

Research Plan 2006–2007

Health and Global Change Project

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Introduction

The World Health Organization (WHO) Commission on Macroeconomics and Health, the UN Millennium Project, and other groups have identified health as an element of global sustainable development. Yet at the same time that health is being recognized as a factor in development, the challenges to improving global health are large. The Health and Global Change (HGC) Project is an exploratory activity to investigate the social, economic, and institutional aspects of global health development at this important point in time. Its long-term goal is to develop health as a programmatic area for IIASA.

At the request of the IIASA Science Advisory Committee, the HGC Project will begin by focusing on a specific issue of importance in the area of infectious disease. The activity proposed is an interdisciplinary assessment of the potential global socioeconomic impacts of pandemic influenza and possible responses. The issue is timely and interest is high; these points need not be elaborated.

Why is IIASA positioned to contribute in a global health field that appears to be crowded already not only with researchers, but with entire research centers, as well (at Harvard Medical School, the London School of Hygiene and Tropical Medicine, WHO, etc.)?

Health, as has been found in analyzing failure to make substantial progress towards health-related Millennium Development Goals (MDGs), is characterized by many synergies with other sectors (World Bank, 2003a). While little health work per se exists at IIASA, existing research areas have many links to health. Areas in which IIASA is already active, and possible links to health, include

- adaptive dynamics – evolutionary dynamics, innovative approaches to disease management’;
- population – demography, household structure, HIV/AIDS;
- land use – animal husbandry in China, zoonoses;
- trans-boundary air pollution – impacts of air pollution in health;
- new technologies – diffusion of innovations;
- international negotiations – transnational health governance issues; and
- vulnerability to global change – risk perception, economics of catastrophic natural events, fairness issues (e.g., vaccine distribution).

IIASA can also build on past involvement in the analysis and reform of social insurance and health systems in countries as diverse as Japan, Russia, Vietnam, and Rwanda. In work supported by the OECD Development Centre, IIASA recently was responsible for a major overview of priorities in global official development assistance for health, HIV/AIDS, and population (MacKellar, 2005).

IIASA is particularly well suited to contribute in this area because of its unique position as an independent voice in the politically divisive global change policy debate. The only institution

that covers the entire field of health and global change, from epidemiology to infectious disease control to technology to global governance and resources tracking, is the WHO. Yet even within WHO, no single team tries to combine all these aspects into a globally consistent view, besides which, WHO is responsive to a board comprised of governments and cannot be considered a truly independent scientific voice. Finally, IIASA's small size and flexible structure make it possible for the institute to devote modest but significant core resources to emerging topics; as in the pandemic influenza assessment study described below.

Background

Health and Sustainable Development

The basket of issues that comprise the global health *problématique* cannot be separated and considered in isolation; they are indissolubly linked and are coming to the fore simultaneously.

The infectious disease environment is changing for the worse. Newly emergent diseases (HIV/AIDS, Severe Acute Respiratory Syndrome or SARS, West Nile Virus, etc.) and anti-microbial resistance or AMR (multiple drug resistant tuberculosis or TB, antibiotic resistant *Staphylococcus* infections, etc.) are eroding decades of gains made against communicable disease. While some countries (such as China) have invested heavily in the past few years, epidemiological surveillance and response is weak in most parts of the world due to low capacity and inadequate budgetary resources (St. John and Plant, 2001; US General Accounting Office, 2001). Increased mobility has contributed to the "globalization of disease" and arguably heightened systemic vulnerability. More intensive human-animal contact due to intensive animal husbandry, expansion of the human population into areas where it comes into contact with new disease reservoirs, and environmental-ecological changes that may be worsened by climate change appear to be increasing the rate at which zoonoses emerge (Karesh and Cook, 2005).

Population aging is bringing pressure to bear on health care systems and elder-care arrangements as the number of elderly suffering from chronic conditions, particularly the "oldest old," rises. While population aging to date has been largely a phenomenon of high-income countries, the rapidity of fertility decline in many low- and middle-income countries means that these societies will experience population aging while still at a relatively low level of economic development. As pointed out in a recent issue of *The Lancet*, chronic disease is now a major problem in developing countries (Strong *et al.*, 2005), yet international resources and attention are focused on problems attractive to the donor and advocacy communities, such as HIV/AIDS and maternal health (MacKellar, 2005). In focusing on diseases of the poor, admittedly a laudable approach, international health policy makers have tended to pass over diseases of the burgeoning Third World middle class, yet this is where the most rapid growth in global demand for health care is likely to occur. Another aspect of demographic change is rapid change in household structure, with implications for elder care as well as disease transmission.

Health research and development (R&D), once largely carried out by the public sector and philanthropic organizations, is now concentrated in private pharmaceutical companies. The demand for "blockbuster," top sales-performing drugs and tests has concentrated research on diseases of the well-to-do, a trend which international initiatives in the form of public-private partnerships has failed to reverse (UK Commission on Intellectual Property Rights, 2002; Global Forum for Health Research, 2004). Vaccine development, including development of a vaccine for HIV/AIDS, is under-funded. Technological innovation in health has not reduced costs, as in other sectors; it has increased them by developing new drugs, tests, and procedures. Yet these have contributed little so far to alleviating the diseases of the most vulnerable segments of the human population.

Institutions for dealing with global public good aspects are not up to the job. Many of the problems cited above arise from the fact some aspects of health have significant global public good aspects. The two criteria that must be satisfied for a good to be internationally public from a mainstream economic point of view are non-rivalry (one country's benefit does not reduce the benefit to another country) and non-excludability (no country can be excluded from benefiting). "Pure" public goods are both in full degree; "impure" public goods are partially excludable and/or partially rival. To quote Sandler and Arce (2001, p. 10–17), health-promoting public goods "run the gamut," representing all degrees of public-ness. Disease eradication (e.g., smallpox, polio) is both non-rival and non-excludable. Vaccination (which taken to the extreme leads to disease eradication) is rival: resources on an immunization program in Country A cannot be expended to finance immunization in Country B. However, it is non-excludable; Country B will benefit from lower disease prevalence in Country A. Epidemiological surveillance and control is also rival but non-excludable (B will benefit if an epidemic is headed off in A). Advances in health technology such as the discovery of new drugs are excludable (pharmaceutical firms can refuse to export a new drug to Country A if patent protection is not in place) but non-rival (the knowledge embodied in the drug is available to Country A, even if the product is not). These are "classic" global public goods.

There is a widespread feeling that the supply of global public goods for health is inadequate. For example, despite initiatives from both WHO and the US Centers for Disease Control (CDC), there has been little progress in fighting AMR (Smith and Coast, 2001; US Centers for Disease Control, 1998, World Health Organization, 2001) and accelerating the development of new antibiotics (Nathan, 2004). Innovative institutions such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; the Global Alliance for Vaccines and Immunization (GAVI), Roll Back Malaria, and others have had little success in mobilizing additional resources for global health development (MacKellar 2005, p. 310), i.e., they have simply diverted existing resource flows. Polio eradication, once confidently expected to be complete in 2005, is proving difficult to attain, and the Stop TB initiative has failed to have anything near the impact originally foreseen. Based on these failures, some authors, e.g., Kaul and Faust (2001) have called for massive expansion of public resources for health, yet often, such calls undermine their credibility by expanding the definition of a public good far beyond its original intent.

In some areas, there has been progress. The impact of SARS effect on global health governance has been tangible (Fidler, 2004). WHO assumed a strong role, independently issuing travel advisories for the first time in its history (to the chagrin of several governments), criticizing, with rare candor, the lack of early reporting on the part of China, and coordinated an unprecedented global research laboratory response. It must never be forgotten that, despite global public good problems that weaken its effectiveness, the scientific arsenal against infectious disease has never been stronger. The identification of the SARS coronavirus within weeks of the disease's emergence and the scientific response to the threats of pandemic influenza (discussed below) are strong evidence of this.

The link between poverty and inadequate health remains unbroken. As the Millennium Project and others have argued, there is no apparent reason why health in poor countries cannot be improved. The World Bank's 1993 World Development Report, a flagship document in the health-and-development field, identified a minimum care package that would cost a mere \$12 (1990 terms) per capita to deliver. The WHO estimates that in low-income countries, the cost of a essential health care package is \$12 per capita, and in middle-income countries \$22 per capita. The comparison between the misery caused by poor health in the Third World and the apparently trivial sums required to improve it could not be more striking. Yet, the health Millennium Development Goals have proven the hardest of all to attain.¹ Health budgets in

¹ The World Bank (2003b) forecast, in its evaluation of progress in 18 low-income countries, that extrapolating current policies and external resources, 11 will not meet a single health MDG, 7 will meet at least 1, but of these seven, none will meet all. In education, by contrast, only 4 of the countries will meet none of the goals and only nine will fail to meet the income poverty goal.

poor countries remain heavily dependent on donor support (Musgrove and Zeramndini, 2002; Nandakumar *et al.*, 2004), and the budgetary impact of HIV/AIDS has hardly begun to be felt in the most seriously affected countries.

Analysis of the socio-economic impacts of disease has far to go in methodological terms. Work to date on modeling economic impacts of infectious disease has usually followed the time-honored approach of applying basic ratio analysis to estimate the number of cases, direct health system costs in the form of hospital days, physician visits, and medical commodities; indirect costs in the form of days of work lost and income foregone, etc. (e.g., Meltzer *et al.*, 1999, further cited below). These approaches give little consideration to macro-economic multiplier effects, to cross-border or global impacts, or to possible feedback effects that might shift the behaviors that underlie the incidence of disease. Much recent work in global health has focused on “costing” needed public health responses. Thus, UNAIDS (2004) estimated 2005 requirements for an adequate response to the epidemic to be US\$ 12 billion, as opposed to actual spending of perhaps US\$ 5 billion.² The WHO Commission on Macroeconomics and Health (2001) estimated needed international assistance for health to be US\$ 27 billion in 2007, divided into US\$ 22 billion for in-country programs, US\$ 3 billion for research and development targeted at diseases of the poor, and US\$ 2 billion in classic global public goods such as collection and analysis of epidemiological data and surveillance of infectious disease. International funding ca. 2000, the Commission estimated, was only US\$ 6 billion per year. The UN High Level Panel on Financing for Development, the so-called Zedillo Commission, estimated that an extra US\$ 7–10 billion per year in additional resources are required as a minimum to fight communicable diseases alone (United Nations, 2001).

Yet “costing” studies, which are usually linked to resource mobilization and advocacy, cannot substitute for realistic global balancing of the potential sources and uses of health care expenditure and analysis of the social and economic characteristics of various scenarios. Resources needed for health in poor countries have not been placed in the context of a global health economy in which health costs in rich countries are growing and accounts must balance. The traditional distaste of public health experts for private out-of-pocket medical expenditure has translated into a dearth of research on this vital component of the health equation. Partial equilibrium studies of the impact of health on economic development (Bloom and Canning, 2003; Bloom *et al.*, 2004) have not been followed up with globally consistent cross-border multiplier analyses. Nor have inter-sector linkages between health and other aspects of global change – ageing, global economic integration, etc. been systematically taken into account. One example of this which needs more study is the migration of health personnel from developing countries – which can ill-afford to lose skilled staff – to developed countries where populations in need of care are growing and, for a range of reasons, nursing and some other segments of the health labor market are unattractive to nationals.

Pandemic Influenza

The picture painted above depicts a global health system that is straining to meet needs and expectations. Against this challenging background has re-emerged the cyclical problem 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). For strategic reasons explained in the following section the main thrust of this project is an assessment of the global impacts of pandemic influenza and policies to address it.

² Summers and Kates (2003) estimated that 2003 spending by donors was \$3.2 billion and that government own-resource spending was US\$ 1 billion; while data are scarce, private out-of-pocket spending might amount to another US\$1 billion.

*Influenza.*³ 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 major infectious disease killer even in normal years, accounting for 1–1.5 million deaths worldwide. The significant human and economic costs, and the cost effectiveness of public health responses, particularly vaccination, have been well established (see Fedson, 2003, p. 1532 for citations).

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 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. 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 one 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 one million.⁴

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.

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.⁵

³ The assistance of Wah Sui Almberg in preparing this section is gratefully acknowledged. As it 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).

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

⁵ In September 2005, Dr. David Nabarro, newly named UN 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.

Smil (2005) ranked an 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. As of this writing (October 2005), a major international conference on the global response to pandemic influenza was recently convened by the US Department of Health and Human Services in Washington; President George W. Bush called for broad latitude to deploy the US military in the fight against influenza; and Mr. York Chow, Health Secretary of Hong Kong, made headlines by referring to pandemic influenza as nature’s “ecological terrorist.” Mr. Andrew Natasios, Administrator of the US 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 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).⁶ H5N1 is 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. A previous outbreak of H7N7 avian influenza in the Netherlands in 2003 was stamped out at great cost to the poultry industry and only after many human infections, one fatal, had been experienced. 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 1968 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).⁷ 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

⁶ 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. Webby and Webster (2003, p. 1519-20) 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 re-assortment with a human-to-human transmissible virus is there.

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. 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.

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 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 very close quarters (Ungchusak *et al.*, 2005).⁸ 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).⁹ 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.¹⁰ 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).

⁸ 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.

⁹ 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.

¹⁰ 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).

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.

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;
- It has acquired genes from influenza viruses that infect other species;
- It is highly pathogenic in humans; and
- The dangerous interaction of animal and human populations in Asia continues apace.

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. In this case, mortality arose from a so-called cytokine storm, an immune system response leading to acute respiratory distress syndrome (Kobasa *et al.*, 2004). Perhaps ominously, the H5N1 strain is also causing cytokine storms and its 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.¹¹ 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 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 high end 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

¹¹ The case-fatality ratio among US 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).

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.¹² This completely atypical pattern remains a mystery. 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 essentially 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 (WHO, 2005, 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.

In the case of 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.

Two recently published high-profile micro-simulation studies have 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.

“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 Centres, of which there are 110 in 80 countries (Hampson, 1997). However, some countries in the Southeast Asia region have virtually no epidemiological surveillance capacity at all, namely Laos and Cambodia. All over the region, farmers are reluctant to report epidemic outbreaks, and local officials are inclined to suppress the news, because livelihoods are at stake. Emergency technical assistance programs to put surveillance capacity in place are underway (for example, USAID has dispatched US\$ 25 million to the region), as is consideration of rural insurance schemes to improve the compensation paid to farmers whose flocks were slaughtered. However, these efforts will take time to bear fruit, and 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

¹² 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.

¹³ Bell and Lewis (2003) describe the sequence of events. The first case was observed in Guandong 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

in such behavior, resulted, but old bureaucratic habits die hard. All in all, countries where countries where pandemic influenza is most likely to emerge are ill equipped to carry out ambitious, cross-cutting interventions of the type envisioned by the authors of the studies cited above.

Once a pandemic is established, anti-virals may be helpful, but they 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 (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, adamantane. It has been argued, however, that Tamiflu is less susceptible to resistance (Ward *et al.*, 2005).

Vaccine development and administration would be the 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 and 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 and consumer acceptance (Webby and Webster, 2003). 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, p. 1383 for references). However, rapid mutation of the virus means that vaccines developed from currently known virus strains may not be effective when a new strain emerges.

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). 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 Programme of Immunization (EPI) goals, that the GAVI was put in place. Adding to the pharmaceutical industry's distaste for vaccines are litigation issues and memories of the 1976 US “swine flu” debacle, in which hundreds of persons suffered serious adverse effects from a mass vaccination programme instituted to head off a pandemic that never happened. In the US, the UK, and Europe, civil society groups opposing 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 million doses per year. 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 US) to universal influenza vaccination as major barriers to

publicly disagreed was arrested and put in jail. By March, SARS was recognized as a previously unknown disease and was spreading throughout Southeast Asia.

pandemic preparedness.¹⁴ His estimate is that vaccine sufficient to vaccinate 500 million persons against a new influenza strain might be available within six 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.

A number of authors have pointed out that the best way to prepare vaccination strategy for a pandemic is to improve inter-pandemic vaccination policies. Yet there has been little progress. 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.

One may envision not only vaccine (and antiviral) shortages, but a more general picture 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.

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.

¹⁴ 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.

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 US to be, to an order of magnitude, US\$ 100 billion, a bit less than one percent of gross domestic product or GDP.¹⁵ 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 labour 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 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 of 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.¹⁶ The authors of the pieces that appeared in the June/July 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.¹⁷ This view is speculative in the extreme, not to mention that it overlooks that fact that in 1918–20, 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.¹⁸ 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

¹⁵ 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.

¹⁶ 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.

¹⁷ 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).

¹⁸ See Bell and Lewis (2004) for a description of the range of relief measures instituted by Southeast Asian countries in response to SARS.

substitution between capital and labour.¹⁹ The instantaneous reduction in labour 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 return to capital.²⁰ 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 would 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. Scuhltz (1964) found that the 1918–20 pandemic significantly increased output per member of the agricultural labour 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. The vulnerability of the poor would be more due to their precarious economic status than their susceptibility to infection – evidence from both 1918–20 (Brainerd and Siegel, 2003) and the Black Death (Cohn, 2002) indicates that all classes of persons were equally susceptible to infection and that wealth was no guarantee of a better clinical outcome.

Because of the many ambiguities, it has proven difficult to estimate with any certainty the economic impact of severe epidemics.²¹ Brainerd and Siegler (2003) find for the US 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.

¹⁹ This discussion of the neoclassical growth model is based on Brainerd and Siegler 2003, pp. 8–11.

²⁰ 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.

²¹ Controversies over the economic impact of pandemic influenza parallel controversies over the impact of natural disasters (floods, earthquakes, etc.) on economic growth.

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.²² In a report published in mid-2003 (Fan, 2003), the Asian Development Bank examined two cases, a one-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 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), using a global general equilibrium model that highlighted the role of expectations, estimated that SARS would reduce GDP in China by one 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.

In summary, the discussion above gives rise to the following thoughts:

- Pandemic influenza is inevitable, although unpredictable. Galloping growth of the swine and poultry population in Asia, mostly in uncontrolled and unsanitary conditions, is the major source of risk for the emergence of pandemic influenza. There is evidence that the world is at a very dangerous stage of the influenza cycle, and the virus of concern, H5N1, appears to be a lethal one. However, the next pandemic could emerge a month from now, a year from now, or ten years from now. It could be a minor episode, or a murderous one.
- There are well-understood policies to lesson the risks of zoonoses. No rocket science is involved – they consist of improving farm conditions; building modern, well-lit, frequently hosed-down and disinfected indoor markets; refrigeration; improving social safety nets and compensation schemes for farmers whose flocks must be destroyed, improved disease surveillance, etc. There are well-defined protocols for the control of disease outbreaks in farm animals when they occur. However, the development efforts needed to substantially improve conditions in Asian agriculture will take years, as will capacity building efforts to improve disease surveillance in areas where it is woefully incomplete. .
- Global health systems are vulnerable to a pandemic event. Population ageing in high-income countries and the combined impact of insufficient budgetary resources and HIV/AIDS in middle- and low-income ones are mostly to blame for this vulnerability. Calls for preparedness are heard on all sides, but deserve to be taken with a grain of salt. No health system, in any country, was designed to handle a situation in which a quarter of the population was sick. Disruptions and shortages, as well as ad hoc approaches to handling them, are inevitable when a pandemic strikes.
 - Unless we are lucky and the next pandemic emerges via a gradual evolutionary process, “ring-fencing” exercises of the sort recently proposed are unlikely to work. The institutional constraints to identifying the area to be ring-fenced are great, as are the logistical challenges of enacting the coordinated policies required.
 - In the more likely (based on history) event of sudden emergence, policies to slow the international spread of influenza are likely to have very limited impact; all the more since there is no evidence that increased global mobility has had any impact on patterns of global influenza transmission.

²² Bell and Lewis (2003) present a cogent account of the development of the epidemic, its clinical aspects and epidemiological progression, and the policy response.

- Unless the next pandemic is years in the future and the current level of policy interest does not abate, the global vaccine (and antiviral) system will not be positioned to respond adequately. Technical, legal, and regulatory issues need to be addressed over the course of years, not months or weeks.

Influenza, like many other problems such as preparation for natural disaster, is characterized by a policy cycle in which there is a flurry of activity when a pandemic looms, accompanied by loud recriminations of incompetence or worse, followed by a period of neglect during inter-pandemic years. Many of the scientific and economic initiatives described above, from genetic engineering to rationalizing the production and distribution of influenza vaccine to improving agricultural conditions in Asia, will be of little help if a pandemic strikes within a few months. The one immediate policy intervention that might bear fruit in the near term – administering “normal” influenza vaccinations to individuals in areas of avian influenza endemicity to prevent mixing of the viruses -- has received no effective policy attention despite its modest cost.

One explanation for policy paralysis is the absence of credible estimates of the economic impacts of pandemics. Available work consists of mechanical sector studies in which health sector costs, foregone tourism, and so on are estimated. Yet no one seriously believes that the economic effect of a major pandemic would be limited to these linear, additive shocks. SARS taught us that expectations and psychology are key factors, and that disruptions can far exceed the actual scale of the disease (estimates of the economic cost of SARS per death are astronomical). Public health experts express apocalyptic visions of economic collapse, but these visions, while they have headline appeal, possess little policy legitimacy. It will be much easier to convince policy makers to undertake forward-looking actions if there are forensically defensible estimates of the damages that can be avoided.

Strategic Goals and Objectives

This proposal takes as its starting point the view that health is an aspect of global change as important as energy, population, and other areas already addressed by IIASA. In order to function effectively as a global change institute, IIASA needs to address global health. The HGC Project proposed here is an exploratory activity whose long-term goal is to put IIASA in a position to contribute to research and deepen international policy dialogue related to health considered as one of the human dimensions of global change. Its target audience is the international health policy community, including researchers in academic institutions and policy makers in international organizations, governments, non-governmental organizations (NGOs) and private firms.

IIASA’s Science Advisory Committee counseled that HGC begin by concentrating on economic and social aspects of infectious disease and responses thereto. Its strategic advice was to break off one piece of the global health picture and study it over the course of a two-year initial phase. In response to this, HGC has chosen to concentrate on pandemic influenza. The HGC project will engage in data collection and modeling, hold a series of workshops, affiliate an international network of researchers, and disseminate research results which, while preliminary during the time frame covered (two years), will nevertheless contribute significantly to global knowledge in this field. The objective is to produce research results that will be credible in their own right while building the capacity and setting the stage for further work.

Research Framework

The approach proposed here is an impact assessment focusing on a specific infectious disease, pandemic influenza. This approach will contribute to achieving the strategic goal by mobilizing

a network of contributors, assembling available data, and identifying modeling approaches while producing significant research outputs in its own right and identifying areas for work in the longer term. The approach exploits IIASA's comparative advantage, which is as an institute where diverse modeling approaches and disciplinary perspectives are synthesized into a comprehensive view of policy challenges and possible responses. It is particularly apposite because, in the explosion of research on pandemic influenza since the late 1990s, the area of economic and demographic impacts has been under-studied; as a result of which, estimates are still largely *ad hoc* and speculative and the assumptions made have not been clearly set forth for debate.

Some of the issues to be addressed are schematized in the following table.

Subject	Aspects
Modelling emergence and international transmission of infectious disease	<ol style="list-style-type: none"> 1. Epidemiological modeling 2. Evolutionary perspectives 3. Mobility / globalization aspects 4. Zoonoses: changing human-animal contact, global environmental change aspects.
Integrating disease impacts into economic models	<ol style="list-style-type: none"> 1. National health accounting and global extensions 2. "Costing" epidemics: traditional and novel approaches 3. Integrating infectious disease into economic growth models (HIV/AIDS, TB, malaria) 4. Impacts of health on development: improving estimates, including global multipliers.
International health governance issues	<ol style="list-style-type: none"> 1. Epidemiological surveillance and response 2. Vaccination / immunization issues 3. Resource mobilisation / international assistance 4. How are global health priorities set?
Population ageing and health	<ol style="list-style-type: none"> 1. Population aging and health care costs 2. Population aging and the shifting burden of disease 3. Disability and long-term care; links with household structure.
Health technology	<ol style="list-style-type: none"> 1. Research and development / intellectual property rights issues (the "90-10 problem"). 2. Diffusion of medical technology 3. The slowdown in antibiotic development.

Research Activities

In order to carry out the impact assessment, HGC proposes to affiliate a group of international researchers and hold a series of workshops, as follows:

- An international “scoping” workshop at IIASA in March / April 2006. This workshop will provide a venue for presenting preliminary and planned papers, exchanging and vetting ideas, identifying crosscutting themes, forming collaborative partnerships, and identifying potential research partners not yet implicated. It will provide an opportunity for “showcasing” possible contributions to the assessment, including contributions by other IIASA researchers who wish to participate. Upwards of a dozen potential international participants have been tentatively identified.
- A China workshop in Beijing in the second half of 2006 at which national research on causes and consequences of, as well as policy responses to avian influenza will be presented. In addition to synthesizing existing research, the workshop will have a focus on developing data on the distribution of human and animal populations in China and possibilities for mapping possible epidemiological “hot spots.”
- An international conference at IIASA in mid-2007 at which papers developed as a result of the previous two workshops will be presented. Selected papers from the conference will be peer reviewed and published in a journal special issue or book in late 2007 or early 2008. Discussions on this possibility have already been held with the journal *Population and Development Review*.

Based on the review above, “question areas” to be investigated have been identified.

Demographic Impacts

What are the potential global demographic impacts of pandemic influenza under various scenarios? What would be the impact of various age-attack profiles on population age structure? How will influenza interact with immuno-suppressing diseases such as tuberculosis and HIV/AIDS? Proposed components of an approach to answering these questions are:

- A review of the demographic impact of past epidemics (the 1918-20 pandemic and Black Death).
- A study on selective mortality and its potential impact on subsequent all-cause mortality, as well as potential synergies between influenza, tuberculosis, and HIV/AIDS.
- A set of population scenarios, derived from the work of IIASA’s Population Project, for global population under different scenarios regarding the next influenza pandemic (including the possibility of a W-shaped age-attack profile). These projections would provide basic input into the economic simulations described below.

Economic Impacts

What are the potential global economic impacts of pandemic influenza under various scenarios? What do neoclassical and endogenous growth theories tell us about the likely impact of pandemic influenza? What insights can be gained from the broad classes of currently available global economic models -- trade-linked macro-economic models and open-economy computable general equilibrium models? What is the scope for new, hybrid approaches that might link epidemiological and economic models? Are there insights to be gained from empirical analysis of previous influenza pandemics and the Black Death? Proposed components of an approach to answering these questions are:

- A review of economic growth theory, perhaps including exploratory work on combined epidemiological-economic modeling.
- A review of the economic impacts of past catastrophic health events, such as the 1918–19 pandemic and the Black Death.
- A global simulation performed in collaboration with Project LINK (see below) focusing on short-and intermediate term impacts of influenza, concentrating on the international economic linkages and disequilibrium dynamics.
- A second simulation, performed in collaboration with IIASA’s Population and Climate Change Project, focusing on long-term impacts and general equilibrium. This simulation would employ the Population-Environment-Technology or PET model, which is well suited because of the wealth of demographic information incorporated. The PET model is not global, however, versions exist for China and the United States. From the standpoint of assessing neoclassical impacts, the model that provided analysis for the IIASA Social Security Project’s analysis of population ageing in Japan (MacKellar *et al.*, 2004) would also be well adapted.

Emergence of Pandemics, Especially the Role of Asian Zoonoses

What factors – demographic increase, growth of consumer demand, rural poverty, failure of the agriculture sector to modernize, etc. – are driving the emergence of zoonoses in Asia? Can danger zones or “hot spots” be identified based on available data? What policies, from improved sanitary inspection to institution of livestock insurance schemes for poor farmers, are available to prevent or slow the process? What are the economic costs of avian influenza in Asia, and what are the potential economic impacts of a pandemic? How much would preventive programmes cost?

These questions will be the subject of the workshop convened in Beijing. In approaching these issues, HGC will cooperate with IIASA’s Land Use Project, which already has available a substantial amount of information, including projections, on population and livestock in China (Ermolieva *et al.*, 2005).

Governance, Global Public Good, and Fairness Aspects of Influenza Pandemics

What is the scope for improved surveillance and control of influenza pandemics at the source? What improvements in governance and institutions at all levels (global, national, and local) would be required and what would be the cost? How can the global system by which vaccines are developed, distributed, and administered be improved to counter pandemic influenza? What insights can be gained from two major recent vaccination fiascos – the US 1976 “swine flu” incident and the global vaccine shortage of 2004–05? What approaches to allocating inadequate resources across uses would be broadly regarded as workable and fair?

These questions will be the subject of a review from the global public goods perspective to be presented at the scoping workshop.

Three papers on economic impacts, three papers on demographic impacts, and four to six papers on assorted other aspects of pandemic influenza, plus a synthetic overview, would provide an excellent basis for the planned 2007 conference. Assuming reasonable attrition, this material would be ample for a journal special issue.

Networking and Collaboration

It will not be possible, in the context of the initial activities of the project to exploit all of the potential IIASA-wide linkages listed earlier. However, HGC will pursue the following in-house collaborations in performing the study:

- It will be an in-house client for data and analyses on Asian animal husbandry produced by IIASA's Land Use Project (LUC).
- It will be an in-house client for data and projections produced by IIASA's Population Project.
- During this activity, possibilities for further collaboration with IIASA's adaptive dynamics project will be explored. This might range from simple scientific oversight of the biological and epidemiological aspects of the work undertaken to more ambitious joint activities.

The project will be led by Dr. Landis MacKellar. Dr. MacKellar is an economist. His most relevant publication (MacKellar, 2005), examined the gap between the composition of official development assistance for health, the burden of disease, and developing-country policy priorities. In previous work, he reviewed global population ageing (MacKellar, 2000) and analyzed macroeconomic impacts of population ageing in Japan (MacKellar *et al.*, 2004).

In coordinating this project Dr. MacKellar will be assisted by Dr. Andrew Noymer of the University of California at Berkeley. Dr. Noymer is a demographer whose prior work (Noymer and Garenne, 2000; 2003) established the tuberculosis selection effect in the 1918–19 pandemic. He was an IIASA Young Scientist in 1997.

Internationally, the HGC Project will incorporate the following collaborations so far agreed upon:

- Collaboration with Modelling and Economics Unit of the UK Health Protection Authority (<http://www.hpa.org.uk/infections/about/dir/smed/modellingunit.htm>) on estimating economic impacts of pandemic influenza and exploring approaches to integrated economic-epidemiological modeling. The Unit, directed by Dr. John Edmunds, has three main areas of work: estimating the current health and economic burden of diseases, evaluating the health and economic impact of interventions to control infectious diseases, and using data and models to improve basic understanding of the epidemiology of infectious diseases. Through this link, the HGC initiative will be informally affiliated with the EU Framework 6 Project SARSControl: "Effective and Acceptable Strategies for the Control of SARS in China and Europe" (<http://www2.eur.nl/fgg/mgz/SARSControl/Start.html>). Coordinated by the School of Public Health at Erasmus University in Rotterdam, the goal of SARSControl is to control possible future outbreaks of SARS and other emerging diseases by developing strategies based on epidemiological and economic modelling.
- Collaboration with the Centre for Population, Health, and Development of the Institute of Population Research, Peking University (<http://www.pkuipr.net/en/ccphd/index.html>), on causes, consequences, and policy responses to zoonoses in China. Directed by Professor Zheng Xiaoying, the Centre is a basic policy research resource for the Government of China as well a focus for international scientific collaboration in the area of public health.
- Collaboration with the School of Health Policy and Practice of the University of East Anglia, specifically with the Health Economics Group, on global public good aspects of health. Directed by Professor Richard Smith, the HEB is a centre of excellence for, inter alia, antibiotic resistance, globalisation and health, and trade in health services.

- Collaboration with Project Link Research Centre at the Institute for Policy Analysis, University of Toronto (<http://www.chass.utoronto.ca/link/>), directed by Professor Peter Pauly. Project LINK is a large cooperative, non-governmental, international research consortium based on a world-wide network of participants in more than 60 countries in the industrial and developing world. Using the Project LINK econometric model based at the United Nations Department of Economic and Social Affairs, Project LINK has for over 30 years been a source of policy-relevant international economic simulations and impact assessments.
- Collaboration with the XpaX research group, Department of Computer and Systems Sciences at the Royal Institute of Technology, Stockholm (<http://www.dsv.su.se/~mab/xpax.html>) on agent-based social simulations and microsimulation models. XpaX is led by Magnus Boman, who holds a professor's chair in Intelligent Software Services and is a founding member of the Stockholm Group for Epidemic Modeling (S-GEM), a newly formed network of epidemiologists, sociologists, mathematicians, statisticians, and computer scientists. XpaX and S-GEM actively cooperate with counterpart groups at Karolinska Institutet, the Swedish Institute for Infectious Disease Control, and the new European Centre for Disease Prevention and Control (<http://www.ecdc.eu.int/>).

Selected Publications

Relevant publications have been cited above. In addition to his work with IIASA, Dr. MacKellar has been responsible for designing social insurance systems in Vietnam, assessing coordination of HIV/AIDS assistance in Rwanda, and estimating sources and uses of HIV/AIDS resources in the Russian Federation.

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