statistics supplied by the Ha Noi Supermarkets' Association, described the rise of large, self-service stores and the decline of traditional open markets. In 2000, supermarkets accounted for some 6 per cent of retail sales, while in 2009, supermarkets had quadrupled in number and now accounted for 16 per cent of these sales.[32]

By mid-2009, then, the government measures to control avian influenza had also had a considerable impact on the marketing structure of poultry, as well as on consumer choices. Consumers clearly eschewed traditional markets in favour of supermarkets because they were more convenient, had longer opening hours, and offered a wider range of safe, hygienic and well-priced products. This movement was facilitated by the press, it seems. In 2009, just before the New Lunar Year, *Thanh Niên* and *Tuổi Trẻ* informed the public that it could purchase 'safe food', including chicken, a traditional dish during the Têt celebration, in the supermarkets and went so far as to list the prices of different supermarket brands.[33]

To vaccinate or not to vaccinate?

In order to protect its fowl, Vietnam also had to decide on whether to undertake mass vaccination of poultry. Here, too, it followed the lead of international biosecurity agencies. As early as February 2004, a conference of experts from international organizations, including the FAO, WHO and the OIE, met in Rome to discuss poultry vaccination.[34] The FAO advocated 'targeted vaccination', arguing that it 'might limit the need for mass sacrifice of flocks outside infected sites, and reduce economic damage'. WHO authorities expressed some reservations about this strategy, estimating that vaccination was only 'a complementary tool', not by itself 'sufficient ... to bring the present outbreaks in poultry under control'. WHO chief influenza expert, Klaus Stohr, argued that poultry vaccination had considerable disadvantages, since only 50 per cent of birds stop shedding virus after vaccination. 'In the longer term,' he opined, 'these birds will continue to excrete the virus and if these birds are moved, they might look completely healthy but they might continue to spread the disease.'[35]

As new outbreaks affected several Asian countries, the FAO, supported by the OIE, revived the debate in late September 2004, indicating that 'countries wishing to eradicate the disease *may choose* to use vaccination as a complementary measure to the stamping out policy' (our emphasis) and published new guidelines.[36] But

country strategies varied. Thailand, the world's first frozen chicken exporter, had already announced weeks earlier that its poultry would not be inoculated against the disease because vaccines offered no guarantee of safety. Simultaneously, Chinese authorities reinforced poultry immunization in some regions.[37] Vietnam, rather than declaring officially its stance to FAO/OIE recommendations as Thailand and China had done, decided to wait for incentives and financial guarantees before making a decision. It appears that some local experiments were carried out before the government took its stand. *Tuổi Trẻ* reported one in Ho Chi Minh City. Despite its apparently satisfying results, the experience was interrupted following local authorities' protests and scientists' objections about the vaccine's uncertainties and the risks of virus mutations.[38]

Tuổi Trẻ was again the first newspaper to report on new efforts to control avian influenza. Following the February 2005 Asian avian influenza conference convened by the FAO and OIE to boost Asian governments' avian influenza control policies, the paper published an interview with the MARD Minister, Cao Duc Phat. Recounting conference discussions about free-range duck flocks (particularly in the Mekong delta) as dangerous sources of infection, the Minister revealed for the first time that the Vietnamese government was studying domestic fowl vaccination as part of a 'concrete plan of action' that could elicit foreign economic aid. To this revelation, the journalist appended his own commentary, sustained by observations of experts attending the conference about the potential dangers of bird vaccination.[39]

But expert opinion was far from united. Other foreign experts emphasized the advantage of poultry vaccination, due to 'the extremely high amounts of virus in the Mekong delta region and the farmers' reluctance to kill their birds'. 'You can't expect farmers to give up their birds at 50 cents', observed Dave Halvorson, an American professor at the Veterinary Biomedical Sciences Department at the University of Minnesota. 'When you're dealing with people whose incomes may be $5 or $6 a day', he continued, 'how do you motivate them to give up their livestock? It's not possible.'[40]

In the months that followed, observations like these helped to strengthen international agencies' support for vaccination. The FAO and OIE announced mass culling as the main means of control is no longer acceptable 'for ethical, ecological and economic reasons' and called for US$100–120 million to assist poor countries in developing their vaccination programmes.[41] Subsequently, WHO fully subscribed to poultry vaccination as one of three pillars of an avian influenza control plan defined by international health agencies in 2005. The other two were the education of small-scale farmers and the segregation of animal species (FAO, 2005).

With international agencies' backing, the Vietnamese authorities now accelerated vaccine testing. After the encouraging results obtained with first inoculations of chicken in the northern province of Hà Tây (March 2005) and of Mekong delta duck flocks (April 2005), the launching of a nationwide vaccination

campaign was declared in June of the same year. The plan was to begin the campaign in August in two heavily affected provinces, Nam Dinh in the north and Tien Giang in the Mekong delta, and then to extend the campaign to 40 other high-risk provinces over the following two years. Poultry in both commercial poultry plants and small household farms would be vaccinated, and small farms were offered incentives to encourage their industrialization.[42]

Despite some delay in the vaccination schedule, in mid-October, 32 provinces and cities were reported to have completed the first round of mass poultry vaccination; in the Nam Dinh and Tien Giang provinces, where the campaign had been initiated, poultry had received two shots of vaccination.[43]

Just as the Vietnamese were welcoming the new lunar year (the year of the Rooster!) in January 2006, the Deputy Director of the National Department of Animal Health, Hoang Van Nam, triumphantly declared 'Vaccination works!' The trial had shown that about 80 per cent of vaccinated poultry had developed some immunity to the H5N1 virus. He added that, 'no outbreaks were reported in areas where poultry were given two shots of vaccine'.[44] The 2006 vaccination campaign, launched from February to July, covered all Vietnam's provinces. That year there was a relative lull in H5N1 outbreaks among poultry, and no human victims. According to the Director of the National Institute of Health and Epidemiology, Nguyên Trân Hiên, mass poultry vaccination had at least partly accounted for the improved situation. While the virus had not disappeared altogether, he observed, its concentration was insufficient for propagation.[45]

Nevertheless, controversy over poultry vaccination continued among Vietnamese scientists. Two senior scientists from the same department of Ho Chi Minh City Pasteur Institute, for example, expressed divergent opinions about its efficacy.[46] Objections to poultry vaccination ranged widely. Some scientists raised concerns about the lack of specificity of certain vaccines used during the campaigns.[47] Others argued that vaccinating all domestic fowl was useless, because it required two injections over the very short lifespan of a bird.

Recurrent avian influenza outbreaks, some of which afflicted new human victims in 2007 and after, offered some support for opposition to vaccination. The print media mostly blamed any reports of its inefficacy on poorly implemented vaccination campaigns, false certificates and the like. But it also tackled more fundamental questions. In the aftermath of a recent death whose suspected cause was avian influenza, *Tuổi Trẻ* provided on 16 June 2007 a detailed report of a debate between a Ho Chi Minh City Pasteur Institute scientist and a representative of the local veterinary service. On the basis of a comparison between countries adopting poultry vaccination (Vietnam, China and Indonesia) and those that had not (Thailand, the Philippines and Cambodia), the Pasteur scientist concluded that vaccinating countries had no fewer outbreaks of AI among poultry and thus were no better off than non-vaccinating ones.[48] The article suggested, however, that the debate was far from settled. Indeed, its writers invoked

the expression *thac mac* ('to be still unclear about a point, to worry, to be uneasy, to be at cross-purposes') (Kim Ngoc Bao Ninh, 2002, p122) to signal to readers that debate was not completely closed.

Still, the FAO continued to strongly recommend vaccination. Acknowledging the difficulties involved in this mass strategy, it also recommended the structural transformation of farming.[49] Nevertheless, by 2008, the FAO had altered its recommended vaccination strategy, advocating age-selective vaccinations throughout the year, instead of mass poultry vaccinations twice a year.[50] Sure enough, two months later, the press echoed these recommended changes, as revealed in a *Thanh Niên* article entitled, 'Vietnam urged to change anti-bird flu vaccination program'; and the Vietnamese government took the decision to experiment with this new vaccination strategy.[51]

Conclusion

Although in the initial phase of the first AI outbreak, Vietnamese authorities did not declare a public health emergency overall, they sought to carry out international biosecurity agencies' recommendations to the letter. This strategy fitted with the country's general politics of global market integration. It is noteworthy that Vietnam applied for admission to the World Trade Organization (WTO) prior to the first AI outbreak and successfully gained entry to this institution in 2006. WTO admission required significant changes in Vietnamese poultry distribution and marketing.

As we have shown in this chapter, however, global health governance has to a certain degree been called into question, by encouraging factory farms to the detriment of backyard farms and using mass poultry vaccination. Its flaws are all the more striking in the case of Vietnam, which was designated as a model by the international health and agriculture agencies. Furthermore, AI management did not simply entail new rules for the regulation, production, processing, transport and conditioning of fowl. It also aimed at changing the 'really basic behaviour that people have been engaged in all their lives', as one Hanoi-based WHO epidemiologist observed, 'It is going to be a slow process... As the H5N1 outbreak expands, planners worldwide are acknowledging that scientific and political efforts to control the virus will fail unless they are accompanied by willing cultural change. Vietnam's attempts to create that change are being closely watched.'[52]

This cultural change, a component of the biosecurity regime whose principal agent is the press, began before the AI outbreak and accelerated during the epidemic. The biosecurity regime extends well beyond poultry production and consumption, for it permeates the entire food sector. In early August 2009, a *Thanh Niên* headline read, 'HCMC bans informal trade in fresh food: Ho Chi Minh city authorities have banned with immediate effect trading in fresh food

outside formal retail channels in a bid to improve food safety and tighten control over food trading in the city.' These regulations would shut down 'spontaneous markets' or 'makeshift shops', according to city authorities. Official statements, widely diffused by the press, abound with antonyms of such descriptors as 'clean', 'tidy' and 'supervised'. The document detailing the new regulations 'aims to put an end to trading in *unhygienic* food and *illegal* occupancy of the street and sidewalks by many *unregistered* small traders' (our emphasis), summarized Truong Trung Viet, the deputy director of the municipal Department of Industry and Trade at a press briefing. As for household businesses, they may engage in the food trade, provided that they meet safety requirements, register with relevant agencies, and take a training course on food safety. At present, there are 238 legal retail markets and three registered wholesale markets. Plans exist to further transform Ho Chi Minh City, with local authorities exercising greater control over the food trade.[53]

Notes

1 *Thanh Niên*, 28 April 2009.
2 *Thanh Niên*, 29 April 2009.
3 *Người Lao Động*, 4 May 2009. The fact that the new virus came from afar increased consumers' preference for local pork meat.
4 Even before the AI, the press quite frequently reported health hazards and especially cases of food contamination.
5 The popularity of these two newspapers results partly from the fact that Vietnam has a highly youthful population, in which over 60 per cent are under 30. The appeal of these two papers lies primarily in their more relaxed and youthful language, contrasting sharply with the administration's stereotypical, formalized rhetoric. We consulted all these papers on their websites. We used the English version of *Thanh Niên*, and generally a French version of *VNA*. As for articles from *Tuổi Trẻ*, quotations were translated from Vietnamese.
6 Quotations from these newspapers, except *Vietnam News* and *Thanh Niên* were translated by us.
7 1st wave: mid-2003–March 2004; 2nd wave: July–November 2004; 3rd wave: December 2004–April 2005; 4th wave: October–December 2005; 5th wave: December 2006–November 2007; 6th wave: December 2007–March 2008; 7th wave: September 2008–April 2009. Outbreaks were declared in the northern Dien Bien Province in early November 2009.
8 www.who.int/csr/disease/avian_influenza/country/cases_table_2009_09_24/en/ index.html.
9 *Tuổi Trẻ*, 9 January 2004.
10 *Tuổi Trẻ*, 12 January 2004.
11 The AI outbreak in Egypt was an occasion for a parliamentary committee to strongly criticize the authorities for their management of the epidemic.

12 It is worth noting that the state has more recently cracked down on journalistic freedom. In 2008, reporters of *Tuổi Trẻ*, *Thanh Niên* and other newspapers had been subjected to repressive measures, including the revocation of press cards, prosecution and heavy prison sentences for violating regulations on media or 'infringing the interests of the state, the legitimate rights and interests of organizations and/or citizens'; see www.queme.net/eng/doc/UPR_Vietnam_2009_English.pdf.
13 *Vietnam News*, 12 February 2004.
14 *Vietnam News*, 3 March 2004.
15 *Vietnam News*, 4 March 2004.
16 *Vietnam News*, 10 March 2004.
17 *Vietnam News*, 19 March 2004.
18 *Tuổi Trẻ*, 16 March 2004.
19 *Le Courrier du Vietnam*, 27 October 2004.
20 VNA, 30 March 2007.
21 VNA, 7 February 2007.
22 The measure's architect, then Hong Kong Director of Health Margaret Chan, was later promoted to serve as the Director-General of the World Health Organization.
23 *Lancet Infectious Diseases*, vol 6, 2006, p185. It is interesting to note that a report published by an Egyptian parliamentary committee stated that 'contrary to WHO aetiology they had found no scientific evidence that migratory birds brought the virus to Egypt' (Bingham and Hinchliffe, 2008, p187.
24 www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html#isthere; *Responding to the Avian Influenza Pandemic Threat*, WHO/CDS/CSR/GIP/2005.8.
25 www.publications.parliament.uk/pa/ld200506/.../88/88.pdf.
26 *Vietnam News*, 25 March 2004.
27 *Vietnam News*, 8 May 2004.
28 *Vietnam News*, 13 February 2004.
29 *Vietnam News*, 12 March 2004.
30 *Thanh Niên*, 31 October 2006. Such a change was not easy to implement, given consumer preferences. Muriel Figuié's 2004–2006 study of consumer poultry preferences in Hanoi and the Hà Tây rural province (Red River Delta) found that consumers believed backyard poultry raised by known farmers or relatives were both tastier and safer than industrially produced chickens (Figuié et al, 2008).
31 Yet one should underline that variations persisted according to social stratum and distance from the city centre, where supermarkets are located. Thus, before and after the AI epidemics, purchasing poultry products in supermarkets sharply increased by income and decreased by distance from city centre (city centre and middle belt vs. peri-urban) (Phan Thi Giac Tam and Reardon, 2007).
32 'Supermarkets hit small shops', *Vietnam News*, 23 July 2009.
33 *Thanh Niên*, 7 January 2009; *Tuổi Trẻ*, 12 January 2009.
34 www.fao.org/newsroom/en/news/2004/36647/index.html.
35 There was a special reference to a report published by *the New Scientist* in January 2004. It suggested that the vaccination of flocks by Chinese poultry producers after the 1997 H5N1 outbreak in Hong Kong may have permitted the virus to replicate without causing symptoms, enabling it to spread without being noticed.

36 www.fao.org/newsroom/en/news/2004/50961/index.html. While the FAO, supported by the OIE, said that the slaughter of infected animals still most effectively controlled the disease, it recognized that this measure was neither practical nor adequate in some countries.
37 See *Chinese Daily*, 29 September 2004, quoted in *CIDRAP News*, 29 September 2004.
38 The paper quoted the opinion of a virologist who stressed the necessity of a careful preliminary study concerning the type of vaccine used as well as vaccination strategy. The MARD would apparently nominate a special commission for this purpose. *Tuổi Trẻ*, 15 January 2005.
39 *Tuổi Trẻ*, 26 February 2009.
40 *CIDRAP News*, 13 April 2005 (Becker, A. L., 'Avian flu widespread in Vietnam flocks: Experts push vaccines'), www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/april13avflu.htm.
41 *CIDRAP News*, 13 April 2005 (Becker, A. L., 'Avian flu widespread in Vietnam flocks: Experts push vaccines'), www.cidrap.umn.edu/cidrap/content/influenza/avianflu/news/april13avflu.htm.
42 Small farm flocks were vaccinated free; a portion of the fees was charged to industrial operators, while the rest was subsidized by the government. *Thanh Niên*, 30 June 2005; 15 July 2005.
43 Small farm flocks were vaccinated for free; part of the fees was charged to industrial operators, the rest being subsidized by the government. *Thanh Niên*, 30 June 2005; 15 July 2005.
44 *Thanh Niên*, 24 January 2005.
45 *Tuổi Trẻ*, 4 December 2006.
46 Personal interviews, January and December 2008. The scientist in favour of vaccination considered that the mass campaign which started in 2005 saved Vietnam from 'the end of the world'.
47 The campaigns used vaccines imported from China (Harbin Institute) and from The Netherlands (Cie Merial). At the beginning, anti H5N1-vaccines were mainly reserved for ducks. Anti-H5N9 and anti-H5N2 vaccines were used to inoculate the chickens.
48 *Tuổi Trẻ*, 16 June 2007.
49 *Thanh Niên*, 19 June 2008.
50 As Tony Forman declared to the *Thanh Niên* reporter, 'Up until now, vaccination has been based on two campaigns each year, which is logistically the easiest way to implement a big vaccination, but technically it is not the most efficient way to immunize all the poultry because they're not all being vaccinated at their best age.' *Thanh Niên*, 16 August 2008.
51 *Thanh Niên*, 16 August 2008.
52 *Thanh Niên*, 31 October 2006.
53 *Thanh Niên*, 11 August 2009.

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Comment: Ethics and Epidemics: Reflections on Contemporary Stakes in Transparency and Equity

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This contribution is a wide-ranging comment on the three preceding chapters. Written in early January 2010, it proposes some reflections generated by these three papers concerning the ethical stakes in pandemics in general, and on influenza in particular. Whether they consider events dating to almost a century ago (the problems of quarantine during the pandemic of 1918) or more recently (the subject of avian influenza), the three chapters concern questions that remain entirely debatable today.

In reading these texts I suggest two angles of reflection: first, transparency in the rationality of decisions; and second, equity of access to resources.

Transparency and rationality: Two ethical public health principles

It is now a platitude to observe that political decisions undertaken within the framework of prevention or of efforts against pandemic influenza are supported simultaneously by public health's primary objective and by scientific expertise. But everything becomes more complex when one wonders exactly what the primary purpose of public health is, and when one accounts for the content and power of experts' scientific discourse. When the ideal 'the best health for the greatest number' cannot easily be achieved without tensions or contradictions – that is, without a certain price to pay – then public health decisions essentially become political reflections, and medical knowledge constitutes just one tool in those reflections. The analysis of the decision making modalities concerning the restriction of movement during the 1918 pandemic presented here (Giles-Vernick, Craddock and Gunn) is exceptionally clear about the 'natural limits' of

scientific discourse. The logics of scientific epidemiology is necessarily the focus of successive, sometimes contradictory, interpretations. Scientific discourse is not the sole actor in this decision-making scenario. The reasoning guiding political choices in establishing restrictions on individual liberty are multiple: scientific, but also social, political and economic. This first layer of complexity in rational public health choices is further compounded by the second, which lies within the epidemiological expertise. Epidemiology does not provide certainties during an epidemic, but is based more on descriptions of uncertainty about what might possibly occur. Although our surveillance and modelling tools are better today than they were in 1918, public health expertise is still marked by great uncertainty. In presenting epidemiological models of Influenza A/H1N1 at an international meeting of the WHO on 13 November 2009, Neil Ferguson (one of the world's prominent public health specialists) insisted on the inability of models to make predictions in real time (Ferguson, 2009). An understanding of the reasoning behind public health choices within the framework of a pandemic requires us to account for these two layers of complexity.

There is general consensus concerning the ethics of public health, in particular about the importance of transparency and rationality in collective emergencies (Daniels, 2000; University of Toronto Joint Centre for Bioethics Pandemic Influenza Working Group, 2005; WHO, 2007; Daniels and Sabin, 2008; O'Malley et al, 2009). Daniels and Sabin initially developed the notion of *accountability for reasonableness* while reflecting upon the ethics of distributing limited health care resources. This notion has been adopted and assimilated into a more general framework concerning public health decision making. The brief definition that Daniels and Sabin offer follows:

> *Accountability for reasonableness is the idea that the reasons or rationales for important … decisions should be publicly available… Specifically, a rationale [of a public health decision] will be reasonable if it appeals to evidence, reasons, and principles that are accepted as relevant by fair-minded people who are disposed to finding mutually justifiable terms of cooperation.* (Daniels and Sabin, 2002)

Their approach to this principle involving both the legibility of public health decision making and public involvement would be taken up again, most notably by the Joint Centre for Bioethics in Toronto, and then by the WHO in their respective reports *Stand on Guard for Thee* and *Ethical Considerations in Developing a Public Health Response to Pandemic Influenza* (University of Toronto Joint Centre for Bioethics, 2005; WHO, 2007). In the WHO document, for instance, the chapter concerning general ethical considerations contains this observation:

> *Public engagement and involvement of relevant stakeholders should be part of all aspects of planning. Policy decisions and their justifications should be publicized and open to public scrutiny.*

A population may well find common public health interventions such as quarantine or prioritization of access to preventive or treatment measures difficult to accept. But popular support for such measures will depend greatly on the trust that a population has in its authorities. Special attention paid to transparency is one of the important conditions that create this trust.

The chapter about the role of the media in managing the H5N1 epizootic in Vietnam (Guénel and Klingberg) contains a fascinating illustration – and without a doubt an exemplary one – of one newspaper's (*Tuoi Tre*, 16 June 2007) effort to communicate uncertainty about the efficacy of poultry vaccination policies. In this case, journalists sought to translate and disseminate scientific knowledge to the public, rendering perfectly clear the ongoing debate between experts over the most appropriate measures against the spread of the H5N1 virus. This example serves as a counterpoint to examples mentioned by Giles-Vernick, Craddock and Gunn, which illuminate what the authors have judiciously called a process of the 'mapping of certainty onto deeply unpredictable [epidemiological phenomena]'.

Guénel and Klingberg's analysis of the media's function in Vietnam richly illustrates several political and sociological dimensions. Most notably, their investigation constitutes an invitation to consider the media's functions, mediations, communication of scientific information, and actors during a public health crisis.

How, then, might we understand the H1N1 pandemic from April to December 2009 in light of these insights about transparency? My sense is that the 'transparency' of justifications for public health decisions constituted an important general concern, as well as a multilateral (WHO, for instance) and national preoccupation. But at the same time, it was a patent failure in many respects. The notion of 'transparency' should be considered in all its complexity; it cannot be reduced to the media's reactions in the face of medical and scientific knowledge.

Two examples can be productively examined. The first involves the politics of vaccination in countries that had them. Vaccination coverage in these countries was highly variable; it proved to be very low in France, where full-scale vaccination had been anticipated (Clavreul, 2010). This simple admission is sufficient for us to understand that the conditions under which a society accepts the usefulness of a vaccine are so complex that a vaccine can be perceived at one moment as a useless danger, and at another, as an indispensable product. At the end of 2009, Nicole Lurie rightly observed:

> *Effective communication with the public is central to any public health emergency response. The widespread misunderstanding of vaccine safety and effectiveness speaks to the need to improve not only safety science but also communication science – to enhance our ability to reach and educate the public, especially those who are at highest risk for disease.* (Lurie, 2009)

A second example concerns the use of the antivirals oseltamivir and zanamivir, known by their commercial names as Tamiflu and Relenza. Recommendations

concerning the use of these drugs were subject to numerous modifications and adaptations between April and December 2009. The changes resulted from the real-time analysis of new evidence over time. And yet, the integration of this new knowledge (composed of certainty and uncertainty) proved to be particularly complex. Communication with the wider public about antivirals, which also took place in real time, introduced an impossible pedagogical exercise, one that could not be resolved. In effect, we remain too wedded to a univocal approach, too positivist in our conception of responses to a crisis. This is particularly characteristic of the medical domain. A medicine is either good or bad, indicated or contraindicated. The 8 December 2009 edition of the prestigious *British Medical Journal* (*BMJ*) reported a lack of proof of oseltamivir's (Tamiflu) efficacy in reducing the number of hospitalizations. These reports raised critically important discussions in the press about the validity of using oseltamivir, about the importance of creating antiviral stocks, and about the efficacy of antivirals in general. For the public, these *BMJ* articles (Doshi, 2009; Freemantle and Calvert, 2009; Godlee and Clark, 2009; Jefferson et al, 2009), which scrupulously examined available data available on the clinical effects of oseltamivir, appeared as a sort of quasi-detective investigation of Roche, with the direct support of the media: Channel 4. An online article, entitled 'New Doubts over Tamiflu', appeared on the television channel's website on the same day as the appearance of the *BMJ*, and it indicated that the investigation was as much journalistic as scientific:

> *Channel 4 News and the BMJ asked Professor Nick Freemantle and Dr Melanie Calvert, from the University of Birmingham, to review these observational studies. They concluded: 'Oseltamivir may reduce the risk of pneumonia in otherwise healthy people who contract flu. However, the absolute benefit is small, and side effects and safety should also be considered.* (Channel 4 News, 2009)

Roche responded with a firm reproach, implying that the *BMJ* had concluded a sort of deal with journalists that compromised its integrity and legitimacy. Mentioning the contact between the *BMJ* and Channel 4, the Roche spokesperson observed, 'We are further concerned that this approach appears to have been supported by the *BMJ*' (Smith, 2009, p5374). Ten days later, the European Medicines Agency published an update to its recommendations concerning antivirals, indicating that its own examination of the risks and benefits came down heavily in favour of using oseltamivir (European Medicines Agency, 2009). It is not possible here to decipher in detail the elements of these apparent contradictions. Nonetheless, this brief public episode compels us to wonder what the most fair and appropriate questions are when it comes to the transparency of public health choices. In this example, it appears that it is less about transparency, and more about the existence of the necessary keys for the public to understand the messages and to integrate complex knowledge. For instance, the precise nature of the *BMJ*

articles' technical conclusions should be carefully studied; this would necessitate most notably a clear idea of the different uses of oseltamivir, of what is known about the effects on both the individual and the collective during a pandemic, and of the importance of the unknown, particularly since the trials in question did not concern the new variant of Influenza A/H1N1.

My conviction is that this example is representative of our lack of capacity to understand collectively the complexity of the Influenza A episode. This incapacity thus renders fundamentally problematic any real popular participation in the decisions that concern them, whatever that form of participation may be. Yet hope is permissible, on condition that we develop the means to include broad social participation in these debates and the broad mobilization needed during a serious crisis.

Equity in resource access

Cassier's analyses of intellectual property and of knowledge sharing about influenza constitutes a stimulating, more thorough consideration of equity and reciprocity in global public health governance during a pandemic threat. An analogous problem existed – and still exists today – in the HIV epidemic, particularly concerning the availability and distribution of antiretroviral treatments. From the very start of the 21st century, these medicines were very scarce resources in countries of the global South. This situation was subsequently more or less corrected with the implementation of global financing, notably the Global Fund. How to distribute these resources was addressed on both global and local levels. On the global level, it has been necessary to understand the ways in which the poorest countries become the focus of initiatives for solidarity. At the local level, it has been imperative to decide who benefits from these resources if their quantities are insufficient to treat all individuals in a population needing them. The stakes of distribution have been the subject of deliberations on both levels, most notably in the elaboration of the 3x5 programme, which aimed to distribute three million antiviral treatments in 2005.

With respect to influenza A/H1N1 in 2009, deliberations at the local level followed those already undertaken within the framework of H5N1 pandemic preparedness plans. But Cassier here underlines the responsibility of global public health governance. The Indonesian stance is effectively symptomatic of a gap in this regard. Cassier's analysis thus invites us to consider the effects of geographical scale on reflections concerning the principle of equity. In its publication on ethical considerations in public health actions undertaken during an influenza pandemic, the WHO defined equity in an interesting way:

> *[as] the fair distribution of benefits and burdens. In some circumstances, an equal distribution of benefits and burdens will be considered fair. In others, the distribution of benefits and burdens according to individual or group need will be considered fair. For example, in some circumstances, it may be equitable to give preference to those who are worst off, such as the poorest, the sickest, or the most vulnerable. Inequities are differences in health that are unnecessary, avoidable, and are considered unfair and unjust.* (WHO, 2007)

This paragraph is much more than a definition: it is possible to find within it a command to act in any way possible against 'unnecessary and avoidable differences'. From an international perspective, the distribution of vaccines or antiviral medications during a pandemic would, according to the logic of this command, raise a daunting question: we would have to agree upon what is inevitable (and thus, beyond our control) and on the other hand what engages our responsibility to act.

The 2009 pandemic influenza episode, which happily has not been very serious after nearly a year of global circulation, has shown us that the global community has not grappled effectively with this public health question. Of course, there are many actions to laud, as in state or manufacturers' donations of vaccines and medicines to WHO (SAGE, 2009). But in the end, these actions of solidarity were not undertaken in a coordinated fashion within the framework of a global effort opposed to the influenza pandemic. There is thus a kind of distance between the knowledge anticipated of a 'lack' on a global level (we know well that it was impossible in 2009 to produce more than three billion doses of influenza vaccine *per year* (Collin and de Radigues, 2009)), and on the other hand, the absence of any real transparent political cooperation among multilateral agencies. This political dimension seems to be 'masked' by the international medical one, clearly marked by what is best called dependence on North–South inequality that has become largely ordinary. An example of this phenomenon of masking can be found in the working out of the distribution programme for non-commercial vaccination stocks at WHO's disposal, amounting to a little more than 200 million doses at the end of 2009. This programme involved 95 countries which were to receive a sufficient vaccine to immunize 10 per cent of their populations, under certain conditions, most notably to vaccinate their health professionals (Kieny, 2009; WHO, 2009). WHO therefore plays the role of vaccine 'distributor', following an appropriate logic, that is, the recommendations by its own international experts of priority groups, and the identification of countries that would receive vaccines, and in what quantity. These criteria, principles and guidelines used by WHO have not been criticized to my knowledge. Nevertheless, it is worth noting that they are not the result of a global process to work out this policy, involving all actors in the international community. The ethical foundations of these criteria are not entirely explicit. This is not to say that they are not fair, but simply that a more explicit elucidation of the ethical underpinnings of these actions would reinforce their credibility and their effectiveness. However,

this distribution programme is a valuable one, and it is necessary to pay homage to the individuals responsible for the influenza and vaccine programmes at WHO headquarters who worked to identify where inequities lay and sought to improve international participation (Kieny et al, 2006; Collin and Briand, 2009). In March 2009, Collin and Briand wrote:

> *[the] WHO is working with industrialized countries, pharmaceutical companies and the international community as a whole to promote global solidarity and cooperation and thus ensure distribution of pandemic vaccine in poor countries with no local production. The current pandemic situation highlights the increasing globalization of public health stakes with regard to influenza vaccination.* (Collin and Briand, 2009)

Cassier, in his contribution to this volume, is right to indicate that new mechanisms must be put into place from this perspective: an important course of action must be taken before we can be sure of being able to undertake coherent actions on a global scale in response to pandemics that could constitute a very severe threat.

Conclusion

The three chapters in this book are rich in numerous lessons, and the few comments proposed here concern only a small part of these lessons. The historical analyses presented on 1918 and on the 21st-century management of the H5N1 virus show at what point it would be useful to consider the moral, social or political continuities in response to pandemics. So too do they invite us to consider how the stakes in globalization and how rapidly expanding science and technology can improve the terms of the debate, provided that we consider our wide-ranging tools to cope with influenza and other pandemics in light of new knowledge.

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Short Comment

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History may repeat itself, but never quite in the same way, and thus the many lessons from the two influenza epidemics in Catalonia, Spain (Chapter 2) are instructive. My first observations are about the viruses themselves and how biomedical researchers develop knowledge about them. We know that influenza viruses are sufficiently variable for it is never clear whether an epidemic will be very important, very powerful and thus very deadly, or on the contrary, whether it will be much more limited, with relatively moderate mortality. Those in charge of predicting how an epidemic will unfold and preparing for it are now faced with this incontestable difficulty, and I believe that we are all obliged to show a certain modesty in the face of such difficult predictions.

Moreover, there exist serious difficulties in determining the first cases of a pandemic, a point raised in the chapters by Esteban Rodríguez-Ocaña and Anne Rasmussen, and that remains one of the major difficulties: When an epidemic phenomenon begins, how do we locate the first cases in foci that might be distant from one another? If we have the means, we should certainly very rapidly identify the linkages that would permit authorities to activate their action plans against pandemic infectious phenomena.

Scientists have also faced considerable difficulties in identifying an infectious agent of past epidemics. From the complete uncertainty in the late 19th century to the early 20th century, there were scientific advances, new explanations, efforts at improving our understandings of infectious agents – but also errors. Such errors are completely normal, but they were adopted, indeed firmly supported by authorities. When scientists in 1918 observed a new illness, they were puzzled whether it was indeed new or due to an infectious agent, Pfeiffer's bacillus, of which they had already been aware for 15 years. Yet in the face of such uncertainty, the authorities, in an effort to reassure the public, expressed absolute certainty about appropriate control measures and care. Their expressed certainty is fascinating, and I think we should remain aware of the dangers of absolute certainty as we reflect upon the changing nature of our current biomedical

knowledge. At the same time, pandemic crises can also stimulate research and the development of new knowledge.

In the midst of pandemics, institutions must contend with epidemic phenomena, and conflicts can arise about how to do so. In 1918, for instance, conflicts erupted between civilian and military authorities, between the Minister of the Interior and the Minister of the Armies. And such conflicts arise now as well: on paper, pandemic plans enumerate the lists of leaders in charge of organization, offices or other structures, each focused on their own concerns. But in reality, it can be difficult to know which structures and which leaders are *really* responsible, which ones can prepare and implement the decisions devised to address an epidemic.

In this process of implementation, certain factors have now acquired considerable importance. When faced with the uncertain progression of a pandemic, we try to do our best with what we have. As Anne Rasmussen's chapter observes, this was the case in previous pandemics, and authorities implemented hygienic and protective measures, that were valued as efficacious. She observes that the French army was experiencing a difficult period and had to contend with multiple infectious phenomena, such as salmonella and typhoid fever as well as vaccination campaigns.

Serious problems in implementing measures can impinge upon their efficacy. Certain measures can be exceedingly difficult to apply, even if they have already been decided upon. They can be especially troublesome to implement fully in contexts where political conflict is heightened, as Rodríguez-Ocaña demonstrates, or even within highly disciplined structures such as the military (see Rasmussen, Chapter 3). A discontented civilian population may not only express dissatisfaction with the measures taken, but can also mobilize political and social claims simultaneously. And these claims are critically important for both implementing measures and for offering medical care during a pandemic.

Authorities face the conflicting impulses of taking responsibility for addressing the pandemic and minimizing the importance of the phenomenon. Authors have underlined the need to communicate messages about protection and to avoid arousing disquiet among the population. We see this same situation today: the media announce pandemic influenza to stimulate public engagement, and yet there exists a desire not to start an infernal spiral of worry that would require authorities to undertake measures that might be judged as disproportionate to the actual risks at hand.

After an epidemic phenomenon has passed, there is a tendency to forget what happened. This amnesia is common during post-epidemic phases, when in fact we should be drawing conclusions that would allow us to prepare and implement our plans better. So I would express the wish that today, in response to the obligation across science, precautionary principles and social development for the greater common good, the obligation is felt to continually advance the organization of

the protection of populations against infectious epidemic phenomena, especially if they are contagious.

To conclude, I would argue that the most important contributions that these historical analyses offer is the lesson of modesty. Past experiences with pandemics illustrate that preparations will always be insufficient and inadequate; and with influenza especially so. Claude Hannoun likes to say that we are always wrong about influenza pandemics. Because we are always wrong, I would add that there is no reason at all for this situation to change. Perhaps that is a little pessimistic, but we must be modest in our preparations. I would hope that we have made sufficient progress so that we do not come to the same conclusion as Léon Bernard: that we failed, and that our failures had catastrophic consequences.

Short Comment

Dr Jean-Marie Cohen, Open Rome (Réseaux d'Observation des Maladies et des Epidémies), which coordinates the Groupes Régionaux d'Observation de la Grippe (GROG)

Open Rome has as one of its objectives to coordinate GROG, the regional network for influenza surveillance. In 2007, we had to teach some 300,000 French health workers about avian flu and pandemic planning, and to illustrate that an influenza pandemic is a serious threat. But to illustrate this point, we needed stories to tell, historical examples that could illustrate what might happen in a future pandemic. What is bewildering to us is that mortality figures can vary so dramatically. Some argue that the Spanish flu caused 10 million deaths, while others argue that it was 20 or 40 million. The mortality figures from the Hong Kong flu are also variable. For physicians and scientists, this variation is a problem that raises questions about the difference between historical facts and supposition.

Historical investigations can also be instructive to help us mobilize for future pandemics. As Claude Hannoun's contribution shows, in 1968 there were no pandemic plans, and so physicians, pharmacists and nurses organized themselves. Historical analyses might tell us what sort of solutions have been used in the past, whether they were efficient, and whether they might be used to organize responses to future pandemics.

Both Sylvie van der Werf's and John Eyler's chapters show that a pandemic can transform scientific knowledge of influenza. It remains entirely possible that the next pandemic will deconstruct our scientific knowledge. Can we prepare for that eventuality? Can we identify which aspects of existing knowledge might be dramatically revised? Relatedly, John Eyler's chapter addressed the development of clinical epidemiology, and the transfer of the laboratory to the patient. We now possess rapid diagnostic tests that may enable us to develop a new field of epidemiology. It isn't clear to me whether this will be the case, but perhaps we can explore both of these possibilities with historians after the next pandemic.

Short Comment

Dr Jean-Claude Desenclos, Scientific Director of the Department of Infectious Diseases, Institut de Veille Sanitaire (InVS), which conducts surveillance of infectious diseases and detects disease threats to mobilize relevant French health authorities and ministries

These debates over pandemics are taking place in a new context of public health. The goal of public health has historically been a global, collective endeavour to improve the health of the community and to increase the lifespan of the population. But after the late 1990s, we shifted from a collective approach to what we call in France *securité sanitaire*. *Securité sanitaire* – health security – puts the security of a nation's population at top priority, which implies an individual perspective before a collective one. Thus, more egalitarian, global and broadly humanistic concerns for public health may be (and in fact) are deemed to be less important. This approach is not exclusive to France. In my work, I have realized that even the World Health Organization has now moved toward a 'health security' approach, but not because it wanted to do so (WHO is, after all, committed to protecting public health). Nevertheless, as a political institution that reflects the priorities of its member states, WHO could not avoid a focus on health security. In particular, in 2005 the World Health Assembly voted for the new International Health Regulations (IHR), legal measures that seek to 'help the international community prevent and respond to acute public health risks that have the potential to cross borders and threaten people worldwide'.[1] But the IHR have introduced management that has increasingly stressed health security issues at the expense of global public health, especially for the most vulnerable and low resource countries.

Therefore, the health security approach requires critical reflection. There is increasingly a primary self-interest that guides policy and resource availability above global and collective priorities. Citizens are informed on a daily basis, often in contradictory ways, and they fear the threat of a pandemic, even when that threat is not so great. Their perception and representation then plays a key role, even more important than the threat itself, in the way decision makers act and

respond. Hence, political concerns guide these public health policies, as well as the distribution of health resources and benefits.

Some of the chapters in this section, however, seek to reintroduce a much broader understanding of public health. Cassier's chapter on intellectual property, and the Giles-Vernick, Craddock and Gunn chapter both address how public health should be structured, how to ensure broader access to biomedicine by all, in particular those that are most vulnerable, and how to implement control measures.

In the case of an influenza pandemic, there may be little that we can do to limit its spread. We may only be able to limit its consequences by reducing the speed of transmission and by using medicines or a vaccine. In the case of H5N1, no screening tests exist, but a rapid test could be developed, and again, the question of who has the right virus from which a patent for a screening test, vaccine or drugs could be developed are critical. This observation raises Cassier's problem concerning intellectual property, capacity and equity of distribution and stockpiling. In a context where most biomedical resources will be available on time only in the most affluent countries, the way that a country like Indonesia reacted [in refusing to share its H5N1 influenza virus samples][2] is not surprising at all! Any country that is disproportionately affected by an influenza pandemic could well observe:

> *Viruses that are in my country are used by WHO labs, but I cannot get anything from them. I cannot get any assurance that I will receive a vaccine in sufficient and affordable quantities. This has been going on since 1947. My country's population has increased from 20 million to more than 200 million now – no more or less than any other country that has sufficient access to the vaccine.*

These are valid social and political concerns that need to be addressed. *Not* taking them into account *will* be a major threat to global public health organization in the interest of all. We therefore need to integrate this political consideration. This is why we need to come back to the basic values of a public health approach where equity is embedded as a fundamental principle.

On the subject of mobility restrictions, isolation and quarantine there has been much evaluation over the past ten years. Modelling studies have shown that these interventions can potentially reduce transmission peaks and slow epidemics. Using basic public health interventions was very effective during the SARS epidemic. There were no tests, drugs or vaccines for this epidemic, but early clinical diagnosis, isolation and care of cases very effectively prevented further transmission. Even the quarantine measures that were widely used and might have been unnecessary had early recognition and isolation been implemented, primarily because cases only became infectious just after the onset of disease. Nevertheless, the combination of quarantine and isolation was scientifically

supported, and when applied very effectively controlled transmission. Chapter 8 on Zimbabwe and the Midwestern US (Giles-Vernick, Craddock and Gunn) raises a critical issue about moving from plans to implementation. All countries have pandemic plans, and in France it is said that we have a very good one, among the best in the European Union. Nonetheless, this plan is quite centralized, and the challenges of implementing it at both local and regional levels remain a major concern.

Finally, the questions raised about media and communications in Vietnam (Guénel and Klingberg) have widespread importance. The media can sometimes react unpredictably; they can amplify a central message and at times assist strategies for controlling public health situations. In my own experience, I have seen how the media covered the chikungunya outbreak in Réunion, when many people fell ill over an eight-week period. The media acted aggressively towards health authorities. Authorities certainly made mistakes, but they did their best in all circumstances. Aggressive media coverage can also have a detrimental impact, and it is difficult to know what will and will not work.

In the end, social sciences can and should play an important role in public health, alongside epidemiology, microbiology and virology. If we cannot account for the world in which we live, for the public's perceptions, for politicians' or physicians' perspectives, we cannot understand the very different ways of representing pandemics. Perhaps that is why public health serves as such an effective bridge between basic science and the life of the community. The examples examined in these chapters illustrate how these different representations of pandemics operate and interact in different parts of the world in the past and present.

Notes

1 'What are the International Health Regulations?' accessed online at www.who.int/features/qa/39/en/index.html.

2 Indonesia subsequently agreed to share its H5N1 virus samples. See 'Indonesia to resume sharing H5N1 avian influenza virus samples following a WHO meeting in Jakarta', (27 March 2007), accessed online at www.who.int/mediacentre/news/releases/2007/pr09/en/index.html.

Short Comment

Pierre-Dominique Lansard, France Telecom and Club de la Continuité d'Activité

I interpret these contributions not as a physician, but as one who comes from a mathematical discipline working within France Telecom, a company of some 200,000 employees, half of whom are located within France, and the other half outside. My responsibility in the France Telecom group is to develop and implement a pandemic plan throughout the world, to adapt different versions of the plan to meet the needs of different countries. In addition, I represent the Club de la Continuité d'Activité, or the Business Continuity Management Group. This group is composed of more than 60 companies, mostly in France, and has undertaken pandemic preparations to ensure the continuity of business activities. Our aim has been to exchange approaches and strategies in developing pandemic preparedness plans and to develop a general framework for other companies that are in the process of creating and implementing their own strategies. In large companies usually one or two employees are dedicated to elaborating such plans, but smaller companies may find that process especially challenging because they have so few employees. Different national plans have not addressed this problem, and we think that it remains critically important to assist small companies in elaborating and implementing plans for the continuity of activities during a pandemic.

To my mind, the perspectives of companies and of the markets in which they operate are not addressed extensively in these chapters, and I would point out that we cannot escape the fact that we are all operating within a market environment. With reference to Chapter 8 (Craddock-Giles, Vernick and Gunn) France and Europe seem to reflect a kind of combination of Zimbabwe and the Midwestern US. As in colonial Zimbabwe, we have companies that simply would like to survive, and citizens want these companies to survive in order to supply critical resources such as water, energy, communications, food and transportation. It always astonishes me to attend gatherings of physicians who somehow overlook the necessity of utilities such as water, transport or food. It would be simply impossible to survive an 8–12-week pandemic emergency without them. At the same time, we resemble Minnesota, with several different organizations competing among themselves. France has a very good plan, well-trained personnel in

both health care and within the government, but there seems to be little information about how various aspects of the plan will be implemented, or how coordination of control strategies (such as distributing and wearing protective masks) is supposed to take place. Even within a single family where two people are working for two different companies, different company plans might put into place very different measures and at different times. This is precisely where coordination across companies and across government agencies would be crucial, and if we don't adopt that sort of coordination, we might be facing considerable panic.

On the subject of intellectual property, Roche, like any other company, is there to make money, and it will do what it can to protect its assets. But we must find a way for developing countries to receive assistance and be compensated for the viruses that they provide. This tension raises a point made in both the Zimbabwe-US chapter and the intellectual property chapter about segregation, both racial and economic. These disparities between developed and developing countries really centre on the existence of a well-trained network of people, something in which the developed world has considerable advantages. At the same time, these differences in education might not be so huge when we consider communication and the media in the developed and developing world. What people on the street in Vietnam know about influenza and its transmission may not be so different from what people on the street in France know, and it would be useful to explore how communication strategies used in one part of the world might be effective in another.

Conclusion

Tamara Giles-Vernick and Susan Craddock

Pandemics are a unique confluence of diverse factors and no single pandemic replicates another. Yet the authors and commentators in this volume have individually and collectively underscored certain patterns – questions, problems and responses – that do cut across pandemics over time. Our conclusion takes stock of these patterns, contending that pandemic planners in the future might productively debate these common questions, problems and responses and adapt them to their own national preparedness plans for influenza, and also for other acute infectious diseases that pose the risk of epidemic or pandemic. The lessons here fall into several wide categories: implementation; the mobilization of non-governmental organizations and institutions; the cultivation of public investment and participation in public health measures; the recognition of non-public health factors in shaping response; factors of globalization changing the nature of epidemics; and inequities characterizing vulnerability to and outcome of infection. Embedded within these broad categories are other important lessons about effective communication, the media and the diverse needs and priorities of multiethnic communities.

We should be clear that our aim here is not to delineate a set of specific recommended actions to be incorporated into national plans. In the first place, pandemics are complex global events that cannot be resolved with a simple 'how to' list. We would also remind readers that historical analysis can offer rich description and comparative evaluation highlighting commonalities over time, and thus provide opportunities for reflection, not precise solutions. Third, detailed, precise recommendations would limit the utility of our analysis because nations have designed their national pandemic preparedness plans differently. Several comparative analyses of preparedness plans have demonstrated important similarities and differences from different perspectives (Mounier-Jack et al, 2007; Garoon and Duggan, 2008; McLeod et al, 2008; Azziz-Baumgartner, 2009; Mensua et al, 2009). National pandemic preparedness plans do display some important commonalities: they seek to slow transmission and to reduce morbidity and mortality; they aim at ensuring the continuity of critical services; they detail an array of prevention, control and care measures; they elaborate the means of coordination

between different sectors; they evolve continually in light of recent changes and shortcomings; they emphasize the necessity of operating ethically and of enlisting active public support (US Health and Human Services, 2005: UK Department of Health, 2007; Azziz-Baumgartner et al, 2009; Premier Ministre, Secrétariat Général de la Défense Nationale, 2009).

Differences between the plans are significant as well, and researchers have evaluated how different national plans measure up to recommendations elaborated by the World Health Organization. For instance, multiple studies – one comparing plans in six south Pacific island nations, another of 15 Latin American nations, and a third of 29 European nations – have identified significant differences in border control measures. While some nations have explicit plans for screening incoming and outgoing travellers, others merely mention but do not specify what border control would entail, and still others discount its utility altogether (Mounier-Jack et al, 2007; McLeod et al, 2008; Mensua et al, 2009). Some studies identify additional differences among surveillance networks, in vaccination and antiviral drug strategies, and in coordination between countries (Mounier-Jack et al, 2007; McLeod et al, 2008; Ortu et al, 2008). In part, these disparities may result from the different ways that power is organized within these states, and how states understand their relations to broader political formations and public health institutions. It should be no surprise, then, that the US plan accords considerable authority to individual states and localities to develop their own vaccination plans; by contrast, the French national plan confers authority to the Prime Minister to 'direct government action', but provides for the Ministry of Interior to designate a Cellule Interministerielle de Crise (Interministerial Crisis Committee, or CIC), a body that coordinates between agencies (Premier Ministre, 2009, p19). The French plan also acknowledges the European Union's power over animal health by 'restrict[ing] imports, increas[ing] ... surveillance, and reinforc[ing] ... biosecurity' (Premier Ministre, 2009, p14). By contrast, a survey of preparedness plans in 15 Latin American countries revealed very little 'operational coordination' between neighbouring countries, and signalled in particular the dearth of coordination of animal surveillance systems (McLeod et al, 2008).

Implementation

The most significant differences between how a pandemic plays out, however, may have less to do with what appears in a national preparedness plan than with actual implementation and global disparities in wealth (a lesson that we address later in this conclusion). While national influenza pandemic plans did not figure in past pandemics, states around the world did in the past elaborate measures to contain or prevent transmission and to care for the sick. But as several contributors to this volume demonstrate, *implementation* was the critical factor that differentiated effective preventive measures from ineffectual ones.

Barcelona authorities' anti-crowding measures in 1918, for instance, were undermined by the church's belated observation of these measures and exceptions made for other holidays. More recently, the Vietnamese government's avian influenza control strategy entailed poultry slaughtering, but the measure applied to backyard poultry growers, and not to large-scale commercial ones, whose flocks ran higher risks of infection. In 1918, incessant conflicts between the French Ministries of War and Interior stymied effective response to pandemic influenza. In Colonial Zimbabwe that same year, officials and missionaries sought to disseminate medical supplies, vaccines and advice to rural populations living in scattered compounds, but their efforts were stymied by poor roads, inadequate supplies, and by people who simply refused to accept their ministrations. Finally, implementation problems also affected the 2009 distribution of vaccines. In the USA, some vaccination clinics had to meet overwhelming demands with fewer available resources, but also had no means of ranking or distinguishing between priority groups in their distribution of vaccines (Bosman, 2009). The French state's initial distribution of vaccines solely through special government clinics incurred the ire of general practitioners, some of whom argued that they should have been involved in vaccine distribution some physicians discouraged patients from being vaccinated. Moreover, neither the WHO nor national governments seemed particularly well prepared for vaccine sceptics, who doubted the safety, efficacy or necessity of an H1N1 vaccine (Gerlin, 2009; Sypsa et al, 2009) or for a rapid decline in vaccine uptake once the pandemic's second wave appeared to have passed, even though historical analyses have demonstrated long-standing public doubts about vaccinations (Moulin, 1996).

By many accounts, the 2009 vaccination campaigns failed for multiple reasons: many governments did not anticipate public scepticism about vaccine safety; some did not create detailed plans for prioritizing vaccine recipients, for efficient delivery of vaccines, or for better communication about the development, effectiveness and safety of vaccines; and finally, communications early on about the risks of H1N1 influenza and of the vaccines seemed out of sync with the perceived mildness of the pandemic (Larson and Heymann, 2010). Moreover, many low income countries faced not only a problem of acquiring vaccines at all, but those that did receive them did so belatedly. Many began receiving vaccines from WHO only in March or April of 2010, several months after vaccine delivery to wealthier countries, and as of May 2010, some had never received vaccines at all. These problems of equitable access and timely delivery of vaccinations will be especially crucial in the event of a more virulent influenza (or other infectious disease epidemic) outbreak.

'Implementation' is thus partly about 'operational' plans and coordination – the specific strategies and contingency plans that allow pandemic measures to

reach a nation's populations. Clearly, vaccination plans in the 2009 pandemic would have run far more smoothly if the US had received the expected number of doses in time and had some clinics screened vaccine recipients more rigorously, if the French government prior to the pandemic had negotiated with a group of health-care providers whose support for widespread vaccination was critical, if developing countries had gained more equal access to vaccinations. Implementation here involves making and publicizing the difficult choices of distinguishing vulnerable groups, but also of setting up mechanisms to screen these groups and medical personnel to usher them through the vaccination process, and of politicking with, or perhaps making concessions to, professional groups upon whom a government relies heavily during pandemic emergencies.

Good communication is more than 'telling the truth'

Moreover, successful implementation necessitates a capacity to communicate clearly both certainties and uncertainties of medical and public health knowledge, together with information about interventions, including vaccination, containment measures or therapies. This communication is a considerably more treacherous problem than simply '[t]elling the public the truth' (Barry, 2009, p325). National and local governments need to convey clearly what they know, what they do not know, and what can and cannot be done. Change, uncertainty and periodic intellectual disarray are inherent to biomedical and epidemiological research. As many virologists and epidemiologists have noted, emerging and mutating pathogens are difficult to predict. Several chapters in this book (van der Werf, Hannoun, Eyler, Rasmussen and Rodríguez-Ocaña) make clear the difficulties and risks of translating change and communicating the uncertainty inherent in any virological, epidemiological or other research, yet doing so without exacerbating public anxieties.

States, too, must also respond to multiple constituencies, to mounting public and media demands for complete (and patently unachievable) biosecurity, and to the economic interests of vaccine or drug manufacturers, who would promote vaccination or medical stockpiling for financial benefit. Public officials in such instances may find themselves obliged to mobilize resources for preparedness, prevention and treatment, even when a disease may be widespread but less severe than previous pandemics or current localized epidemics. They may also miscalculate their priorities, making significant investments to control one disease threat at the expense of other, deadlier ones. Indeed, some critics have castigated American and European health authorities for investing heavily in H1N1 pandemic preparedness and vaccination, when other diseases account for far more morbidity and mortality than H1N1 influenza, and they express deep scepticism that these investments are justified (see Duclos, 2009; Gostin, 2009). As Denis Duclos (2009) has recently suggested, such criticisms have the potential to generate serious and productive debate about public health priorities in investing and distributing limited resources, although he appears convinced that this scepticism has played a central role in *preventing* such debate.

Open discussions about public health priorities and the realities of epidemiological uncertainty remain crucial topics for a post-pandemic phase. Indeed, some states, and particularly those with limited access to vaccines or antiviral therapies to mitigate influenza transmission or its severity, might well resist relinquishing certainty as a political, rhetorical strategy, for they may have little else to offer their citizens. Nevertheless, better adherence to public health measures is more likely to be attained through channels of communication that acknowledge and capitalize upon public capacity to accept the limitations of what public health officials can do when these limitations are clearly explained rather than hidden under the guise of scientific certainty.

Media and the management of communication

The print, radio, television and internet media all have an important role here in facilitating this communication. Guénel and Klingberg show that the Vietnamese press had a critical role in galvanizing the Vietnamese government to acknowledge that it had an avian influenza epidemic on its hands. In the 1968 pandemic, media reports from Hong Kong provided important indicators of an unusual respiratory illness well before the official recognition that a pandemic had erupted (Wilson et al, 2009). But the influence of the media is not always salutary. A Swiss hospital-based survey conducted during the early wave of the 2009 pandemic suggested that extensive media coverage had provoked many people to present themselves to the hospital with flu-like symptoms, but that only 5 per cent tested positive for the novel H1N1 virus (Nickel et al, 2009). The authors, however, did not conduct any analysis of the press at all. Moreover, as Daniel Drache and David Clifton have recently argued concerning the 2003 SARS epidemic, media reporting can reflect a complex mix of strategic interests involving political authorities, public health officials and medical personnel, and economic stakeholders that inevitably generated competing messages (Drache and Clifton, 2008). The media's own competitive reporting and its selective juggling of different, and sometimes entirely contradictory messages not only undermined important public health communications, but also aggravated 'public fear and misunderstanding ... even though public health officials and health professionals, such as nurses, demanded accountability and transparency' (Drache and Clifton, 2008, p121). In the end, Drache and Clifton argue for 'focused communication strategies, proactive public health systems, and a realistic understanding of the global reach of local communication' as well as some critical reflection on the part of the media about its assumptions of fairness and objectivity (Drache and Clifton, 2008, p121). We would encourage international, national and local health

authorities to work with print, television and web journalists before, during and after pandemics to collaborate in the framing of pandemic communications, virological, epidemiological and medical evidence, and the understanding of threats, containment measures, vaccinations and treatment. But this, too, requires that the press reflects upon certainty and uncertainty in all these domains, and take stock of its own role and interests in galvanizing unproductive fear.

Implementation is thus far more than the already considerable task of elaborating good plans and contingency plans and of coordinating between agencies. It requires good communication, which entails acknowledging openly the certainties and uncertainties that underpin any public health intervention, and working more concertedly with the press.

Contributions of non-governmental organizations

This collection also reveals the significant influence of non-governmental institutions and organizations in managing pandemic challenges. These influences are clearly multifarious: Pierre-Dominique Lansard has highlighted the critical importance of private corporations that must ensure the continuity of their services during pandemics. Maurice Cassier underscores ways in which pharmaceutical companies have shaped the development, production and distribution of drugs and vaccines, and the variegated implications; in the upper Midwestern USA and colonial Zimbabwe, non-governmental organizations such as the Red Cross provided care and distributed medicines in the gaps left by rural health care and public health infrastructures, but at times could undermine the coordination that state authorities sought to effect in managing pandemic interventions.

The work of non-governmental institutions, enterprises and organizations can have a crucially important impact on the success of pandemic interventions, and this significance has been clearly recognized in recent years. To an unprecedented extent, the 2009 pandemic plans incorporated the active contributions and participation of the private sector and other associations and organizations, and as Lansard has indicated, many private sector enterprises developed their own plans for continuing operations during a pandemic. Such recent developments are crucially important, of course, and should be built upon. Associations and organizations can reach populations that might otherwise reject official interventions because of their poor relations with the state. Non-profit organizations may be better situated to understand particular communities and to assist with outreach efforts and interventions that may be more appropriate and acceptable to these communities. The private sector frequently can more rapidly mobilize infrastructural and technical resources and networks of facilities, including laboratories or manufacturing plants which may already have global reach. In other words, every sector – governmental, non-profit, private – possesses certain strengths and limitations, and thus their active contributions to preparedness necessitates collaborative planning.

Gaining public participation and support

The historical analyses in this collection illustrate well the variegated ways in which the public has engaged with governments, public health authorities and public health measures, including particular technologies. The tendency among government officials, health authorities and analysts has been to emphasize the importance of 'public trust' for the success of pandemic interventions. We have opted not to use the term 'trust' here, primarily because we remain convinced by Melissa Leach and James Fairhead's contention that the term is much too broad to be of real use. Instead, they argue that we need to distinguish between the multiple relationships that are covered by this undifferentiated category of 'trust', to consider the more nuanced ways in which 'people themselves consider their relationships with technologies and technocracies, in all their rich diversity and texture' (Leach and Fairhead, 2007, p30).

Chapters in this volume illuminate that in certain historical contexts populations accepted or rejected pandemic interventions for multiple reasons that 'trust' cannot solely explain. In 1918, some African subjects in colonial Zimbabwe rejected official counsel and medical supplies for several reasons: fear, an inability to adhere to colonial advice, alternative explanations of the illness, perceptions that medical and public health interventions were ineffectual, and mistrust of colonial authorities. At times, governments have been acutely aware of the importance of buttressing social or national cohesion, even at the expense of public health. In the highly disciplined context of the 1918 French military, about which Anne Rasmussen writes, the military and government authorities shied away from coercive measures such as rescinding military leaves, recognizing that the war effort required the active support of both troops and civilian populations.

Mobilizing the public's active support and engagement for pandemic interventions raises here another aspect of good communication between governments and their citizenry. In addition to recognizing and attending to inequalities among social groups, it also necessitates that authorities understand how social groups themselves conceptualize their own bodies, their strategies for safeguarding their health, the specific ways that they evaluate risk, and the ways in which they understand the place of particular technologies such as vaccination or particular therapies in efforts to safeguard health (Leach and Fairhead, 2007). Only by taking such factors into account can public health and other authorities tailor public health communications in ways that are meaningful to these populations.

Pandemic response and extra-public health factors

Certain chapters in this book also illustrate that pandemic response involves factors that often do not fall within the purview of public health. Military priorities (Rasmussen), political rivalries (Rodríguez-Ocaña), economic aspirations of states and economic needs of particular industries (Wallace et al, Cassier, Guénel and Klingberg), the necessity of adhering to the demands of international institutions (Ali, Cassier, Guénel and Klingberg), intellectual property rights (Cassier), racial politics (Giles-Vernick, Craddock and Gunn) all shaped the formulation of responses and populations' access to medical and public health resources. During pandemic emergencies, state officials are no doubt acutely aware of the multiple sources of demands they must respond to and between which they must shuttle. Yet when engaged in planning for such emergencies, preparedness plans still tend to focus primarily on those factors that have traditionally fallen into the realm of public health: surveillance systems, surge capacities of health-care facilities, the training of health-care workers, the distribution of limited antiviral medications and vaccines, and school and workplace closures, for instance.

Global currents

Elaborating on this point, Harris Ali (Chapter 1) and others writing on infectious diseases today (Davis and Lederberg, 2001; Knobler et al, 2006) note that increased levels and speed of population mobility, higher volumes of animal transport across national borders, and complex global networks of commodity manufacture and exchange have produced new challenges for infectious disease prevention. Ali argues persuasively that we have entered a 'historically specific epoch defined by the forces of globalization', which in turn has changed how outbreaks emerge and the speed with which they spread. By default, then, factors of globalization have changed the nature of public health. Some factors of the overarching term 'globalization' are not so new: epidemics across time have required attention to the movement of people and pathogens across borders, and more recently have been accompanied by the supranational exchange of information. It is first the higher level and speed of population mobility and the increased potential for the rapid global spread of pathogens that have compressed the time frame for responding to epidemics. They have also amplified the possibilities for local outbreaks to become pandemic, which, as Ali argues, makes globally coordinated interventions even more imperative and isolated, regionally specific responses to outbreaks less tenable (Ali, this volume; Ali and Keil, 2008).

Wallace, Bergmann, Hogerwerf and Gilbert (Chapter 4) complement Ali by making a good case for why public health must expand its purview to encompass social and economic practices that have shifted in recent decades under new technological and corporate regimes. As these authors contend, the recent explosion

of huge industrial chicken farms and the diminution in the diversity of poultry species has shaped viral mutation and pathogenic spread, since now relatively few companies ship a highly reduced variety of chickens throughout the world. The role of poultry processing and export in spreading influenza lends forceful support for the argument for WHO, and not just WTO, surveillance of industrial livestock production. Even in the recent H5N1 outbreaks, wild migratory birds gained at least as much attention as potential agents of viral spread, even though industrial chicken breeding and exports proved a more dangerous threat but a greater political liability.

Extending WHO's reach to economic practices of global capitalism points to the limits of what global public health agencies can do, however. WHO and national public health and veterinary agencies have monitored infectious agents in animals for some time now, a practice bolstered by recent anthrax, BSE and e-coli outbreaks. By the late 1990s, WHO was sending teams to Guangdong province in China, collaborating with the Chinese Ministry of Health to test chickens on farms throughout the province for evidence of H5N1 (*WHO Bulletin*, 1998). Infected chickens were either slaughtered or prohibited from export. Wallace and colleagues' analysis indicates that the trend of fewer producers concentrating animals in higher densities on larger farms is creating virtual laboratories for influenza production. It is not simply the occasional influenza outbreak that WHO must monitor; Wallace and colleagues' point is that infectious outbreaks are not an occasional industrial accident, but rather will be inevitable and continual. Yet although WHO is the pre-eminent global public health agency, it cannot intervene in the configuration of an industry. Doing so would trespass on the political leverage of privatized industry and the rights of national governments to support particular economic sectors; it would also introduce conflict between WHO and the WTO and its regulations governing commodity exchange.

The question remains, then, about how to manage the changing nature of pandemic production and transmission: how can WHO – in collaboration with other agencies and governments – intervene in pandemics that may emerge from global economic practices that are buttressed by national and supranational regulations protecting the privatization of industries and commodity exchange? Extending the purview of WHO and increasing collaborations among WHO, WTO, corporate executives, national governments and other entities, such as FAO, might pave the way for acknowledging the pathogenic effects of large-scale livestock production and other global economic practices. Under such circumstances, it could be possible for these institutions and industries to identify collaboratively the means to change aspects of production that may stimulate viral incubation and transmission, without putting companies and workers out of business. Institutionalized collaborations across global agencies, governments and private industries could also potentially prevent other kinds of outbreaks such as

BSE or *E. coli*, effectively thwarting misguided decisions on the part of national governments to ban imports or slaughter livestock needlessly.

Acceleration of pathogenic mobility may also worsen the unpredictability of geographic diffusion discussed by Claude Hannoun for the 1968 pandemic (Chapter 7). In that epidemic, influenza outbreaks did not suggest a logic or pattern of geographic spread. Instead, influenza showed up simultaneously in distant parts of the world, while transmission to more proximate regions often occurred more slowly. SARS and the rapid spread of H1N1 both testify to the increasing difficulties that public health agencies and surveillance networks will face in identifying outbreaks and stopping them before it is too late. More robust surveillance networks will help to achieve this task, but as we indicated in the introduction, sizeable regional gaps in surveillance coverage still exist. Clearly, any significant gap in surveillance networks will significantly weaken the overall capacity for intervention. Since surveillance systems confer substantial benefits extending well beyond national borders, countries without infectious disease surveillance networks require technical and infrastructural assistance, which might productively come from World Bank or Global Fund-style grants or aid packages rather than loans.

In addition to locating and communicating infectious disease outbreaks, as Hannoun's chapter indicates, there is a need for standardizing the methods for determining approximate numbers of infected persons across geographic regions. As in 1968, countries still employ various means, from hospital admissions to school absences, for monitoring how many people are sick with seasonal or epidemic influenzas. Keeping accurate track of large numbers of people during a pandemic will always pose significant challenges, especially when they are as mild and as easily transmissible as the 2009 H1N1 outbreak. It makes sense, however, for WHO to create a set of criteria to harmonize data collection, so as to improve the accuracy in comparing numbers across regions and determining an outbreak's extent.

As Eyler's piece (Chapter 6) and the revised estimates of H1N1 infection demonstrate, epidemiologists and biostatisticians have been working for years to improve the accuracy in determining numbers of those infected, but also in determining precisely who the infected are. Eyler's point was to show a shift in epidemiology from a focus on population to one on the individual and immune response. The goal with either approach, however, is a better understanding of which subgroups are more vulnerable in each outbreak, and why. Eyler has noted that epidemiologists studying excess mortality among certain ethnic groups in the USA after the 1918 pandemic suggested that socio-economic factors may have contributed to higher mortality among Russian, Austrian, Polish and Italian immigrants than among Irish, English and German immigrants.

Recent studies that have organized statistics around population subgroups have consistently found ethnic minorities and other marginalized groups to be at higher risk of infection and of more serious complications from influenza. One clear indication from these studies is that further research is needed into why ethnic minorities in the US, New Zealand, Canada and elsewhere are more vulnerable. Although these groups may display some similarities that can explain such vulnerabilities, they may also be subject to factors specific to national histories, social policies and economic support structures. Nevertheless, these occasional studies underscore the need for epidemiological data to reflect more sensitively a population's subgroups. Knowing whether the young or the elderly are at higher risk in each new outbreak is important, but equally significant is knowing whether or which underserved groups require targeted attention and resources. Incorporating the insights of community members themselves is also critically important to gaining a better understanding of vulnerability, as well as which intervention measures and resources would be most appropriate.

Questions concerning the production and distribution of resources such as vaccines and drugs during epidemics extend beyond underserved communities, however. Chapter 9 (Cassier) makes clear that current global regulatory mechanisms protecting pharmaceutical industries have driven the prices of vaccines and antivirals up, diminished possibilities for collaborative production, and made it exceedingly difficult to manufacture cheaper generic versions. The result is that inequities in resource allocation occur between countries as well as between subgroups within countries. In 2009, the US Congress, for example, allocated $7.65 billion towards vaccines and antivirals such as Tamiflu, a sum of money that most lower income countries cannot afford. This sum, though considerable, is insufficient to purchase enough vaccine to cover the entire US population, thus leading to the identification of priority populations in state influenza preparedness plans. But the 250 million doses obtained by the US, with just over 4 per cent of the world's population, still compares favourably to the 200 million vaccine doses procured by WHO for 95 low-income countries that comprise over 30 per cent of the world's population. As major pharmaceutical companies like GlaxoSmith-Kline and Roche reap windfall profits from vaccine and antiviral purchases before and during epidemics (Gostin, 2009; Padlock, 2009), millions of people will go without these needed interventions.

What is clear is that better mechanisms must be developed to address the inequities characterizing every influenza epidemic. Lowering the prices of vaccines and antivirals by invoking built-in national and global policies to break patent laws under conditions of emergency would be a step in the right direction. So, too, would be concerted efforts to more comprehensively include underserved populations in national influenza preparedness plans. Acknowledging and accounting for the economic impacts of surveillance measures, especially on the poor, would be a third. History might not offer easy solutions for the complex causes of multiple inequities, but it does display all too poignantly what happens when they go unchecked. It is thus best to remember, in the words of law

professor and bio-ethicist Lawrence Gostin, that 'responding to swine [or any other] flu is quintessentially a problem of social justice' (2009, p10).

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