Pandemic Influenza: A Review

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LANDIS MACKELLAR

THE YEAR 2007 marks the tenth anniversary of the first human fatality from Highly Pathogenic Avian Influenza, a three-year-old boy who died in Hong Kong. Epidemiologists have warned for some time that an influenza pandemic is practically certain to recur (Webster 1997; Webby and Webster 2003). Smil (2005) ranked an influenza pandemic as the single most likely "transformational" catastrophe, that is, one with potential to change the course of history.

In contrast, say, to their reaction to climate change, policymakers have not only quickly taken scientific fears to heart, but if anything have amplified them. US President George W. Bush called for broad latitude to deploy the US military in the fight against influenza. Andrew Natsios, then Administrator of the US Agency for International Development, declared avian influenza, a likely source of the next pandemic, the agency's main global priority, thus displacing, at a stroke, Iraq, Afghanistan, and HIV/AIDS. The editors of the opinion-leading journal *Foreign Affairs* committed the July/August 2005 issue to the theme, whose staying power was confirmed by its return to the pages of the same journal two years later (Osterholm 2007). At least in the United States, pandemic influenza has been packaged as a security issue, an area in which the exercise of sovereign power is a matter of survival. The very nature of the viral enemy, constantly mutating or "emerging," seems to call for a permanent state of mobilization.

Is the level of concern about the next influenza pandemic justified? This review assesses the current state of knowledge regarding this potentially deadly event and the state of policy responses to it.

Influenza

Influenza is a respiratory infection caused by an RNA virus.[1] There are three main types of influenza virus (A, B, and C); A is the main cause of influenza in humans. Influenza A is further divided into subtypes on the basis of the

two classes of surface proteins comprising the outer coat of the virus—hemagglutinin (H) and neuraminidase (N). Virus subtypes are identified by the order in which the protein was discovered; for example, the subtypes now established in the human population are H1N1, H1N2, and H3N2. Although these proteins are attacked by the human immune system, new protein types allow the virus to escape the human body's defenses. Virus subtypes can, in turn, be subdivided into various strains.

Influenza is a significant infectious disease killer even in normal years. In the United States, the "attack rate" (the proportion of the population experiencing clinical symptoms of disease) in a normal influenza season is about 10 percent. The human and economic costs, and the cost effectiveness of public health responses, particularly vaccination, have been assessed by public health experts (see Fedson 2003: 1532 for citations), although rigorous reviews find a wide gap between policy and the quality of the empirical evidence (Jefferson et al. 2005; Jefferson 2006). Studies suffer from multiple flaws, among which perhaps the most serious is nonrandomness: for example, extrapolation to the entire community of results from a study of nursing home residents, or to all flu seasons from evidence pertaining to a single year.

Influenza virus is transmitted by direct contact with secretions, large droplets, and aerosols, each of which calls for its own response—hand washing, surgical masks, and respirators, respectively. Tellier (2006) has argued that aerosol transmission has been downplayed in pandemic preparedness planning, with two ominous implications: the public will be less protected than they think by mass wearing of surgical masks, and health professionals should be equipped with personal respirators, a step not foreseen in pandemic preparedness plans.

Influenza is a seasonal disease concentrated in the cold months of the year in temperate zones and, less strongly, in wet and rainy seasons in tropical zones, although pandemics can emerge at any time during the year. The reasons for its seasonality remain unknown.

Pandemic influenza: Emergence and spread

Pandemic influenza refers to a situation in which a new and highly pathogenic viral subtype, one to which no one (or few) in the human population has immunological resistance and which is easily transmissible between humans, establishes a foothold in the human population, at which point it rapidly spreads worldwide. Historically, influenza pandemics have struck, on average, every 28 years, with extreme values of 6 and 53 years.[2] In the twentieth century, there were three major pandemics (Lazzari and Stöhr 2004; Kilbourne 1987):

—a severe one in 1918–20 ("Spanish flu," caused by the H1N1 subtype) in which 20–40 million persons died in the space of 18 months, an estimate now viewed as conservative (Johnson and Mueller 2002)[3];

—a mild one in 1957–58 ("Asian flu," caused by the H2N2 subtype), in which excess mortality was about one million;

—a mild one in 1968–69 ("Hong Kong flu," caused by the H3N2 subtype), when excess mortality was also on the order of one million.[4]

In the 1918–20 and 1957–58 pandemics, infection rates on the order of 50 percent and attack rates on the order of 25 percent were observed. Perhaps just as important as these three epidemics, when its impact on policy is considered, is the 1976 swine flu epidemic, which failed to materialize after US policymakers had launched a mass vaccination campaign in anticipation.

How do new influenza viruses appear? There are two processes by which the influenza A virus undergoes evolution: antigenic drift and antigenic shift. Drift is gradual; thus, influenza vaccine produced on the basis of last year's strain will likely confer reasonable protection if only drift has occurred. Pandemics are ascribed to antigenic shifts, which are abrupt variations leading to universal susceptibility to the disease.[5] A likely scenario for producing a shifted influenza strain is the combination of segments from a human virus and an avian virus, resulting in a reassortment of genetic material. One way for this to happen is for swine, susceptible to both human and avian influenza, to serve as an intermediary host in which reassortment can occur. Therefore, the coresidence of the "Three P's"—people, pigs, and poultry—in rural Asia is conducive to the emergence of pandemic influenza, leading some researchers to refer to this region (specifically, China) as an "influenza epicenter" (Hampson 1997). Osterholm (2005a, 2005b) refers to Asia as "an incredible mixing vessel" for the production of new viruses.

Current pandemic fears focus on the H5N1 variant of avian influenza, a disease of domestic and wild fowl that is now endemic among bird populations in Asia (Li et al. 2004) and is increasingly infecting humans (World Health Organization 2005a, 2005b; Writing Committee of the WHO 2005).[6] Having started its existence as a relatively benign virus, H5N1 has evolved to be highly pathogenic to domestic fowl, leading to the term Highly Pathogenic Avian Influenza. It may or may not make wildfowl sick, allowing them to spread the disease widely. Domestic ducks can also remain asymptomatic, making them an especially dangerous disease vector. Although H5N1 avian influenza emerged in Asia, migratory wildfowl have spread the disease to Russia, Turkey, Romania, Nigeria, Egypt, and other countries (including western European countries). The World Organisation for Animal Health (OIE), the international organization tasked with global animal health, has a clear protocol for the isolation and slaughter of infected flocks. Over 100 million birds have been slaughtered in Southeast Asia in recent years, at enormous economic cost and impact on poor farmers, yet the H5N1 virus is nowhere near being contained, let alone eradicated.

The 1957 and 1968 pandemic viruses (H2N2 and H3N2) both arose from genetic reassortment. Some have found it encouraging, if mystifying, that H5N1 has not reassorted despite having had ample chance to do so (Stöhr

2005).[7] Perhaps the viruses resulting from reassortment, if such has taken place, have been so benign as to escape notice. However, reassortment in an intermediary host is not necessary for the emergence of a pandemic strain. The deadly 1918 virus appears to have been an avian virus that adapted directly to humans (Taubenberger et al. 2005). This is disquietingly similar to what has been observed with H5N1, which has infected humans directly, with no evidence of reassortment having occurred (World Health Organization Global Influenza Program Surveillance Network 2005). So far, H5N1 does not appear to be easily transmissible between humans, but this could change at any time. Or, the virus, having established a foyer in a geographically limited human population, could mutate gradually in the direction of greater human-to-human transmissibility.

H5N1 was first observed in the human population in 1997, when it infected 18 persons, six of whom died, in Hong Kong. This was the first known example of the direct transmission of influenza from birds to humans (Class et al. 1998). Since then, human cases have been observed mainly in China, Thailand, Indonesia, and Vietnam. All known cases of human avian influenza to date appear to represent bird-to-human transmission, with the exception of a few cases of person-to-person transmission at very close quarters (e.g., Ungchusak et al. 2005). No case of casual transmission via nasal aerosols has been confirmed, risks to health care workers appear to be modest, and blood tests of persons in contact with human avian influenza sufferers have been negative (Writing Committee of WHO 2005, especially Table 2).[8] These facts suggest that the virus has not yet become broadly transmissible from human to human (Liem et al. 2005). However, if the virus attains the ability to pass easily between human hosts—and the H5N1 virus is known to mutate rapidly[9]—this will represent the beginning of a potentially catastrophic pandemic. The genetic changes necessary to adapt the H5N1 virus from avian to human receptors are minor (Harvey et al. 2004).[10]

The World Health Organization (2005a) has divided the influenza cycle into six phases, as shown in Figure 1. Based on this scheme, H5N1 influenza is in Phase 3, where some cases of person-to-person transmission have been observed, but human-to-human transmissibility is low. Some epidemiologists believe, however, that the true scope of H5N1 has not been recognized because of poor testing; that, in fact, H5N1 is well into Phase 4 or even Phase 5 (see Henry Liman's «www.recombinomics.com» for this argument). Even if this pessimistic view is incorrect, the World Health Organization has listed five points that give cause for grave concern (WHO 2005b):

—H5N1 has spread rapidly among poultry in Asia and is now endemic to the region. (WHO might have added that H5N1 is now known to spread by migratory wildfowl.)

—It mutates rapidly, as witnessed by its rising virulence in poultry.

—It has acquired genes from influenza viruses that infect other species.

FIGURE 1 Six phases of the influenza cycle

Inter-pandemic period

Phase 1: No new influenza virus subtypes have been detected in humans. An influenza virus subtype that has caused human infection may be present in animals. If present only in animals, the risk of human infection or disease is considered to be low.

Phase 2: No new influenza virus subtypes have been detected in humans. However, a circulating animal influenza virus subtype poses a substantial risk of human disease.

Pandemic alert period

Phase 3: Human infection(s) with a new subtype has been detected, but no human-to-human spread, or at most rare instances of spread to a close contact ("person-to-person").

Phase 4: Small cluster(s) with limited human-to-human transmission but spread is highly localized, suggesting that the virus is not well adapted to humans.

Phase 5: Larger cluster(s) but human-to-human spread still localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible (substantial pandemic risk).

Pandemic period

Phase 6: Pandemic: increased and sustained transmission has been detected in general population.

—It is highly pathogenic in humans.

—The dangerous interaction of animal and human populations in Asia continues apace.

Stöhr (2005) writes that the warning signs of an imminent pandemic have never been higher since 1968; nearly five years ago, Webby and Webster (2003) derived the same conclusion from the cluster of avian-to-human influenza transfers since 1997. However, the precise etiology of influenza pandemics remains unknown and, as the 1976 swine flu episode demonstrates, the emergence of a novel influenza strain together with cases of animal-to-human transmission does not necessarily result in a pandemic (Dowdle 2006).

Pandemic influenza: Clinical aspects

Most strains of influenza do not kill the victim outright; rather, secondary infections such as pneumonia, treatable with antibiotics, are responsible for mortality. Pandemic influenza, by contrast, is characterized by a high prevalence of primary viral pneumonia (Ward et al. 2005). The 1918–20 viral strain was a strikingly efficient killer. Mortality arose from a "cytokine storm," an

immune system response leading to acute respiratory distress syndrome (Kobasa et al. 2004). Perhaps ominously, H5N1 hemagglutinin shares molecular characteristics with that of the 1918 virus (Hatta et al. 2001). Laboratory animals infected with the H5N1 virus become far sicker than control-group animals infected with H3N2 (Ward et al. 2005: i7 for references).

As of September 2006, the World Health Organization recognized 309 human cases of avian influenza, of which 188 resulted in death. This case–fatality rate of over 50 percent is inflated because not all cases have been reported; however, even it is five times too high, it would rank with that of the 1918–20 virus.[11] There is no established clinical protocol for treatment of the disease other than broad-spectrum antibiotics and the antiviral agents oseltamivir and zanamivir (Tamiflu and Relenza), manufactured by the pharmaceutical firms Roche and GSK respectively (see Ward et al. 2005 on Tamiflu). The drugs appear to be of low efficacy if the infection is well established (Hien et al. 2004). Tamiflu may also be taken as post-exposure prophylaxis in a six-week course of 75 milligrams twice daily. Demand for Tamiflu has soared and Roche has broadly licensed governments and other firms to manufacture it.[12]

It is practically unavoidable, if arguably deplorable, that in public health, life-years at the extremes of the age spectrum are less valued than life-years in the middle range. The perceived severity of a pandemic will greatly depend on its age-attack curve, that is, the age groups at greatest risk. The typical age profile of influenza mortality is U-shaped, meaning the very young and the very old are at highest risk. In 1957–58, children were at greater risk than the aged, perhaps because older persons had some degree of immunological protection from previous exposure to a similar strain. In 1968–69, the very young and very old were equally at risk. The frightening specter of the 1918–20 pandemic is in part attributable to the fact that attack rates followed an idiosyncratic W-shape—added to the traditional peaks at the extremes of the life span was a peak for young adults.[13] This completely atypical pattern remains a mystery (Taubenberger and Morens 2006). Stöhr (2005) notes with concern that most cases of human H5N1 infection have been children and young adults, although this may in part have to do with their close contact with poultry in farmyards.

The unlucky few who to date have suffered from Highly Pathogenic Avian Influenza have infected only persons in very close contact with them because the H5N1 virus affects the lower respiratory tract, immediately leading to debilitating pneumonia. A mutation increasing human-to-human transmission probabilities might well see the virus affecting the upper respiratory tract instead, with the welcome side effect of reducing pathogenicity (Smith 2006). In any event, it is not warranted to assume that pandemic influenza will be characterized by the astronomical case–fatality rates that have so far been observed in H5N1 Highly Pathogenic Avian Influenza. Nor should we assume that it will have an atypical age-attack curve.

Policy responses to pandemic influenza

There is another reason to be at least moderately optimistic. In their review of the 1918 pandemic, citing improved response capabilities, Morens and Fauci (2007) are succinct: "Almost all 'then versus now' comparisons are encouraging." Policies to respond to pandemic influenza fall into three time frames—measures that can be taken before the emergence of a new virus, measures that can be undertaken in the immediate aftermath of its emergence, and measures that can be taken once the pandemic has been established.

Under the lead of the Food and Agriculture Organization (FAO), the World Health Organization, and the World Organisation for Animal Health, a number of initiatives have been proposed to reduce the risk of Asian zoonoses (FAO and OIE 2005). Officials of the Association of South East Asian Nations (ASEAN) have even committed themselves to an ambitious effort to eradicate avian influenza. This strategy is unlikely to succeed given the endemic nature of the disease and the possibilities of long-range transmission by migratory wildfowl; however, the improvements in agricultural and market conditions resulting from the initiative, as well as the improved capacity for surveillance, represent steps in the right direction. Interventions affecting agriculture and rural development have the distinct advantage of being win–win options—regardless of their impact on human influenza, they will improve the lives of many poor households, as well as those of farm animals. Indeed, the under-allocation of public health resources to veterinary health has been commonplace (Martinot et al. 2007).

In the case of Severe Acute Respiratory Syndrome, or SARS, isolation and quarantine measures were effective in stamping out the epidemic. Influenza, however, is characterized by a much shorter incubation period, and the onset of infectiousness is known to occur before the onset of symptoms. The dangers of disease transmission were shown dramatically during the SARS epidemic when 16 persons on a single airline flight became ill. Air filters can reduce the likelihood of transmission (Pavia 2007). One study based on a stochastic model (Cooper 2005) found that travel restrictions would delay the international spread of pandemic influenza only if they were virtually instantaneous and 100 percent effective, which is exceedingly unlikely to be the case. Other studies lead to different conclusions; for example, some believe that restrictions on air travel following the September 11th, 2001 attacks resulted in a mild influenza season (Brownstein et al. 2006). Yet, historical data suggest no change in the speed of influenza's spread over recent centuries, despite the massive proliferation in travel and human-to-human contact.

Two high-profile micro-simulation studies concluded that rapid policy measures could successfully "ring-fence" influenza outbreaks within Southeast Asia (Ferguson et al. 2005; Longini et al. 2005). The main intervention foreseen was targeted post-exposure prophylaxis with antiviral drugs, combined with "social distancing" (school and workplace closures, etc.) and

quarantine. Opinions differ: Monto (2006) takes the idea seriously; Mills et al. (2006) warn that, like forest fires, pandemics may represent the cumulation of multiple outbreaks, effectively swamping any "ring-fence" strategy. *The Lancet*, in an editorial for 13 May 2006, was flatly dismissive of ring-fencing. Flauhault et al. (2006) used a different approach to assess strategies for reducing the impact of a pandemic assuming that it could not be ring-fenced and concluded that the combination of complementary measures, timing, and global coverage were key factors determining effectiveness. The use of mathematical modeling to design optimal response strategies is complicated by the fact that epidemiological dynamics can be perverse. If interventions to prevent transmission are too effective, a large number of susceptible persons are left in the population, leading to the likelihood of a second peak (Bootsma and Ferguson 2007).

The value of the reproduction coefficient R_0 is the key assumption in model simulations. R_0 is the number of persons infected by each infectious individual in a completely immuno-naive population (i.e., at the onset of a pandemic; hence the subscript zero). As such, it is held to be a characteristic of the virus and the mixing characteristics of the population. R, by contrast, is the number of persons infected by an infectious person at a given point in time, and it declines as an epidemic progresses and growing numbers of persons in the population acquire immunity. A simulation study for the United States suggested that for a relatively low R_0 coefficient of 1.7, a stockpile of 10 million courses of Tamiflu, twice the current US stockpile, would be required to keep the total attack rate below 10 percent (Germann et al. 2006). For $R_0 = 1.9$, by contrast, the required stockpile would be an astronomical 182 million courses. R_0 for pandemic influenza has been estimated, based on San Francisco data from autumn 1918, to be 2.0–3.0 at the city level (Chowell et al. 2007).

The higher the R_0, the greater the need for comprehensive approaches involving antivirals, vaccination, social distancing, and travel restrictions. The key to ring-fencing, though, is not implementing measures so much as targeting them. Wu et al. (2006) stress the need for aggressive contact tracing and implementation of household protection measures, while McCaw and McVernon (2007) show the large payoff to proper targeting of antiviral prophylaxis.

Ring-fencing an epidemic presupposes that the surveillance necessary to pinpoint the epidemic has taken place. The first line of defense against a pandemic is WHO's National Influenza Centers, of which there are 110 in 80 countries (Hampson 1997). But centers in many poor countries lack equipment and human capacity (Meijer 2006). Some countries in Southeast Asia (e.g., Laos and Cambodia) have virtually no epidemiological field surveillance capacity. Emergency technical assistance programs to put surveillance capacity in place are underway (for example, USAID has dispatched US$25 million to

the region). Capacity building will be in vain, however, if reasonable public health governance is not in place (Calain 2007a). During the SARS episode, China incurred widespread disapprobation when Ministry of Health officials tried to cover up the epidemic.[14] A number of high-profile sackings and public commitments never again to engage in such behavior resulted, but old habits die hard. China's decision in 2006 to make press reporting of "unexpected occurrences" subject to criminal action is proof of this. Even if there is a commitment to transparency at the center, implementation in the provinces may be weak. Throughout Southeast Asia, regardless of central government policy, farmers are reluctant to report epidemic outbreaks because compensation for slaughtered birds is low, and local officials are inclined to suppress the news because livelihoods are at stake. The keys to making surveillance work are (1) rewarding or at least reimbursing those whose flocks must be destroyed and (2) empowering those who surveil. Few countries are willing to do either.

The control of infectious disease is a clear example of a health-related global public good (Smith et al. 2003), and supra-national collective action is required in areas ranging from surveillance and reporting to immunization. Much has been written on the globalization of disease, typically construed to mean heightened vulnerability to infectious disease. Much less has been written on the globalization of the response to disease. The remarkably effective global response to SARS, particularly the coordinated international laboratory effort, which saw the virus identified within a matter of weeks, gives cause for optimism. Since then, however, the emphasis on security aspects of infectious disease has led to perceptible tension and an atmosphere of confrontation, nowhere better illustrated than in Indonesia's temporary refusal to make virus strains available for analysis (Calain 2007b; Normile 2007). Why, Indonesian policymakers reasoned (until they were placated), should we provide the raw material to develop vaccines that pharmaceutical firms will then sell at prices we cannot afford? The World Health Organization, the lead international agency in this area, can set policies, but it has no power to implement or enforce them. At best it can act as an advocate for more vigorous policy response, but these policies are enacted by national governments and pharmaceutical firms.

Once a pandemic is established, antiviral drugs will play a major role. The World Health Organization has issued clinical recommendations for the use of antivirals against H5N1 Highly Pathogenic Avian Influenza, but acknowledges that because of the small number of cases, the evidence base is poor (WHO 2007). Nuno et al. (2007) advise that countries with limited antiviral stocks should use them only therapeutically; countries with large stocks should use them prophylactically as well. A major advantage of antivirals is that they will be effective from the very beginning of a pandemic, whereas efforts to develop and deliver a vaccine will take many months (Monto 2006), as described below. As vaccine efficacy and coverage increase, the effective-

ness of antivirals to reduce morbidity and mortality increases *pari passu*. Thus, the idea that antivirals are only a stopgap measure to be applied early in the pandemic cycle is wrong.

Some strains of the H5N1 virus are already resistant to another antiviral agent, adamantine, and despite arguments that oseltamivir is less subject to resistance (Ward et al. 2005), mildly resistant strains have already been found in a clinical setting (de Jong et al. 2005). The worst-case scenario is that a resistant transmissible strain emerges, attempts to control use of the antiretroviral agent fail, nonresistant strains are killed off, and only the resistant strain is left in place. Yet simulations by Lipsitch et al. (2007) found that even when resistance emerges, widespread use of antivirals can significantly delay and reduce total morbidity and mortality.

Vaccine development and administration would be a key response to a pandemic, but Fauci (2006) aptly described the entire pandemic influenza vaccine development and manufacturing process as "fragile." It is often pointed out that, using traditional approaches, it takes the global pharmaceutical industry six to eight months to develop an influenza vaccine from the time the viral strain to be protected against is isolated. As stated above, in normal years the genetic mutation from last year's virus is small. Thus, when patients are immunized with a vaccine based on last season's influenza strain, they are reasonably well protected against the strain that will be prevalent in coming months. These favorable conditions will not be present in the case of pandemic influenza: vaccine development would have to commence after the new virus had emerged and been identified. Given a lag of 6–8 months, the pandemic would already be globally established (Stöhr and Esveld 2004). One need not be overly pessimistic, however. While it takes the pharmaceutical industry 6–8 months to fill an entire national order, significant batches of vaccine are available weeks or even months earlier. Pandemic spread is variable and tends to occur in waves. While a vaccine might have little impact on the first wave (particularly in the country or region of origin), its effectiveness in subsequent waves as they spread around the world might be considerably greater.

Genetic engineering techniques ("reverse genetics") might permit scientists to speed up vaccine development, allowing a vaccine to be developed within weeks after the viral strain had been identified (Webby et al. 2004). Reverse genetics raises issues of intellectual property rights, regulatory regimes, and consumer acceptance (Webby and Webster 2003).[15] Early development of candidate vaccines is another prudent step, and several candidate vaccines generated from H5 isolates have been under study for some time (Writing Committee of WHO 2005: 1383 for references). Subbarao and Joseph (2007), reviewing the difficulties of developing a vaccine against avian influenza, cite the importance of maintaining a "library" of candidate vaccines. The problem of removing the highly pathogenic component of the H5N1 virus has already been solved (Monto 2006). However, rapid muta-

tion of the virus means that vaccines developed from currently known virus strains may not be effective when a new strain emerges. One of the main challenges is not vaccine development per se but minimizing the need for multiple vaccinations (ibid.). The arithmetic is not complex: a given stock of vaccine requiring one immunization will make it possible to protect twice as many persons as a vaccine requiring two. The role of "adjuvants," substances that increase the potency of vaccines, will be crucial.

Laboratory development of a vaccine will be only the beginning of the challenge. While high-value specialized vaccines (against human papillomavirus, for example) are a profitable line of business for pharmaceutical firms, commodity vaccines (basic vaccines administered to children, for example, or influenza vaccine) are not. Part of the reason is that the main customers are governments, which take little interest in public immunization programs (Fedson 2003, 2005; Hinman et al. 2006). It was to counter this general indifference, and the resulting failure to meet WHO Enhanced Program of Immunization (EPI) goals, that the Global Alliance for Vaccines and Immunisation (GAVI) was established. Adding to the pharmaceutical industry's distaste for vaccines are memories of the 1976 US "swine flu" debacle, in which hundreds of people suffered serious adverse effects from the mass vaccination program instituted. In the United States, Britain, and elsewhere in Europe, civil society groups opposing mass compulsory immunization have become a political force.

Under these adverse conditions, it is perhaps not surprising that industry capacity to produce influenza vaccine is only about 300–350 million doses per year.[16] A chaotic situation can be foreseen in which major countries attempt to lock in supplies by negotiating forward contracts with individual suppliers. Osterholm (2005a) cites "1950s egg-based technology" and the lack of national commitment (in the United States) to universal influenza vaccination as major barriers to pandemic preparedness.[17] His estimate is that supplies sufficient to vaccinate 500 million persons against a new influenza strain might be available within six months of the beginning of a pandemic (this refers to conventional egg-derived unadjuvanted vaccine). Given the limited number of doses and the concentration of manufacturing capacity in fewer than a dozen countries, there will be thorny questions of how to allocate inadequate vaccine stocks. It is difficult to imagine national policymakers freeing vaccine from national stocks in order to vaccinate populations in greater need elsewhere in the world. Poor and middle-income countries will be able to obtain vaccines (and antivirals) only by means of binding orders with pharmaceutical firms (if they have the money) or local production (if they have the capacity). Most have neither, and global institutions are ill-prepared to cope with the outcry that will follow.

A number of authors have pointed out that the best way to prepare vaccination strategy (as well as production capacity) for a pandemic is to

increase inter-pandemic vaccination coverage. As of this writing, one of the easiest steps that could be taken to head off a pandemic would be vaccinating persons, especially those exposed to poultry, in areas where the H5N1 avian influenza is endemic (to prevent the possibility of reassortment in a human host). Yet there is no serious effort to do this.

A recent expert meeting convened by the World Health Organization on enhancing the vaccination response to pandemic influenza examined the entire range of options from novel vaccine development technologies to vaccine-sparing modes of injection. A summary of the meeting reports that an investment of US$3–10 billion might begin to bear fruit in three to five years (Kieny et al. 2006). Not considered by the World Health Organization, but another means of boosting effective supply, would be harmonization of regulatory standards among countries (Gronvall and Borio 2006). Perhaps most important, from an industry perspective, is the assurance that demand for vaccine will materialize. Existing capacity can be (and has been) expanded; even existing capacity and technology can produce far more vaccine than it currently does, but all of this requires that pharmaceutical firms have a high expectation of profit.

One may envision not only vaccine (and antiviral) shortages, but a more general situation of distress throughout the health care system. Hospital beds, ventilators, surgical masks, and other equipment would be in short supply. Personnel problems would be felt as doctors, nurses, and hospital workers (or their families) became sick and missed work. An influenza pandemic is a classic "surge" problem, and public health systems have traditionally been unprepared for peak demand. Surge aspects aside, national public health systems are chronically underfunded (Garrett 2007), and they have retooled for health promotion rather than for the classic infectious disease control missions that they were originally mandated to carry out (MacDougall 2007).

Some 50 countries have responded to the call to devise pandemic preparedness plans, but very few of these are operationally credible, even in Europe (Mounier-Jack and Coker 2006). A "checklist" approach, in which countries attempt to address the measures identified in the WHO national pandemic preparedness template, dominates. A survey of EU member countries led experts to conclude that countries were "moderately" well prepared, but this amounted to certifying that they had ticked off those boxes on the list that were identified by expert opinion as the most important. The specification of audiences and objectives in the plans was found to be generally weak. Cross-border aspects of pandemic preparedness were conspicuously absent from national plans.

In developing countries, planners meticulously enumerate interventions, estimate target populations, set coverage targets, multiply by unit costs to calculate resource needs, and present international donors with their estimates of the funding gap. Given the near collapse of public health systems in

many poor countries after decades of government indifference (and the unforeseen devastation of HIV/AIDS), the exercise appears divorced from reality. Nowhere is the gap wider between rhetoric, heavily tinged with off-the-shelf protocols and model policy guidelines, and grim reality. The World Health Organization, which answers to a board consisting of representatives named by governments, can hardly be expected to adopt a critical perspective.

Demographic impacts of pandemic influenza

The general public has scant appreciation of the lethality of pandemic influenza (Kristiansen et al. 2007). Scaling up the global population in 1918 (1.8 billion) to current levels, it is not inconceivable that 200 million or more persons would die in the event of a hyper-virulent pandemic.[18]

Whether the next pandemic will have a U- or a W-shaped mortality profile is essentially irrelevant to its overall toll—population growth alone since 1918 suggests that pandemic influenza has the potential to kill 100–300 million persons if the case–fatality rate is high enough. However, the age profile of mortality could have a significant impact on population age structures and on age-based transfer systems such as pensions. A pandemic in which excess mortality among the working-age population exceeded excess mortality among the elderly (as in 1918–20) would worsen the problems currently faced by pension and health care finance systems.

Equally important could be selective mortality. In the French heat wave of 2003, most heat-related deaths were among the frailest elderly (whose survival prospects were already poor), so the total person-years of life lost was less than what would have been expected by applying a population-wide actuarial table to the age distribution of heat wave deaths. In the 1918 pandemic, tuberculosis infection was one condition that enhanced mortality, so that TB death rates fell sharply after the epidemic—so many of the tuberculous died in 1918 that there were fewer left to die years later. Today, especially in developing countries, tuberculosis remains a highly prevalent disease, and similar selective mortality cannot be ruled out. Individuals with compromised cell-mediated immunity (those with HIV/AIDS, for instance) may likewise be highly affected by an influenza pandemic. The point is open to discussion, however: some have argued that an overly vigorous immune response to the virus (the "cytokine storm") caused the W-shaped 1918–20 mortality profile, in which case the immuno-compromised might actually be better off.

Links to fertility also need to be considered. For reasons not understood, the 1918–20 pandemic was ruthlessly lethal to pregnant women. If a pandemic led to high mortality among women of childbearing age, the result might be a temporary drop in fertility. After the pandemic had passed its peak, fertility might rise above its long-term trend as parents sought to

replace lost children; alternatively, it might drop below its trend as a result of reduced economic expectations or lagged health effects of the pandemic.

Economic impacts of pandemic influenza

Like developing-world pandemic preparedness plans, estimates of the economic costs of pandemic influenza are somewhat surreal, since the perceived loss will be more human than material. Nonetheless, and predictably, estimates of economic impacts have played a large role in the attempt to mobilize governments and the private sector in pandemic preparedness. Their magnitude, and whether their estimation rests on sensible approaches, are therefore not unimportant questions. For example, the authors of the articles that appeared in the 2005 special issue of *Foreign Affairs* appeared to be unanimous in the view that the global economy would "shut down" in the event of pandemic influenza.[19] This view is speculative in the extreme, and indeed it overlooks that fact that in 1918 the global economy demonstrably did not skid to a halt.

Economic impacts of disease can usefully be classified as direct and indirect. Direct impacts, which have been widely studied, would include hospital costs, lost days of work, costs of medication consumed, and so on. In a much-cited piece Meltzer et al. (1999) estimated the direct costs of pandemic influenza in the United States to be, to an order of magnitude, US$100 billion, a bit less than 1 percent of gross domestic product.[20] As is usual in health impact evaluation studies, the major component of direct costs was the present value of future lifetime earnings of persons in the prime working ages who died. Much of the labor force impact of pandemic influenza would depend on whether excess mortality affected the old and the young, as in 1957–58 and 1968–69, or those in the prime of life, as in 1918–19; Meltzer et al. made the assumption that the old and the young would be most at risk. Declining tax revenues and the need for increased expenditure in response to the epidemic (both health spending and economic relief to distressed sectors) would increase government fiscal deficits.[21]

Indirect costs would include the economic multiplier effects of the direct costs, plus the results of shifts in the structural parameters governing such fundamental economic behavior as consumption. A wide range of such effects might be expected. Private consumption would be reduced not only as a direct result of illness, but also as consumer confidence was reduced and demand for precautionary balances rose. Investment might decline along with business sentiment; at some point, however, depleted inventories would have to be rebuilt. Home bias, that is, the preference for domestic goods and assets over foreign ones, would increase, the latter perhaps reducing foreign direct investment, which has been the main instrument of global economic integration and growth in Asia. Trade would suffer and supply chains would

be disrupted. To judge from experience with SARS, the travel, tourism, hotel, and restaurant sectors would probably suffer severe losses. There might be a global flight to quality, perhaps short-term US government debt, in asset markets. The equity premium would everywhere rise, and impacts on currency markets might be considerable.

All of these hypothesized macroeconomic impacts augur a significant decrease in gross domestic product around the world as a result of a pandemic, with some "connected," outward-looking countries faring worse than less open ones.

A number of recent reports have estimated the consequences of pandemic influenza. The Asian Development Bank has considered an Asian pandemic with a 20 percent attack rate and a 0.5 percent case–fatality rate (Bloom et al. 2005). Depending on how long the psychological shock of the pandemic persisted, the Bank estimated an economic impact of about 2–7 percent of GDP in the region. In New Zealand, the Treasury examined a pandemic with a 40 percent attack rate and a 2 percent case–fatality rate, concluding that GDP in the year of the event would be reduced by 5–10 percent (Douglas et al. 2006). Of interest in both simulations is that the demand effect mediated through consumer and investor behavior is held to be much stronger than the direct supply side effect, most of the latter due to lost days of work. The US Congressional Budget Office (CBO 2006) estimated that, on the assumption that 30 percent of all US workers became ill, 2.5 percent died, and those who survived missed three weeks of work, US GDP would decline by 5 percent. McKibben and Sidorenko (2006) estimated that a mild pandemic might reduce global output by 1 percent, while a very serious one on the scale of 1918–20 might reduce it by 10 percent.

The example of SARS, especially its impacts on the region most affected, Southeast Asia, should provide some indication of what consequences pandemic influenza might have.[22] In a report published in mid-2003 (Fan 2003), the Asian Development Bank examined two cases, a SARS epidemic lasting one fiscal quarter and a SARS epidemic lasting two quarters. In the first case, the 2003 annual GDP growth rate was estimated to be reduced by 0.4 percentage points against a no-epidemic baseline in East Asia (China, Hong Kong, South Korea, Taiwan) and by 0.5 percentage points in Southeast Asia (Indonesia, Malaysia, Philippines, Singapore, and Thailand). A two-quarter epidemic was estimated to reduce annual GDP growth by 1.0 percentage point in East Asia and 1.4 percentage points in Southeast Asia. Lee and McKibbin (2004) estimated that SARS would reduce GDP in China by 1 percent in 2003 (the epidemic emerged in November 2002) if economic agents expected the epidemic to be short-term, but by over twice that if such agents expected that it would persist (diminishing steadily) over ten years. It is an open question whether the impact of SARS—a new disease for which authorities were entirely unprepared—on expectations and confidence would be greater or less

than the impact of pandemic influenza. SARS resolved itself quickly, whereas pandemic influenza would remain in the headlines month after month, with depressingly high mortality and morbidity.

Switching to a microeconomic perspective, the impact on GDP per capita is open to debate: it would depend on the age profile of mortality and morbidity and on the elasticity of substitution between capital and labor.[23] The instantaneous reduction in the labor force as a result of the pandemic would lead to an increase in capital per worker and a corresponding increase in wages and decline in the rate of return to capital.[24] In a simple neoclassical model, characterized by diminishing marginal returns, an exogenous saving rate, and an exogenous rate of total factor productivity growth, the investment required to maintain the higher capital–output ratio would exceed available savings. Therefore the capital–output ratio would gradually decline to its baseline value (and the wage rate along with it). The process of shock and re-equilibration would consist of an immediate increase in output per worker, followed by negative growth as the capital–output ratio returned to its equilibrium value, following which there would be no impact on the long-run equilibrium rate of growth.

Even in a simple model, however, a number of factors could complicate the picture. An increase in household demand for precautionary balances might offset the decline in public savings, so the overall effect on savings is indeterminate. If the aggregate saving rate increased, the long-term equilibrium capital–output ratio would be increased, and vice versa in the case of a decline. Effects of pandemic mortality on the age structure might influence the household saving rate by changing the ratio of persons in the main saving age bracket (20–64 years) to those in the main dis-saving age bracket (65+ years). The age profile of excess mortality would also, as mentioned above, affect age-based transfer systems (pensions and health).

A medium-term shift in the rate of population growth would also mean that the capital–output ratio would not return to its original equilibrium. Finally, the simple neoclassical model is one in which prices adjust to instantly clear markets. In a macroeconomic context, where wages, interest rates, and commodity prices are likely to be sticky, additional impacts of the type described above, often with a significant role of expectations, would be possible.

Even laying aside the claim by Murray et al. (2007) that mortality and morbidity would be greatest in the developing world, it seems likely that economic impacts in low-income countries would be especially severe. Schultz (1964) found that the 1918–20 pandemic significantly increased output per worker in the agricultural labor force in India. However, it is the household, not the worker, that is of most interest. Poor households would suffer immediate losses from lost wage income, in addition to which they would be forced to sell assets in order to care for the sick. Much research indicates that

episodes of illness push families on the brink of poverty into poverty and prevent those in poverty from climbing out.

Because of the many ambiguities, it has proven difficult to apply growth theory to estimate with any certainty the economic impact of severe epidemics.[25] Brainerd and Siegler (2003) find for the United States that the 1918–20 pandemic significantly raised (not lowered, as the unadorned neoclassical model would suggest) growth of GDP per capita for about a decade after the event. Perhaps the concentration of mortality among the most productive members of the population (the middle spike of the W) reduced per capita income (despite presumably having increased per worker output) and led to ill-defined catch-up effects.

Closing thoughts

This review began with the question whether the current near-crisis level of concern over the likelihood of an influenza pandemic was justified. The range of issues raised by pandemic influenza is wide, and different readers may well, based on the discussion above, arrive at different answers. For the author, the answer is captured by the German colloquialism *Jein*—yes and no.

That there will be another pandemic, and perhaps soon, is not in question. The key issues are its pathogenicity and its age-attack curve, which are difficult if not impossible to predict. A mild pandemic, or one affecting only the very young and the very old, even if deadly, will attract relatively little attention. On the other hand, a repetition of the 1918–20 W-shaped pattern, even if overall pathogenicity is rather mild, will be a severe event.

Pandemics may be expected, albeit not predicted. The issues raised here should not be addressed on the basis of "preparing for the next one," an approach that is bound to lead to policy fatigue if the looked-for pandemic does not emerge soon and to a boom–bust policy cycle if it does. This is especially true in the developing world, where pandemic influenza should rather be addressed as part of a sustained medium-term program for strengthening health systems, a win–win option that bears fruit even in the absence of a pandemic. Overall rural development, and veterinary health in particular, are key to alleviating the problem and, again, can be considered win–win options. The scientific arsenal has never been stronger, yet gaps in availability of antiviral drugs and vaccines are inevitable and the world is poorly prepared to deal with the politics of shortage. Some studies suggest that emerging pandemics can be "ring-fenced," but this conclusion is not universally accepted. It is agreed, however, that the entire of range of complementary responses, from antiviral prophylaxis to social distancing, all targeted to maximize effectiveness, should be deployed as needed. A theme that cuts across all aspects of pandemic influenza is governance (at both the national and global levels), which is as important as capacity issues. Governance problems, such as the

fragility of health systems, represent structural weaknesses and are not best addressed by crisis-mentality preparedness planning.

Notes

1 This essay had its origin as the overview paper of the workshop "Policy and Social Aspects of Pandemic Influenza," held at IIASA on 4–5 August 2006. Assistance from Wah-Sui Almberg is gratefully acknowledged. General background sources on influenza consulted include Cox and Bender (1995), Cox and Subbarao (2000), Earn et al. (2002), and Kilbourne (1987).

2 It was once accepted wisdom that pandemics occurred in a 10–11-year cycle (which fueled concerns over a possible 1976 pandemic), but this is now known to be false (Dowdle 2006).

3 A pandemic in 1830–32 was as deadly, in relative terms, as the 1918–20 pandemic.

4 Some researchers also cite 1946 and 1977 as years in which relatively minor pandemics occurred.

5 This is an oversimplification: in past pandemics susceptibility has varied by age group according to exposure to previous influenza viruses.

6 H5N1 is, however, not the only candidate for causing the next pandemic; Bartlett and Hayden (2005) list five avian influenza viruses that have caused human infection since 1997. Dowdle (2006) is particularly concerned by H2N2. Webby and Webster (2003: 1519–1520) discuss different viral subtypes at length.

7 H5N1 has been found in pigs in China and Indonesia; H3N2 is endemic in pigs in the region, so the opportunity for reassortment with a human-to-human transmissible virus exists.

8 The Writing Committee (2005) adds that the most sophisticated assay method, the reverse transcriptase polymerase chain reaction test for viral RNA, is increasingly detecting mild and asymptomatic cases among persons in contact with known cases. This development contains both good and bad news. It suggests that the virus is becoming increasingly transmissible from human to human, at least at the local level (placing us in Phase 4 of the WHO influenza cycle—see Figure 1). However, factoring in mild cases would also reduce the elevated case–fatality rates estimated to date.

9 The highly pathogenic H5N1 virus that caused deaths in Vietnam in 2004 was genetically distinct from the strain that caused deaths in Hong Kong in 1997, suggesting that vaccines prepared on the basis of the 1997 strain are unlikely to be effective against today's virus (Horimoto et al. 2004).

10 The HA protein determines the receptor preference of the virus. Classic avian influenza strains preferentially bind to intestinal epithelial cells of fowl; human pathogenic strains such as the 1918 H1N1 virus contain HA variants that preferentially bind to the epithelial cells of the human upper respiratory tract (Stevens et al. 2006). A minor mutation of two points on the HA protein array was found to be sufficient to revert a strain of the 1918 virus to a classic avian virus.

11 The case–fatality rate among US Army troops in 1918–20 was 5–10 percent. Mortality in some sub-populations, for example, the population of some Pacific islands, was far higher, ranging from 5 percent in Fiji to 20 percent in Western Samoa (Wilson et al. 2005 for references).

12 Another antiviral agent, Relenza, has received less attention than it perhaps deserves. GSK had shut down production capacity for the drug, which is administered via a nasal spray, but reopened it under pressure from the international public health community. Many countries have increased stocks of Relenza to diversify their portfolio of responses and as a fallback in the event of Tamiflu-resistance. I am indebted to an anonymous reviewer for these points.

13 There was excess influenza mortality (i.e., mortality over that expected in a normal year) for the very old and very young as well, but enormous excess mortality for young adults.

14 Bell and Lewis (2004) describe the sequence of events. The first case was observed in Guangdong Province in November 2002. Local public health officials downplayed the seriousness of the outbreak, and there was insufficient information flow between the provincial and central levels. In February 2003 Ministry of Health officials in Beijing announced that there had been an outbreak of "atypical pneumonia" but that it was under control. A physician who publicly disagreed was arrested and jailed. By March, SARS was recognized as a previously unknown disease and was spreading throughout Southeast Asia.

15 Implications of intellectual property rights (IPRs) for new techniques of vaccine development would appear to be the major link between intellectual property rights and vaccines. A WHO conference concluded that, to date, Trade-related Aspects of Intellectual Property Rights (TRIPS) have neither stimulated the development of new vaccines relevant to the developing world nor reduced demand for vaccine in poor countries (Milstein and Kaddar 2006).

16 Taking account of the potential to convert avian influenza vaccine production to human vaccine might triple this figure. A reviewer commented that this approach, much advocated by public health experts, is regarded as impractical by the pharmaceutical industry.

17 Current practice is to allow reassortment to take place in embryonated chicken eggs until the desired genetic profile is observed (Webby and Webster 2003). These strains are then grown, again in embryonated chicken eggs, to produce vaccine stocks. There are two elements to the time delay. First, random reassortment must take place until a suitable viral strain emerges. Second, it takes time to obtain the needed large number of chicken eggs. To make matters worse, the H5 virus kills chicken embryos, requiring arduous measures to produce vaccines.

18 In September 2005, Dr. David Nabarro, then the newly named UN coordinator for influenza, was sharply criticized by WHO for scaremongering when he warned that 150 million persons might die. Yet, predictions have ranged from 2 to 360 million, and WHO itself commented that there was too much uncertainty to choose one number over another. Murray et al. (2007) applied 1918 mortality rates to current population to estimate possible mortality of 62 million (their median estimate). Provocatively, Murray et al. predict that almost all of these deaths would be in developing countries.

19 One of those authors, Osterholm (2005b), does not mince words in another article: "The global economy would come to a halt ..." (Osterholm 2005a: 1840).

20 Balicer et al. (2005), applying a similar approach to Israel, estimated the direct costs of pandemic influenza to be 0.5 percent of Israel's GDP.

21 See Bell and Lewis (2004) for a description of the relief measures instituted by Southeast Asian countries in response to SARS.

22 Bell and Lewis (2004) present a cogent account of the development of the epidemic, its clinical aspects and epidemiological progression, and the policy response.

23 This discussion of the neoclassical growth model is based on Brainerd and Siegler (2003: 8–11).

24 Bloom and Mahal (1997) found no impact of the Black Death on land rents, but Bell and Lewis (2004) attribute the negative finding to small sample size. The latter authors are also dismissive of Bloom and Mahal's finding that the 1918–20 influenza pandemic had little impact on Indian agricultural output (a finding that contradicted earlier work by Schultz cited below). The decline in the rate of return to capital would be consistent with a decline in asset prices—perhaps a steep one for housing, where the market might take years to adjust to the downward demand shock.

25 Controversies over the economic impact of pandemic influenza parallel controversies over the impact of natural disasters (floods, earthquakes, etc.) on economic growth.

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