

PANDEMIC INFLUENZA ISSUES

Landis MacKellar

International Institute for Applied Systems Analysis, Vienna

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The global health system is straining to meet rising needs and expectations with limited resources. Against this challenging background has re-emerged the predicament of pandemic influenza, which epidemiologists warn is practically certain to recur within a matter of years if not months (Webster 1997, Webby and Webster 2003). Pandemic influenza is not a problem (problems have solutions) so much as it is a predicament – a situation with negative consequences that can, at best, be kept to a tolerable minimum.

*Influenza.*¹ Influenza is a respiratory infection caused by an RNA virus of the family Orthomyxoviridae. There are three main types of influenza virus (A, B, and C). It is A that 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 virus' outer coat – Haemagglutinin (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. It is these proteins that are attacked by the human immune system, so 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, accounting for perhaps one million deaths worldwide (about 65,000 in the U.S.) In the U.S., the “attack rate” (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 proclaimed by the public health community (see Fedson 2003, p. 1532 for citations), although epidemiologists and laboratory scientists sometimes express doubts.

One of the challenges of influenza is that little is known about its transmission. It is generally held that the virus is spread during the symptomatic stage by respiratory secretions in the form of droplets. However, it is difficult to explain the explosive trajectory of influenza pandemics without some form of airborne transmission. Historical data suggest no change in the speed of influenza's spread over recent centuries, despite the explosion in travel and contact. 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. 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

¹ Assistance from Wah-Sui Almberg is gratefully acknowledged. As this section is non-technical in nature, full citations are not given. General sources consulted include Cox and Bender (1995), Cox and Subbarao (2000), Earn *et al.* (2002), and Kilbourne (1987).

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);
- a mild one in 1957-58 (“Asian flu,” caused by the H2N2 subtype), in which about 1 million died;
- and a mild one in 1968-69 (“Hong Kong flu,” caused by the H3N2 subtype), when mortality was also on the order of 1 million.³

In the 1918-20 and 1957-58 pandemics, infection rates on the order of 50 percent and attack rates, i.e. the proportion of the population experiencing clinical illness, on the order of 25 percent were observed. Perhaps just as important as these, when its impact on policy is considered, is the 1976 swine flu epidemic, which failed to materialize after U.S. policy makers had launched a mass vaccination campaign.

Scaling up the global population in 1918 (1.8 billion) to current levels, it is not inconceivable that 200 million or even more persons would die in the event of a hyper-virulent pandemic.⁴ Smil (2005) ranked influenza pandemic as the single most likely “transformational” catastrophe which might change the course of history. Fear of a devastating pandemic is strong enough that the editors of the opinion-leading journal *Foreign Affairs* devoted its March 2005 issue to the theme. President George W. Bush called for broad latitude to deploy the U.S. military in the fight against influenza. Mr. Andrew Natasios, Administrator of the U.S. Agency for International Development (USAID) 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.

How do new influenza viruses appear? The processes by which the influenza A virus undergoes evolution are two: 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. A likely scenario for producing a shifted influenza strain is combination of segments from a human virus and an avian virus, resulting in a re-assortment of genetic material. One way for this to happen is for swine, susceptible to both human

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

³ Some researchers also cite 1946 and 1977 as years in which relatively minor pandemics occurred.

⁴ In September 2005, Dr. David Nabarro, newly-named U.N. coordinator for influenza, was criticized by the WHO for warning that 150 million persons might die. Yet, predictions have ranged from 2-360 million and WHO itself commented, in the course of the flap over Nabarro’s comments, that there was too much uncertainty to choose one number over another. A pandemic in 1830-32 was as deadly, in relative terms, as the 1918-20 pandemic.

and avian influenza, to serve as an intermediary host in which re-assortment can occur. Therefore, the co-residence of the “Three P’s” – people, pigs, and poultry – in rural Asia is a risk for the emergence of pandemic influenza, leading some researchers to refer to this region (specifically, China) as an “influenza epicenter” (Hampson 1997). Osterholm (2005a and b) 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).⁵ 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 or HPAI. 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. While H5N1 avian influenza emerged in Asia, migratory wildfowl have spread the disease to Russia and, most recently, to Turkey and Romania. The Office International des Epizooties (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, and yet the H5N1 virus is nowhere near being contained, let alone eradicated.

The 1957 and 1967 pandemic viruses (H2N2 and H3N2) both arose from re-assortment. Some have found it encouraging, if mystifying, that H5N1 has not re-assorted despite having had ample chance to do so (Stöhr 2005).⁶ Perhaps the viruses resulting from re-assortment, if such has taken place, have been so benign as to escape notice. However, re-assortment 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 re-assortment 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, 6 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 in China, Thailand, Indonesia, and Viet Nam. As yet, all known cases of human avian influenza appear to represent bird-to-human transmission, with the exception of a possible case of person-to-person transmission at

⁵ H5N1 is, however, not the only candidate for causing the next pandemic; Bartlett and Hayden (2005) list five different avian influenza viruses that have caused human infection since 1997. Dowdle (2006) is particularly concerned by H2N2. Webby and Webster (2003, p. 1519-20) discuss different viral subtypes at length.

⁶ H5N1 has been found in pigs in China and Indonesia; H3N2 is endemic in pigs in the region, so the opportunity for re-assortment with a human-to-human transmissible virus is there.

very close quarters (Ungchusak *et al.* 2005).⁷ 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 This suggests 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, this will represent the beginning of a potentially catastrophic pandemic -- and the H5N1 virus is known to mutate rapidly.⁹ The genetic changes necessary to adapt the H5N1 virus from avian to human receptors are minor (Harvey *et al.* 2004).

The WHO (2005a) has divided the influenza cycle into six phases, as follows:

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 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, 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 in general population.

Note that, while inter-pandemic influenza is highly seasonal, pandemic influenza can emerge at any time.

⁷ See Writing Committee of the WHO (2005), Table 3 for a synopsis of 52 confirmed avian influenza cases in humans. 42 of the 52 had confirmed exposure to sick poultry. Others may have contracted the disease from asymptomatic infected poultry such as ducks.

⁸ The Writing Committee (2005) adds that the most sophisticated assay method, the reverse transcriptase polymerase chain reaction test for viral RNA, is increasingly picking up 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). However, factoring in mild cases would also reduce the elevated case-fatality ratios estimated to date.

⁹ The highly pathogenic H5N1 virus that caused deaths in Viet Nam 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).

Based on this scheme, H5N1 influenza appears to be in Phase 3, where some cases of person-to-person transmission have been observed, but human-to-human transmissibility is low. Some 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 Dr. Henry Liman's www.recombinomics.com for this argument). Even if this maverick view is incorrect, WHO has listed six points that give cause for grave concern (WHO 2005b):

- H5N1 has spread rapidly among poultry in Asia and is now endemic to the region. The authors might have added that it is now known that H5N1 is 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.
- 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; Webby and Webster (2003) derive the same conclusion from the cluster of avian-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 do 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 killing machine. Some argue that mortality arose from a "cytokine storm," an immune system response leading to acute respiratory distress syndrome (Kobasa *et al.* 2004). Perhaps ominously, H5N1 haemagglutinin shares molecular characteristics with that of the 1918 virus (Hatta *et al.* 2001). Laboratory animals infected with the H5N1 virus become much, much sicker than control-group animals infected with H3N2 (Ward *et al.* 2005, p. i7 for references).

As of September 29, 2005, the WHO recognized 116 human cases of avian influenza, of which 60 resulted in death. This case-fatality rate of roughly 50 percent is inflated because cases have not been reported; however, even if it is four or five times too high, it would rank with the 1918-20 virus.¹⁰ There is no established clinical protocol for treatment of the disease other than broad-spectrum antibiotics and the antiviral agents oseltamavir and zanamivir (Tamiflu and Relenza), manufactured by the pharmaceutical firms Roche and GSK respectively (Ward *et al.* 2005 for the case of 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 (*ibid*). Demand for the

¹⁰ The case-fatality ratio among U.S. Army troops in 1918-19 was 5-10 percent. Mortality in some sub-populations, for example, the population of the Pacific Islands, was staggering (Wilson *et al.* 2005 for references).

drug has soared and Roche is considering licensing governments and other firms to manufacture it. Relenza has generally attracted less interest, partly because, since it is taken intra-nasally, it is difficult to stockpile.

It is practically unavoidable, if sometimes 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 be greatly dependent on its age-attack profile, i.e. the age groups at greatest risk. The typical age profile of influenza mortality is a U, i.e. 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 evil reputation of the 1918-19 pandemic is in part due to the fact that attack rates followed an idiosyncratic W-shape; i.e., to the traditional peaks at the extremes of the life span was added a peak for young adults.¹¹ 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 close contact with poultry in farmyards.

Policy responses to pandemic influenza. Policies to respond to pandemic influenza fall into three time frames – measures that can be taken before emergence of the 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 WHO, and the OIE, 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 is a strategy 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.

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 thought to occur before the onset of symptoms. 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 occur.

Yet, two recently published high-profile micro-simulation studies concluded that timely policy measures could successfully “ring-fence” influenza outbreaks in Southeast Asia (Ferguson *et al.* 2005, Longini *et al.* 2005). The main intervention foreseen was targeted post-exposure prophylaxis with the anti-virals, combined with “social distancing” (school and workplace closures, etc.) and quarantine. Opinions

¹¹ Note that there was excess influenza mortality (i.e., mortality over a normal year) for the very old and very young as well, but enormous excess mortality for young adults.

differ: Monto (2006) takes the idea seriously; *The Lancet*, however, in its lead editorial for 13 May, 2006, was openly dismissive.

The value of R_0 is the key assumption in model simulations.¹² A simulation study for the United States suggested that for a relatively low R_0 coefficient of 1.7, the model a stockpile of 10 million courses of Tamiflu, twice the current U.S. 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 utterly unrealistic 182 million courses. The higher R_0 , the greater the need for comprehensive approaches involving antivirals, vaccination, social distancing, and travel restrictions.

“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 the Southeast Asia (e.g., Laos and Cambodia) have virtually no epidemiological field surveillance capacity at all. Emergency technical assistance programs to put surveillance capacity in place are underway (for example, USAID has dispatched US\$ 25 million to the region). However, these efforts will take time to bear fruit.

Capacity in place will not help unless governance issues have been resolved. During the SARS episode, China experienced what can only be called an embarrassing fiasco when Ministry of Health officials tried to cover up the epidemic.¹³ A number of high profile sackings, and public commitments never again to engage in such behavior resulted, but old habits die hard. China’s recent decision 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 centre, implementation in the field may be weak. All over the region, regardless of central government policy, farmers are reluctant to report epidemic outbreaks and local officials are inclined to suppress the news, because livelihoods are at stake.

Once a pandemic is established, antiviral drugs will likely play a major role. While not yet tested under pandemic conditions the indications are that antivirals will be effective. Best of all, they will be effective from the very beginning of a pandemic, whereas efforts to develop and deliver a vaccine will take time to bear fruit (Monto 2006). However, anti-viral drugs are not a panacea. Global stocks are nowhere near enough to meet the demand that would arise in the event of a pandemic. There is no guarantee that antiviral resistance would not emerge during the course of a pandemic (Tamiflu-resistant strains of H5N1 have already been found). If a resistant

¹² R_0 is the number of persons infected by each infectious individual in a completely immuno-naïve population (i.e. at the onset of a pandemic; hence the sub-script). 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 declines as an epidemic progresses and growing numbers of persons in the population acquire immunity..

¹³ Bell and Lewis (2003) 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. 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 put in jail. By March, SARS was recognized as a previously unknown disease and was spreading throughout Southeast Asia

(and transmissible) strain did emerge, all use of the antiretroviral agent would need to be stopped immediately; otherwise non-resistant strains would be killed off and only the resistant strain would be left in place. The H5N1 virus is already resistant to another antiviral agent, adamantine. It has been argued, however, that Tamiflu is less susceptible to resistance (Ward *et al.* 2005).

Vaccine development and administration would be a key response to a pandemic. Using traditional approaches, it takes the global pharmaceutical industry 6-8 months to develop an influenza vaccine from the time that the viral strain to be protected against is isolated. In normal years, the genetic mutation from last year's virus is small. Thus, when patients are immunized with a vaccine based on the last flu 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 to 8 months, the pandemic would already be globally established (Stöhr & Esveld 2004).

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). However, reverse genetics raises issues of intellectual property rights (IPRs) and consumer acceptance (Webby and Webster 2003).¹⁴ Early development of candidate vaccines is another prudent step, and several candidate vaccines generated from H5 isolates are already under study (Writing Committee of WHO 2005, p. 1383 for references). The problem of removing the highly pathogenic component of the H5N1 virus has already been solved (Monto 2006). However, rapid mutation 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 mathematics is not complex – a given stock of vaccine requiring one immunization will make it possible to protect twice as many persons as one requiring two.

Laboratory development of a vaccine will be only the beginning of the challenge. Vaccines in general are not a profitable line of business for pharmaceutical firms, which take little interest in them (Fedson 2003, 2005; Hinman *et al.* 2006). So do governments, whose purchases of vaccines have generally been low. 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 put in place. Adding to the pharmaceutical industry's distaste for vaccines are memories of the 1976 U.S. "swine flu" *débaclé*, in which hundreds of persons suffered serious adverse effects from the mass vaccination program instituted. In the U.S., the U.K., and Europe, civil society groups opposing immunization have become a political force.

¹⁴ Implications of 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) has neither stimulated the development of new vaccines relevant to the Third World nor reduced demand in poor countries for vaccine (Milstien and Kaddar 2006).

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.¹⁵ A chaotic situation in which major countries attempt to lock in supplies by negotiating forward contracts with individual suppliers can be foreseen. Osterholm (2005a) complains of "1950s egg-based technology" and the lack of national commitment (in the U.S.) to universal influenza vaccination as major barriers to pandemic preparedness.¹⁶ His estimate is that vaccine sufficient to vaccinate 500 million persons against a new influenza strain might be available within 6 months of the beginning of a pandemic. Between the limited number of doses and the concentration of manufacturing capacity in less than a dozen countries, there will be thorny questions of how to allocate inadequate vaccine stocks. It is practically impossible to imagine national policy makers freeing vaccine from national stocks in order to vaccinate populations in greater need elsewhere in the world.

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 re-assortment 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 3-5 years and would need to be sustained over a timeframe of 10 years to reap full benefits (Kieny *et al.* 2006). Not considered by WHO, but another means of boosting effective supply, would be harmonization of regulatory standards among countries (Gronvall and Borio 2006).

One may envision not only vaccine (and antiviral) shortages, but a more general situation of health system-wide distress. 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. Some 50 countries have responded to the call to prepare pandemic preparedness plans (PPPs), but very few of these are operationally credible, even in Europe (Mounier-Jack and Coker 2006).¹⁷ The UK and Canada are reckoned to represent the state of the art in pandemic planning.

¹⁵ Taking account of the potential to convert avian influenza vaccine production to human vaccine might triple this figure.

¹⁶ Current practice is to allow re-assortment 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 re-assortment 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.

¹⁷ In a letter to *The Lancet* (July 2, 2006, the Irish doctor's trade union acidly remarked that no resources are available in Ireland to pay for overtime for public health physicians.

Demographic impacts of pandemic influenza. 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 1918-20 suggests that pandemic influenza has the potential to kill 100-300 million persons if the case-fatality ratio is high enough. However, the age-profile of mortality could have a significant impact on population age structures, and along with it, age-based transfer systems such as pension systems. 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. The heat wave in France in 2003 is currently being studied by demographers as an example of this, with preliminary findings pointing to the fact that year-on-year comparisons show that the heat-related deaths were among the most frail elderly, so the total person-years of life lost was less than what would be expected by applying an actuarial table of life expectancy to the age distribution of heat wave deaths. In the 1918-20 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 to die years later. Today, especially in developing countries, TB 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 a group highly affected by an influenza pandemic. However, the point is open to discussion: there is an argument that an over-vigorous immune response to the virus ((the “cytokine storm”) is what 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 expectations or lagged health effects of the pandemic.

Economic impacts of pandemic influenza. Based on the discussion above, even if an influenza pandemic is some years in the future, and even if it is far less severe than feared, there is likely to be significant economic disruption. Economic impacts of disease can usefully be classified as direct and indirect. Direct impacts, which have been widely studied, would include direct hospital costs, loss of days of work, costs of medication consumed, etc. In a much-cited piece Meltzer *et al.* (1999) estimated the direct costs of pandemic influenza in the U.S. to be, to an order of magnitude, US\$ 100 billion, a bit less than 1 percent of gross domestic product or GDP.¹⁸ 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

¹⁸ Balicer *et al.* 2005, applying a similar approach to Israel, estimated the direct costs of pandemic influenza to be 0.5 percent of Israeli GDP.

1968-69, or those in the prime of life, as in 1918-19; Meltzer *et al.* made the assumption that it would be the old and young who were most at risk.

Indirect costs would include the economic multiplier impacts of these costs, plus the results of shifts in the structural parameters fundamental economic behaviors such as consumption. It is striking that, apart from one thought-piece (Bell and Lewis 2004), there has not been any serious consideration of the potential economic effects of an influenza pandemic.¹⁹ The authors of the pieces that appeared in the March 2005 special issue of *Foreign Affairs* all one way or another expressed the view that the global economy would simply freeze up in the event of pandemic influenza.²⁰ This view is speculative in the extreme, not to mention that it overlooks that fact that in 1918-19, the global economy demonstrably did not skid to a halt.

However, looked at from a macroeconomic point of view, a wide range of important effects might be expected. Private consumption would be reduced not only as direct result of illness, but as consumer confidence was reduced and demand for precautionary balances rose. 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 Investment might decline along with business sentiment; at some point, however, depleted inventories would have to be rebuilt. Home bias, i.e., the preference for domestic goods and assets over foreign ones, would increase, the latter perhaps reducing the FDI which has been the main instrument of global economic integration and growth in Asia. Trade would suffer, and supply chains would be interrupted. To judge from experience with SARS, the travel, tourism, hotel, and restaurant sectors would probably suffer severe losses (Bell and Lewis 2004). There might be a global flight to quality, perhaps short-term US government debt, in asset markets. Currency market impacts might be considerable.

All of these hypothesized macroeconomic impacts argue in favor of a significant decrease in world GDP as a result of a pandemic, with some regions presumably being more seriously affected than others. Much evidence suggests that “connected,” outward-looking countries fare better in the long run; in the event of a pandemic, it might be autarchic countries that better withstood the shock.

Switching to a microeconomic perspective, the impact on *per capita* GDP would be contentious, as it would depend on the age-profile of mortality / morbidity as well as the elasticity of substitution between capital and labor.²² The instantaneous reduction in labor force as a result of the pandemic would lead to an increase in capital per worker and corresponding increase in wages and decline in the rate of

¹⁹ In this section, we leave to one side the sizeable literature on the economic impacts of HIV/AIDS (well summarized by Bell and Lewis 2004), which is of limited relevance. HIV/AIDS is a slow-onset, wasting disease, spread by modifiable behaviors, whose economic impacts are spread over many years. Pandemic influenza is a short, sharp shock spread by casual contact.

²⁰ One of those authors, Osterholm (2005b), is succinct and to the point in another article: “The global economy would come to a halt ...” (Osterholm 2005a, p. 1840).

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

²² This discussion of the neoclassical growth model is based on Brainerd and Siegler 2003, pp. 8-11.

return to capital.²³ 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 return 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.

However, even in a simple model, a number of things could complicate the picture. An increase in the 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. Impacts of pandemic mortality on the age structure might affect the household saving rate by changing the ratio of persons in the main saving age bracket (20-64) to those in the main dis-saving age bracket (65+). 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, such as described above in discussing demographic impacts, 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.

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 member of the agricultural labor force in India. However, from a welfare point of view, it is the household, not the worker, which is of 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 estimate with any certainty the economic impact of severe epidemics.²⁴ Brainerd and Siegler (2003) find for the U.S. 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

²³ Bloom and Mahal (1997) found no impact of the Black Death on land rents, but Bell and Lewis (2004) blame the negative finding on small sample size. The same authors are also rather 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.

²⁴ Controversies over the economic impact of pandemic influenza parallel controversies over the impact of natural disasters (floods, earthquakes, etc.) on economic growth.

income (despite presumably having increased per worker output) and led to ill-defined catch-up effects.

The case of SARS, especially its impacts on the region most affected, Southeast Asia, should provide some indication of what impacts pandemic influenza might have.²⁵ In a report published in mid-2003 (Fan 2003), the Asian Development Bank examined two cases, a 1-quarter SARS epidemic and a two-quarter SARS epidemic. In the first case, the 2003 annual GDP growth rate was estimated to be reduced by 0.4 percentage point against a no-epidemic baseline in East Asia (People's Republic of China, Hong Kong, Republic of Korea, Taiwan) and by 0.5 percentage point in Southeast Asia (Indonesia, Malaysia, Philippines, Singapore, and Thailand). A 2-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), using a global general equilibrium model that highlighted the role of expectations, estimated that SARS would reduce GDP in China by 1 percent in 2003 if agents expected the epidemic to be short-term, but by over twice that if agents expected that it would persist (diminishing steadily) over ten years. It is an open question whether the impact of SARS -- a totally 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 quarter after quarter, with depressingly high mortality and morbidity.

Two recent reports have estimated impacts of pandemic influenza. In Southeast Asia, the Asian Development Bank has considered a pandemic with a 20 percent attack rate and a 0.5 percent case-fatality ratio (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 regional GDP. In New Zealand, the Treasury examined a pandemic with a 40 percent attack rate and a 2 percent case fatality rate, and concluded 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 demand effect mediated through consumer and investor behavior are held to be much stronger than direct supply side effect, most of them due to lost days of work.

Closing thoughts. The range of issues raised by pandemic influenza is wide, and different readers may well arrive at different conclusions based on the discussion above. A few thoughts that occurred to the author are as follows:

- The key issues are the pathogenicity of the pandemic (how deadly it is) and its age-attack curve. A mild pandemic, or one affecting only the very young and very old, even if deadly, will attract relatively little attention. A repetition of the 1918-19 W-pattern, even if overall pathogenicity is rather mild, will be a severe event.
- In many cases, overall health system strengthening will be preferable to vertical pandemic preparedness planning. Strong health systems will not only be able to respond better to pandemic influenza, but will be better able to maintain normal operations during the height of the event. Health system strengthening is also a win-win option; it bears fruit even in the absence of a pandemic.

²⁵ Bell and Lewis (2004) present a cogent account of the development of the epidemic, its clinical aspects and epidemiological progression, and the policy response.

- In improving surveillance, governance issues are as important as capacity issues.
- Even if the global vaccine system is enhanced, it is necessary to plan for extreme shortages of vaccine (and antivirals). Contingency planning and prioritization now will reduce the level of chaos and recrimination later.

Perhaps most important, pandemics are events that may be expected, albeit not predicted. The issues raised by pandemic influenza should not be addressed on the basis of “preparing for the next one,” but as part of a sustained medium-term program for strengthening the world health system.

References Cited

Balicer R.D., M. Huerta, N. Davidovitch, and I. Grotto 2005 (August). Cost-benefit of stockpiling drugs for influenza pandemic. *Emerging Infectious Diseases*. Available online at <http://www.cdc.gov/ncidod/EID/vol11no08/04-1156.htm>

Bartlett, J. and F. Hayden 2005. Influenza A (H5N1): Will it be the next pandemic influenza? Are we ready? *Annals of Internal Medicine* 143(6): 460-62.

Bell, C. and . Lewis 2004. The economic implications of epidemics old and new. *World Economics* 5(4).

Bloom, D. and A. Mahal 1997. AIDS, flu, and Black Death: Impacts on economic growth and well-being. In D. Bloom and P. Godwin, eds., *The Economics of HIV and AIDS: the Case of South and South East Asia*. New York: Oxford University Press.

Bloom, E., V. de Wit, and Mary Jane Carangal-SanJose 2005. *Potential economic impact of an avian flu pandemic on Asia*. ERD Policy Brief No. 42. Manila: Asian Development Bank.

Brainerd, E. and M Siegler 2003 (February). The economic effects of the 1918 influenza epidemic. Centre for Economic Policy Research Discussion Paper 3791. London: CEPR.

Class, E. *et al.* 1998. Human influenza A H5N1 virus related to a highly pathogenic avian influenza virus. *The Lancet* 351:472-7.

Cooper, B. Delaying the international spread of pandemic influenza. Manuscript, Modelling and Economic Unit, Health Protection Agency, London, UK.

Cox, N. and C. Bender 1995. The molecular epidemiology of influenza viruses. *Seminars in Virology* 6: 359-370, 1995.

Cox, N and K. Subbarao 2000. Global epidemiology of influenza: past and present. *Annual Review of Medicine* 51: 407-421.

Dowdle, W.R. 2006. Influenza pandemic periodicity, virus recycling, and the art of risk assessment. *Emerging Infectious Diseases* 12(1): 34-39.

Earn, D., J. Dushoff, and S. Levin 2002. Ecology and evolution of the flu. *Trends in Ecology and Evolution* 17(7): 2002.

Ermolieva, T., G. Fischer, and H. van Velthuis 2005. *Livestock production and environmental risks in China: scenarios to 2030*. Laxenburg, Austria: IIASA.

- Fan, Emma Xiaoquin 2003. SARS: economic impacts and implications. *ERD Policy Brief* 15. Manila: Asian Development Bank. Available online at <http://www.adb.org/economics>
- Fedson, D. 2003. Pandemic influenza and the global vaccine supply. *Clinical Infectious Diseases* 36:1552-61.
- Fedson, D. 2005. Preparing for pandemic vaccination: an international policy agenda for vaccine development. *Journal of Public Health Policy* 26:4-29.
- Ferguson, Neil M., Derek A.T. Cummings, Simon Cauchemez, Christophe
- Fraser, Steven Riley, Aronrag Meeyai, Sapon Iamsirithaworn and Donald S. Burke 2005. Strategies for containing an emerging influenza pandemic in Southeast Asia. *Nature* 437: 209-214.
- Fidler, David P. 2004. Germs, governance, and global public health in the wake of SARS. *Journal of Clinical Investigation* 113:799-804. Available online at <http://www.jci.org/cgi/reprint/113/6/799.pdf>.
- Food and Agriculture Organization and Organization International des Epizooties 2005 (May). *A global strategy for the progressive control of Highly Pathogenic Avian Influenza (HPAI)*. Rome: FAO.
- Germann, Timothy C., Kai Kadau, Ir M. Longini, and Catherine A. Macken 2006. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Sciences* 103(15): 5935-40.
- Gronval, Gigi Kwik and Luciana L. Borio 2006. Removing barriers to global pandemic influenza vaccination. *Biosecurity and Bioterrorism: Biodefense Strategy Practice, and Science* 4(2):168-75.
- Hampson, A. 1997. Surveillance for pandemic influenza. *Journal of Infectious Diseases* 176 (Suppl.1): S8-13.
- Harvey, R., A. Martin, M. Zambon, and W. Barclay 2004. Restrictions to the adaptation of influenza A virus H5 hemagglutinin to the human host. *Journal of Virology* 78:502-07.
- Hatta, N., P. Gao, P. Halfmann Y. Kawaoka 2001. Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. *Science* 293:1840-2.
- Hien, T.T. *et al.* 2004. Avian influenza (H5N1) in 10 patients in Viet Nam. *New England Journal of Medicine* 350(12): 1179-88.
- Hinman, Alan R., Walter A. Orenstein, Jeanne M. Santoli, Lance E. Rodewald, and Stephen L. Cochi 2006. Vaccine shortages: history, impact, and prospects for the future. *Annual Review of Public Health* 2006 27:235-59.
- Horimoto, T. *et al.* Antigenic differences between H5N1 viruses isolated from humans in 1997 and 2003. *Journal of Veterinary Medical Science (Tokyo)* 66:303-05.
- Johnson, N. and J. Müller 2002. Updating the accounts: Global mortality of the 1918-1920 "Spanish" influenza pandemic. *Bulletin of the History of Medicine* 76(1): 105-115.
- Kibourne, E. 1987 *Influenza*. New York and London: Plenum Medical Book Company

- Kieny, Marie-Paule, Alejandro Costa, Joachim Hombach, Peter Carrasco, and Yuro Pervikov 2006. A global pandemic influenza action plan. Meeting report. *Vaccine* article in press, accessed on www.sciencedirect.com.
- Kobasa, D. et al. 2004. Enhanced virulence of influenza A viruses with the haemagglutinin of the 1918 pandemic virus. *Nature* 431:70307.
- Lazzari, S. and K. Stöhr 2004. Avian influenza and influenza pandemics. *Bulletin of the World Health Organization* 82(4): 242-42A.
- Lee, Jong-Wha and Warwick J. McKibbin 2004. Globalization and disease: the case of SARS. *Brookings Discussion Paper in International Economics* No. 156. Washington, D.C.: The Brookings Institution.
- Li, K.S. et al. 2004. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. *Nature* 430: 209-13.
- Liem NT, World Health Organization International Avian Influenza Investigation Team, Vietnam, Lim W. 2005. Lack of H5N1 avian influenza transmission to hospital employees, Hanoi, 2005. *Emerging Infectious Diseases* 11(2). Available online at <http://www.cdc.gov/ncidod/EID/vol11no02/04-1075.htm>
- Longini, Ira M, Jr., Azhar Nizam, Shufu Xu, Kumnuan Ungchusak, Wanna Hanshaworakul, Derek A. T. Cummings, and M. Elizabeth Halloran 2005. Containing Pandemic Influenza at the Source. *Science* 309(5737): 1083 – 1087.
- Meijer, Adam 2006. Importance of rapid testing to combat the global threat of bird flu. *Expert Review of Molecular Diagnostics* 6(1): 1-4.
- Meltzer, Martin I., Nancy J. Cox, and Keiji Fukuda 1999. The Economic Impact of Pandemic Influenza in the United States. *Emerging Infectious Diseases* 5(5). Available online at <http://www.cdc.gov/ncidod/eid/vol5no5/meltzer.htm>
- Milstien, Julie and Miloud Kaddar 2006. Managing the effect of TRIPS on availability of priority vaccines. *Bulletin of the World Health Organization* 84(5): 360-65.
- Monto, Arnold S. 2006. Vaccines and antiviral drugs in pandemic preparedness. *Emerging Infectious Diseases* 12(1): 55-60.
- Mounier-Jack, Sandra and Richard Coker 2006. *How prepared is Europe for pandemic influenza? An analysis of national plans*. London: London School of Hygiene and Tropical Medicine.
- Osterholm, M. 2005a. Preparing for the next pandemic. *New England Journal of Medicine* 352:1839-42.
- Osterholm, M. 2005b. Preparing for the next pandemic. *Foreign Affairs* 84(4): 24-37.
- Schultz, T. 1964. *Transforming traditional agriculture*. New Haven: Yale University Press.
- Smil, V. 2005. The next 50 years: fatal discontinuities. *Population and Development Review* 31(2): 201-36.
- Stöhr, K. 2005. Avian influenza and pandemics – research needs and opportunities. *New England Journal of Medicine* 352:405-7.
- Stöhr, K. And M. Esveld 2004. Will vaccines be available for the next influenza pandemic? *Science*. 306: 2195-2196.

- Taubenberger, Jeffery K. and David M. Morens 2006. 1918 influenza: the mother of all pandemics. *Emerging Infectious Diseases* 12(1): 15-22.
- Taubenberger, J., A. Reid, R. Lournes, R. Wong, G. Jin, and T. Fanning 2005. Characterization of the 1918 influenza virus polymerase genes. *Nature* 437:889-93.
- UK Commission on Intellectual Property Rights 2002. Final Report. London. Available online at <http://www.iprcommission.org> .
- Ungchusak K, Auewarakul P, Dowell SF, Kitphati R, Auwanit W, Puthavathana P, et al. 2005. [Probable person-to-person transmission of avian influenza A \(H5N1\)](#). *New England Journal of Medicine* 352:333-40.
- Ward, P., I. Small, J. Smith, P. Suter, and R. Dutkowski 2005. Oseltamivir (Tamiflu®) and its potential for use in the event of an influenza pandemic. *Journal of Antimicrobial Chemotherapy* 55, Suppl. S1:i15-i21.
- Webby, R. and R. Webster 2003. Are we ready for pandemic influenza? *Science* 302:1519-22.
- Webby, R. et al. 2004. Responsiveness to a pandemic alert: use of reverse genetics for rapid development of influenza vaccines. *The Lancet* 363:1099-103
- Webster, 1997. Predictions for future human influenza pandemic. *Journal of Infectious Diseases* 176 (Suppl. 1) S14-19.
- World Health Organization 2005a. WHO global influenza preparedness plan. Geneva: WHO. Available online at http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf
- World Health Organization 2005b. Avian influenza: assessing the pandemic threat. Geneva: WHO. Available online at <http://www.who.int/csr/disease/influenza/H5N1-9reduit.pdf>
- World Health Organization Global Influenza Program Surveillance Network 2005 (October). Evolution of H5N1 avian influenza viruses in Asia. *Emerging Infectious Diseases*. Available online at <http://www.cdc.gov/ncidod/EID/vol11no10/05-0644.htm>.
- Writing Committee of the World Health Organization 2005. Avian influenza A(H5N1) infection in humans. *The New England Journal of Medicine* 353:1374-85.