MULTI-DISCIPLINARY ISSUES

INTERNATIONAL FUTURES PROGRAMME

OECD/IFP Project on
"Future Global Shocks"

"Future Global Shocks: Pandemics"

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This report was prepared by Harvey Rubin as a contribution to the OECD project "Future Global Shocks". The opinions expressed and arguments employed herein are those of the author, and do not necessarily reflect the official views of the OECD or of the governments of its member countries.

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I. INTRODUCTION:

Classifying *pandemics* as a Future Global Shock is consistent with considering certain aspects of public health and infectious diseases as "existential threats" to human security as described in the United Nations Development Programme (UNDP) of 1994 and reaffirmed in the 2003 UN Commission on Human Security. The UNDP conceptualizes security as human-centric rather than the traditional state-centric and includes protection from the shocks that affect human safety and welfare, such as disease, hunger, unemployment, crime, social conflict, political repression and environmental hazards. The consequence of such a definition, as Ole Weaver points out (Weaver 2009) is, "... that action according to the normal procedures will not be able to offset this in time, and therefore extraordinary measures are both needed and justified." In this formulation, the nature of an existential threat depends in part on the particular threatened sector. In considering the traditional national security threat, the survival of the sovereignty, territory and physical condition of the nation is at stake; to the environmental community, the sustainability of an ecosystem is at risk; to the economic sector, survival includes protecting the means of production. To the medical community in general and especially to the public health and infectious diseases sectors, survival under a pandemic global shock clearly refers to taking every action to minimize morbidity and mortality *as well as* to minimize the effect of the pandemic on the economic, social and political stability of communities, nations and transnational organizations. In this view, analyzing a pandemic future global shock must be informed by its effect on a broad range of key resources and critical infrastructure. Therefore, we argue that the global shock to public health in the form of a pandemic is unique among global shocks in having profound positive and negative externalities and interdependencies.

HIV/AIDS is probably the most well studied pandemic in history. It is frequently discussed in the context of securitizing public health issues. This discussion originated with the UN Security Council Resolution 1308 (2000) on the Responsibility of the Security Council in the Maintenance of International Peace and Security: HIV/AIDS and International Peace-keeping Operations, adopted by the Security Council at its 4172nd meeting, on 17 July 2000 in which HIV/AIDS was placed squarely in the cross-hairs of the security debate.

The wisdom of securitizing certain infectious diseases has been analyzed predominantly in the political science literature. Arguments are made that such a process will 1) widen the domain of security thereby weakening the traditional military agenda, 2) unnecessarily remove the debate and discussion of policy issues regarding

infectious diseases from the biomedical and public health practitioners and place it in the hands of the diplomats, the military and possibly even the intelligence community, 3) focus attention on the needs of the economically and militarily stronger countries and not on global health and 4) inhibit rather than encourage infectious diseases data sharing among nations ((Maclean 2008); (McInnes and Lee 2006); (Feldbaum 2009); (Pereira 2008); (Elbe 2006); (Elbe 2005); (Elbe 2008)). Securitization of public health issues generated a heated international dispute centering on the equitable access to vaccines in a multilateral context with respect to a highly anticipated, but fortunately not realized H5N1 pandemic. An excellent review of the events surrounding this dispute can be found in Stefan Elbe's 2010 book Security and Global Health: Towards the Medicalization of Insecurity. Professor Thomas Pogge (Yale University) has examined the philosophical foundations of access to medicines and vaccines in the context of human rights and global justice (http://pantheon.yale.edu/~tp4/index.html).

We recognize the controversy over declaring certain infectious diseases as security issues, however we agree with Dr. Lincoln Chen's comments in his address to the Helsinki Process Track on Human Security (Chen 2004):

> "…human security which may be defined as consisting of human survival, livelihoods, and dignity. Poor health – illness, injury, disability, and death – are critical threats to human security. And of many health problems, those considered most germane to human security are health crisis during conflict and humanitarian emergencies, infectious diseases, and the health problems of poverty and inequity.
> These three cluster of health problems were selected as being most relevant to human security based on four criteria – scale, urgency, intensity, and externalities. … Especially important are health problems that create emergencies or crises, such as an epidemic or war. The severity of social and economic impact of disease also is an important criterion. Finally, those health threats that generate "spillover effects" onto other problems (and are thus not purely medical problems) are also prioritized. Classical examples of health problems with high externalities are transmitted infectious diseases. One divergent viewpoint was that health was either too broad or too vague to be considered a core aspect of human security. Rather, some believed that the military security of the nation state should retain its primacy. If human security were to expand the types of threats to be prioritized, some stretching of threats to other forms of violence or conflict could be considered. But if health, education, and all sorts of other threats are considered human security challenges, the concept would lose its meaning, since everything ultimately means nothing!
> That is why the Commission established the four criteria for prioritizing which health problems are linked to human security, … Thus, the concept's breadth should be seen as a strength, not a weakness. …
> Another deliberated issue was the "securitization" of health. This term implies an implicit effort to argue for higher political and budgetary prioritization for health as a sector; "securitization" suggests that just as defense and military expenditures are prioritized in the concept of state security, so too should health be prioritized in the concept of human security. …"

A Look Ahead—jumping to the conclusions and recommendations of the report:

Four major lessons emerged from the data and risk analyses described in this report:

1) there is not sufficient interoperable, globally shared information available in real-time about pandemic risk inventories, hazards or threatened segments of the built or natural infrastructure,

2) there is a dramatic lack of forward thinking and planning for the creation and distribution of medical countermeasures—including drugs, vaccines and surge capacity, which, in part, arises because of the lack of real-time information,

3) there is a serious requirement for international harmonization of regulations across the pandemic spectrum, and

4) there needs to be financially sustainable basic research efforts upon which is based the preparation, mitigation, response and rebuilding that will be required before, during and after a pandemic.

A series of recommendations that address these lessons learned are presented in the concluding section of the report.

Historical examples of pandemics

Consideration of the complexities of planning for, responding to, and mitigating a pandemic global shock reveal extensive interdependencies, including sustaining and protecting national sovereignty, ensuring commercial and economic growth and continuity of household activities. This is not a new problem. Pandemics have been documented from well before the common era (BCE). The Plague of Athens (430 BCE), widely believed to have contributed to the fall of the Golden Age of Greece, has been attributed to epidemic typhus or perhaps typhoid fever. The Antonine Plague or the Plague of Galen (165-180 CE), attributed to either smallpox or measles, devastated the Roman Empire. Perhaps one of the most famous pandemics, the bubonic plague, caused by the bacterium *Yersinia pestis,* started around 540 CE, returned with a vengeance in the 1300s and continued in cycles until the 18th century. Cholera, caused by *Vibrio cholerae*, with a pandemic between 1816-1826, is now in its eighth cycle that began in 1992 with a new serogroup –a genetic derivative of the EI Tor serogroup (*V. cholerae* 0139 Bengal) that emerged in Bangladesh and has now been detected in 11 countries. The WHO reported protracted cholera outbreaks in Angola, Ethiopia, Somalia, Sudan and northern Vietnam. An epidemic in Zimbabwe lasted almost 1 year and spread throughout the country as well as to Zambia and South Africa with an estimated global burden of diseases to be 3–5 million cases and 100,000–130,000 deaths per year. (Weekly epidemiological record 26 March 2010, No. 13, 2010, 85, 117–128).

Other documented pandemics have been caused by typhus, measles, smallpox, tuberculosis, malaria and yellow fever. In addition to the documented pandemics, potential pandemics loom as possibilities including those that might be caused by

known infectious agents--the viral hemorrhagic fevers (Lassa, Rift Valley, Marburg, Ebola), antibiotic resistant bacteria including *Staphylococcus aureus*, *Enterococcus* species, *Mycobacterium tuberculosis*, *Serratia marcescens*, *E. coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. In addition to these known agents, there exists on the immediate horizon the dreadful threat of engineered or synthetic bioterrorist agents. While not reaching the level of a pandemic, the spread of a corona virus that caused severe acute respiratory syndrome (SARS) can teach a number of lessons about disease reporting, the international response and economic consequences of a new and unexpected communicable disease.

The 2009 H1N1 influenza pandemic is a rich case study that offers a modern context of the risk of a global shock from a pandemic. It provides an opportunity to learn how pandemics are addressed, what works well and what does not, how macro socioeconomic trends, such as increasing population, globalization, social networking, changing demographics, and interdependencies influence the risk. Therefore we will use the 2009 H1N1 pandemic as the most relevant model on which to build the analysis of a Pandemic Global Shock.

Influenza A -- the disease:

Influenza, the symptoms of which were described as early as 412 BCE by Hippocrates, causes pandemics approximately every 10-30 years. The 1889 Asiatic flu was followed by the famous 1918 Spanish flu H1N1 pandemic that claimed an estimated 100 million lives worldwide. In 1957, an H2N2 pandemic and in 1968 an H3N2 pandemic caused approximately two million deaths and one million deaths respectively worldwide.

The incubation period for the 2009 H1N1 virus was between 1 and 7 days; virus is shed 1 day before the onset of symptoms and persists until symptoms resolve. Children, young adults and immunosuppressed individuals shed, or release the virus for a more prolonged period. It is noteworthy, in the context of the global problem of antibiotic resistance, that on September 29, 2009 the CDC reported that 22 of 77 fatal H1N1 cases had evidence of bacterial coinfection, including 10 cases with *S. pneumoniae*, six with *S. pyogenes*, seven with *S. aureus*, two with *Streptococcus mitis*, and one with *H. influenzae*; four cases involved multiple pathogens. Antibiotic resistance among these bacteria is on the rise, which will complicate the planning for any future pandemic.

The influenza A – the virus:

The genetic material in the influenza A virus is composed of 8 segments of negative-sense RNA. Negative sense RNA cannot be directly translated into protein and must be converted, or transcribed, into positive-sense RNA by an RNA polymerase that is encoded by the virus. The genome of influenza A encodes 11 proteins, the functions of which have been determined. The HA, or hemagglutinin protein, helps bind the virus to the host cell and the NA, or neuraminidase protein, helps the fully formed, infectious,

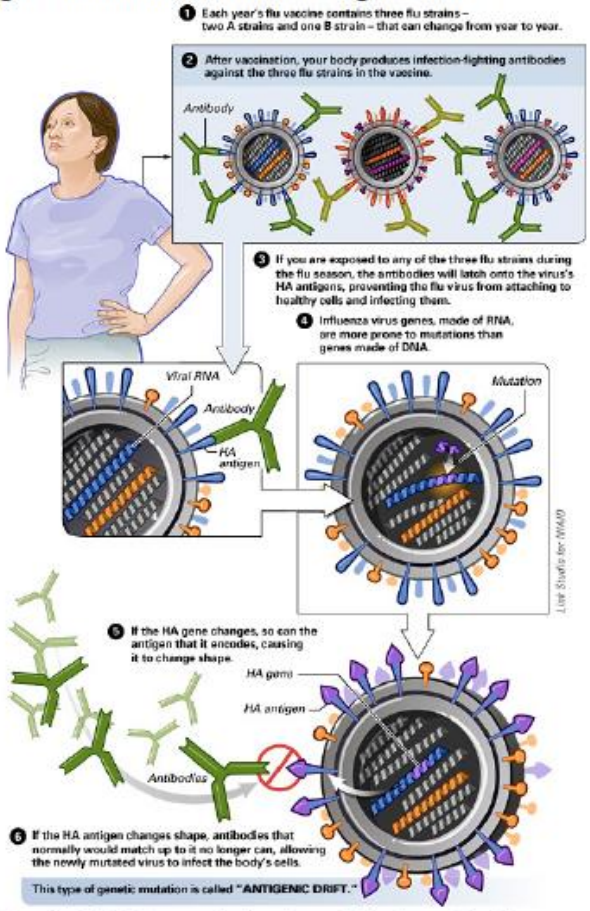
virus escape from the host cell. These proteins account for the defining HxNx nomenclature that has now become familiar to the world. The HA and NA proteins change over time and over geographic location. Both proteins can undergo minor mutations, called antigenic drift, creating a subtype of virus that causes seasonal influenza disease. People infected with the new subtype are not completely protected by the previous season's vaccine. In addition, HA and NA can undergo major changes creating an influenza A virus subtype to which the population has no preexisting immunity. The viruses that result from these shifts are associated with pandemics. The US National Institutes of Health offers a good description of these genetic processes:

"Antigenic Drift

Each year's flu vaccine contains three flu strains -- two A strains and one B strain -- that can change from year to year.

1. After vaccination, your body produces infection-fighting antibodies against the three flu strains in the vaccine
2. If you are exposed to any of the three flu strains during the flu season, the antibodies will latch onto the virus's HA antigens, preventing the flu virus from attaching to healthy cells and infecting them.
3. Influenza virus genes, made of RNA, are more prone to mutations than genes made of DNA.
4. If the HA gene changes, so can the antigen that it encodes, causing it to change shape

If the HA antigen changes shape, antibodies that normally would match up to it no longer can, allowing the newly mutated virus to infect the body's cells. This type of genetic mutation is called "antigenic drift."



Credit: This image is in the public domain. Please credit the National Institute of Allergy and Infectious Diseases (NIAID). **Illustrator:** Links Studio.

“Antigenic Shift

The genetic change that enables a flu strain to jump from one animal species to another, including humans, is called antigenic shift. Antigenic shift can happen in three ways:

Antigenic Shift 1

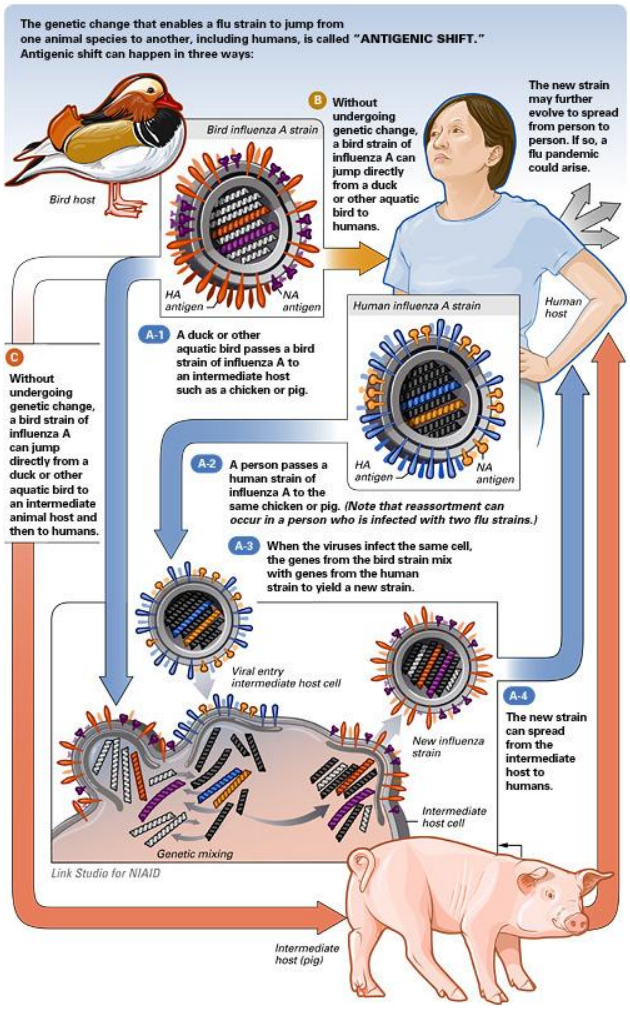
- A duck or other aquatic bird passes a bird strain of influenza A to an intermediate host such as a chicken or pig.
- A person passes a human strain of influenza A to the same chicken or pig.
- When the viruses infect the same cell, the genes from the bird strain mix with genes from the human strain to yield a new strain.
- The new strain can spread from the intermediate host to humans.

Antigenic Shift 2

- Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to humans.

Antigenic Shift 3

- Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to an intermediate animal host and then to humans.

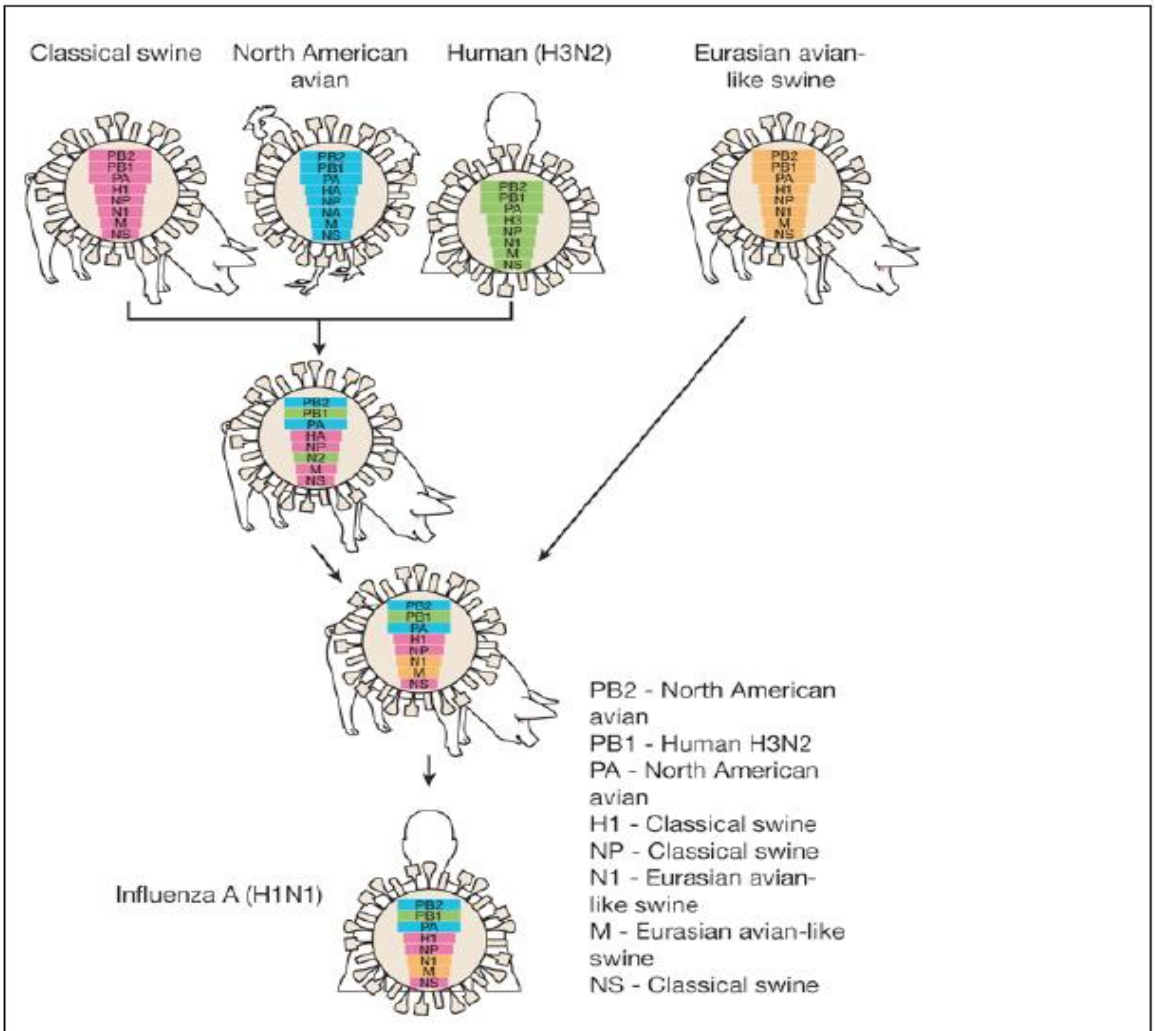


The new strain may further evolve to spread from person to person. If so, a flu pandemic could arise. “

Credit: This image is in the public domain. Please credit the National Institute of Allergy and Infectious Diseases (NIAID). **Illustrator:** Links Studio.

II. HOW 2009 H1N1 EMERGED

The genetic segments of the virus can move between viruses if two or more viruses infect the same cell. With this mechanism, reassortant between human H3N2, North American avian, and classical swine viruses resulted in the reassortant H3N2 and H1N2 swine viruses that circulated in North American pigs. Then a triple reassortant swine virus reassorted with a Eurasian avian-like swine virus that formed the H1N1



***Nature* 459, 931-939 (18 June 2009) Published online 14 June 2009. Emergence and pandemic potential of swine-origin H1N1 influenza virus. Gabriele Neumann, Takeshi Noda & Yoshihiro Kawaoka.**

causing the 2009 pandemic. *This highlights the need for real-time biomedical information including clinical and scientific biosurveillance—isolation and sequence determination of influenza strains in the animal and human populations in order to stay ahead of the wave of any future pandemic.* We return to this in the final section of this report where we make recommendations.

Immune Protection Against and Evolution of the 2009 H1N1 influenza virus—returning to its 1918 roots

A recent study mapped the evolutionary pathway that led to the 2009 H1N1 subtype that caused the pandemic (Wei, Boyington et al. 2010). The authors of the study observed that a vaccine for the 1918 strain of flu protected mice against the 2009 strain and conversely, a vaccine for the 2009 flu strain protected animals against the 1918 strain. They discovered that the protective antibodies generated by the vaccine, the neutralizing antibodies, were directed against a region of the HA protein that is remarkably similar in both the 1918 and 2009 strains. This region is quite altered in the seasonal flu strains. Antibodies that protect against seasonal flu strains offer no protection against the 1918 and the 2009 strains, as would be predicted. *This work has significant implications for vaccine development and is an example of the need for ongoing, sustainable basic research in emerging and re-emerging infectious diseases in general.*

A compendium of basic medical research findings on H1N1 can be accessed at http://www.niaid.nih.gov/topics/flu/research/basic/Pages/default.aspx.

Declaration of a Pandemic—truth and consequences

Given the molecular detail that is now known about influenza A, it would seem that declaring a pandemic should be the result of a set of direct observations. However, it is not that simple. In fact, the declaration of a pandemic has profound social, political, and economic consequences. The World Health Organization (WHO) defines a disease an ***epidemic*** when there are more cases of that disease than normal. A ***pandemic*** can range from mild to severe with the level of severity possibly changing over time, is the geographic extension of an epidemic (http://www.who.int/csr/disease/influenza/pandemic/en/). According to the current WHO guidelines there are six phases of a pandemic, a post peak period and a post pandemic period (http://www.who.int/csr/disease/avian_influenza/phase/en/index.html):

WHO Pandemic Influenza Phases

Phase	Description
Phase 1	No animal influenza virus circulating among animals have been reported to cause infection in humans
Phase 2	An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
Phase 3	An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of diseases in people but has not resulted in human-to-human transmission sufficient to sustain community–level outbreaks
Phase 4	Human to human transmission of an animal or human-animal influenza reassortant virus able to sustain community-level outbreaks has been verified.
Phase 5	The same identified virus has caused sustained community level outbreaks in two or more countries in one WHO region.
Phase 6	In addition to the criteria defined in Phase 5, the same virus has caused sustained community level outbreaks in at least one other country in another WHO region.
Post peak period	Level of pandemic influenza in most countries with adequate surveillance have dropped below peak levels; during this period additional waves of the pandemic may recur.
Post pandemic period	Levels of influenza activity have retuned to the levels seen for seasonal influenza in most countries with adequate surveillance.

Perceived trouble with the WHO pandemic guidelines:

The WHO announced the start of the H1N1 pandemic on June 11, 2009 noting that the virus quickly spread to 120 countries and territories in about 8 weeks. Nevertheless, the WHO came under attack from several quarters accused of succumbing to the pressures of the pharmaceutical industry to "fake" a pandemic in order to drive up profits from vaccine production. This prompted a statement by Dr Keiji Fukuda on behalf of WHO at the Council of Europe hearing on pandemic (H1N1) 2009 on 25 January 2010 emphatically denying that the WHO were improperly influenced by the pharmaceutical industry and that to label the pandemic as fake "is to ignore recent history and science and to trivialize the deaths of over 14,000 people and the many additional serious illnesses experienced by others".

Many reviews of the response to 2009 H1N1 pandemic are underway

On April 12, 2010 the WHO began a review of the response to the 2009 H1N1 pandemic in the context of the 2005 International Health Regulations (IHR, described below) with the following three objectives:

1. Assess the functioning of the International Health Regulations (2005);
2. Assess the ongoing global response to the pandemic H1N1 (including the role of WHO); and
3. Identify lessons learned important for strengthening preparedness and response for future pandemics and public health emergencies.

The review is to be wide-ranging and without preconditions. Dr Margaret Chan, Director-General of the WHO commented, "We are seeking lessons, about how the IHR has functioned, about how WHO and the international community responded to the pandemic, that can aid the management of future public health emergencies of international concern…We want to know what can be done better and, ideally, how." The review panel is independent of the WHO and will be chaired by Dr. Harvey Fineberg, President, The Institute of Medicine, Washington D.C., USA and is composed of an international panel of experts. It is expected that the review committee will advise the Director-General and based on the committee's advice, the Director-General will provide an interim report to the World Health Assembly (WHA) in May 2010, and a final report to the WHA in May 2011.

Several agencies within the US government are initiating reviews of the response to the 2009 H1N1 pandemic as well.

The WHO pandemic staging system has also come under criticism for not including a severity index. This was by design because of the correct understanding that there is no reliable way yet to predict severity. The US has prepared a staging system that is based on the hurricane warning system that does include anticipated severity. This is no general agreement on which of these two pandemic staging algorithms is most useful.

The U.S. CDC pandemic staging algorithm—one that includes severity:

On February 1, 2009, the CDC released a staging algorithm or pandemic severity index (http://pandemicflu.gov/professional/community/commitigation.html) fashioned after hurricane warning system and uses case fatality ratio as the critical driver for categorizing the severity of a pandemic. These criteria were developed with the purpose of, "…(providing) interim planning guidance for State, territorial, tribal and local communities that focuses on several measures other than vaccination and drug treatment that might be useful during an influenza pandemic to reduce its harm. Communities, individuals and families, employers, schools, and other organizations will be asked to plan for the use of these interventions to help limit the spread of a pandemic, prevent disease and death, lessen the impact on the economy, and keep society functioning."

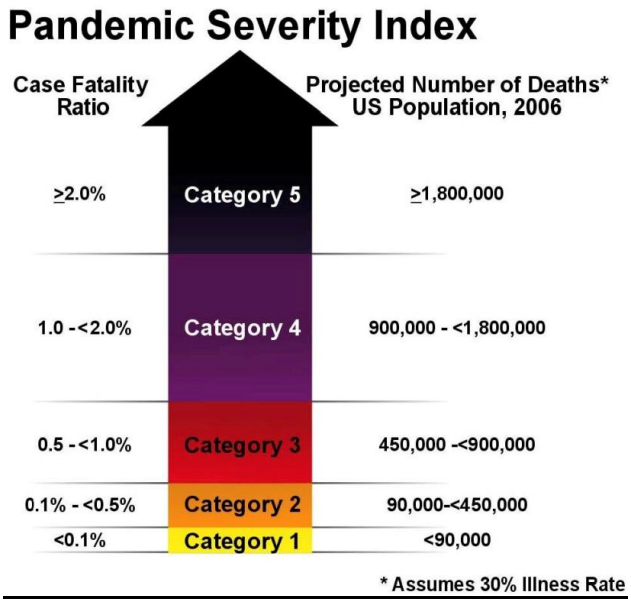


Table 1. Summary of the Community Mitigation Strategy by Pandemic Severity

	Pandemic Severity Index		
Interventions* by Setting	**1**	**2 and 3**	**4 and 5**
Home **Voluntary isolation** of ill at home (adults and children); combine with use of antiviral treatment as available and indicated	Recommend†§	Recommend†§	Recommend†§
Voluntary quarantine of household members in homes with ill persons¶ (adults and children); consider combining with antiviral prophylaxis if effective, feasible, and quantities sufficient	Generally not recommended	Consider**	Recommend**
School **Child social distancing**			
-dismissal of students from schools and school based activities, and closure of child care programs	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
-reduce out-of-school social contacts and community mixing	Generally not recommended	Consider: ≤4 weeks††	Recommend: ≤12 weeks§§
Workplace / Community **Adult social distancing**			
-decrease number of social contacts (e.g., encourage teleconferences, alternatives to face-to-face meetings)	Generally not recommended	Consider	Recommend
-increase distance between persons (e.g., reduce density in public transit, workplace)	Generally not recommended	Consider	Recommend
-modify postpone, or cancel selected public gatherings to promote social distance (e.g., postpone indoor stadium events, theatre performances)	Generally not recommended	Consider	Recommend
-modify work place schedules and practices (e.g., telework, staggered shifts)	Generally not recommended	Consider	Recommend

III. ARE THERE EXISTING MANAGEMENT STRUCTURES THAT HELP PREPARE, MITIGATE AND RESPOND IN THE EVENT OF A PANDEMIC?

An issue of great importance for an analysis of pandemic future global shocks is the question of "What management structures/regulations/international cooperation mechanisms are already in place for dealing with the risk?" With respect to this question, the WHO investigation will be an important study not only for analyzing the specific response to the 2009 H1N1 pandemic but perhaps even more importantly for the analysis of the 2005 international health regulations (http://www.who.int/ihr/9789241596664/en/index.html). The IHR were designed to:

> "prevent, protect against, control and provide a public health response to the international spread of disease in ways that are commensurate with and restricted to public health risks, and which avoid unnecessary interference with international traffic and trade." The IHR (2005) contain a range of innovations, including: (a) a scope not limited to any specific disease or manner of transmission, but covering "illness or medical condition, irrespective of origin or source, that presents or could present significant harm to humans"; (b) State Party obligations to develop certain minimum core public health capacities; (c) obligations on States Parties to notify WHO of events that may constitute a public health emergency of international concern according to defined criteria; (d) provisions authorizing WHO to take into consideration unofficial reports of public health events and to obtain verification from States Parties concerning such events; (e) procedures for the determination by the Director-General of a "public health emergency of international concern" and issuance of corresponding temporary recommendations, after taking into account the views of an Emergency Committee; (f) protection of the human rights of persons and travellers; and (g) the establishment of National IHR Focal Points and WHO IHR Contact Points for urgent communications between States Parties and WHO."

The International Health Regulations (IHR) 2005

The International Health Regulations (IHR) of 2005 represent an international legal instrument updated from the IHR (1969), for the purpose of helping the international community prevent and respond to public health risks that threaten the global community. The instrument is legally binding on 194 countries across the globe, including all the Member States of WHO, and entered into force on 15 June 2007. One of the main goals of the IHR is to optimize a system of surveillance, alert and response to various infectious disease emergencies such as pandemic influenza, as well as other public health emergencies such as chemical spills, leaks and dumping, or nuclear incidences. The specific innovations are detailed above. A goal of the IHR is also to limit interference with international traffic and trade with its system of response, i.e. "prevent, protect against, control and provide a public health response to the international spread of disease and which avoid unnecessary interference with international traffic and trade." Specifically, the IHR require countries to report certain

disease outbreaks and public health events to WHO. The IHR also require countries to strengthen their existing capacities for public health surveillance and response. They define the rights and obligations of countries in the context of their global health contributions, and in return establish a number of procedures and obligations that WHO must follow in its work to uphold global public health security.

In implementing IHR 2005, WHO is working closely with countries and partners to provide technical guidance and support to mobilize the resources needed to implement the new rules in an effective and timely manner. In 2009 the Secretariat planned to establish a new web-based system for States Parties to report progress in implementation. Establishing and reinforcing existing resource infrastructures such as new WHO Influenza Collaborating Centres and national influenza centres also play a role in IHR. The intended downstream effects include supporting member stakeholders in:

- boosting national capacities in disease surveillance and response
- the development of regional surveillance networks
- the promotion of laboratory quality systems, as well as the training in field epidemiology, laboratory biosafety and instituting laboratory certification for transport of infectious substances
- the establishment of effective risk communication strategies.

WHO, through its regional and country offices, continues to adapt its regional strategies for national disease surveillance and response systems to the requirements of the Regulations. WHO Collaborating Centres for reference and research on influenza have been updating and distributing influenza diagnostic reagents for surveillance to national influenza centres. Networks of National IHR Focal Points and WHO IHR Contact Points are used for rapid communication of public health information between WHO and States Parties. In addition, WHO has organized field meetings designed to strengthen the surveillance capabilities of designated international airports, ports and ground crossings.

However, key issues in implementing the IHR include the need to continue to increase awareness by national and regional stakeholders. A recent survey by WHO (http://apps.who.int/gb/ebwha/pdf_files/A62/A62_6-en.pdf) detailed the progress achieved in implementation of the IHR. While considerable progress has been made in establishing a reliable channel of reporting to the WHO by state parties and identifying relevant national stakeholders for sector-specific implementation, only 21% of the countries indicated that they had examined the possible need for additional financial resources in order to implement adequately the requirements of the IHR. This is particularly essential, as the impediments to implementation in many of the poorer countries are lack of funding, manpower and other critical infrastructure and key resources, which needs to be reviewed and resolved. Specific concerns (see for example (Editors 2007)) include:

1) the infrastructure that is required for surveillance, reporting and responding is expensive and generally unavailable in many developing countries,
2) developing countries need the capacity to respond to their own public health emergencies in addition to those of international concern as defined in the IHR,
3) nations with a federalist-style governance structure, including the US, Canada, India, Germany, modern Russia, Mexico, South Africa, Australia, Switzerland, Belgium, Argentina, may have difficulty harmonizing powers and responsibilities between the central national government and those remaining with states or regions within the country, especially those that require surveillance and reporting,
4) what happens to, and for, countries that are not members of WHO, and
5) can the IHR be harmonized with the surveillance and reporting guidelines that already exist?

Dr. Guenael Rodier, the director of the IHR coordination programme at the WHO, gave a candid discussion of these issues. He commented, "Funding is critical. Technology transfer will play a role. Much of this work is likely to be funded on a bilateral basis and many countries in need are already in touch with institutional development partners. Development partners are interested, but the challenge is to find out how much it will cost and for how long." (Rodier 2007).

Interdependencies and Critical Links

The Global Burden of Disease Study indicates that infectious diseases accounts for 22% of all deaths and 27% of disability adjusted life years (DALYs) with a disproportionate impact on the developing world where infectious diseases account for 52% of deaths and 50% DALYs in sub-Saharan Africa and only 11% of deaths and 5% of DALYs in established market economies (Globalization and Infectious Diseases: A review of the linkages. found at http://www.who.int/tdr/cd_publications/pdf/seb_topic3.pdf).

While progress has been made on a number of fronts, especially at the basic science level in understanding the pathogenesis of many diseases, the overall situation in controlling infectious diseases has deteriorated for a number of interdependent reasons including:

Biological: 1) the increase in antibiotic resistant bacterial infections, 2) zoonotic and foodborne infections must be taken into consideration in the increased incidence of the spread of infectious diseases

Corporate/financial: 1) the pipeline of new molecular entities that lead to effective anti-infective agents is quite sparse, 2) large pharmaceutical companies have, in many cases, abandoned anti-infective drug development and discovery, 3) global financial crises divert scarce resources from health related issues

Governmental/policy/infrastructure: 1) the absence of harmonized regulatory processes hinders rapid development of anti-infective agents, 2) in many parts of the

world the distribution of anti-infective agents to clinics and to patients is woefully underdeveloped, 3) the infrastructure that is necessary for rapid and accurate diagnostic testing in the developing world is woefully inadequate, 4) there are an insufficient number of well-trained medical workers that are necessary to ensure proper diagnosis, prescribing and monitoring practices, 5) the increased incidence of national insurgencies and of failed states worsens the global communicable disease situation, 6) individual nations have different motivations in generating policy for the use of first, second and third line anti-infective agents, 7) globalization—economic globalization, demographic globalization (urbanization and refugee movement), technological global changes and environmental/climate global changes, all contribute to altered patterns of communicable diseases, frequently in unpredictable ways, 8) agencies that work for increased access to anti-infective agents must coordinate goals and policies with agencies that work to limit the emergence of resistance to anti-infective agents,

Research/information: 1) while antiviral research and development is progressing, work developing antibacterial, anti-fungal and especially anti-parasitic agents lags far behind, 2) global infectious disease surveillance and reporting is incomplete and shared, interoperable, real-time databases are also inadequate, 3) the emergence of new research in synthetic biology generates an entirely new threat space with the synthetic creation of new infectious agents, the reintroduction of infectious agents that no longer exist in nature or in generating infectious agents that exist in nature but are hard to isolate.

Illegal activities: 1) increased number and availability of counterfeit drugs contribute substantially to the spread and emergence of drug resistance of communicable diseases

Social unrest: 1) social disruptions would hinder if not completely prevent an adequate response and mitigation of any outbreak of an infectious disease.

(see page 33, http://www.istar.upenn.edu/PDF-literature-photos/HR_HOL_Testimony.pdf).

IV. WHAT IS THE STATE OF THE ART REGARDING RISK ANALYSIS, POTENTIAL IMPACTS, EXISTING MODELS?

Let us define the following: *risk* is some measure of the probability of an event and its consequence; *threat* is the basis, origin or agent of an unwanted impact to a system and *vulnerability* is any condition or weakness that makes an asset susceptible to a threat. With these in mind we can consider risks, threats and vulnerabilities as either symmetric or asymmetric. For example, the investment community would consider it an asymmetric risk environment when, for a given investor, the probability of gain is greater when an asset moves up compared to the amount that investor would lose if the asset moved down--Heads I win, tails, I don't lose. It has been argued that this asymmetry was at the heart of the subprime mortgage crisis.

In the world of infectious diseases, one might safely say that the *risk*, the probability, of contracting Ebola virus and a subsequent local outbreak in the South Pole is vanishingly small. If an Ebola infection did arise in an individual or community in the South Pole, the probability of devastating consequences would be high. In this example, the *threat agent*, the Ebola virus, the single stranded RNA hemorrhagic fever virus, is the same as it is in the South Pole as it is in Africa. Similarly, it is very clear in the domain of infectious diseases, that vulnerabilities are frequently asymmetric and depend on a host of social, economic and political factors, many of which are interdependent. Therefore, recognizing the nature of asymmetric/symmetric risks, threats and vulnerabilities vastly complicates the analysis of the onset characteristics, root causes and propagation paths in defining the relationship between pandemics and global shocks.

The WHO recognizes the inadequacy of the scientific and clinical data on which risk analyses are based and published a set of six public health recommendations that it proposes are essential for public health decision–making (WHO Working Group 2009).

1. Measuring age-specific immunity to infection.

2. Accurately quantifying severity.

3. Improving treatment outcomes for severe cases.

4. Quantifying the efficacy of interventions.

5. Capturing the full impact of the pandemic on mortality.

6. Rapidly identifying and responding to antigenic variants.

We would add to this list sharing of complete genetic sequences before and especially during a local outbreak, as difficult as this may be in our fractious world (see for example, (Franklin 2009), (Sedyaningsih, Isfandari et al. 2008), (Bhattacharya 2007), (Enserink and Normile 2007), (Elbe 2010)).

Risk analysis:

We follow here a framework for risk analysis suggested by our colleagues at the Wharton School Risk Management and Decision Processes Center (Kunreuther and Useem 2009). First, a *risk assessment* is informed by the science, medical knowledge and engineering aspects of a pandemic. Second, *risk perception and choice* utilizes psychology, sociology, experimental economics and communication theory to analyze how individuals, organizations, and local, state and national governments perceive risks and make decisions. Third, carrying out a *risk management* program will necessarily employ a multidisciplinary team to develop strategies to minimize losses and optimize mitigation, response and recovery.

V. RISK ASSESSMENT PART 1:

There are four basic elements for assessing risk: 1) inventory, 2) hazard, 3) vulnerability and 4) loss. Within *inventory* we consider the inventory of properties, humans, physical environment and critical infrastructures at risk. In *hazard* we will consider geographic origin of pandemics, pathway to spread, spread rate. Together, *hazard* and *inventory* allow a consideration of *vulnerability* of the population and the built and natural resources leading to and estimation of *loss*.

Inventory and hazard: The individual--Who was at risk for 2009 H1N1?

The full extent of the economic, social and political impacts of a human pandemic depend critically on the number of people who: 1) become infected, 2) can transmit the disease, 3) develop symptoms, 4) cannot work for a certain period of time either because they are ill or because they are at home caring for the sick and, 5) eventually die.

Even in the absence of a pandemic, infectious diseases physicians, epidemiologists and basic scientists try to establish a prioritized list of those who might be more susceptible to acquiring a disease, those who will become symptomatic and those who will become severely ill. Genetics, biochemistry, concomitant diseases, other therapies, comorbidities, and infections with other infectious agents inform these studies. In addition, those at higher risk are stratified according to the likelihood of extensive exposure to an individual or community in which infections are frequent, for example, health care workers, teachers, correction officers, agriculture workers and the military to name but a few (see for example (Chen, Lee et al. 2010); (Chevalier, Pepin et al. 2010); (Stanforth, Krause et al. 2010)). Prior to an expected outbreak of an infectious disease, such as seasonal flu, the exercise of setting priorities for early distribution of vaccine and drugs to selected populations is carried out at the highest levels of government with input from the biomedical community (Goldstein, Miller et al. 2010). During and after each epidemic or pandemic, clinicians and scientists review categories of at-risk populations in order to gain basic biomedical information on the pathophysiology of the disease and to plan for the next outbreak.

On the individual level--What was done? Did it work well?

The following are the CDC recommendations for at risk populations based on prior and ongoing studies of influenza outbreaks (found at: Patients at Increased Risk for Complications (http://www.cdc.gov/h1n1flu/recommendations.htm):

"Prompt empiric antiviral drug treatment is recommended for persons with confirmed or suspected influenza who are at increased risk for serious morbidity and mortality. Based on currently available data, approximately 70% of persons hospitalized with 2009 H1N1 are in one or more of the following groups:
Children (see below) younger than 2 years old
Adults 65 years of age or older
Pregnant women and women up to 2 weeks postpartum (regardless of how the pregnancy ended [live birth, pregnancy termination, preterm birth, miscarriage, fetal death])

Persons with certain medical conditions, described below.
Children: Children younger than 2 years of age are at higher risk for influenza-related complications and have a higher rate of hospitalization compared to older children. Children aged 2 to 4 years are more likely to require hospitalization or urgent medical evaluation for influenza compared with older children and adults, although the risk is much lower than for children younger than 2 years old. From April through September 2009 hospitalization rates for laboratory-confirmed 2009 H1N1 influenza were 4.5-fold higher among children < 2 years of age, 2-fold higher among children 2-4 years of age, and 1.6-fold higher among children 5-17 years of age than among adults (see Weekly Flu View). In April, 2009, the FDA authorized oseltamivir use in children younger than 1 year under an Emergency Use Authorization (EUA) in response to the current public health emergency involving 2009 H1N1 influenza. Use of oseltamivir in children younger than 1 year is subject to the terms and conditions of the EUA. Retrospective safety data on oseltamivir treatment of seasonal influenza in children younger than 1 year old are limited and suggest that severe adverse events are rare. Prospective data continue to be collected on safety and efficacy of oseltamivir in this age group. Dosing for children younger than 1 year is based on the EUA guidance. Details are provided in Table 1, below. (See also: Emergency Use Authorization of Tamiflu (oseltamivir) available at /h1n1flu/eua/). Children and adolescents under 19 years of age who are receiving long-term aspirin therapy are also at increased risk. For more detailed information, see "Updated Recommendations for Health Care Providers of Children and Adolescents on the Use of Antiviral Medications for the Management of 2009 H1N1 and Seasonal Influenza for the 2009-2010 Season".

Adults aged 65 years and older: Even though persons aged 65 years and older are less likely to become ill with 2009 H1N1 influenza compared to younger persons, when they do acquire influenza, they are at higher risk for severe influenza-related complications.
Pregnant women: Pregnancy increases the risk of complications, hospitalization, and severe disease. One study estimated the risk of hospitalization for 2009 H1N1 to be four times higher for pregnant women than for the general population (Jamieson DJ, et al. Lancet. 2009;374:451-458). While oseltamivir and zanamivir are "Pregnancy Category C" medications, meaning no clinical studies have been conducted to assess the safety of these medications for pregnant women, available data suggest pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy, and pregnancy should not be considered a contraindication to treatment with oseltamivir or zanamivir. Oseltamivir is preferred for treatment of pregnant women because of its systemic activity. Anecdotal reports suggest postpartum women, similar to pregnant women, might be at increased risk for severe complications and death from 2009 H1N1 influenza. The transition to normal immune, cardiac, and respiratory function occurs quickly, but not immediately after delivery. Therefore, the increased risk associated with pregnancy should be considered to extend for 2 weeks postpartum regardless of the outcome of the pregnancy (including live birth, premature birth, termination of pregnancy, miscarriage, fetal death). Prompt empiric antiviral treatment is indicated for suspected or confirmed 2009 H1N1 influenza in women who are up to 2 weeks postpartum regardless of how the pregnancy ended.
Medical conditions: The following medical conditions have been associated with increased risk of complications from influenza:
1. Asthma
2. Neurological and neuro-developmental conditions [including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury].
3. Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
4. Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
5. Blood disorders (such as sickle cell disease)
6. Endocrine disorders (such as diabetes mellitus)
7. Kidney disorders
8. Liver disorders
9. Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
10. Weakened immune system due to disease or medication (such as people with HIV or AIDS, or cancer, or those on chronic steroids)
11. People younger than 19 years of age who are receiving long-term aspirin therapy"

A 2010 study (Siston 2010) analyzed the severity of illness (hospitalizations, intensive care unit [ICU] admissions, and deaths) in 788 pregnant women in the United States with 2009 influenza A (H1N1) who developed the disease between April through August 2009. The study showed that among these women, 30 died (5% of all reported 2009 influenza A (H1N1) influenza deaths in this period). 115 of 509 hospitalized women (22.6%) were admitted to an ICU. Pregnant women who had delayed antiviral treatment (more than 4 days after symptom onset) were more likely to be admitted to an ICU (56.9% vs 9.4%) compared to those treated early--within 2 days after the onset

of symptoms. 1 death occurred in a patient who received treatment within 2 days of the beginning of symptoms. Additional data on pregnant women with symptom onset through December 31, 2009, identified 165 women for a total of 280 women who were admitted to ICUs, 56 of whom died. 4 deaths occurred in the first trimester (7.1%), 15 in the second (26.8%), and 36 in the third (64.3%). A study published in September 2010 in the Mayo Clinic Proceedings (vol. 85 pp 798-805) reviewed the Mayo Clinic experience and found that the patients hospitalized with H1N1 infection were relatively young, many required intensive care unit admission and mechanical ventilator support, the three most common co-morbidities were hypertension, obesity and diabetes mellitus.

Lessons learned from the 2009 H1N1 pandemic include the identification of obesity as a high-risk for severe illness. In Australia, it was found that indigenous populations were also at particularly high risk for poor outcomes. The Australian experience also showed a distinguishing feature of the pandemic was the relatively large number of patients who were an intensive care unit with confirmed cases of H1N1 disease. The peak of the pandemic lasted approximately 3 weeks in Australia and while the health system there was stressed, there was sufficient surge capacity with enough ICU and regular hospital beds to care for the patients (Bishop, Murnane et al. 2009).

Mild or Severe— it depends on how do you count

As discussed above, there were, among some commentators, serious concerns that national governments and world health organizations, including the WHO, overreacted to the potential of an H1N1 pandemic in 2009. Now that the pandemic has been confirmed by the current WHO criteria, some commentators continue to fault these agencies because the clinical characteristics of the disease, while widespread, were actually quite mild. However, characterizing the 2009 H1N1 pandemic as mild is not correct if one considers years of life lost rather than simply mortality as the metric of severity. A recent study recommends using years of life lost (YLL) as a

Age group (yrs)	No. deaths	Proportion of deaths	Life expectancy in 2000 (yrs)
0-4	24	5.1%	76.5
5-9	32	6.8%	72.5
10-19	45	9.6%	65.1
20-29	84	17.9%	55.5
30-39	72	15.4%	46
40-49	82	17.5%	36.7
50-59	71	15.2%	28.1
> 60	58	12.4%	14.9

Age distribution of pandemic-related deaths in 2009 [9] and life expectancy estimates in the US used for calculation of years of life lost (Viboud and Miller, 2010)

	Numbers of deaths (adjusted to 2000 population)	Mean age of deaths (yrs)	Years of life lost (adjusted to 2000 population)
2009 pandemic	7,500-44,100 *	37.4	334,000-1,973,000
	12,000 (8,500-17,600) **		463,300 (328,900-680,300)
1968 Pandemic	86,000***	62.2	1,693,000
1957 Pandemic	150,600***	64.6	2,698,000
1918 Pandemic	1,272,300***	27.2	63,718,000
Average A/H3N2 season, 1979-2001	47,800***	75.7	594,000

* Range is based on estimates of excess P&I deaths (lower) and all-cause deaths (upper), based on projections from the 122 cities mortality surveillance
** Estimates based on CDC's probabilistic estimates, using 2009 pandemic survey data [8] (different from CDC's excess mortality method for measuring seasonal influenza burden)
*** Estimates based on excess mortality approach applied to final national vital statistics and adjusted to the 2000 population age structure

Estimates of number of deaths, mean age of deaths, and years of life lost attributable to the 2009 pandemic in the US. Estimates for historical pandemics and typical A/H3N2 seasons are provided for comparison purposes. (Viboud and Miller 2010)

more significant metric for analyzing the impact of a pandemic (Viboud, Miller et al. 2010). As explained in Viboud, "YLL is calculated by multiplying the number of age-specific deaths attributable to the 2009 pandemic to standard life expectancy at age of death in 2000 from the mid-point of each age category. Our algorithm follows a

standard approach for estimating Disability Adjusted Life Years (PLoS Med. 2006 Nov;3(11):e442. Projections of global mortality and burden of disease from 2002 to 2030.Mathers CD, Loncar D.) but without weighing a social discount rate that favors life saved in the near future, nor using age-specific coefficients to weight deaths in young adults more heavily than in children or seniors. " It has been estimated that more than 85% of laboratory-confirmed A/H1N1 deaths occurred in people under the age of 60, with a mean age of deaths of 37 compared to seasonal influenza epidemics where 90% of deaths occur in people over 65 and the mean age of influenza-related deaths is estimated at 76 yrs.

Local to Global Propagation--How is the virus spread ?

A recent study of the diffusion of pandemic human influenza A (H1N1) 2009 in Hong Kong, using geographic information system (GIS) methodology found that diffusion of the virus was closely associated with population structure and mobility. Students were the primary disseminators of the 2009 H1N1 across Hong Kong, similar to previous observations in other countries and for seasonal flu (Lee and Wong 2010). Investigations of the SARS outbreak clearly identified superspreaders (Lloyd-Smith, Schreiber et al. 2005), (Galvani and May 2005) (Shen, Ning et al. 2004), (Wong 2004). A suggestion that coinfection with other respiratory viruses could partially explain the observation of superspreaders of SARS (Bassetti, Bischoff et al. 2005). Except for the prevalent and not unreasonable hypotheses that certain healthcare workers and students may represent H1N1 superspreaders, there are no data yet to confirm or falsify the hypothesis. Nor is there any data on the basic biology of potential H1N1 superpreaders that could help identify a pathophysiologic mechanism for superspreading.

Human superspreaders notwithstanding, the role of transportation clearly serves as a superspreading technology. It is clear that air travel is the major route of local to global propagation (Khan, Arino et al. 2009). While it is evident that air travel is a major means of local to global propagation, the impact of restricting air travel once a major outbreak is identified is debatable. Several mathematical models have questioned the effectiveness of such restrictions (Lim 2006), (Grais, Ellis et al. 2003), (Cooper, Pitman et al. 2006). One study (Hollingsworth, Ferguson et al. 2006) concludes, "Our analysis also indicates that restrictions on travel will be of limited benefit in slowing global spread of a pandemic influenza outbreak that is not contained at its source. There may be a role for travel restrictions applied to the source country while containment efforts are underway— minimizing the chance that one of the first few hundred infections of an outbreak might be exported to a region where containment would be less feasible."

Spread a pandemic?--Consider criminals and animals and not just transportation technology

There are yet other ways in which a local outbreak can go global. In the case of HN51, the so-called Avian flu, while the virus has yet to mutate to efficiently allow human to human spread, cases of human H5N1 have been reported to the WHO from 15 countries accounting for at least 495 cases with 292 deaths. To some extent this reflects migratory bird patterns but it also reflects robust, international smuggling activity. Therefore it is very hard to predict the major means or trajectory of local outbreak to global pandemic. As we discussed above, the international community must make surveillance and reporting a priority.

Planes, trains, people and pets—what about the virus?

Identifying the genetic and biochemical properties of the virus that correspond to transmissibility and virulence is critically important and, fortunately, is a hotly pursued research area in a number of labs around the world (see for example: (Tumpey and Belser 2009), (Miotto, Heiny et al. 2010), (Taubenberger, Reid et al. 2005). The ultimate success of these multidisciplinary research programs will depend on sustained international scientific and political cooperation.

We can see from the above that ultimately any globally successful mitigation program has to be based on additional basic biomedical and epidemiologic research on:

1) the epidemiological dynamics of spread

2) the properties and activities of certain hosts that correspond to increased transmission—e.g., are there individuals who are so called "superspreaders"?

3) the genetic and biochemical properties of the virus that correspond to transmissibility

4) the possibility of developing a truly universal vaccine that will be safe and effective in preventing any strain of influenza A, obviating the need for the mad scramble whenever a new strain appears either through antigenic drift or even shift.

Developing a universal vaccine for influenza A is one of the holy grails of vaccine research. This is a very difficult research project yet progress is being made, albeit slowly and funds should continue to be identified to support this effort (see for example, (Taubenberger, Reid et al. 2005) (Du, Zhou et al. 2010), (Gerhard, Mozdzanowska et al. 2006).

VI. RISK ASSESSMENT PART 2: VULNERABILITY AND LOSS: HOW LIKELY IS A PANDEMIC GLOBAL SHOCK AND WHAT COULD BE THE ECONOMIC CONSEQUENCES?

It is extremely difficult to predict the likelihood of a pandemic. However models of the economic consequences of an influenza pandemic have been studied extensively over the past 5 years. Prior to the 2009 H1N1 pandemic, the World Economic Forum estimated that the likelihood of a pandemic to be between 5 and 10% with an impact in the 250 billion US dollar range.

The United States Congressional Budget Office (CBO) Assessment of the Macroeconomic Effects of a Pandemic Flu

A 2005 CBO study, revised in 2006, estimated that in a severe pandemic there would be about 4.25 percent reduction in GDP and about 1 percent reduction in a mild pandemic compared to what it would have been in the absence of a pandemic (www.cbo.gov/ftpdocs/69xx/doc6946/12-08-BirdFlu.pdf). The impact on the supply side of a potential pandemic: about 2.25 percent in the severe scenario and about 1/2 percent in the mild scenario (see Table A1). The impact on the demand side would depend on the industry—those that depend on intense interpersonal contact would suffer more than those industries that do not require person-to-person contact, except for health-care industry, which would actually show an increase in demand (see Table A2). In both the severe and mild pandemic models, it was concluded that economic activity would rebound in the post pandemic period pandemic as businesses increased production to meet new demand.

Supply-Side Effect

To evaluate the supply-side impact of a pandemic, CBO calculated the effect of the loss of employee work days on GDP in five sectors of the economy—nonfarm business, farm, households, nonprofit institutions, and general government—using average productivity per employee calculated in 2004. The specific values for the assumptions that went into the model are given in Table A-1.

Table A-1.

Assumptions Underlying Estimates of the Supply-Side Impact of an Avian Flu Pandemic

	Gross Attack Rate (Percent)		Weeks Out of Work		Case Fatality Rate (Percent)	
Economic Sector	Severe	Mild	Severe	Mild	Severe	Mild
Nonfarm Business	30	25	3	0.75	2.5	1.14
Farm	10	5	1	0.25	2.5	1.14
Household	30	25	3	0.75	2.5	1.14
Nonprofit Institutions	30	25	3	0.75	2.5	1.14
Government	30	25	3	0.75	2.5	1.14

Source: Congressional Budget Office.

Note: The gross attack rate is the percentage of the population that is infected with a disease. The case fatality rate is the percentage of infected persons who eventually die from the disease or complications.

case fatality rate was unchanged). Using data for 2004, CBO used average productivity per worker, by sector, to compute the impact on GDP of the employment lost to the pandemic.[3]

For the mild pandemic CBO assumed a 25 percent attack rate (except in the farm sector, which was assumed to be 5 percent), a case fatality rate of just over 0.1 percent, and cut the time out of work to one-quarter of the duration assumed for the severe scenario (i.e., just under four days absent, on average).

Demand-Side Effect --Table A-2

To calculate the demand-side effect, CBO examined GDP by industry and assumed different declines in demand for different industries, based on judgments about the degree of social interaction required in different industries. The CBO recognized that there is little data to arrive at these estimates and therefore the estimates may not be robust. Industries that require interpersonal contact are assumed to have the largest declines in demand.

Table A-2.

Assumed Declines in Demand, by Industry, in the Event of an Avian Flu Pandemic

(Percent)

	Severe Scenario	Mild Scenario
Private Industries		
Agriculture	10	3
Mining	10	3
Utilities	0	0
Construction	10	3
Manufacturing	10	3
Wholesale trade	10	3
Retail trade	10	3
Transportation and warehousing		
Air	67	17
Rail	67	17
Transit	67	17
Information (Published, broadcast)	0	0
Finance	0	0
Professional and business services	0	0
Education/health care		
Education	0	0
Health care	-15	-4
Arts/entertainment/ accommodation/food		
Arts and recreation	80	20
Accommodation	80	20
Food service	80	20
Other services except government	5	1
Government		
Federal	0	0
State and local	0	0

Source: Congressional Budget Office.

Note: The severe scenario describes a pandemic that is similar to the 1918-1919 Spanish flu outbreak. It incorporates the assumption that a particularly virulent strain of influenza infects roughly 90 million people in the United States and kills more than 2 million of them. The mild scenario describes a pandemic that resembles the outbreaks of 1957 to 1958 and 1968 to 1969. It incorporates the assumption that 75 million people become infected and about 100,000 of them die from the illness or complications.

A number of studies of the potential macroeconomic impact of an influenza pandemic similar to that carried out by the CBO have been published; some conclude that the impact would be greater than that estimated by the CBO (Kennedy, Thomson et al. 2006), (McKibbin and Sidorenko 2006).

A study published by Dr. Sherry Cooper of BMO Nesbitt Burns (March 13, 2006) pointed out that the CBO estimate considered only the loss of labor and labor productivity in its supply shock and did not take into account the effect of trade disruptions that would negatively influence the supply chain. Cooper's model considered the trade and supply chain and predicted that a mild pandemic would reduce

annual GDP growth by 2 percentage points and a severe pandemic, would reduce global GDP growth by 6 percentage points.

A study by the New Zealand Treasury estimated that a severe pandemic would reduce GDP in New Zealand by between 5 percent and 10 percent in the year that it occurred (Douglas, Szeto et al. 2006).

Other studies estimate effects on the economy that are roughly the same size or slightly lower that those calculated by the CBO (James and Sargent 2006)) estimate that a severe pandemic, with mortality similar to that seen in 1918, would reduce Canadian GDP by an amount that ranged from 0.3 percent to 1.1 percent in the year of the pandemic.

How would a pandemic impact the economy sector by sector?

The potential impact of a pandemic on each segment of the economy and infrastructure depends on information about the details of the pandemic: What is the predominant mode of spread? Are there animal hosts? Who are the at risk populations? Is the pandemic predominantly urban or rural? Is it primarily limited to the developed world or developing world? Do adequate supplies of drugs and/or vaccines already exist or do they have to be developed, manufactured and distributed?

A 2007 study by the US Department of Homeland Security (see Figure 3-1 below) estimated the impact on the individual sectors. The study found that manufacturing would suffer the largest hit losing $95 billion in output, finance and insurance would lose $40 billion, and retail trade would lose $32 billion.

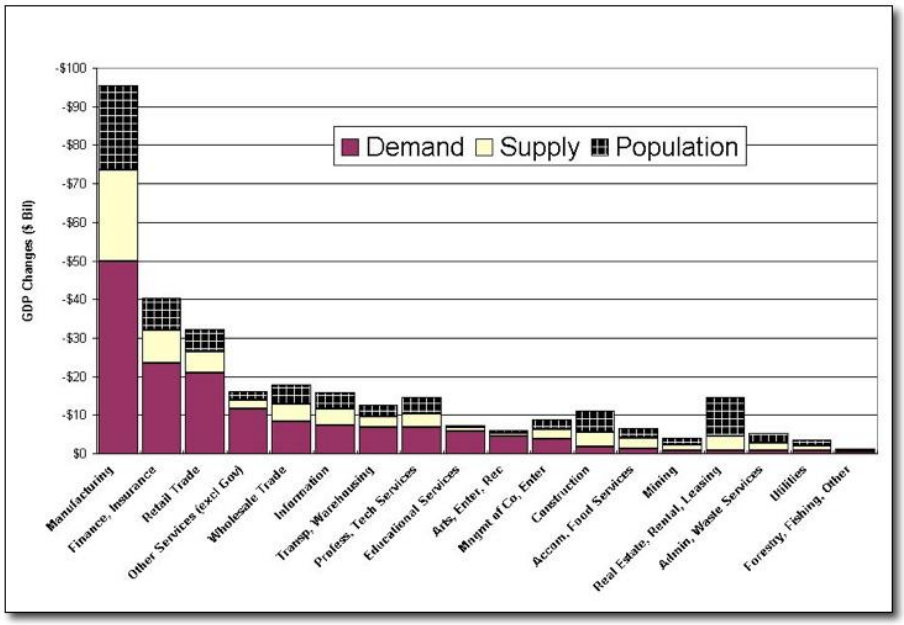


Figure 3-1: Average gross domestic product (GDP) losses, by type of shock and industry: year 1, baseline scenario (Economic Modeling for the Analysis of Pandemic Influenza.

Supplement to the National Population and Infrastructure Impacts of Pandemic Influenza Report. 15 October 2007. Prepared by National Infrastructure Simulation & Analysis Center. Infrastructure Analysis and Strategy Division. Office of Infrastructure Protection, Department of Homeland Security)

The full 2007 DHS report (National Population, Economic, and Infrastructure Impacts of Pandemic Influenza with Strategic Recommendations 10 October 2007) describes seven influenza epidemiological scenarios in order to model the impact of a pandemic on the critical infrastructure sectors:

1. *Baseline:* No intervention, unconstrained pandemic
2. *Fear-40:* Only strong voluntary self-isolation as a result of normal caution or fear (beginning on day 57, ramping up to 40 percent on day 63, then ramping back down to 0 on day 70), no intervention
3. *Community Mitigation Guidance (CMG):* Unlimited antivirals, strong social distancing, complete student dismissal for duration of epidemic, no circulating symptomatic people ("liberal leave"), partial quarantine of the families of sick people from day 1, partial reduction in children's activities, and no voluntary self-isolation
4. *Community Mitigation Guidance-Selected Elements (CMG-SE):* Unlimited antivirals and strong social distancing only
5. *Antivirals:* Application of stockpile antivirals only
6. *Pre-pandemic Vaccine:* Partially effective vaccine at a reasonable production rate
7. *Anticipated:* Stockpile-only antivirals, mild social distancing, limited student dismissal, weak voluntary self-isolation, and normal vaccine production and timing. (Note: *Social distancing* encompasses a variety of behavioral modifications that can reduce disease transmission, including improved hygiene, handshake avoidance, maintenance of interpersonal space, and mask-wearing; changes in activities, such as following bans on public events, are treated as separately distinct interventions and are not included in social distancing as defined in this analysis.)

Table 2-1. Epidemiological scenarios

Inter-vention / Scenario	Medical intervention	Non-household transmission reduction by social distancing	Student dismissal	Home isolation by fear or choice	Other interventions
1. Baseline	None	None	None	None	None
2. Fear-40	None	None	None	12.5 days x 40% (day 57)	None
3. Community Mitigation Guidance (CMG)	Unlimited antiviral therapeutic plus household prophylaxis	50% starting when 0.1% of population is symptomatic (day 48)	100% starting when 0.1% of population is symptomatic (day 48)	None	Household quarantine (30% percent (day 1); children's activity curtailment (30%) and liberal leave (day 48)
4. Community Mitigation Guidance-Selected Elements (CMG-SE)	Unlimited antiviral therapeutic	50% starting when 0.1% of population is symptomatic (day 33)	None	None	None
5. Antivirals (AV)	Strategic National Stockpile (SNS) antiviral (20 million courses) therapeutic plus household prophylaxis	None	None	None	None
6. Pre-pandemic vaccination	Half-effective pre-formulated vaccine, 10% of population vaccinated per week	None	None	None	None
7. Anticipated Intervention	SNS antiviral (20 million courses) therapeutic plus household prophylaxis	10% starting when 0.1% of population is symptomatic (day 44)	20% starting when 0.1% of population is symptomatic (day 44)	53 days x 15% (day 44)	Strain-specific vaccine. Delivered to 5% of the population per week (day 150)

Table 3-2. National absenteeism rates for CI/KR sectors in pandemic influenza scenarios[8]

CI/KR Sector	Baseline Peak Rate % Day of peak is day 70 for all sectors	Fear-40 Peak Rate % Day of peak is day 70 for all sectors	CMG Peak Rate % (Day of peak)	CMG-SE Peak Rate % (Day of peak)	Antiviral Peak Rate % (Day of peak)	Anticipated Peak Rate % Day of peak is day 98 for all sectors
Commercial Facilities	5.9	28.4	2.6 (63)	1.8 (91)	6.1 (112)	13.6
Public Health and Healthcare	5.9	28.4	2.6 (63)	1.8 (91)	6.1 (112)	13.6
Agriculture and Food	5.7	28.3	2.4 (63)	1.71 (91)	5.8 (112)	13.7
Banking and Finance	5.8	28.4	2.6 (63)	1.76 (91)	6.0 (105)	13.5
Government Facilities	5.9	28.4	2.6 (63)	1.8 (91)	6.1 (112)	13.6
Defense Industrial Base	6.0	28.4	2.6 (77)	1.82 (91)	6.2 (112)	13.6
Transportation Systems	5.8	28.3	2.6 (84)	1.8 (91)	6.1 (105)	13.7
Information Technology	5.9	28.3	2.6 (63)	1.8 (91)	6.0 (105)	13.3
Chemical	5.7	28.5	2.7 (56)	1.74 (91)	5.9 (112)	13.5
Energy, including Dams	6.0	28.6	2.6 (84)	1.9 (91)	6.2 (112)	13.4
Telecommunications	5.9	28.7	2.4 (105)	2.0 (91)	6.3 (112)	14.1
Commercial Nuclear Reactors, Materials, and Waste	5.9	28.6	2.8 (112)	1.9 (91)	6.4 (112)	13.7
Drinking Water and Water Treatment Systems	6.2	28.8	2.8 (91)	2.0 (91)	6.3 (112)	13.1
Postal and Shipping	6.5	28.3	2.6 (154)	1.9 (98)	6.5 (112)	13.6
Emergency Services	7.0	28.4	1.7 (70)	1.9 (84)	7.2 (105)	13.5
National Monuments and Icons	7.3	29.0	1.7 (112)	2.0 (91)	7.9 (105)	13.2
Total or Average	5.9	28.4	2.6 (63)	1.8 (91)	6.1 (112)	13.6

Given the impact of a pandemic on workforce across the economic sectors, several mitigation measures have been proposed:

- Extend shifts and overtime for healthy workers
- Postpone voluntary leave
- Postpone elective surgeries, healthcare, and dental care
- Hire temporary workers
- Hire permanent workers to replace deceased workers
- Split shifts to decrease social density in the workplace
- Cross-train staff to fill in for absent staff
- Reassign critical workers (such as certified plant operators) to other locations
- Defer regularly scheduled maintenance projects
- Permit employees to work from home
- Pay ill workers to stay home
- Enact social distancing measures such as mask-wearing

Impact on Specific Sectors

1. Impact on Food and Agriculture

A DHS study found that overall, the food and agriculture sector (1) is relatively labor-intensive, (2) contains a large number of small firms that are generally less resilient to workforce disruptions, (3) relies upon special handling and relatively quick transport of products between links in the value chain, (4) has insufficient excess capacity to offset production losses resulting from absenteeism, (5) may suffer from

increased shipping distances and times generating increased volatility in inventories and productivity. It is clear that any disruption of flow of the commodity by rail or road, by enforced or individual quarantine, illness, entry point closures or delivery point closures would have a profound impact on the manufactured food sector. The study also concluded that wholesale and retail subsectors in large metropolitan areas will be hit earlier than suburban or rural areas but full food supplies would be restored within 2 weeks of labor levels returning to normal. Limitations on the food and agriculture sector arising from the bulk materials industries (e.g., flour milling operations) were found not to be a factor at even the higher absenteeism levels, because of the assumption that food industry usage would receive priority over nonfood industry usage. This however is an assumption that may require legislative enforcement.

RESULTS OF DHS MODEL

*"**Estimates of Impacts***

NISAC estimated the impacts of only 2 scenarios in this study: Scenario 1, a 10-percent labor shortage, and Scenario 2, a 40-percent labor shortage. The scenarios assume a pandemic duration of 7 weeks, affecting the entire food chain, the entire country, and all sectors simultaneously.

Scenario 1: A 10-Percent Labor Shortage

Simulations indicate few impacts to the food value chain from a 10-percent lost of labor across the value chain for 7 weeks. There are sufficient on-site inventories at primarily the wholesale and secondarily the manufacturing levels, as well as shipments (or in-transit inventories) between manufacturing and wholesale and between wholesale and retail, to prevent food shortages at retail locations. Still, due to the inherent dynamic cycling in large value chains where production, inventories, shipments, and purchasing repeatedly rise and fall, the simulations indicate that there could be intermittent, relatively innocuous outages in select industries and regions of the country.

The qualitative performance of the food industry in response to a 10-percent labor shortage for a period of 7 weeks corresponds to a Stage-1 disruption (Table 2-3). There is little disruption to end-consumption, markets, transportation, and the production of most firms. Affected industries should recover within weeks of the end of the disruption.

Scenario 2: A 40-Percent Loss of Labor

Simulations of a 40-percent loss of labor for 7 weeks, however, indicate there would be shortages at a number of retail food locations across the country. Industry and wholesale sectors experience shortages that last most of the disruption period, with some industries requiring up to 4 months recovering. The overall performance corresponds to a Stage-3 disruption (Table 2-3), during which markets are restructured and industries experience bullwhips; retail firms experience shortages, but do not close. Many of the simulated regional and sectoral dynamics are generalized (and are described as such) because of the stylized assumptions made about how the pandemic progresses across the entire nation in a single wave and to all sectors simultaneously."

Table 2-3: Progressive failure of national value chains

Stage	Dynamics	Economic Impacts
1	Industry and wholesale sectors: intermittent purchasing, production, and sales decrease, but purchasing and selling markets (that is, supplier/buyer relationships) remain unchanged. Retail sectors: experience no or few shortages, as retail sector sells from on-site inventories and in-transit inventories (shipments).	Low
2	Industry and wholesale sectors: specific sectors in specific regions of the country cannot purchase from their local suppliers, causing them to purchase from farther away; in-transit inventories increase to accommodate longer shipping distances, causing surges in remaining suppliers' productions and further disruption of new suppliers' markets. Retail sectors: experience regional, intermittent shortages, as on-site inventories are drained, but intermittent shipments replenish inventories.	Low
3	Industry and wholesale sectors: regular shortages of materials from local suppliers across the country cause some regional goods markets to become national in nature; baseline structure of regional supplier/buyer relationships is disrupted, causing irregular market dynamics, shipping patterns, shipping distances and costs, and ultimately the reliability of materials resource planning, production, and sales in many parts of the country. Retail sectors: unreliability of supply causes minor, regional hoarding, further exacerbating value chain "bullwhips."	Moderate
4	Industry and wholesale sectors: regional and national bullwhips dominate purchasing patterns and markets, tempered only by production capacity constraints, on-site inventory constraints, and in-transit inventory constraints (that is, limited availability of trucks, trains, and water transport vessels); markets are highly irregular, further exacerbating difficulties in acquiring supplies; firms with intractable purchasing, production, sales, and shipping problems temporarily close their doors. Retail sectors: lack of supply causes some stores to close their doors until supply returns.	Moderate
5	Industry and wholesale sectors: systemic lack of reliable material inputs causes major sectors to shutdown, with many firms unable to restart due to lack of cash flow and lack of reliable upstream markets (suppliers) and downstream markets (customers); due to their regionally distributed nature (that is, their heavy focus on customers in their region), wholesalers operate at minimal levels until supply returns. Retail sectors: due to their fixed physical proximity to regular customers, they close temporarily until wholesale supply returns.	High

Knock-on effects on Bulk Materials Firms

The DHS report concluded that the bulk-materials industries have adequate production capacities to supply the needs of manufactured-food firms and would not experience material input shortages or maximum production levels.

The DHS report made the following policy recommendations (based on the 40% loss of labor scenario):

- Knowledge of an impending pandemic would allow manufacturing and wholesale food establishments to overstock inventories that can ride it out. Given that a pandemic-induced workforce disruption could temporarily eliminate a significant fraction of all food manufacturing industries' inventories and a significant fraction of all wholesale food firms' inventories, particularly in metropolitan regions of the country, and that wholesale food distribution is spatially located across the nation, city and state authorities could implement effective pre-pandemic food continuity strategies by working with their local and regional wholesalers to overstock inventories of food to ensure local delivery of food through the pandemic period. Many of these additional foods would likely have to be the types that do not require refrigeration or other constraints during storage or transportation.
- A food-stock plan would require some planning at the federal level, but execution of the plan would need to occur at the local or regional level. Given sufficient planning by food industry officials through the U.S. Department of Homeland Security (DHS), sufficient food could be produced and distributed to regional wholesalers potentially well in advance of the pandemic. The *Homeland Security Act* [HAS] *of 2002*,[1] "National Infrastructure Protection Plan [NIPP],"[2] and Homeland Security Presidential Directive (HSPD)-9, "Defense of the United States Agriculture and Food," provide the basis for coordinating, at a federal level, the insurance of an adequate and safe food supply. Actual execution of such a plan, however, could occur very well at the state or regional level, between the localities that have high food demand and the wholesale firms that supply that food.

(Economic Impacts of Pandemic Influenza on the U.S. Manufactured Foods Industry Supplement to the National Population and Infrastructure Impacts of Pandemic Influenza Report, 15 October 2007)

Geographic origin of the pandemic

The estimates of the impact on the food agriculture sector discussed above are based on the effects on the US. However, the geographic origin of the pandemic and the role that animals play in the source of the pandemic will have tremendous local impact. For example, in May 2006 the Asia Pacific Economic Cooperation Ministers released a document in which they state:

> "There have been direct economic costs related to the mass culling of poultry throughout the affected economies. These costs are borne both upstream and downstream in the poultry industry, affecting both independent farmers and the feed and grain industries as well as processing plants and wholesale exporters. Many economies will need to invest and will require financial and technical support in: human resources and infrastructure for veterinary and human health systems; implementing well-established disease control strategies such as culling, bio-security and movement controls; and, safe and effective vaccinations. There is concern about general and pre-emptive bans on poultry imports adopted in response to avian influenza, and in particular, import bans on poultry that do not distinguish between infected and non-infected economies. It is important that APEC economies commit to

[1] Specifically, the HAS gives DHS governance over the protection of the national food system; Title II, Section 201 assigns DHS primary responsibility for recommending "the measures necessary to protect the key resources and critical infrastructure of the United States in coordination with other agencies of the Federal Government and in cooperation with State and local government agencies and authorities, the private sector, and other entities."

[2] Under the NIPP, the sector-specific agencies in charge of food are the USDA for agriculture and meat, poultry, and eggs, and HHS for food other than meat, poultry, and eggs.

> the application of science-based standards for international trade, in order to avoid unnecessary restrictions on trade in agricultural goods and services."

2. Impact on the rail and port system

A detailed mathematical model showed that the rail system, which operates at near capacity with very little buffer ability, would be subject to fairly substantial disruptions as a consequence of absenteeism with the effective capacity of the major rail yards reduced by approximately 45% in the face of 28.2 % absenteeism. Similarly, total time in the Port of Los Angeles for shipments would increase by 40-50% if absenteeism reaches 28.2% (Jones DA, Mark A. Turnquist et al. 2008).

3. Impact on the Insurance sector

The insurance industry sector is naturally concerned that in the event of a pandemic, "there will be a search for deep pockets and possibly an increase in fraudulent claims. Some will be looking to claim on any policy they believe could be valid and will be creative in their interpretation of the policy wording. It is also important to note that whilst the impacts discussed below may not all be capital damaging issues on their own, taken together they will have a larger impact. This is an example of "tail dependency" that we witnessed with the terrorism attacks of 9/11; for very large scale events, things tend to go wrong at the same time. A global pandemic potentially affects every industry, every person and every country at the same time." (Pandemic Potential Insurance Impacts, prepared by Lloyd's emerging risk team). The Lloyd's paper considered a wide range of businesses and suggested that, "a global recession will result in a reduction in economically active stakeholders leading to a reduced demand for insurance". The analysis also predicted that premium income would be reduced but many overheads would remain, and a reduction in available capital may cause a hardening of premium rates.

The impact on life and health insurance business is predicted to be very significant with profitability damaged for several years. One study (Weisbart, 2006) concluded that "If the death pattern in the United States caused by an H5N1 influenza pandemic were to follow the HHS severe forecast and the life insurance coverage situation remains as described above, it is possible that the dollar value of death claims from the flu for group life insurance would be $54 billion and for individual life insurance $79 billion, for a total of $133 billion." A series of knock-on effects on the insurance industry have been predicted: There is concern that while

> "capital may be adequate to withstand the rush of life assurance claims, payments may cease earlier than expected and the balance sheet of life and health re-insurers may be weakened at a time when P&C cedants are also looking to claim. Industries that involve a significant amount of close interaction between humans entertainment, hospitals, hotels, travel and universities will be expected by third parties to have thought through the impact of pandemic fully and have robust and tested plans in place. Those that don't plan adequately and perform badly in a pandemic, putting others at risk, may face legal action. Similarly, any company that did not properly plan and was disproportionately financially impacted, when compared to their peers, may see their directors sued for loss of shareholder value. A company with weak worker protection plans compared to their peers

might be considered as having failed in their duty of care to their employees. This may impact healthcare facilities disproportionately. Medical malpractice claims may be subject to an increase given the potential for inadequate surge capacity. Claims involving the hotel and hospitality business interruption, event cancellation and travel disruption may increase. Credit Insurance payments resulting from company insolvencies may increase."

In summary the consequences of a moderate to severe pandemic would be devastating to insurance industry for two reasons—1) a result of the general downturn in the economy and 2) more specifically a result of increased claims. This would hit the health insurance, life insurance, and pension insurance sectors especially hard. The nonlife insurance sectors would not be severely impacted except for certain special lines such as business interruption. The reinsurance industry would suffer severe impact especially those members who write life reinsurance policies.

4. Impact on Telecommunications

Vulnerabilities of the telecommunications sector occur primarily in its exposure to absenteeism among workers in the operations center and among field technicians who repair the facilities of critical components in the network infrastructure. "The operations of wireline voice telecommunications would only be slightly affected by even the worst-case pandemic scenario. In the worst-case scenario for absenteeism (the fear-based self-isolation scenario), there would be a slight increase in the equilibrium damage level in the network. This impact is somewhat artificial because the model does not allow for hiring additional workers to make up for those that do not return after the pandemic has ended. After the pandemic is over, the infrastructure could hire additional workers to bring that level back down to the original nominal level (Modeling and Analysis of Pandemic Influenza Impacts on Telecommunications Operations Supplement to the National Population and Infrastructure Impacts of Pandemic Influenza Report, 26 October 2007, Prepared by National Infrastructure Simulation & Analysis Center Infrastructure Analysis and Strategy Division Office of Infrastructure Protection Department of Homeland Security)."

5. Hospital surge capacity in the event of a pandemic or overwhelming attack

A great deal of thought and planning has focused on the thorny problem of medical care and laboratory support surge capacity (Nap, Andriessen et al. 2008; Hick, Christian et al. 2010; Joynt, Loo et al. 2010; Meltzer, McNeill et al. 2010) (Rubinson, Nuzzo et al. 2005). Suffice it to observe that this sector would be critically impaired in the event of a severe pandemic, with the obvious and profound knock-on effects for the rest of society. Even if all the financial resources were available to carry out the plans, absenteeism and uncertainty in the supply chain could cripple the healthcare sector in the event of a severe pandemic.

Risk Analysis: Risk perception, choice and management

In recent years, governing bodies of every sector of the economy and of every component of the critical infrastructure and key resources have developed a pandemic preparedness plan with the goals of readiness, response, and recovery. The pandemic plans across these key resources and critical infrastructures are all quite similar. They depend on risk communication, availability of resources and medical countermeasures and non-pharmaceuticals interventions.

Given the economic, social and political consequences of a pandemic briefly reviewed above, how should the global communities respond? Response to a pandemic or a potential pandemic is generally divided into two broad categories: 1) pharmaceutical responses including the production and distribution drugs and vaccines and 2) non-pharmaceutical responses including personal hygiene, quarantine, school closings, use of personal protective gear, social distancing, education and communication programs, continuity of business and government planning. The question to be investigated is, how good is this advice and how well is it understood and accepted?

Pharmaceutical Interventions:

Vaccination against influenza:

On July 29, 2009, the CDC's Advisory Committee on Immunization Practices established priority groups to receive 2009 H1N1 vaccine—1) pregnant women, 2) caregivers for and cohabitants of infants younger than 6 months, 3) health care and emergency services personnel, 4) persons aged 6 months through 24 years, and 5) persons aged 25 through 64 years with medical conditions that increase risk of influenza-related complications. Recognizing that vaccine production may not be sufficient to meet the demand by these 5 priority groups, the Advisory Committee on Immunization Practices designated 5 population subsets for highest priority in receiving vaccine: 1) pregnant women, 2) caregivers for and cohabitants of infants younger than 6 months, 3) health care and emergency services personnel in direct contact with patients or infectious material, 4) children aged 6 months to 4 years, and 5) children or adolescents aged 5 to 18 years at higher risk of influenza-related complications. Once demand among all high-priority groups has been met, vaccination should be extended to other persons aged 25 through 64 years, followed by those older than 65 years.

A troubling delay in manufacturing enough vaccine in the beginning of the 2009 H1N1 pandemic revealed a serious vulnerability in protecting the population. The 2009 H1N1 seed strains grew slowly in eggs and larger inocula were needed in the scale-up process (http://cdc.gov/h1n1flu/vaccination/qa_vac_supply.htm),(http://cdc.gov/h1n1flu/vaccination/vaccinesupply.htm). As expected, this resulted in numerous accusations and finger-pointing with the usual news conferences, press releases and testimonies.

On February 1, 2010, Donald G. McNeil reported in the New York Times ("Progress Is Slow on Moving Surplus Swine Flu Vaccine to Countries That Need It", http://www.nytimes.com/2010/02/02/health/02flu.html) that,

> "Of the 95 countries that told the WHO last year that they had no means of getting flu vaccine, only two, Azerbaijan and Mongolia, have received any so far. Afghanistan is expected to be next. Early last month, W.H.O. officials said they hoped to have shipped vaccine to 14 countries by now, and even then it would have been only enough to protect 2 percent of the countries' populations. While the flu has waned in North America, it is still affecting North Africa, Central Asia and parts of Eastern Europe. This imbalance between rich and poor countries, and the inefficiency of global vaccine transfers, frustrate many experts." He went on to observe, "But the W.H.O. is stuck with the world as it is: countries that can afford vaccines save themselves first and, when the worst has passed, transfer their leftovers to the poor, using the W.H.O. as a clearinghouse. That transfer "turns out to be an incredibly difficult logistical action," said Dr. Keiji Fukuda, the W.H.O.'s chief of pandemic influenza. "It's a mammoth effort by an awful lot of people and organizations and countries but holy moly, it's a very complex operation."

The possibility that these problems could arise were not unexpected and were discussed in the Congressional Budget Office report on the macroeconomic implications of a pandemic flu (The Congressional Budget Office: A Potential Influenza Pandemic: Possible Macroeconomic Effects and Policy Issues December 8, 2005; revised July 27, 2006).

Antiviral H1N1 drugs:

The use of antiviral agents in the contexts of seasonal influenza and pandemics is the subject of intense study and controversy concerning the use of these agents upon exposure to an infected person and prior to symptom development. This is evident at the start of every seasonal flu cycle and was especially evident at the start of the 2009 H1N1 pandemic. H1N1 antiviral agents can be used for prophylaxis against the disease or for treatment. The selection of agents depends critically on the observed resistance of the virus to the known antiviral agents. According to the revised February 2010 WHO advisory documents:

As of January 2010, the antiviral susceptibilities of circulating viruses are:

	Oseltamivir	Zanamivir	M2 inhibitors[b]
Pandemic (H1N1) 2009	Susceptible[a]	Susceptible	Resistant
Seasonal A (H1N1)[c]	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant

a. See text below
b. Amantadine and rimantadine
c. Seasonal A (H1N1) refers to the human influenza A (H1N1) viruses that were circulating prior to the introduction of pandemic influenza A(H1N1) 2009 virus and which continued to circulate during 2009.

Based on this, the WHO guidelines for prophylaxis are (note the quality of evidence):

- When risk for human-to-human transmission of influenza is high or low, and the probability of complications of infection is high, either because of the influenza strain or because of the baseline risk of the exposed group, use of oseltamivir or zanamivir may be considered as postexposure chemoprophylaxis for the affected community or group, for individuals in at-risk groups, or for healthcare workers (weak recommendation, moderate-quality evidence).
- Individuals in at-risk groups or healthcare personnel need not be offered antiviral chemoprophylaxis if the likelihood of complications of infection is low. This recommendation should be applied independent of risk for human-to-human transmission (weak recommendation, low-quality evidence).

The WHO guidelines of patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009 are:

- Oseltamivir should be prescribed, and treatment started as soon as possible, for patients with severe or progressive clinical illness (strong recommendation, low-quality evidence). Depending on clinical response, higher doses of up to 150 mg twice daily and longer duration of treatment may be indicated. This recommendation is intended for all patient groups, including pregnant women, neonates, and children younger than 5 years of age.
- Zanamivir is indicated for patients with severe or progressive clinical illness when oseltamivir is not available or not possible to use, or when the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir (strong recommendation, very low quality evidence).
- Antiviral treatment is not required in patients not in at-risk groups who have uncomplicated illness caused by confirmed or strongly suspected influenza virus infection (weak recommendation, low-quality evidence). Patients considered to be at risk are infants and children younger than 5 years of age; adults older than 65 years of age; nursing home residents; pregnant women; patients with chronic comorbid disease including cardiovascular, respiratory, or liver disease and diabetes; and immunosuppressed patients because of malignancy, HIV infection, or other diseases.
- Oseltamivir or zanamivir treatment should be started as soon as possible after the onset of illness in patients in at-risk groups who have uncomplicated illness caused by influenza virus infection (strong recommendation, very low quality evidence).

Details of the CDC recommendations can be found at: http://www.cdc.gov/h1n1flu/recommendations_pediatric_supplement.htm.

The pandemic continues to evolve and the global community is sure to see more papers reporting rapid emergence of drug resistance in H1N1 (Memoli, Hrabal et al. 2010); (Harvala, Gunson et al. 2010)).

How local communities plan and respond: are the plans based on reliable data?

Non-pharmaceutical interventions

In addition, the Department of Health and Human Services developed a "Business Pandemic Influenza Planning Checklist" that includes no fewer than 35 recommendations including identifying a pandemic coordinator, the essential employees and supplies, establish training and education programs, generate emergency communications plans, forecast and allow employee absences that result from personal illness, family member illness, community containment measures and quarantines, school and/or business closures, and public transportation closures.

To be sure, for every pandemic plan that has been published there are observations on how those plans may fail. Take for example, the address given to the Corporate Pandemic Planning Congress (Sydney 27 July 2006) by Athol Yates, Executive Director of the Australian Homeland Security Research Centre where the title of his talk was: "What could go wrong with Australia's pandemic planning and response". He listed six issues that could derail Australia's pandemic response "resulting in large scale deaths, massive unemployment and economic devastation".

1. Waiting too long to raise the pandemic alert level
2. A lack of confidence in governments' ability to manage a pandemic
3. A lack of focus on the post-pandemic recovery phase
4. Too little attention given to the fall back strategy of the *Maintenance of Social Function*
5. Failure by critical infrastructure organisations to consider the unique factors of pandemics in their response planning
6. Businesses fail to have business continuity plans and those that do, fail to incorporate pandemic mitigating activities into their plans

Nevertheless, while pandemic plans proliferate and are no doubt necessary, it is clear that many are based on historical, social and political considerations and are not based on rigorous, evidence-based analysis. Consider for example the recommendation to *Forecast and allow for employee absences during a pandemic due to factors such as personal illness, family member illness, community containment measures and quarantines, school and/or business closures, and public transportation closures.* A research group from the Brookings Institution Center on Social and Economic Dynamics analyzed the CDC's Community Strategy for Pandemic Influenza Mitigation

recommendations to close schools for up to 4 weeks in the event of a Category 2 or 3 pandemic and up to 12 weeks in the event of a Category 4 or 5 pandemic in "Cost and Health Care Workforce Effects of School Closures in the U.S." (Lempel, Epstein et al. 2009). As background, the authors of the Brookings report note that two previous studies (Sadique, Adams et al. 2008), (Sander, Nizam et al. 2008)) calculated that closing all schools for four weeks in the United Kingdom would cost between 0.1% and 0.4% of GDP and the net cost of closing schools in the United States for 26 weeks is $2.72 million per 1,000 persons respectively. The Brookings study used the Current Population Survey to identify households where an adult is likely to miss work to provide child care and included adults that are most likely to miss work based on their gender and relationship to children and added data on absentees' earnings and industry to value the effect of their absence on the economy and the health care system. They found that closing all schools in the U.S. for four weeks could cost between $10 and $47 billion dollars (0.1-0.3% of GDP) and lead to a reduction of 6% to 19% in key health care personnel (see Tables 1, 2 and Chart 1 below).

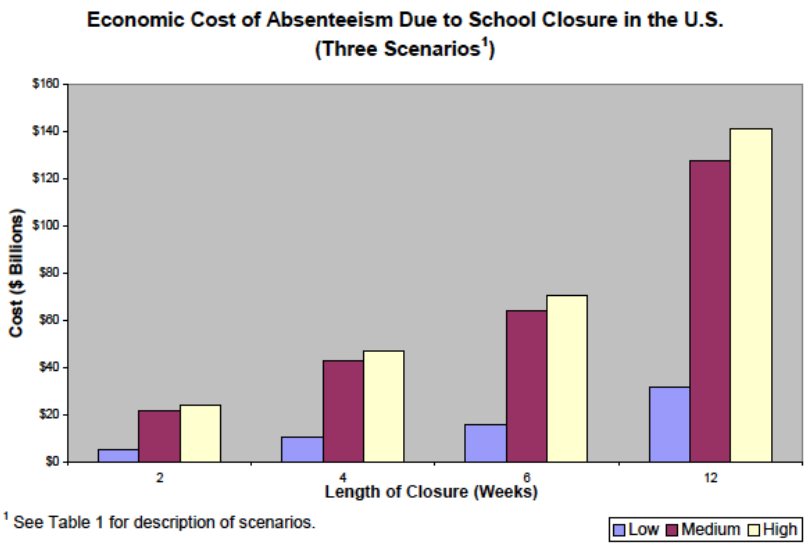
Table 1

Economic Costs of Absenteeism Due to School Closure in the United States (Billions of 2008 US dollars and Percent of 2008 GDP)				
Closure Length		Low Cost Estimate[1]	Base Estimate[2]	High Cost Estimate[3]
2 weeks		$5.2 (<0.1%)	$21.3 (0.1%)	$23.6 (0.2%)
4 weeks		$10.6 (0.1%)	$42.6 (0.3%)	$47.1 (0.3%)
6 weeks		$15.6 (0.1%)	$ 63.9 (0.4%)	$70.7 (0.5%)
12 weeks		$31.3 (0.2%)	$127.8 (0.9%)	$141.3 (1.0%)
Sources: 2007 and 2008 CPS Outgoing Rotation Groups; 2008 CPS March Supplement; Child Care Module of the 2004 SIPP; Sadique et. al.; Harvard School of Public Health Project on the Public and Biological Security's *Pandemic Influenza Survey*.				
[1] Allows for use of informal care and work-from-home and assumes the elasticity of output with respect to hours worked is 0.8. If a male and female are equally closely related to a child, the female misses work. [2] Assumes that an adult must miss work in each household with at least one child and the elasticity of output with respect to hours worked is 1. If a male and female are equally closely related to a child, the female misses work. [3] Assumes that an adult must miss work in each household with at least one child and the elasticity of output with respect to hours worked is 1. Assumes that households randomly choose whether males or females care for children.				

Table 2

Weekly Cost Per Student[1] of School Closures (2008 US Dollars)		
Low Cost Estimate[2]	Base Estimate[3]	High Cost Estimate[4]
$35	$142	$157
Sources: 2007 and 2008 CPS Outgoing Rotation Groups; 2008 CPS March Supplement; Child Care Module of the 2004 SIPP; Sadique et. al.; Harvard School of Public Health Project on the Public and Biological Security's *Pandemic Influenza Survey*.		
[1] Cost per student is calculated as the total cost of absenteeism in the United States divided by the number of persons under 16 years of age or currently in high school. [2] Allows for use of informal care and work-from-home and assumes the elasticity of output with respect to hours worked is 0.8. If a male and female are equally closely related to a child, the female misses work. [3] Assumes that an adult must miss work in each household with at least one child and the elasticity of output with respect to hours worked is 1. If a male and female are equally closely related to a child, the female misses work. [4] Assumes that an adult must miss work in each household with at least one child and the elasticity of output with respect to hours worked is 1. Assumes that households randomly choose whether males or females care for children.		

Chart 1



[1] See Table 1 for description of scenarios.

Another study (Smith, Keogh-Brown et al. 2009)) designed to estimate the potential economic impact of pandemic influenza, associated behavioural responses, school closures, and vaccination on the United Kingdom found that "the costs related to illness alone ranged between 0.5% and 1.0% of gross domestic product (£8.4bn to £16.8bn) for low fatality scenarios, 3.3% and 4.3% (£55.5bn to £72.3bn) for high fatality scenarios, and larger still for an extreme pandemic. School closure increases the economic impact, particularly for mild pandemics. If widespread behavioural change takes place and there is large numbers workers not showing up, the economic impact would increase with few health benefits. Vaccination with a pre-pandemic vaccine could save 0.13% to 2.3% of gross domestic product (£2.2bn to £38.6bn); a single dose of a matched vaccine could save 0.3% to 4.3% (£5.0bn to £72.3bn); and two doses of a matched vaccine could limit the overall economic impact to about 1% of gross domestic product for all disease scenarios."

In a study of non-pharmaceutical interventions, (Aledort, Lurie et al. 2007), the authors carried out an independent analysis of the published literature as well as collected expert opinions on the use of non-pharmaceutical public health interventions in a variety of settings (healthcare facilities; community-based institutions; private households) and pandemic phases (no pandemic; no US pandemic; early localized US pandemic; advanced US pandemic). They concluded: 1) good hand hygiene and respiratory etiquette in all settings and at all should be promoted, 2) the capability and capacity for early rapid viral diagnosis should be a high priority, 3) healthcare providers should receive infection control training, including use of masks, respirators, and other personal protective equipment; the use of personal protective equipment by the general public was not recommended, 4) widespread government mandates to segregate individuals would not be recommended however voluntary reduction in social contact, should be supported, 5) well-controlled observational and especially interventional studies are needed.

Risk Communications: Was there a believable message out with regard to H1N1 pandemic? Did the public trust the message?

An analysis of the public response to the 2009 H1N1 influenza pandemic was carried out by reviewing the information gathered through national telephone public opinion polls that were conducted from April 2009 to January 2010 (N Engl J Med. 2010 Jun 3;362(22):e65. Epub 2010 May 19. The public's response to the 2009 H1N1 influenza pandemic. SteelFisher GK, Blendon RJ, Bekheit MM, Lubell K.). Two major reasons for not accessing the vaccine were found: 1) concerns over safety and 2) the impression that vaccination was not needed. It is of interest and concern that 31% of the parents polled would not get vaccine for their children and 19% would not themselves take the vaccine because of "distrust that public health officials would provide correct information about vaccine safety".

VII. RESEARCH RECOMMENDATION: DESIGNING THE OPTIMAL STRATEGY FOR RISK COMMUNICATION –FINDING TRUST IN INFORMED LEADERSHIP AND THE CROWD.

It is widely recognized that the role of the traditional print, television and radio media, as well as internet sites and social networking sites are key in crafting and disseminating reliable, trustworthy health communications and is absolutely central to optimizing the public participation in pandemic planning and response. Coverage the recent "avian flu"--H5N1 and the "swine flu" H1N1 has only intensified the debate on the role that the media should and does play. See for example, Media coverage of health issues and how to work more effectively with journalists: a qualitative study, BMC Public Health 2010, 10:535 Leask, Hooker, King in which the authors interviewed a number of Australian journalists. The authors found that early morning interactions with reporters lead to more efficient information transfer, especially when the reporter was a "specialty reporter" with specific knowledge of health issues.

A recent analysis of adequacy and effectiveness of public information on pandemics from the Fogarty International Center; National Institutes of Health (Alonso and Paim 2009) notes: "… as far as a severe crisis is believed to be plausible, the guidelines for such a scenario should be clearly available for citizens looking for that information." After a careful analysis of the risk communications in 10 countries, the authors concluded that, "… while many positive recommendations were provided, the set of recommendations issued by most countries was not comprehensive enough for severe influenza scenarios. Moreover, … some of the recommendations provided have proven to be inadequate to reduce transmission and enable an efficient allocation of limited resources to attend the most in need."

It is evident from the above that many public and private organizations have implemented education programs designed to elicit behavioral changes in their population that will allow them to withstand a disruption in their everyday lives and be prepared for the most likely disasters. However, it is well established that *preparedness knowledge* is often not converted into *preparedness action*. A series of questions remain unanswered:

1. Are there recommended actions, generally agreed upon by experts, that individuals should adopt prior to an emergency? How general are these actions?
2. What is the community-member mental model of preparedness actions?
3. How do the community-member and expert models compare—is there a misalignment between the expert and community-member models that may arise from

misconceptions, omissions and what additional information needs to be included in these models?
4. What is the broader community's perspective on preparedness decision-making? What special attention is required with respect to vulnerable-population communities, including the aged and populations for whom English is a second language?

Designing a risk communications strategy that will optimize community compliance is a difficult task that requires additional research. Noncompliance can arise from single or multiple influences including confusion, inability to access public communications, competing priorities, and uncertainty in the utility of recommended actions. One method that has been used to overcome these difficulties is the ***mental models*** approach pioneered by the group from Carnegie Mellon University (Morgan, Fischhoff et al. 2002). This method addresses individual decision making in the face of a complex decision-making environment using qualitative interviews to compare the intuitive theories of complex domains held by an individual without expert knowledge with expert opinions of factors relevant to the decisions. This approach has been applied to many diverse risks, including climate change electromagnetic fields and HIV/AIDS.

Why is risk communication in the domain of infectious diseases so hard? Here is what Baruch Fischhoff, one of the leading academic lights of risk management, had to say about "Scientifically Sound Pandemic Risk Communications" in testimony to the House Science Committee Briefing on Dec 14, 2005: "People want to know the truth, even if it is worrisome; people can assimilate only a limited amount of new information at a time so identify the critical facts and organize them according to their audiences' natural way of thinking; accommodate the known strengths and weaknesses of its audiences thought processes; treat audiences respectfully; pre-test prototype messages; experts exaggerate their ability to predict other people' behavior; experts must provide relevant information in a timely fashion." Yes, but how and even knowing all this, why does it not work? The answer is that the "public" is not homogeneous, it is fragmented along countless lines—educational background, fears, belief systems, financial position, access to information, utilization of information systems, and on and on and on. Compounding this is the structure of the media, it too is enormously fragmented—TV, radio, print, blogs, facebooks, yelps, twitters, youtubes, googles, again, on and on. Applying Prof. Fischhoff's first dictum, the bad news is --the old ways of communicating risks concerning potential, real or hypothetical pandemics will almost certainly never work and new ways have to be developed to think about risk communication. So far, the recommendations and advice tinkers around the edges of the same old approach. Formal pandemic declarations and communications by governments and their representatives, the CDC and WHO and by the professional associations and the specialty societies and the public and private organizations—corporations, schools, NGOs will continue. However, as discussed above, this was tried in the 2009 H1N1 pandemic with only limited success. While it appears that governments, societies, associations are doing as good a job as possible in the old style, they have not gotten the message. However, there is one group that has seen the light--the advertising industry.

Papers on the inadequacies of traditional advertising discuss the fragmentation of the consumer base, fragmentation of the media, metrics of success and quantifying outcomes. The "…future of advertising … is emerging from the interplay of emerging new media channels and a world in which consumers are in charge" (from the Wharton/SEI Future of Advertising project).

In summary, a single risk communication message will not work; many fragmented messages find their way into the public domain immediately. Research on understanding the fears, knowledge, cultural attitudes and media usage of diverse populations in the context of infectious diseases needs to be carried out. This is true not only for a possible influenza pandemic but in general. What is the public understanding of the danger of the emerging resistance to antimicrobials? What are the potential benefits and dangers of synthetic biology? How contagious is tuberculosis? Do vaccines cause autism? The public needs clear and accurate answers to these questions delivered in a fashion that is believable. This will require the use of new communication technologies, possibly crowdsourcing and the use of the new and rapidly changing social media. The world is connected and many individuals get their information in Important lessons can be learned from the new gaming and social networking software companies that are still among the hottest items in the "Silicon Valleys" around the world.

So many variables, so many outcomes, so few certainties. An example of computer modeling--The Wharton-ISTAR Plague Modeling Project
(This section was written jointly with Dr. J. Shin Teh)

Effective strategies for infectious disease control rely on knowing 1) the dynamics of disease spread within the human population taking into account contributions by organic vectors of disease, and 2) how best to employ public health measures such as vaccinations, antibiotics, quarantine as well as vector control in order to stem the spread of disease and mitigate its effects. In addition, the science of such strategies must also incorporate the principles of economics, as the individual's choice to ultimately adhere to public health advisories depends upon economic indices such as cost of countermeasures, risk and cost assessment of disease, and many other factors of decision-making.

Our team (Rubin, Teh, Professors Howard Kunreuther and Geoffrey Heal and Peter Finin) is developing a computational model that simulates the spread of disease in the context of a multi-agent interdependent security (IDS) strategy. The work is based on Kunreuther and Heal who introduced a game-theoretic model for problems of IDS, in which a large number of agents must make individual decisions related to security, but the payoff to each agent may depend on the decisions of the entire population.

The bubonic plague epidemic of India in the late 19th century was selected as a real-life case scenario on which the model could be built and its accuracy assessed. Plague is a rodent-associated, flea-borne zoonosis caused by the gram-negative bacterium Yersinia pestis. The disease is often fatal in humans, particularly when antimicrobial

treatment is delayed or inadequate. Since the last pandemic began in the late 1800s, plague's geographic range has expanded greatly, posing new threats in previously unaffected regions, including the western United States, portions of South America, southern Africa, and Madagascar, and certain regions of India and Southeast Asia Bubonic. In term of disease dynamics, in addition to contracting the disease from infected fleas, humans can transmit it to other humans especially if the disease spreads to the lungs. The Indian bubonic plague was selected because it possesses an environmental disease transmission risk as well as a human-to-human disease transmission risk, in addition to being an important public health case scenario. There is also detailed data on population sizes of the various cities and provinces of India as well as mortality data of the epidemic with which to parameterize the model.

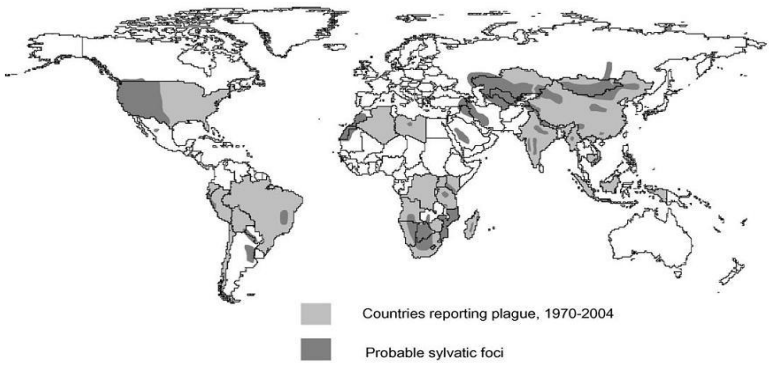


Figure 1 Distribution of plague foci and countries reporting plague.

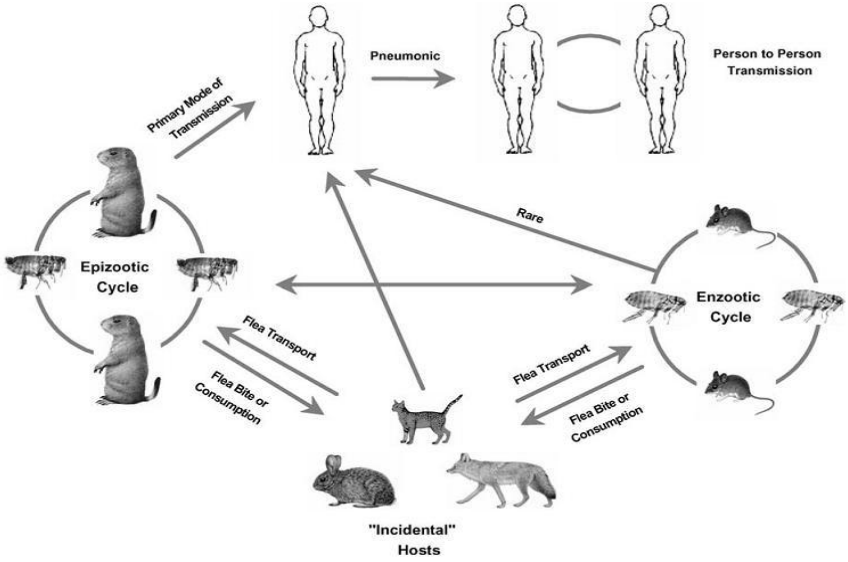
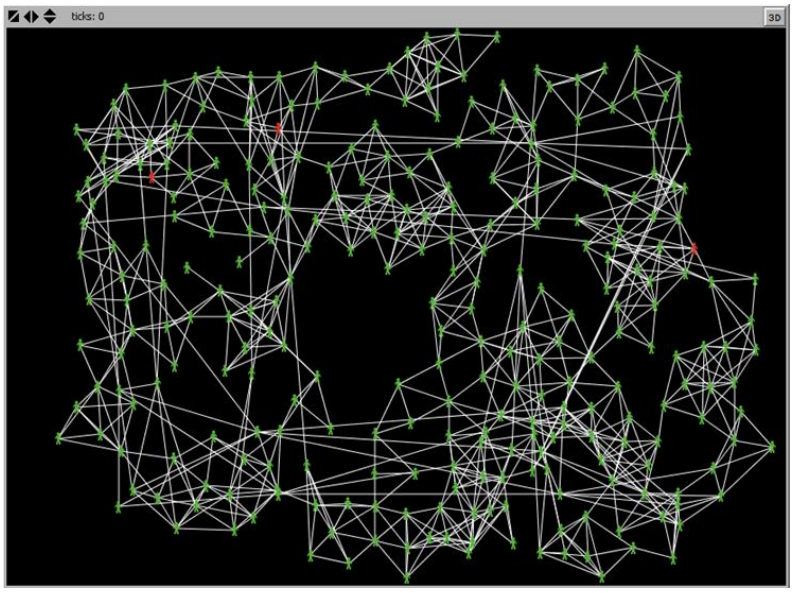


Figure 2 Natural cycles of plague.

The model involves creation of a network of humans (as nodes) with a scale-free distribution of human-to-human contacts. In the scale-free model, a small fraction of nodes are very highly connected. It also exhibits preferential attachment, where new nodes preferentially attach to nodes that are already highly connected. The scale-free nature of networks, so called because of a lack of a typical value (or range of values) for

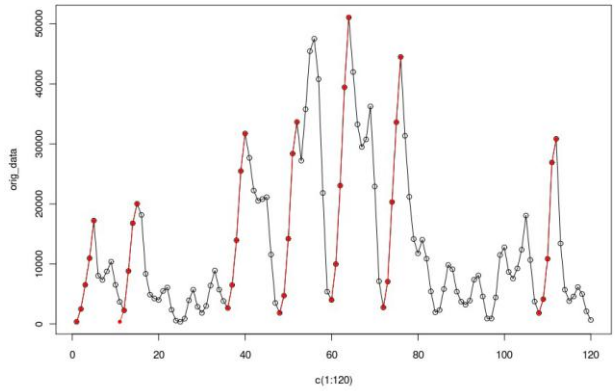
a network's degreeness, provides closer approximations of the self-organization of complex networks in reality; the observed degree distribution follows a power-law. This scale-free topology has been found to be characteristic of many natural and manmade network systems. In fact, the spread of infectious diseases is highly heterogenous, sometimes with only certain carriers efficiently spreading the disease (the "superspreaders") through their extensive contacts with other people, while most others spread the disease more locally.



In the simulation, the susceptible–infective-removed (SIR) macro model was employed. The main assumption of this model is that the population, in which a pathogenic agent is active, comprises three subgroups: the healthy individuals who are susceptible (S) to infection, the already infected individuals (I) who can transmit the disease to the healthy ones, and the individuals who are removed (R) from the infection cycle, either having been immunized after infection and cured, or through their demise. The interpretation of the model is straightforward. The population of susceptible individuals decreases through their interaction with the infected agents, the number of which correspondingly increases through the infection. On the other hand, the population of infected individuals decreases since some individuals either are cured or died, and therefore populate the class of removed. The model examines the temporal dynamics of the infection cycle and should thus be appropriate for the description of bubonic plague. In addition, the model uses prevalent consensus values for the required variables such as human-to-human transmission rate and death rate from bubonic plague.

The work is focused on determining the right combinations of the simulation variables (environmental risk (p), human-to-human risk (q), Δp, Δq) as well as determining the best method to determine these variables. In order to reduce the influence of, for example, seasonal factors that may complicate disease modeling, the model focuses on the initial portion of the disease spread graphs. The scalability of the network model

with sensitivity analyses was investigated, as the initial attempts to model the disease spread in the whole of India involved millions of nodes which is quite time consuming to compute.



The initial portions of the disease spread graphs.

The ultimate goal of modeling is to construct a robust computational system with which to assess the best strategies for employing life saving public health measures. As discussed above, a critical factor of the success of mass vaccination programs is individual decision-making, i.e. if an individual faces the possibility of catching an infectious disease and has the option of a completely effective vaccine against it; will s/he choose to be vaccinated? In deciding whether to vaccinate themselves, individuals consider the cost and the risk of vaccination, the probability that they will become infected, and the risk of morbidity from such an infection. Individuals often refuse or avoid vaccinations they perceive to be risky. Demand for vaccination can also increase when individuals perceive limited vaccine supply or increasing infection risk. During a measles epidemic in Chicago in 1989-90, for instance, physicians observed increased compliance in childhood measles vaccinations. In October of 2004 the British government suspended the license of the company contracted to produce half of the influenza vaccine used in the US. Subsequent news reports indicate that demand for influenza vaccination spiked for a short period following announcements of the impending shortage, before returning toward normal levels. The decisions of individuals are indirectly influenced by the decisions of all other agents, because the sum of these decisions yields the vaccine coverage levels in the population and hence the course of epidemics. Game theory attempts to predict individual behavior in such a setting, where the payoff of strategies chosen by individuals depends on the strategies adopted by others in the population.

Tradeoffs—how to calculate them and what to recommend

The work focuses on policy choices that can be examined by the model. Each policy choice carries with it an appraisal of the costs and benefits of various public health interventions including:

1) Vaccination—the incentives to vaccinate are protection from the disease after a period of about two weeks, no longer being a source of human to human spread of disease and the subsequent financial and social gain from the ability to stay in the network. The cost of vaccination includes the actual monetary value of the vaccine as well as potential medial side effects.
2) Antibiotic therapy—the incentives to take antibiotics are similar to those for the vaccination intervention however there is no lag phase of two weeks that is required to mount an adequate immune response. The costs again are side effects and the monetary outlay for the drugs.
3) Quarantine—here the incentives include protection from contracting the disease from another human however not from fleas but no exposure to adverse events from drugs or vaccine. The costs are removal from the social network and subsequent potential financial loss and social isolation.
4) Kill the rats—this incentive obviously removes the zoonotic source but may have the unintended consequence of actually increasing exposure of humans to flea borne disease as the remaining fleas hunt for an alternative to the rat for its blood meal. Furthermore there is the monetary cost of instituting a rat elimination program.
5) Combinations of these interventions.

The full model for plague is still in development and will be submitted for publication. Extending the model to other infectious diseases is quite straightforward and will be carried out resources permitting.

VIII. LESSONS FROM OTHER OUTBREAKS:

The Global HIV/AIDS Pandemic

The acquired immunodeficiency syndrome (AIDS) emerged in 1981 and is now at pandemic proportions, with approximately 65 million infected individuals and 25 million deaths. There is a large and growing literature on the economic, social, and political impact of HIV/AIDS. In fact, UNAIDS published a series of guidelines for research on this very topic (Guidelines for Studies of the Social and Economic Impact of HIV/AIDS. Tony Barnett and Alan Whiteside. UNAIDS, Geneva, Switzerland 2000). A full review of all this literature is outside the scope of the present paper. However a compelling view as of 2001 can be found at The global impact of HIV/AIDS (Piot, Bartos et al. 2001). Piot's conclusions in 2001 are still relevant:

> "The great historical advances in public health have all involved a radical reconceptualization of the social as well as the medical technologies associated with particular diseases. Recognizing and responding to the issues of social organization that are specific to particular disease entities have been the key to effective responses to major epidemics (for example, quarantine between towns in the case of plague, and urban sanitation in the case of cholera)…. HIV/AIDS has its particular biological and social characteristics that dictate the shape of an effective response: its impact is greatest among young adults; the virus is transmitted through intimate behaviours; its impact ramifies across every field of human endeavour; infection may remain invisible for many years; and overcoming the stigmatization of people with HIV infection, or thought to be at heightened risk, is a precondition for explicit action against the disease…. The types of effective responses to HIV epidemics around the world derive from these specific biological and social characteristics. What is required is nothing less than a sustainable social mobilization. Its key elements are the involvement of affected communities, including individuals who are infected; restructuring of global finance flows so that the essential commodities required for the response can be made available universally; and systematically targeting social exclusion. .. Responding to HIV/AIDS on a scale commensurate with the epidemic is a global imperative. The task has barely begun, but at least we are at the end of the beginning, with the needs recognized together with the proven elements of an effective response. The imperative now shifts to garnering the requisite global, national and community leadership that will be the

only basis on which the total social mobilization against AIDS can be sustained."

SARS

The Severe Acute Respiratory Syndrome (SARS) started in the Guandong province of China and enveloped the world by 2003. The infectious organism, later determined to be a previously unrecognized coronavirus, is a non-segmented, positive strand RNA virus. Approximately 9,000 individuals were infected, with very high mortality rate (Donnelly, Ghani et al. 2003). While the immediate economic, social and political impact was considered quite large at the time with disruption of air travel, suspicion of international travelers, distrust of certain governmental motivations, hospital closings and stresses placed on health care surge capacity, the longer term impact is still a matter of investigation (see for example, The economic impact of SARS: How does the reality match the predictions? (Keogh-Brown and Smith 2008)). Using GDP, growth of GDP, government budget and export revenue or total trade as indicators, the authors analyzed total health expenditures for the country, total revenues from tourism, hotels and or boarding houses, the airline sector, retail sales, food and restaurants, leisure and entertainment and computer or information technology sector activities. They found the largest economic impact of SARS was related to overall GDP and investment, and sectors representing hotels and restaurants and tourism with the major losses in China and Hong Kong, with more minor effects in Canada and Singapore. (see Table 4, reproduced below) Importantly, they found that the losses were generally limited to no more than one quarter.

Table 4
Summary of main SARS impacts

	GDP (US$ billion)	Growth	Exports and trade (US$ billion)	Tourism, food and travel (US$ billion)
China	←	↓3% in Q2	↓7.12 (FDI) but 0 (Exports)	↓5 (International) 3.5 (Domestic)
Hong Kong	↓3.7	↓4.75% in Q2	↓23.1 (Outward FDI)	↓0.86 (Tourism) 0.2 (Hotels) 0.26 (Restaurants)
Canada	↓3.2–6.4	↓1% for 2003	↓5.2 (Investment Outflow)	↓0.03 (Tourism) 6.25% (Airline) 4.33 (Accommodation and food)
Singapore	↓4.9	↓1% for 2003	←	↓0.2 (Hotels) 17.4% (Airline)
Malaysia	←	←	←	↓1.7
Vietnam	←	←	←	↓0.14 (Hotels and restaurants)
Thailand	←	?	←	←33.5 (Tourism)
United States	←	←	←	←
Taiwan	←	←	←	←
Australia	←	←	↓10.1% (2001–2002 decline also)	↓0.119 (Accommodation and food)
Germany	←	←	←	←
Japan	←	?	↓0 Exports but 3.5 (FDI out) and 2.9 (FDI in) but 2001–2002 decline also	←
Mongolia	?	?	←	←
Philippines	←	?	↓1.2 or 3%	←
France	←	?	←Losses in Q1–3 = Iraq war?	←
Sweden	↓Notable loss, probably not SARS	?	?	←

KEY: ↓ = SARS related loss, ← = no evidence of a loss, ? = missing data.

Bioterrorism

In 2008 the National Research Council of the National Academies published a far reaching report on bioterrorism threat risk assessment entitled, "Department of Homeland Security Bioterrorism Risk Assessment: A CALL FOR CHANGE" from the Committee on Methodological Improvements to the Department of Homeland Security's Biological Agent Risk Analysis. Recognizing that the terrorists and not just the responders are intelligent actors, the committee was charged to develop a methodology that could incorporate changing probability distributions with large degrees of uncertainty that reflect how the terrorists as well as the responding public health community would adjust their choices over time or in different contexts. The committee was also asked to show how the methodology could be extended to risks associated with classes of agents, including enhanced or engineered agents. (Disclosure—H. Rubin was a reviewer of the 2006 report that the 2008 report was commissioned to replace). A full analysis of the risks and consequences of a pandemic initiated as a bioterrorist attack is quite complex and is well beyond the scope of the current paper.

IX. THE KNOCK-ON EFFECT OF ANTIBIOTIC RESISTANCE.

The knock-on effect of the emergence of bacterial antibiotic resistance must be considered in any analysis of the possibility pandemics to cause a global shock. The medical as well as the popular literature is replete with reports of life-threatening infections caused by bacteria that are increasingly resistant to currently used antibiotics. In 2004, the Infectious Diseases Society of America (IDSA) released a report demonstrating the dramatic rise in human infections caused by methicillin resistant *Staphylococcus aureus (MRSA)*, vancomycin resistant enterococcus, fluoroquinolone and third generation cephalosporin resistant *Pseudomonas aeruginosa*, penicillin resistant *Streptococcus pneumoniae*, multi-drug resistant *Acinetobacter*, cephalosporin resistant *Salmonella*, third generation cephalosporin resistant *E. coli* and *Klebsiella pneumoniae,* and multi-drug drug resistant *Mycobacterium tuberculosis* (BAD BUGS, NO DRUGS, Infectious Diseases Society of America July 2004 http://www.idsociety.org/badbugsnodrugs.html). The IDSA reported that more than 70% of the 90,000 deaths from bacterial infections were attributable to antibiotic resistant strains (and that) "For many patients, there simply are no drugs that work…" Moreover, the pipeline of new antibiotics is very sparse and major pharmaceutical companies have stopped developing new agents because antibiotics are not as profitable as drugs that treat chronic (long-term) conditions and lifestyle issues.

The health care and public policy communities recognize the public health and national security significance of this problem. In fact, national and regional leaders in health and public policy as well as in pharmaceutical and basic scientific research have written forcefully about the problem, including the Directors of the CDC and NIAID http://www.cdc.gov/drugresistance/actionplan/index.htm). Indeed, senior scientists are writing about this problem in the medical literature, "The pipeline of novel-mechanism antibacterials is still empty and will remain that way for a considerable time..." (Payne, Gwynn et al. 2007).

Who Suffers?

A recent study of adults with pneumonia in the five county region surrounding Philadelphia identified Hispanic ethnicity as an independent risk factor for infection with a drug resistant bacteria, specifically macrolide resistant *S. pneumoniae*, (Metlay, Fishman et al. 2006). The elderly are also at higher risk to develop antibiotic resistant infections. In one of the many studies that examine this issue one study showed that risk factors that were significantly associated with levofloxicin resistant *Streptococcus*

pneumoniae included an older age, residence in a nursing home, multiple hospitalizations, prior exposure to fluoroquinolones, and presence of chronic obstructive pulmonary disease. (Ho, Tse et al. 2001). In fact, the elderly are at greater risk of developing infections in general. A recent review concludes that, "Compared to younger adults, elderly individuals have unique predispositions to infectious diseases as a result of multiple risk factors… impairments in innate and adaptive immunity … increased prevalence of underlying co-morbid disease…(and) increased prevalence of functional limitations…" (High, Bradley et al. 2005)). The report published in The Journal of the American Medical Association in mid October on MRSA in which it was found that incidence rates were highest among persons 65 years and older, blacks, and males (Klevens, Morrison et al. 2007) generated enormous national print, TV and radio coverage. Significantly, it is now realized that MRSA is found not only in hospital settings, but in the community as well, prompting a number of school closures for massive cleaning efforts.

It is also important to recognize that infectious diseases and especially the problem of antibiotic resistance complicate many other medical problems including chronic diseases such as diabetes, obstructive and restrictive pulmonary diseases, stroke, heart disease, cancer, blindness and behavioral diseases, particularly substance abuse disorders. Indeed, drug resistant community and hospital acquired infection are one of the major causes of morbidity and mortality in patients with chronic diseases. In addition to the effects on public health, the problem of antibiotic resistance negatively impacts the cost of healthcare systems. Antibiotic resistant microbes require more expensive and often more toxic second-line drugs, and patients often have poor prognosis. A recent study at one Chicago hospital discovered that antibiotic resistant infections cost $18,588 to $29,069 per patient in extra healthcare costs and prolonged hospital stay by 6.4 - 12.7 days, as well as incurred $10.7 - 15 million combined hospital and societal costs for just 188 patients (Roberts, Hota et al. 2009). It is estimated that the direct costs to the US healthcare system from antibiotic resistant infections runs into the tens of billions of dollars.

What is being done? Antibacterial agents

An interesting situation exists in the antibiotic discovery vertical that represents a market size of approximately $25-$28 billion. The well documented need for new antibiotics that will be effective against increasingly drug-resistant organisms and against resistant organisms that may have been genetically engineered by either state sponsored or rogue terrorists, has been met by most major pharmaceutical companies by eliminating their in-house antibiotic drug discovery activities (Spellberg, Powers et al. 2004).

A number of explanations have been offered for the flight from antibiotics by big pharmaceutical companies:

1. The development time line to Phase One studies is can take up to 15 years with an almost vanishingly small success rate (See Figure 1 from "Drugs for bad bugs: confronting the challenges of antibacterial discovery" (Payne, Gwynn et al. 2007))

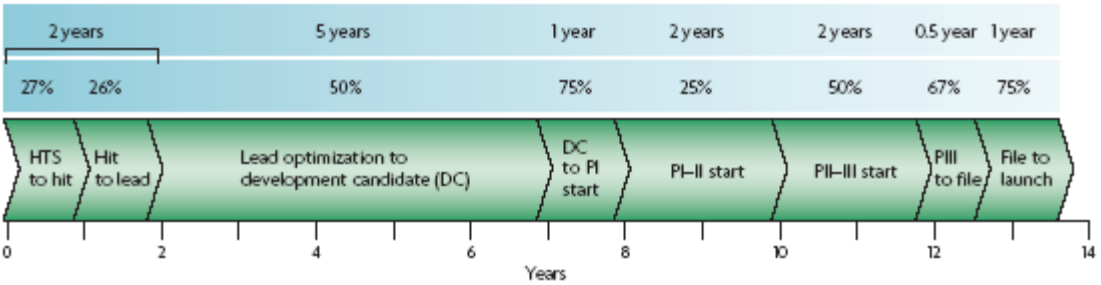


Figure 1 | **Estimated success metrics and timelines for the development of a systemic broad-spectrum antibacterial.** The figure shows timelines and risks associated with antibacterial drug discovery. The probability of success (percentages) up to the beginning of Phase I trials are based on GlaxoSmithKline (GSK) metrics and the clinical success rates are based on industry averages (data taken from reports by the Centers for Medicines Research (CMR); see Further information). Lead optimization is the most challenging and lengthy phase in antibacterial drug discovery. Probability of success during lead optimization is strongly linked to the size of the medicinal chemistry effort devoted to the project. GSK committed large teams of chemists for an uninterrupted period of 5 years to achieve a 50% success rate. Lead optimization efforts with less resources could easily take considerably longer.

2. Antimicrobial agents do not command the price in the marketplace that other prescription drugs achieve. A recent analysis of the cost of a ten-day treatment of all new drugs approved by the FDA during the period between January 1997 and July 2003 showed that new antimicrobial drugs generate a median ten day drug-treatment cost of $137 (all anti-microbial agents) and $85 (anti-microbial agents excluding anti-HIV medications). By comparison, anti-cancer agents were the most expensive drugs compared to all other therapeutic categories, with a median ten-day drug-treatment cost of $848 (Falagas, Fragoulis et al. 2006).

3. There is an ongoing debate over the extensive regulatory requirements for new antibiotics that has not yet been resolved (Shlaes and Moellering 2002), (Powers 2003).

4. There is disappointment in some of the newer technologies that were initially heralded as the drivers for discovery of new and effective therapies. In particular in the post-genomics era, the availability of completely sequenced pathogens and the ability to carry out high-throughput screening (HTS) was to provide a rich panoply of new and validated "druggable" targets, and the capabilities of combinatorial chemistry was expected to generate highly diverse libraries of compounds that would lead to new molecular entities. However, after an investment many millions of dollars across the pharmaceutical industry and many hours of research scientists' time, these expectations have all been reevaluated (Payne, Gwynn et al. 2007).

While big pharmaceutical companies are avoiding large antibiotic drug discovery programs, this has opened an opportunity for the smaller biotech companies that have seized the occasion to enter the anti-infective vertical in a significant way (Monaghan and Barrett 2006). It has been noted that large pharmaceutical companies may be

returning to the hospital market, the more rapidly growing segment of the infectious diseases market through acquisition of companies.

Returning to our opening comments on the securitization of infectious diseases, we go a step further and maintain that discovering new antibiotics is as much a matter of national security as any discovery in military hardware. The Infectious Diseases Society of America commented in 2004,

> "…nearly 2 million people in the United States will acquire bacterial infections while in the hospital, and about 90,000 of them will die, according to CDC estimates. More than 70 percent of the bacteria that cause these infections will be resistant to at least one of the drugs commonly used to fight them. In a growing and frightening number of cases, these bacteria are resistant to many approved drugs, and patients have to be treated with new, investigational compounds or older, toxic alternatives. For many patients, there simply are no drugs that work. *… Resistant bacterial infections are not only a public health problem; they have national and global security implications as well. The Institute of Medicine and federal officials have identified antibiotic resistance and the dearth of antibiotic R&D as increasing threats to U.S. public health.* (italics added)."

A study of United States national security issues conducted by the Woodrow Wilson School of Public and International Affairs at Princeton University unequivocally states that, "American national security in the 21st century … is likely to be threatened by pathogens as much as people. New diseases and antibiotic-resistant strains of old ones are on the rise…" (Ikenberry and Slaughter 2006).

The deliberate spread of infectious diseases has emerged as one option for terrorists and is a major national security concern. However non-deliberate spread is more likely and also constitutes a severe threat to security, more broadly defined. In 1992, the Institute of Medicine published the first comprehensive report, *Emerging Infections: Microbial Threats to Health in the United States*. In its new version published in 2003, the global environment and microbial agents are brought into focus as threats to health in general. An unclassified report from the National Intelligence Council in 2000 examined *"The Global Infectious Disease Threat and Its Implications for the United States."* Similarly, an unclassified 2003 CIA document analyzed *"The Darker Bioweapons Future*" in which the many benefits of modern molecular biology are weighed against the danger that "the effects of engineered biological agents could be worse than any disease known to man." This vexing problem was raised quite clearly in the 2006 *National Security Strategy*: "Public health challenges like pandemics (HIV/AIDS, avian influenza) ... recognize no borders. The risks to social order are so great that traditional public health approaches may be inadequate, *necessitating new strategies and responses. ..."* (italics added).

A report released in 2010 by the Center for Global Development Drug Resistance Working Group, entitled "The Race Against Drug Resistance" (disclosure: H. Rubin was a member of the working Group) addresses 1) the health and economic consequences of global drug resistance, 2) the drivers of drug resistance, 3) the current response to the problem of drug resistance and 4) four recommendations to counter drug resistance. There is a large literature of the biochemical and genetic mechanisms of drug resistance that will not be reviewed in the current report. However, we will consider the economic, social and political drivers of drug resistance that is discussed in the Center for Global Development (CGD) report. First, CDG recognized that absence or inadequate technology contributes to drug resistance. This includes the weak pipeline of new agents including vaccines and the lack of cheap and accessible diagnostics and drug susceptibility testing. The second driver of drug resistance covered in the CGD report was behavioral considerations of 1) manufacturers—lack of incentive to carry out post-marketing monitoring of drug quality and effect, lack of incentive to discover resistance-specific technologies; 2) drug prescribers—pressure form patients and manufactures to prescribe drugs, inadequate information on which to base drug choice secondary to poor diagnostics of drug testing; 3) drug dispensers—wide range of training and levels of professionalism in dispensers, especially in certain parts of the world; 4) and even patients—psychological impact of taking medications, costs, side effects and cultural preferences and beliefs. Weak health systems are another driver of drug resistance that includes inadequately trained professionals, weak or nonexistent laboratory infrastructure, poor disease and resistance surveillance, and poor regulation and enforcement, especially of agents on "the street" that could be counterfeit, adulterated or outdated. The fourth, and very important driver of drug resistance is the use of these agents in animal health and especially in food production. The financial incentive of the use of sub-therapeutic levels of antibiotics in promoting animal growth and earlier marketing accelerates the emergence antibiotic resistant organisms that could be spread to humans. Antibiotics are also found in use in aquaculture and in food crops.

As mentioned above, there are national and international calls for "…new strategies and response" to the threat of pandemics. Specifically referring to the threat of antibiotic resistance, the Center for Global Development concludes with 4 recommendations. 1) Improve surveillance by collecting and sharing resistance information across networks of laboratories (The Race Against Drug Resistance p 48), 2) Secure the drug supply chain to ensure quality products and practices by a) establishing an expert technical group to develop a global standard to maintain, monitor and report on drug quality and b) the creation of a multidisciplinary group to improve decisions on drug provision and use through accreditation of dispensers and improved consumer information(page 51) , 3) create strengthened regional networks of national drug regulators (page 55) and 4) catalyze research and innovation to speed the development of resistance-fighting technologies (page 56). These recommendations will be amplified and expanded in the final set of recommendations in the final section of this report.

Therefore, we conclude, along with every major policy organization that has studies this issue that a crisis exists in the emergence of clinically significant multidrug

resistant bacteria and the potential of deliberately engineered pathogens. The large and small pharmaceutical and biotech companies as well as academia must be incentivized to develop new research programs and new molecular entities that will be rapidly pushed into the development pipeline. The short-term outlook is just barely optimistic with a number of small and mid size biotech companies actively engaged in this critical space of antibiotic development. In this regard, we strongly support the work on the Health Impact Fund (http://www.yale.edu/macmillan/igh/) as one of the creative and practical solutions to the problem of incentivizing the discovery and distribution of new drugs and vaccines (disclosure: H. Rubin is the Chair of the Scientific Advisory Board of the Health Impact Fund). The purpose of the Fund is to reward innovators of new drugs and vaccines for diseases that are now neglected because innovators are not able to recover their R&D costs from sales. The reward would be based on the health impact of their products, creating an effective market for medicines for the poor. Innovators could elect to charge the usual patent-protected mark-ups, or to opt in to the Fund. Opting in would mean that the firm would sell its product at a low price--around the average cost of production, and be compensated through direct payments from the Health Impact Fund based on the product's health impact. The Fund would offer a fixed reward pool each year, financed by governments. Each participating firm would be given a share of the reward pool in each of the 10 years following the introduction of its product. Each product's share would be equal to its share of total QALYs generated by all participating products. The health impact assessment will rely on data from clinical trials, pragmatic or practical trials, audited data on sales, stratified sampling of use of the product in different environments, and global burden of disease data.

X. LESSONS LEARNED CONCERNING CONTROL POINTS: INCREASING SOCIETAL RESILIENCE WHILE MAXIMIZING RESOURCES PRIOR TO, DURING AND AFTER A PANDEMIC. A PROPOSED SOLUTION TO THE PROBLEM

Simply stated there are four major lessons learned about control points from the data and risk analyses presented above:

1) there is not sufficient interoperable, globally shared information available in real-time about pandemic risk inventories, hazards or threatened segments of the built or natural infrastructure,

2) there is a dramatic lack of forward thinking and planning for the creation and distribution of i) medical countermeasures—including drugs, vaccines and surge capacity, and ii) non-medical countermeasures—including public information programs, and recommendations for regulating restrictions on travel and social gatherings (school and work closures, boarder closures),

3) there is a serious requirement for international harmonization of regulations across the pandemic spectrum and

4) there needs to be financially sustainable basic research efforts upon which is based the preparation, mitigation, response and rebuilding that is required before, during and after a pandemic.

We detail the relevant control points in a pandemic event along with the preparedness measures necessary for mitigation, many of which incorporate the four gaps listed above:

<table>
<tr><td></td><td colspan="3">Control Points</td></tr>
<tr><td rowspan="6">Preparedness Measures</td><td><u>At Origin</u>
(Source Country or Locale of Infection)</td><td><u>In Passage</u>
(Transit to Other Locations)</td><td><u>At Destination</u>
(Other Countries or Locales the Infection has Reached)</td></tr>
<tr><td rowspan="2">Enhance Real-time Biosurveillance
• Improvement of livestock operational standards and veterinary inspection
• Viral genotyping
• Establishing reporting infrastructure with established points-of-contact
• Syndromic tracking, including new mobile phone technologies (Gates and Skoll Foundations initiated such projects)</td><td>Mobilizable Infra-red Detectors at Airports of Origin Country*</td><td>Mobilizable Infra-red Detectors at Airports and Ports of Entry*</td></tr>
<tr><td>Comprehensive List of Outbound Ships Provided to Receiving Countries*
• Carrying people
• Carrying livestock</td><td>Enhance Biosurveillance and Reporting System with Public Involvement
- Usage of existing IT technologies
- Leverage existing health infrastructures, e.g. CDC</td></tr>
<tr><td>Livestock Culling Best Practices
- Better targeted with Enhanced Biosurveillance, and will decrease economic hardships</td><td rowspan="4">*Embargo, partial or otherwise, on travel is not feasible or effective, as no measure is leak-proof. Aim should be to reduce count of infected travelers and to better track potential transport routes for transmission.</td><td>Education and Risk Communication
- E.g. address public skepticism re: vaccines</td></tr>
<tr><td>Political Commitment
- For adequate supply of antivirals +/- vaccines
-</td><td>Activate Basic Science Research Into Vaccine Production</td></tr>
<tr><td>Education and Risk Communication
- Vital for instituting practices to minimize transmission, e.g. message re: spitting in public</td><td>Continuing Basic Science Research Into Developing More Antivirals and Rapid Diagnostic Technologies</td></tr>
<tr><td>Clear Plan on Treatment of the Infected
- Where to seek treatment
- Contact tracing and prophylaxis</td><td>Clear Plan on How Medical and Health Workforce Treat the Infected
- E.g. PODS
- Vulnerable communities</td></tr>
</table>

	2nd	3rd	1st
Prioritization	Rationale: Strengthening biosurveillance at the source country may be the most efficacious, as early warning systems may reduce lag period for mitigation efforts. Subsequently, prompt treatment of infected with appropriate public health measures to reduce transmission will reduce global load of infected. However, there are many potential hot spots that can be the source and therefore investments in these countries may still not be comprehensive to cover every single one.	Rationale: Placing restrictions on travel is yields the least returns, as no measure or combination of measure will be nearly comprehensive enough to justify the huge economic, societal and political costs. Investment should be directed to enhancing diagnostic technologies at ports of entry/exit in order to institute a targeted approach to travel restriction, e.g. scanners at airports and ports. There is still an important role for such travel restrictions as a means of reducing disease dissemination globally.	Rationale: By the time the initial signs of a pandemic are evident, the disease will most probably have travelled beyond the borders of origin country. This necessitates robust destination country preparedness as the practical first-line defense. Furthermore, this is the most achievable target in the near future as most destination countries are well developed in terms of infrastructure and this will allow for convenient upgrade of pandemic preparedness. Lastly, self-investment is the most socio-politically palatable when justifying allocation of precious resources.

Distribution of Vaccines in a Multilateral Context

There was great concern that an inequitable distribution of H1N1 vaccines exisited, with the majority of vaccines going to developed countries while poorer countries awaited shipment of vaccines from WHO, resulting in persistence of the pandemic in areas of North Africa, Central Asia and Eastern Europe (http://www.nytimes.com/2010/02/02/health/02flu.html). In fact, the production and distribution of vaccines to WHO member countries represent an enormous logistical undertaking. Furthermore, vaccine-producing countries are hard pressed not to prioritized their own citizens above others. But countries that do not receive adequate countermeasure support will argue against the rationale for their cooperation in biosurveillance, and may withhold sharing of such items such as viral samples thus jeapordizing global public health security. An example is Indonesia's decision not to share with WHO viral samples during the H5N1 outbreak in 2007 (J. Aglionby and A. Jack). The situation was diffused after a high level meeting between Indonesia's health ministry and the WHO which led to a detailed terms of reference for sharing samples and underscored again WHO's 'activities to increase safe and effective pandemic vaccine access, including efforts to mobilize the financial support required to develop a vaccine stockpile and to develop guidelines for the equitable and appropriate distribution of stockpiled vaccines to countries if an influenza pandemic occurs.' WHO also promises to facilitate the collaboration between vaccine manufacturers and recipient countries to speed up the transfer of vaccine manufacturing technology. WHO also stated the possibility of establishing a vaccine stockpile for developing countries, which will enter into a feasibility study (**http://www.who.int/mediacentre/news/releases/2007/pr09/en/index.html**).

A mutually agreeable system of commodity exchanges is one way of ameliorating this impasse. Here, value is assigned to the various contributions towards global pandemic preparedness made by origin and destination countries. For example, the viral samples provided by origin countries for genotyping can represent a specific value in terms of countermeasure support or a specific met obligation that must be matched by specific returns in the event of a disease outbreak. Measurable enhancements in their biosurveillance systems may be another example of contributions meriting specific value amounts. This semi-quantitative valuation system may be tremendously helpful in reducing subjective perceptions of inequity and can be built-in into an international compact that also emphasizes the establishment of multinational research resource centers, which we will describe in principle below. The need for such an ad hoc compact is particularly necessary as diplomatic solutions to solve inequitable access to vaccines are difficult (**http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000247**).

What is a solution to a comprehensive apparatus for preparedness against pandemics and major infectious disease epidemics?

Consider the following observation: "Energy, food, and water crises; climate disruption; declining fisheries; increasing ocean acidification; emerging diseases; and increasing antibiotic resistance are examples of serious, intertwined global-scale challenges spawned by the accelerating scale of human activity. They are outpacing the development of institutions to deal with them and their many interactive effects. The core of the problem is inducing cooperation in situations where individuals and nations will collectively gain if all cooperate, but each faces the temptation to take a free ride on the cooperation of others." (Walker, Barrett et al. 2009).

Beyond influenza and its associated statistics discussed so far, the realities of infectious diseases confronting communities worldwide are overwhelming. Each year 300 million cases of malaria kill two million people. An estimated 3% of the world's population - 170 million people- are chronically infected with hepatitis C virus. About four million people are newly infected each year, 80% of whom will progress to a chronic infection associated with cirrhosis in about 20% and liver cancer in about 5%. 2 billion people have been infected with hepatitis B (1 out of 3 people). Approximately 400 million people are chronically infected with the virus and an estimated 1 million people will die each year from hepatitis B and its complications. One third of the world is infected with the bacterium that causes tuberculosis with 10 million cases every year accounting for two million deaths. Approximately 50 million people worldwide are infected with HIV, which killed 3.9 million people in 2005. Despite the attention given to diseases like HIV/AIDS and avian influenza, some outbreaks are still relatively unknown to the general public yet represent a serious burden on global health. Cholera, for example, still causes close to 120,000 deaths per year. (See page 2 – 3, http://www.istar.upenn.edu/compact/ISTAR_Compact_WP.pdf)

The daunting challenge of tracking, detecting, preventing and treating infectious diseases is the arms race of the 21st century. The race is not between states; the race is

between the global community and pathogens found in nature or pathogens nefariously disseminated. The challenge calls for new solutions that integrate basic science, technology, and social, political, legal and economic realities. The solution should optimize tradeoffs in the interplay of international security, global health, the creation and open dissemination of new knowledge and the maintenance and enhancement of the positive role of modern molecular biology on the economy of the developing world.

In addition to the undeniable moral significance of this state of affairs, the collective global failure to give this problem the attention it deserves has implications for the economic wellbeing of both the developed and developing world. International development scholars have described the role of infectious diseases play in the perpetuation of poverty in the developing world: destroying family structures and limiting economic and educational opportunities. However, infectious diseases are not merely an "over there" problem, but a symmetric threat that imperils the economic security of all nations. While the social disintegration that accompanies an epidemic has filtered into the public consciousness, the resulting economic disruption is less well-known. A few weeks after the identification of SARS, the disease had already cost nearly $30 billion, an amount sufficient to prevent 8 million deaths from infectious disease worldwide.[3] A potential H5N1 pandemic carries an even higher cost, with economic losses approaching 600 billion dollars in the United States alone, depending on the virulence and mortality rate of the pandemic strain.[4] Even without an epidemic, the spread of antibiotic resistant strains of bacteria imposes a persistent cost in terms of both health and dollars. Medical and popular literature is replete with reports of life-threatening infections caused by bacteria that are increasingly resistant to existing antibiotics. The recent Infectious Diseases Society of America report observed, "in a growing and frightening number of cases, these bacteria are resistant to many approved drugs, and patients have to be treated with new, investigational compounds or older, toxic alternatives."[5] (see page 482 – 483 http://books.google.com/books?id=gjq4mC3hW1QC&pg=PA482&lpg=PA482&dq=The+daunting+challenge+of+tracking,+detecting,+preventing+and+treating&source=bl&ots=LBdDi6OFd6&sig=eY2R-K4gpOVxPRxSVrx-sL0rR30&hl=en&ei=LqraS8KzJ5aiOOCg_cMP&sa=X&oi=book_result&ct=result&resnum=1&ved=0CAoQ6AEwAA#v=onepage&q=The%20daunting%20challenge%20of%20tracking%2C%20detecting%2C%20preventing%20and%20treating&f=false).

A study by Sandra Lawson and Douglas Gilman from Goldman Sachs, published Dec. 3, 2009, "Health Buys Wealth" analyzing the relationship between health and economic growth makes the following arguments: 1) six diseases, pneumonia, diarrhea, HIV/AIDS, tuberculosis, malaria and maternal kill more than 11 million people, 2) the

[3] I. Kickbusch. A Wake-Up Call for Global Health, International Herald Tribune April 29, 2003. Cited in M. Selgelid, Ethics and Infectious Disease, Bioethics Vol. 19, Number 3, 2005

[4] M. Lipsitch, W. Nordhaus, H. Rubin et al, A Potential Influenza Pandemic: Possible Macroeconomic Effects and Policy Issues, Report Presented to the Congressional Budget Office December 8, 2005; revised July 27, 2006 http://www.cbo.gov/ftpdocs/69xx/doc6946/12-08-BirdFlu.pdf

[5] Bad Bugs, No Drugs, the Infectious Diseases Society of America, July 2004

knowledge and technology to treat or prevent these diseases exists, 3) prevent and therapy are highly cost effective, 4) health systems in low-income countries are understaffed and under-funded, 5) governments and donors also need to strengthen health systems, expand infrastructure and extend education.

Exhibit 26: Death and disability by region and income aggregate
Rates and relative share of death and disability (disease-adjusted life years) caused by the 6 diseases covered in this paper

Death shares. Estimated share of total deaths (%), by cause, 2004

	Europe	The Americas	Western Pacific	South-East Asia	Eastern Mediterranean	Africa	High-income economies	Upper-middle income economies	Lower-middle income economies	World	Low-income economies
Tuberculosis	0.8%	0.7%	2.5%	3.4%	2.6%	3.6%	0.2%	1.6%	2.9%	2.5%	3.7%
HIV/AIDS	0.3%	1.2%	0.4%	1.3%	0.7%	14.7%	0.3%	4.8%	1.8%	3.5%	9.6%
Diarrheal diseases	0.4%	1.1%	0.9%	4.5%	6.0%	8.9%	0.2%	1.0%	3.6%	3.7%	8.5%
Malaria	0.0%	0.0%	0.0%	0.2%	0.9%	7.2%	0.0%	0.0%	1.2%	1.5%	4.7%
Lower respiratory infections	2.5%	4.2%	3.7%	9.1%	9.6%	12.6%	3.7%	3.4%	7.0%	7.1%	12.6%
Maternal conditions	0.0%	0.3%	0.1%	1.1%	1.4%	2.3%	0.0%	0.2%	0.9%	0.9%	2.1%
Sum of all 6 death shares	4.1%	7.6%	7.7%	19.7%	21.2%	49.3%	4.3%	11.1%	17.4%	19.2%	41.2%

Death rates. Estimated deaths per 100,000 population, by cause, 2004

	Europe	The Americas	Western Pacific	South-East Asia	Eastern Mediterranean	Africa	High-income economies	Upper-middle income economies	Lower-middle income economies	World	Low-income economies
Tuberculosis	8.8	5.2	17.5	31.0	21.3	55.0	1.5	13.9	25.2	22.8	45.8
HIV/AIDS	3.5	8.4	2.6	12.3	6.0	223.8	2.2	41.6	15.4	31.7	119.2
Diarrheal diseases	4.4	8.0	6.2	40.9	49.3	136.3	1.5	9.0	31.1	33.6	104.9
Malaria	0.0	0.2	0.3	2.2	7.4	109.3	0.1	0.3	10.0	13.8	58.0
Lower respiratory infections	26.6	29.6	26.0	83.4	79.8	192.2	31.1	30.0	60.5	64.9	155.9
Maternal conditions	0.4	1.9	1.0	10.1	11.7	35.1	0.2	1.9	7.5	8.2	26.3
Sum of 6 death rates	43.6	53.3	53.7	179.9	175.5	751.7	36.6	96.8	149.7	175.1	510.0

DALYs shares. Estimated share of total DALYs lost (%), by cause, 2004

	Europe	The Americas	Western Pacific	South-East Asia	Eastern Mediterranean	Africa	High-income economies	Upper-middle income economies	Lower-middle income economies	World	Low-income economies
Malaria	0.0%	0.1%	0.1%	0.3%	1.0%	8.2%	0.0%	0.1%	1.6%	2.2%	5.6%
Tuberculosis	1.1%	0.6%	2.1%	2.8%	1.9%	2.9%	0.2%	1.6%	2.5%	2.2%	2.8%
Maternal conditions	0.6%	1.6%	1.1%	2.9%	3.6%	4.0%	0.5%	1.3%	2.5%	2.6%	4.1%
HIV/AIDS	0.8%	1.5%	0.5%	1.4%	0.6%	12.4%	0.5%	6.0%	1.9%	3.8%	8.3%
Diarrheal diseases	0.9%	1.8%	2.0%	5.2%	5.9%	8.6%	0.4%	1.6%	4.6%	4.8%	8.4%
Lower respiratory infections	1.7%	2.5%	2.1%	6.4%	8.5%	11.2%	1.0%	2.4%	5.7%	6.2%	11.2%
Sum of all 6 DALY shares	5.1%	8.1%	7.9%	19.0%	21.5%	47.2%	2.6%	13.0%	18.7%	21.9%	40.4%

DALY rates. Estimated DALYs lost per 100,000 population, by cause, 2004

	Europe	The Americas	Western Pacific	South-East Asia	Eastern Mediterranean	Africa	High-income economies	Upper-middle income economies	Lower-middle income economies	World	Low-income economies
Malaria	0	10	10	80	272	4,193	4	15	376	528	2,242
Tuberculosis	196	102	324	741	523	1,468	19	330	575	532	1,140
HIV/AIDS	134	246	84	365	177	6,326	65	1,218	452	910	3,347
Maternal conditions	98	258	167	771	978	2,021	68	274	581	605	1,637
Diarrheal diseases	158	295	301	1,375	1,606	4,366	46	323	1,071	1,130	3,402
Lower respiratory infections	296	414	323	1,694	2,321	5,722	128	477	1,333	1,469	4,516
Sum of all 6 DALY rates	882	1,324	1,208	5,026	5,877	24,096	330	2,637	4,388	5,174	16,284

Source: Goldman Sachs Research, World Health Organization.

Goldman Sachs Global Investment Research and World Health Organization. Sandra Lawson, Douglas B. Gilman

XI. AN INTEGRATED APPROACH TO THE PROBLEM

An example of a new approach is a new strategy based on the creation of a four-point *International Compact*[6] *for Infectious Diseases*. The recommendations include a number of similar recommendations discussed above in the various sections of this report.

The Core Missions of the Global Compact for Infectious Diseases

Compact Core Mission I: Establish, maintain and monitor international standards for surveillance and reporting of *data and knowledge of infectious diseases* using advanced information technology to ensure timeliness, interoperability and security, including but not limited to:

–Epidemiological data,
–Information about new and ongoing clinical trials
–Data regarding new compounds and targets
–Standardized material transfer agreements
–Services and skills

Compact Core Mission II: Establish, maintain and monitor a network of international basic science research centers that will support fundamental investigations into the pathophysiology of certain microbial threats to global health.

Compact Core Mission III: Expand capabilities for the production and distribution of vaccines and therapeutics expressly for emerging and reemerging infections

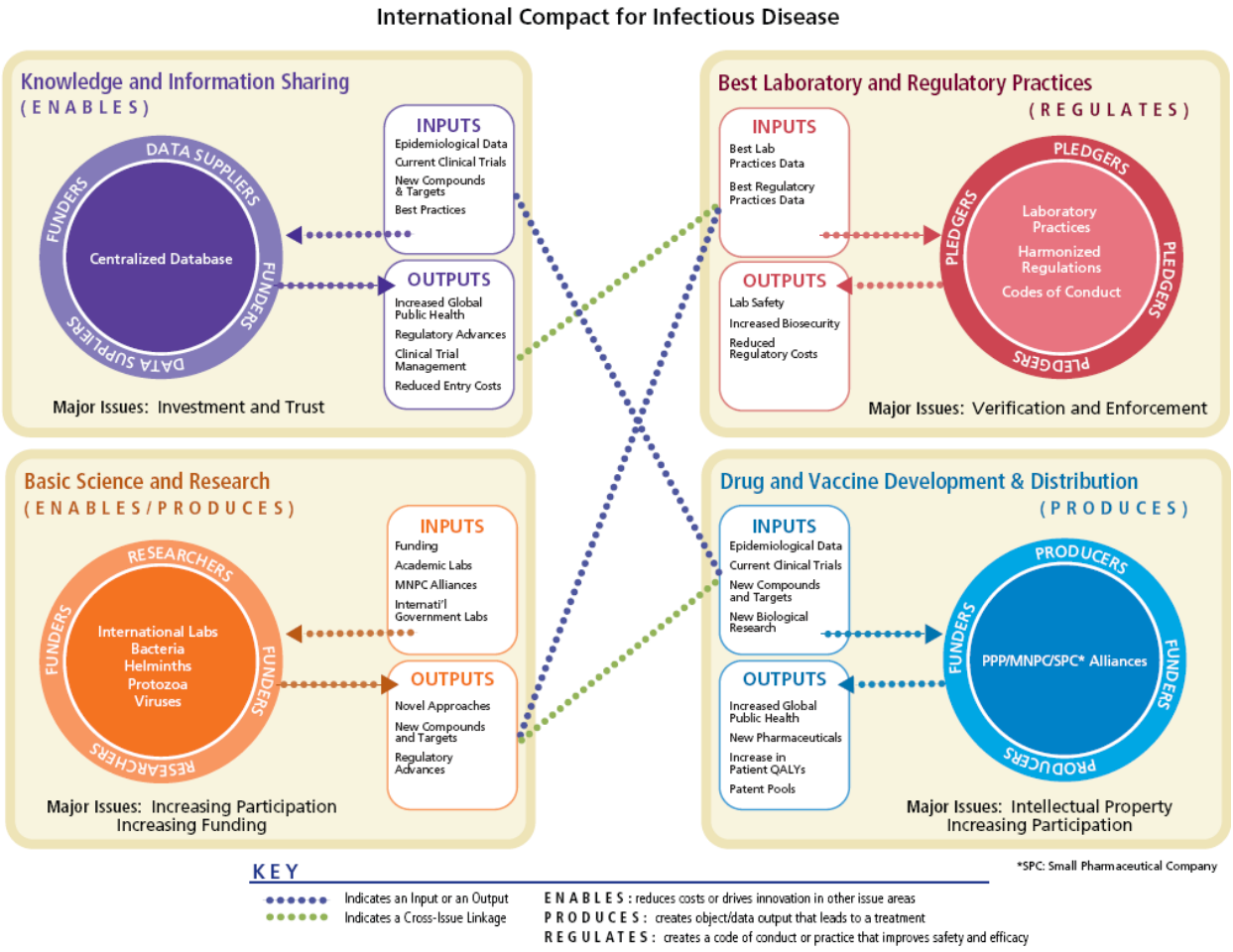
Compact Core Mission IV: Establish, maintain and monitor international standards for best laboratory, regulatory and ethical practices

[6] We deliberately use the concept of "compact" in order to avoid the term "treaty" for many of the reasons discussed by Jean-François Rischard in Global Issues Networks: Desperate Times Deserve Innovative Measures THE WASHINGTON QUARTERLY _ WINTER 2002-03, 26:1 pp. 17–33. We expect that the compact will have a structure resembling networked governance as described in Rischard's paper. We also do not rule out on the alternatives, both legal and political.

Through the implementation of these four core missions, the Compact will minimize the impact of infectious diseases on national and international health, social and economic development and international security. The key benefit of the Compact is to drive innovation and progress in four core areas: information and knowledge sharing, basic science, drug and vaccine development and best laboratory and regulatory practices. As shown in Figure 1, these missions are interconnected; without a strong foundation of basic science, the drug and vaccine pipelines dry up. Similarly, in the absence of effective biosurveillance it becomes difficult to project which strain of an emerging disease represents the most significant threat, which in turn hampers our ability to create countermeasures. Information technology and knowledge sharing will drive new science, which in turn can modify and inform regulatory initiatives. Standardized regulatory regimes enable new drugs and vaccines that will change global epidemiological patterns and these patterns must be reintegrated into a central database, beginning the cycle again (See page 4 http://www.istar.upenn.edu/compact/ISTAR_Compact_WP.pdf)

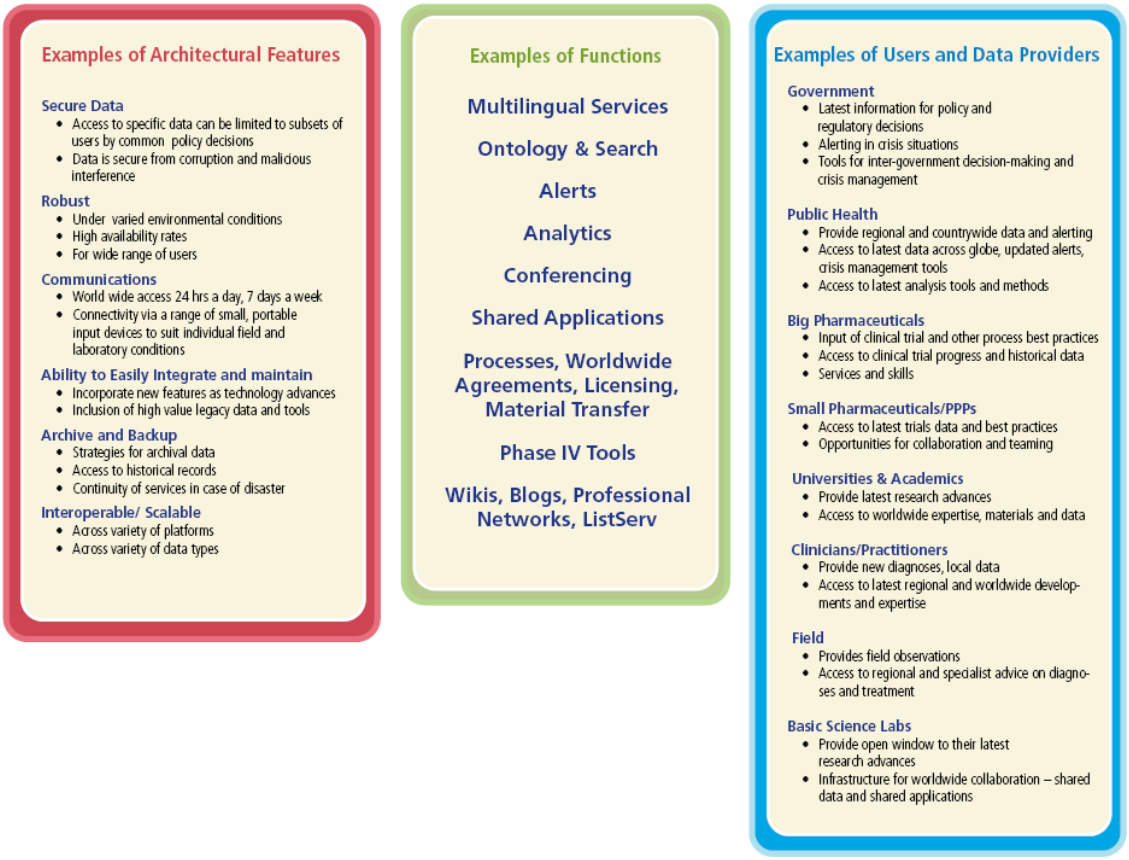
Addressing the problem as a whole creates powerful incentives for stakeholders to participate. For example, in order to access a central database containing information on current clinical trials, epidemiological data and new compounds and targets, participants would pledge to implement best laboratory and regulatory practices. By bringing together government, the private sector and academia the Compact allows each group to institutionalize their relations with the others. Pharmaceutical companies and public-private development partnerships can find partners to help take promising leads through to development. With the inclusion of post marketing/post distribution clinical trial data in the database, philanthropic organizations and governments will be able to understand the effects their investments are having throughout the world. Academics will acquire additional funding streams for their research as well as input from their colleagues all over the world. Finally, all parties will work together to harmonize regulatory processes across the board, reducing barriers to market entry for much needed therapeutics and ensuring their wider distribution (Page 662 http://www.ias.ac.in/currsci/mar102009/658.pdf)

FIGURE 1



There already exist a large number of databases that address one or more of these issues, e.g., the revised 2005 International Health Regulations (IHR). An information technology architecture (Figure 2) that will seamlessly integrate these databases, make them user friendly yet provide the necessary security and add new data as recommended by the wide user community needs to be developed. The challenges here are formidable, but hardly insurmountable. The greatest obstacle is the need for trust between signatory nations and a willingness to share data. There are technical challenges as well. Any attempt to create a common architecture for information systems would require common ontologies. New algorithms and models of disease spread need to be developed and validated. Lastly, the language of the Compact has to address the issue of member states that do not report, or significantly under-report, the incidence of communicable diseases (Page 660 http://www.ias.ac.in/currsci/mar102009/658.pdf).

FIGURE 2



International bio-surveillance and reporting certainly faces certain challenges[7] including:

1. Integrating current initiatives into a national health IT strategy and federal architecture to reduce the risk of duplicative efforts;
2. Developing and adopting consistent interoperability standards;
3. Creating an open architecture that maximizes the use of off-the-shelf tools;
4. Creating enough flexibility to bring together disparate underlying IT languages and technologies to provide a common operating picture;
5. Generating the ability to accept multiple data formats used by agencies that provide the bio-surveillance information;
6. Generating the ability to feed information back to the originating agencies providing bio-surveillance information in a format each agency can accept;
7. Identifying data flows that will evolve during the developmental process;
8. Allowing the methods of analysis to evolve and adapt as new data become available or existing data sets are improved; and

[7] Points 1-2 found in http://www.gao.gov/new.items/d05308.pdf, 3-9 found in the RFQ#RIRM-06-00020 from DHS.

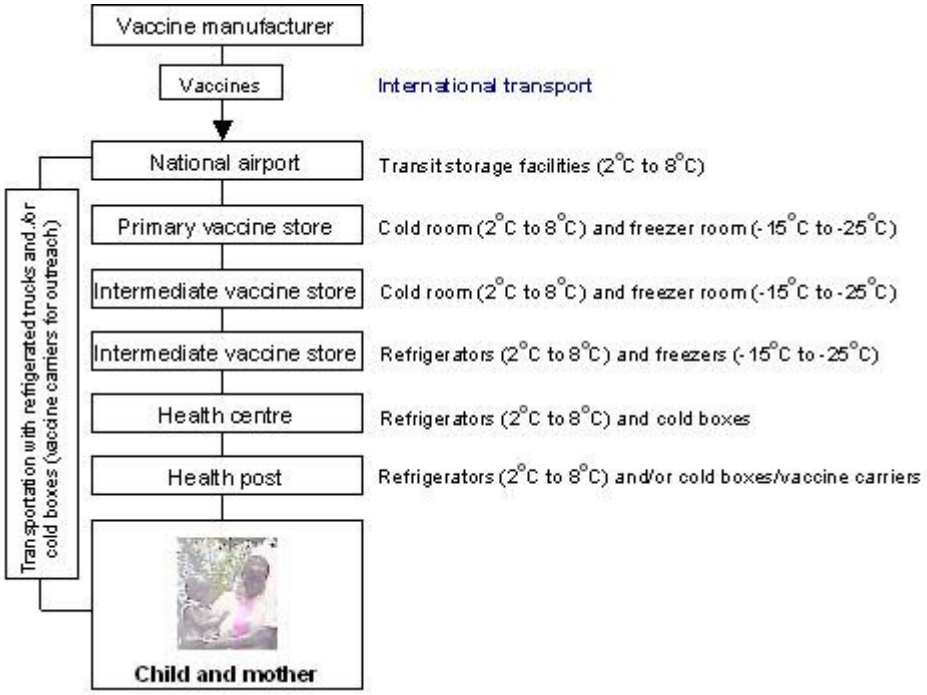
9. Knowing and evaluating the effectiveness of the current underlying algorithms, methods, and structures for biosurveillance data analysis. (See page 661 http://www.ias.ac.in/currsci/mar102009/658.pdf).

Implementing Core Mission III also faces challenges, including identifying sufficient funding, resolving conflicts arising from the need to protect intellectual property and incentivizing innovation. A creative approach to these problems is the health impact fund (HIF) as described in Aidan Hollis and Thomas Pogge, *The Health Impact Fund: Making New Medicines Accessible for All* (Hollis and Pogge 2008); and in "The Health Impact Fund: incentives for improving access to medicines" (Banerjee, Hollis et al. 2010). The HIF is designed to provide incentives and resources for medical research and development of drugs and vaccines, especially for the poor that would not require revision of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. The fund would be resourced by a percentage of GDP from participating countries. Research and development participants who register a particular product would receive funds from the HIF according to the contribution that the product provides toward global health calculated with an as yet to be determined set of outcome metrics. In exchange for these funds, the participants would agree to sell the product wherever needed for the lowest production and distribution cost. After the reward period the participant would also agree to offer free licenses so that a generic version of the product could be manufactured and sold. This plan stimulates the production and distribution of lower priced drugs and vaccines because high priced agents would limit their access and therefore their impact. There are additional benefits of the program—it would add incentive to develop drugs and vaccines that have been neglected, ignored or abandoned by the pharmaceutical industry. It is symmetrical, it benefits the poorer countries without penalty to the wealthier countries, it discourages the production and distribution of counterfeit agent and it encourages the drug developer to ensure safe and efficient delivery and proper patient compliance so that the full health benefit is realized.

(The following section on the cold chain was co written by Harvey Rubin and Alice Conant). Full implementation of Core Mission III requires the successful delivery of drugs and vaccines to the relevant populations. Under certain scenarios, e.g., pandemics or local outbreaks caused by new or difficult to treat agents, bioterrorist attacks, disruptions caused by environmental or governmental dislocations, successful delivery is not yet guaranteed in the developed countries. It is a far distant certainty that vaccines and drugs can be delivered to the populations in developing countries even under usual circumstances. The reason for this is the requirement that many of these drugs and vaccines must be kept cold and the so-called cold chain, the appropriate refrigeration units from the source of the vaccine or drug to the individual recipients, is inadequate. The lack of electrical infrastructure in underdeveloped countries has a direct correlation to the high death rates from preventable diseases in these regions. We propose a solution to this problem that is economically and technically sustainable and which can be implemented immediately.

Cold Chain

In order for vaccines to maintain their potency and effectively immunize a patient, they must be stored at specific temperatures. When medicines and vaccines are distributed, they must be transported from the point of delivery in the country to the point of delivery to the patient, which is frequently in a rural location. During this transfer, the medicines and vaccines must be transported in a series of refrigeration and storage units that maintain very specific temperature ranges. This maintenance of the medicines and vaccines at critical temperatures is referred to as the cold chain, as illustrated here. [1]

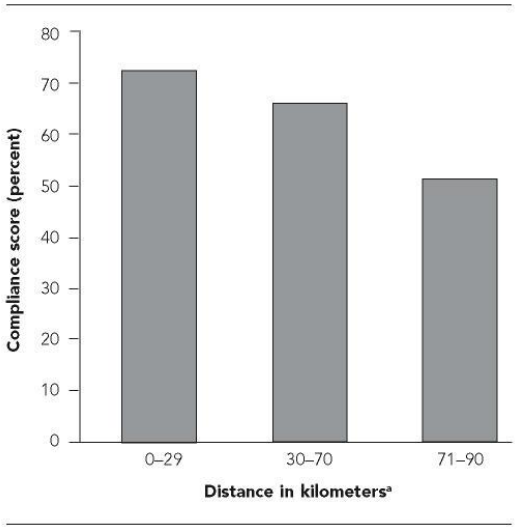


At least 2 million people die each year from vaccine preventable diseases. Generally, these deaths are not because there is a lack of vaccines and medications in the world, but because there is an inadequate vaccine distribution process. Maintaining the cold chain is an overwhelming challenge in countries where the energy infrastructure is limited. A study by Dr. Subhash C.Arya pinpointed this unanswered problem:

> The cold-chain maintenance is indeed a Herculean task as the transportation and storage facilities are as a rule unsatisfactory in most if not all developing countries. There are difficulties in obtaining spares and accessories and carrying out day-to-day repairs. There are insurmountable problems in satisfactory execution of the cold chain since power supplies tend to be erratic. Constant appraisal of personnel and appliances is required at the central and peripheral vaccine storage sites.[2]

The cold chain becomes increasingly unreliable as the distance between primary health centers and sub-health centers increases because of the lack of reliable power

sources in the rural areas. A study done in 2007 evaluating the success of the cold chain for the oral polio vaccine in a rural district of India showed that as the distance between sub-health centers from the primary health centers increased, the effectiveness of the cold chain decreased by .16% per one-kilometer (see below).[3]



The study further analyzed the relationship between effective cold chains and reliable power:

> Electrical power or an alternative source of energy is crucial to the maintenance of the cold chain, and our data indicate 90% of all primary/community health centers reporting frequent power failures (5–10 hours) during summer months. This is compounded by the fact that only 45% of these primary/community health centers have a power generator that can help maintain the cold chain (Samant, Lanjewar et al. 2007).[3]

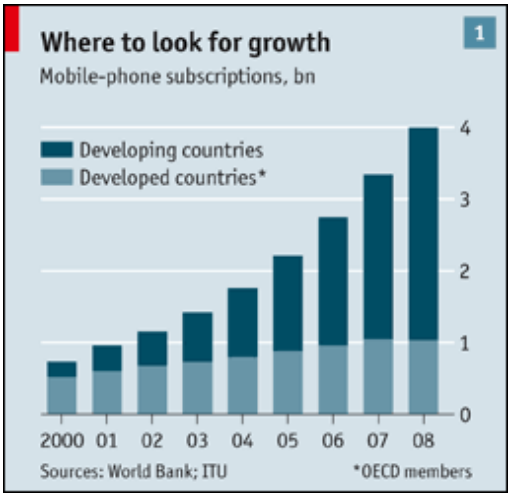
Several other studies evaluating the efficiency of the cold chain and vaccine potency in developing countries agree with this observation (Adu *et al.*[4], Hanjeet *et al.*[5], Senanayake *et al*[6].). The study performed by Adu *et al.* evaluated the cold chain in Nigeria from the National Cold Store (NCS) to rural village clinics, maternity centers, dispensaries and hospitals. The study identified that "all the locations [from the NCS to rural vaccine destinations] had formally trained and sufficient cold store staff", however significant loss of vaccine potency still occurred between the local government cold stores and the rural vaccination centers due to inadequate energy infrastructure.[6]

Although cold chain efficacy is not the only impediment to global immunization, it is a major concern. A technology that could allow penetration of the cold chain into rural regions where sub-health centers are located would significantly impact the effectiveness and distribution of critical medicines and vaccines.

The Solution to the cold chain problem:

The millions of deaths due to insufficient access to viable vaccines demonstrate a major need in the global immunization movement for sustainable energy sources and infrastructure. At the University of Pennsylvania, the collaborative project "Energize the Chain" addresses this dilemma by connecting access to clean water and viable vaccines to an absolute juggernaut of current global technology - cell phones.

Cell phones are the fastest spreading technology in the world, and customers in developing countries account for two thirds of the universal mobile phones in use. This global growth is illustrated below.[8]



Cell phones rely on cell towers, and each tower has its own supply of power. The cell tower facilities usually draw their power from the electrical grid, but this energy can also be converted to direct current (DC) power at 24 volts for the wireless networks.[9] Each cell tower is also connected to a backup power source in case the electrical grid fails. In recent years, however, the global mobile network expansion has been increasingly present in off-grid cell tower projects due to the lack of grid connectivity in many locations.[10] By 2012, the Global System for Mobile Communications (GSMA) estimates that approximately 639,000 off-grid mobile towers will be established in the developing world.[11] In these locations, where access to the electrical grid was previously unavailable, cell towers will introduce a private sector sustainable energy source.

The Energize the Chain project focuses on harnessing an adequate portion of this electrical energy from cell towers to power refrigeration units and water filtration systems. Although providing energy to non-tower related sources is not part of the mobile network design, the GSMA Development Fund recently initiated a new movement called "Community Power" founded upon this idea. In the Community Power January 2010 report, the potential global impact of the mobile expansion on energy infrastructure was recognized.

> A significant opportunity exists to provide environmentally sustainable energy to people in the developing world who live beyond the electricity grid. And it is the mobile telecoms industry – which has already brought phones beyond the fixed telecoms grid – which holds the key to this next infrastructure innovation.[11]

Currently, with the support of Community Power, mobile network operators are exploring ways of using excess cell tower power to charge mobile handsets, large household batteries and rechargeable lanterns. There is recognition, however, for the potential to power an entire village with the reliable energy supply from cell towers.[11] It is this innovative power source that Energize the Chain identifies as the solution to global healthcare's need for sustainable energy. Initially, the project looks to solve the cold chain problem due to the straightforward and minimal energy requirements. This synergy between global healthcare and mobile expansion clearly benefits the cell phone service provider as well as the local population.

Other solutions are being explored to address the global health issue of inadequate power supply in developing countries. Heat stable vaccines, solar powered refrigeration units, and mobile immunization teams with refrigerated cars are under development, however, these methods are very expensive, location specific and require many more years of research. Up until now, no outstanding progress has been made because too often the research has been in the domain of philanthropy and government and is not yet globally comprehensive. Energize the Chain provides a solution with a global drive that is present in all regions of the world and is independent of government funding and targeted philanthropic initiatives. Cell tower, refrigeration and vaccine technologies will continue to evolve, however, as long as the cell towers are maintained by private infrastructure there will be sustainable energy for viable vaccines wherever mobile coverage is present.

This idea has received enthusiastic support for its potentially transformative impact on world health and human security. By piggybacking access to viable vaccines, medications onto the fastest spreading industry in the world, we could solve a perplexing global health problem and save up to 5 million lives. According to the 2010 World Telecommunications/ICT Development Report, approximately 75% of the world's rural inhabitants are covered by a mobile cellular signal, and it is estimated that close to 100% of the world will have mobile coverage by 2015.[13] In order to have mobile coverage you must be within the range of a cell tower-a matter of only a few kilometers, depending on the territory, which means that if the power from the towers can be utilized to sustain cold chains and water filtration units, by 2015 close to 100% of the world could have access to viable vaccines and medications.

Organization and Governance

In order to accommodate the various interested parties and work within the limits of international law, a two-pronged approach is suggested—1) working with states in the form of a treaty and 2) working with other interested parties (NGOs, academic institutions and the private sector) as a softer, pledge-based agreement. While these

differences are structural rather than substantive, both approaches have their limitations. Treaties must be ratified through domestic processes that vary widely from state to state and take an extended amount of time to enter into force. Furthermore, states jealously guard their sovereign prerogatives and thus enforcement regimes must be devised in a manner that maximizes both effectiveness and feasibility.[8] However, once in force a treaty creates a body of "hard law" around an issue, providing a legal basis for international enforcement. A compact structure, in contrast, allows NGOs, the private sector and academic institutions to submit a pledge of membership and voluntary compliance, making it quick to set up and allowing interested parties to coalesce around an issue.[9]

By providing parallel frameworks for different parties, the overall project will, over time, achieve the benefits of each. Domestic groups that pledge their membership can apply pressure to their home states, hopefully speeding ratification of the treaty framework. By bringing together both state and non-state actors, the overall aims of the Compact will be debated from a variety of different viewpoints, thereby enhancing the legitimacy of the project and promoting a thorough understanding of its goals (see page 661 http://www.ias.ac.in/currsci/mar102009/658.pdf)

[8] See George W. Downs, David M. Rocke, Peter N. Barsoom, *Is the Good News about Compliance Good News about Cooperation?* International Organization, Vol. 50, No. 3 (Summer, 1996), pp. 379-406

[9] See Rischard, Matthew, *Global Issues Networks: Desperate Times Deserve Innovative Measures*, The Washington Quarterly Vol. 26, No. 1 pp. 17-33 and *High Noon: We Need New Approaches to Global Problem-Solving, Fast*, J Int Economic Law 4: 507-525.

XII. LESSONS FROM THE PAST

Over the past 25 years, projects with international scope and impact demonstrate that efforts at resolving complex and sometimes overlooked international issues are feasible from the perspectives of both implementation and end-stage achievements. We briefly discuss two of them below.

In October of 1992, six NGOs met in New York City and founded the International Campaign to Ban Landmines (ICBL). By the end of 1997, a mere five years later, the Convention on the Prohibition of the Use, Stockpiling, Production and Transfer or Anti-Personnel Mines and on Their Destruction entered into force and the ICBL was awarded the Nobel peace prize "as a model for similar processes in the future."[10] Of particular relevance for the struggle against infectious diseases is the way in which the ICBL – a coalition of non-state actors – used normative rhetoric to compel government action on a previously neglected issue of little importance to the developed world. The essential issues surrounding infectious diseases possess similar normative force, which hopefully indicates a similar potential for progress.

In the science and development domain, the Consultative Group on International Agricultural Research (CGIAR) achieved tremendous successes with a similarly broad approach to agricultural issues. Reacting to a projected crisis in the food supply a series of high-level consultations were held in Bellagio, Italy and elsewhere to devise a framework for addressing the situation. As a result of CGIAR's efforts the world experienced a massive increase in cereal yield in the second half of the 20th century, and the crisis was averted.[11] CGIAR is an important antecedent combining North/South representation with innovative research and a truly lasting impact in some of the poorest regions in the world. The magnitude of the threat of infectious diseases also necessitates a major global, investigative effort. The example of the "Rice Institutes" funded by the Rockefeller Foundation for fifteen years[12] and sustained by the Consultative Group in International Agricultural Research, provides a framework for an interdisciplinary, collaborative and synergistic network of Infectious Disease International Research Centers. These should have a permanent faculty and staff as well as visiting fellowships and studentships. The lasting positive impacts of international research centers are many, including fostering long-term relationships between

[10] Cited in Sigal, Leon, *Negotiating Minefields, The Landmines Ban in American Politics*, p. 4

[11] http://www.cgiar.org/who/history/index.html

scientists, establishing a culture of research responsibility and serving as the nucleus for safe applications of interdisciplinary sciences globally.

The key to any progress against infectious diseases is a structure that brings together these diverse interests in a lasting fashion. Without such a structure, the commitment to reducing the impact of infectious diseases on our national, economic and personal security will be subject to the political vagaries of the moment, leaving us unprepared for the next global health crisis (see page 659 http://www.ias.ac.in/currsci/mar102009/658.pdf).

Below is a list of just some of the benefits to signatory nations:

1. Provide access to specific therapeutics and vaccines that are relevant to the signatories.
2. Ensure better quality control of vaccines, therapeutics and diagnostics in the developing world, leading to fewer expired or counterfeit agents.
3. Provide access to and participation in high-level research.
4. Provide developing and developed states with a voice in the direction of research and development.
5. Distribute the costs and risks of research and development across a number of countries
6. Provide more complete datasets on emerging infections and potential pandemics.
7. Create a more competitive market for vaccine and therapeutic development targeting diseases of relevance to signatory nations.
8. Enhance and enable human health and well-being, economic development, and basic biological research.

(see page 662 http://www.ias.ac.in/currsci/mar102009/658.pdf).

[12] RICE BIOTECHNOLOGY: Rockefeller to End Network After 15 Years of Success Dennis Normile *Science* 19 November 1999: Vol. 286. no. 5444, pp. 1468 – 1469

RECOMMENDATIONS

Recommendations (includes examples)	**Risk Phase Affected** (Assessment, Monitoring, Prevention, Response, Communication, Recovery)
Unshakable Commitment to Multidisciplinary Research *Basic Science:* • pathophysiology underlying superspreading, antiviral development, new vaccine development targeting essential and common epitopes (all-in-one vaccine), expanding viral genotyping capability *Clinical/veterinary research:* • epidemiological research into patterns of outbreak and spread, risk factors involved (e.g. vectors, comorbidities), farm best practices and monitoring *Sociology research:* • mental models of individual decision making in advance of a pandemic, survey research into receptiveness of message and trust in media sources, as well as types of media engaged *New research:* • network-based analysis of spread, strategic vaccination patterns	All Phases
Establishment of a One-stop Real-time Information Resource for Global Infectious Disease Control and Emergency Preparedness • this resource should address the sharing of vital information for preparedness and response measures: sharing of key research info (viral strains, best practices, disease mapping and spreading), sharing of resource	All Phases

info (availability of as well as need for vaccines, antivirals, manpower) • allows sharing and planning of necessary steps in optimized fashion	
Engagement of Pharmaceutical Industry • to help recruit efforts in countermeasure production capacity. **Establish National/International Research Centers** • dedicated to countermeasure research and production using taxpayer money	Prevention, Response, Recovery
Engaging Partner Countries In Concrete Measurable Terms • a system of symbiotic contribution towards global public health security, with a valuation system that is amenable to stakeholders (e.g. contribute viral samples = assurance of X% vaccine stockpile)	All Phases
Pre-pandemic preparation and contingency planning • absolutely essential to minimize disruptions to public services and established pandemic response procedures. Each locale is unique in their pre-pandemic planning preferences but this is more of a cultural asset that must be inculcated through dialog.	Prevention, Response, Communication, Recovery

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