

The Effectiveness of Policies to Control a Human Influenza Pandemic:

A Literature Review

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Abstract

The studies reviewed in this paper indicate that with adequate preparedness planning and execution it is possible to contain pandemic influenza outbreaks where they occur, for viral strains of moderate infectiousness. For viral strains of higher infectiousness, containment may be difficult, but it may be possible to mitigate the effects of the spread of pandemic influenza within a country and/or internationally with a combination of policies suited to the origins and nature of the initial outbreak. These results indicate the likelihood of containment success in ‘frontline risk’ countries, given specific resource availability and level of infectiousness; as well as mitigation success in ‘secondary’ risk countries, given the assumption of inevitable international transmission through air travel networks. However, from

the analysis of the modeling results on interventions in the U.S. and U.K. after a global pandemic starts, there is a basis for arguing that the emphasis in the secondary risk countries could shift from mitigation towards containment. This follows since a mitigation-focused strategy in such developed countries presupposes that initial outbreak containment in these countries will necessarily fail. This is paradoxical if containment success at similar infectiousness of the virus is likely in developing countries with lower public health resources, based on results using similar modeling methodologies. Such a shift in emphasis could have major implications for global risk management for diseases of international concern such as pandemic influenza or a SARS-like disease.

This paper—a product of the Poverty Team, Development Research Group—is part of a larger effort in the group to understand the benefits and costs of public health policy responses to highly infectious diseases, and foster international cooperation and coordination in their control. Policy Research Working Papers are also posted on the Web at <http://econ.worldbank.org>. The author may be contacted at dutta@prgs.edu.

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The Effectiveness of Policies to Control a Human Influenza Pandemic: A Literature Review

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Policy
AVE_I: Antiviral Efficacy in Reducing Infectiousness
AVE_S: Antiviral Efficacy in Reducing Susceptibility
BMR: Blanket Movement Restrictions
CDC: Centers for Disease Control (US)
CFR: Case Fatality Rate
DHHS: Department of Health and Human Services
GAR: Gross Attack Rate
GTAP: Geographically Targeted Antiviral Prophylaxis
H5N1: Hemagglutinin-5, Neuraminidase-1
H2N1: Hemagglutinin-2, Neuraminidase-1
HCW: Healthcare Workers
IATR: International Air Travel Restrictions
MIDAS: Models of Infectious Disease Agents Study
NPI: Nonpharmaceutical Intervention
NVAC: National Vaccine Advisory Committee
 R_0 : Basic Reproductive Number
RMR: Reactive Movement Restrictions
ROW: Rest of the World
SARS: Severe Acute Respiratory Syndrome
SE: Southeast
SEIR: Susceptible Exposed Infectious Removed
TLC: Targeted Layered Containment
TAP: Targeted Antiviral Prophylaxis
VE_I: Vaccine Efficacy in Reducing Infectiousness
VE_S: Vaccine Efficacy in Reducing Susceptibility
WB: The World Bank
WHO: World Health Organization

GLOSSARY OF EPIDEMIOLOGICAL TERMS USED

Asymptomatic transmission: For influenza, the transmission from person-to-person where the infecting individual does not manifest visible/detectable symptoms of influenza illness.

Basic Reproductive Number, R_0 : The mean number of secondary cases caused by a typical single infectious case in a completely susceptible population (i.e., with no prior immunity), in the absence of public health interventions.

Case Fatality Rate:* The proportion of persons with a particular condition (cases) who die from that condition. The denominator is the number of incident cases; the numerator is the number of cause-specific deaths among those cases.

Chemoprophylaxis: Using antivirals or other drugs to prevent infection with the disease (can be pre- or post-exposure to the disease-causing agent, e.g., the influenza virus).

Epidemic: A generalized epidemic; or, a sequence of outbreaks in a large geographically defined area such as a city, a province, or a country.

Gross Attack Rate: The proportion, usually of a country population, that has a clinical case of the infectious disease during a defined period of time, such as the duration of the epidemic.

Herd Immunity:* The resistance of a group to invasion and spread of an infectious agent, based on the resistance to infection of a high proportion of individual members of the group. The resistance is a product of the number susceptible and the probability that those who are susceptible will come into contact with an infected person.

Incubation period (influenza): The longest period between the introduction of the virus into a host and the occurrence of the first clinical signs of the disease.

Outbreak: A localized epidemic; or, a sequence of related infectious disease cases in a geographically defined area such as a neighborhood, town, or city. Sometimes considered synonymous with epidemic.

Pandemic: An epidemic that is geographically widespread; occurring throughout a region or even throughout the world.

Physical prophylaxis: Using masks or other physical devices to prevention infection with the disease.

Prophylaxis: Prevention of infection with a disease, pre- or post-exposure to disease-causing agent.

Quarantine: The physical separation of healthy people who have been exposed to an infectious disease – for a period of time – from those who have not been exposed.

Social distancing: A disease prevention strategy in which public health authorities limit social (face-to-face) interaction to reduce exposure to and transmission of a disease. These limitations could include, but are not limited to, school and work closures, cancellation of public gatherings and closure or limited mass transportation.

Virulence:* The proportion of persons with clinical disease, who after becoming infected, become severely ill or die.

* Source: CDC Epidemiological Glossary. www.cdc.gov/reproductivehealth/EpiGlossary/glossary.htm

**THE EFFECTIVENESS OF POLICIES TO CONTROL A HUMAN
INFLUENZA PANDEMIC: A LITERATURE REVIEW**

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INTRODUCTION

The recent efforts for pandemic influenza preparedness at local, country, and international levels exemplify rapid, research-driven creation and execution of an agenda for a disease of international concern. A prominent part of the research on a potential pandemic of influenza has focused on strategies to prevent or mitigate such an event. Much of this research has been highly technical and not adequately surveyed such that policymakers can make choices fitting the context of their city or country. This paper reviews this field, focusing on policies to control – i.e., prevent or mitigate – a human pandemic of influenza, and presents the major conclusions from the literature.

A rationale for this literature review is that research on the effectiveness of control policies is driving multilateral and national strategies at three levels. First, the World Health Organization (WHO), and the EU and US agencies responsible for pandemic preparedness have recommended strategies (*sets of policies*) for controlling a human pandemic of influenza. The recommended actions in certain contexts aim at containing an outbreak rapidly before it can spread; in others the emphasis is on mitigating the overall attack rate. The WHO has recently issued an Interim Protocol for containment measures under the title *Rapid Operations to Contain the Initial Emergence of Pandemic Influenza*¹. Recommended policies here substantially derive from insights from mathematical modeling studies^{3,5} that compare policies for containing pandemic outbreaks. Second, there are studies focusing on particular policies, such as limiting international air travel, vaccination, or community-level policies. These studies have informed specific WHO guidelines, e.g., for recommending a restriction on flights from certain cities; as well as country governments' choices of implementing such guidance. Third, policymakers have learned from research on the 2003 SARS outbreak. The emphasis on these three background literature sources in this review follows the order in which they were mentioned.

Before the aims of this review can be discussed, it is necessary to clarify some nomenclature. In general, effectiveness for a containment-focused strategy refers to the reduction of the spread of pandemic influenza within a country or internationally. For a mitigation strategy, effectiveness refers to reducing the overall number of cases, i.e., the attack rate, and to delay and reduce the peak rate of cases per day. A mitigation strategy lowering the overall illness attack rate unambiguously reduces hospitalizations and deaths that are related to human and economic losses. For two strategies achieving similar reductions, the one more feasible is more effective. In this review, effectiveness of a policy (used here interchangeably with 'intervention') is differentiated from baseline *efficacy*, as established in theory or in the laboratory. Efficacy is an important determinant of policy effectiveness in modeling studies. However, effectiveness accounts for likelihood of use, feasibility, transmission dynamics, etc., in an outbreak or an epidemic. Given the rationale above and the definition of terms, this review has three specific aims as specified below.

- I. Link in one document the current research on the efficacy of specific policies; the properties of a potential pandemic-capable influenza virus relevant to its infectiousness and virulence; the assumptions and methods behind mathematical or other models of pandemic influenza spread and control; and the results of studies of the effectiveness, cost (or cost-effectiveness), and ethical dimensions of policies and strategies. For example, such linkage can help refer the claims of modeling studies to the baseline efficacy of particular policies, and to assess the generalizability of the results given modeling assumptions, the assumed properties of the virus, etc.

- II. Provide a taxonomy of control policies and to collate as completely as possible the results of modeling studies that assess their effectiveness in specific or in combination. This allows the comparison of the effectiveness of the same policy when viewed in isolation, or as part of a strategy group of policies aimed at containment or mitigation. This difference is relevant if particular countries may afford only one or few of the policies rather than the most effective group of policies.
- III. Further the debate on the appropriate international mix of funding for pandemic influenza preparedness that reduces the global risk of such an event. As per the current distribution of funding, countries with past outbreaks and at risk of future outbreaks are spending less per capita than some countries with no outbreaks but larger resources. This imbalance in preparedness spending is driven by large pre-investments in the latter group in mitigation policies such as vaccine development and antiviral stockpiling. These are resource intensive and hence disproportionately the preserve of wealthier countries. Such spending is driven by a logic summarized as 'hope for the best but prepare for the worst'. This assumes that containment policies after a pandemic outbreak in the frontline states (those with current or past outbreaks) will fail and hence the spread to the West is inevitable; and further that subsequent containment policies at airports or other entry points in the West will also fail. Discussion of the modeling results below, especially from studies that address a global redistribution of resources⁸⁰, should illuminate this debate.

Ethical and cost considerations can make the choice complex between two similarly effective and feasible control policies. For example, some mitigation policies are selective in terms of who is pre-protected from infection, raising ethical issues that require review. Cost-effectiveness studies of policies for pandemic influenza have been rare, reflecting the difficulty in rigorously estimating the benefits or costs, or negotiating the ethical issues in valuing sickness and death. The few such studies available will be reviewed. A different angle is taken by studies that estimate the general benefit of preventive policies in terms of the avoided macroeconomic costs of a potential pandemic. Such studies of potential national and international losses to economic activity are beyond the scope of this review.

Immediately below, a section surveys what is currently known about the properties of a pandemic influenza virus that determine the ease of containment or mitigation in an outbreak. Also in the same section, the results from published reviews of efficacy for a few policies are summarized. The next section provides a broad overview of the major methods for modeling the transmission of pandemic influenza and for the prospective comparison of control policies. The main section of the paper follows, initially providing the taxonomy of interventions. On this basis, studies that compare various control policies – for containment and mitigation – are analyzed, and those that evaluate a specific policy. The penultimate section reviews cost and cost-effectiveness studies. Ethical issues are briefly discussed in the concluding section, which can be read as an executive summary of the review. The intended audience includes public health practitioners, policymakers, and researchers involved in health. No detailed knowledge of pandemic influenza epidemiology is assumed.

DETERMINANTS OF A PANDEMIC INFLUENZA OUTBREAK AND ITS CONTROL

The properties of a future pandemic influenza virus relevant to the containment and mitigation of outbreaks may be uncertain, but studies have attempted to create scenarios for policy analysis based on three sources of information. First, clinical, epidemiological, and laboratory data exist in the form of tissue samples from patients, records of public health measures, as well as overall morbidity and mortality estimates from influenza pandemics of the 20th century: in 1918-20, 1957-58, and 1968-69. Second, researchers have been tracking the evolution of the current avian influenza A (subtype H5N1) virus and the associated human cases. This virus is considered the prime candidate for generating a pandemic capable strain. Predicting potential mutations in the H5N1 strain helps create new scenarios of the properties of a pandemic virus and inform prevention and control measures. Third, there are extensive studies of the transmission of seasonal influenza (various subtypes), which can help model the transmission of a more efficient human communicable strain of any avian influenza A virus that attacks people.

A discussion of how an avian virus of subtype H5N1 may potentially mutate to pandemic capable form is omitted. Assuming that this mutation occurs, a substantial proportion of the world population – some studies assume 60%⁶² – would be susceptible. The two basic properties of a pandemic influenza virus relevant to prevention and mitigation are considered below: *infectivity* and *virulence*. Thereafter, some concepts related to infectivity – or more generally, transmissibility – used in modeling outbreaks are discussed with reference to pandemic influenza viruses (e.g., the effective contact rate, the basic reproduction number). Connected to both infectivity and virulence, the current science on antiviral, vaccine, and personal protective equipment efficacy is discussed.

Infectivity: The more intrinsically infectious a virus, the higher the likelihood that when an infected person meets an average uninfected person, a second infection will occur. Here, an infection is defined as developing antibodies to the viral presence in the body – also known as ‘exposure’ – and is prior to developing a clinical case of the disease (i.e., symptoms). Given a level of base infectivity of the virus, the likelihood of a secondary infection is modified by several factors - the effectiveness of the contact between infected and uninfected, environmental conditions, and the presence of preventive barriers (i.e., prophylaxis via pharmaceuticals, or physical protection). The issue of effective contact is briefly considered after *virulence* below.

There are three types of human influenza viruses: A, B, and C. Of these, only influenza A viruses, which have subtypes based on the hemagglutinin (HA) and neuraminidase (NA) protein combinations on the viral surface, have caused pandemics. Influenza B virus strains may be widely transmitted in seasonal epidemics, but usually do not cause pandemics. Influenza C virus generally causes mild illnesses in humans². In this review, only influenza A is considered. The base infectivity of influenza A viruses depends on the rate at which the average infected person ‘sheds’ the virus, the timing of the ‘peak shedding’ period, the mode of transmission for the shed virus, minimum size of an infectious dose of virus, and survivability of the virus on surfaces and in the air.

Table 1. Determinants of the Base Infectivity of Influenza Virus Strains

<i>Characteristic</i>	<i>Conclusions for seasonal influenza A</i>	<i>Implication for epidemic control</i>	<i>Review study source</i>
Virus shedding rate & duration	<ul style="list-style-type: none"> ▪ High virus load in respiratory secretions ▪ Shedding up to 24-48 h <i>before</i> symptoms ▪ Virus shed for up to 5 days ▪ Volume & duration higher in children 	Symptom-based control insufficient. Schools may be foci of transmission.	Bell <i>et al.</i> 2006, Tellier 2006 ²⁸
Timing of peak shedding	<ul style="list-style-type: none"> ▪ First 1-3 days since symptoms (illness) 	More rapid transmission*	Bell <i>et al.</i> 2006 ⁵⁵
Mode of transmission (rank order)	<ol style="list-style-type: none"> 1. Virus-laden large droplet in cough/sneeze 2. Virus-laden small aerosol in cough/sneeze 3. Direct contact with secretions, fomites** 	Surgical face masks may not offer complete protection	Tellier 2006
Survivability	<ul style="list-style-type: none"> ▪ Infectious for <24-48 h from steel/plastic ▪ Infectious for <8-12 h from tissue/cloth ▪ Humidity, heat reduce survivability in air 	Malls and crowded transport a source of infection	Bell <i>et al.</i> 2006, CDC 2006 ¹³

* In comparison, SARS has peak infectivity 5-10 days after onset of symptoms.

** Any inanimate object that transfers the virus person to person, e.g. dust particles in a sneeze.

Table 1 presents conclusions from recent review studies of the basic infectivity of influenza A viruses, themselves based on the literature on seasonal (interpandemic) epidemics in the West. Any deficiencies in this literature are noted in the review studies cited in Table 1. If it is assumed that a pandemic capable virus would have similar properties, then some implications for pandemic control can be gleaned. These will be later put into the context of specific policies for local/community or international preparedness. It can be noted that some aspects of infectivity for the influenza A virus seem higher than the SARS coronavirus from 2003. The caveat should be reinforced that Table 1 is based on historical studies of seasonal influenza A/B, across many different subtypes. Any future pandemic-capable strain may have different properties.

An additional characteristic of infectivity is the presence of age-related patterns in attack rates. Based on data from the US, attack rates were much higher in children than in adults during the 1957-58 (subtype H2N2) pandemic, but were equalized in the 1968-69 (subtype H3N2) pandemic³. It is unclear if the 1957-58 pattern was driven by the variation in basic infectivity across age groups (of which there is some evidence vis-à-vis viral shedding in seasonal influenza), by subtype-specific properties, or by the variation across ages in modifiers of basic infectivity such as contact rates. It may be difficult to predict an age pattern of attack rates in a future pandemic, though such a prediction would help setting prevention priorities by age group and locations (e.g., schools vs. offices).

Virulence: The base virulence of a pandemic influenza virus refers to its ability to cause serious health outcomes in an untreated clinical case of the disease. Given virulence, the likelihood of severe outcomes in a case depends on individual level factors (e.g., a complicating comorbidity), and the use and efficacy of pharmaceuticals in treatment. There are several operational measures of basic virulence based on the particular outcome, e.g., deaths per hundred cases or case fatality rate (CFR), hospitalizations per hundred cases, etc. Virulence is directly connected to the ultimate impact on individuals and the economy if an outbreak becomes an epidemic. In theory, virulence is also connected to the duration and attack rate of an epidemic in the no intervention scenario. If a virus incapacitates or kills those infected so rapidly that they do not transmit it to many susceptibles then the epidemic grows slowly. In modeling, this is shown by holding the infectivity constant and increasing the death rate, which usually increases the total duration of a wave of the epidemic, and

depending on the model, reduces the total infections⁴. In the intervention scenario, higher virulence may actually assist control as case detection becomes faster and easier⁵.

Since virulence during an epidemic of influenza is even more affected by personal characteristics of the individual, it should be discussed in terms of population-level averages. In this context, the projected population-level virulence of a future pandemic could compare to that in prior pandemics or seasonal epidemics. The data from individual human cases of the current avian H5N1 subtype, an overall CFR of about 60%⁶, are not as useful, since a pandemic capable virus may trade off some virulence for transmissibility.

The total cases and deaths in the historical pandemics are unknown, but they have been categorized by their estimated CFR, with 'Category 5' being the most devastating⁷. In a study, the ranges of CFR for each historical pandemic were shown as 'lower, medium, and upper' scenarios (Table 2) relevant for a future pandemic⁸. Another study used mortality from seasonal influenza epidemics in the US as a basis for projecting the CFR for a pandemic in the US⁹. From that study, the modeling estimates of CFR for two risk categories in the 0-19 age group (based on the presence of a complicating comorbidity) are shown below.

Table 2: Historical Estimates and Modeling Estimates of CFR by scenario

Scenarios based on history	Lower	Medium	Upper	'Ultra'
Category 5 or Like 1918-20	0.2-0.5	2.5	4	
Category 2 or Like 1957-58	0.04		0.27	
Category 1 or Like 1968-69	0.01	0.013	0.07	
Other modeling estimates				
US, Std Risk 0-19 yrs	0.001	0.002	0.013	} Meltzer <i>et al.</i> ⁹
US, High Risk 0-19 yrs	0.013	0.022	0.765	
US, McKibbin & Sidorenko*	0.023	0.233	1.166	

* Same for all age groups, and run for Mild/Moderate/Severe/Ultra.

Similar to infectivity, any projected patterns in virulence – across age groups, location, or ethnicity – are important for setting priorities in prevention and mitigation of a pandemic. These patterns are also significant towards the macroeconomic impact. It is uncertain which factor, if any, will cause the definitive pattern in a future pandemic. It is now known that mortality in a case of pandemic influenza A virus of close avian origins – as suspected for 1918-20¹⁰ – results from an inimical feedback process in the immune system, termed a ‘cytokine storm’. This response has also been observed in human cases of the current avian H5N1 virus. Here, a healthier immune system, as in younger people, may result in higher risk for severe health outcomes. Still, the age pattern of excess mortality in the 1918-20 pandemic – higher in young adults compared to the elderly – was not repeated in 1957-58 or 1968-69 (these pandemic virus strains had some avian influenza genes). For other patterns, a regression study using international data from 1918-20 found that low per-capita income was a statistically significant explanatory factor of higher mortality¹¹. A study of the same pandemic in Iran found significant rural-urban differences in mortality¹².

Effective contact: Given the recurrence of the idea of effective contact in the modeling of influenza transmission, a short discussion is provided. An effective or sufficient contact between an infected and an uninfected, susceptible individual is one able to transmit infection. Depending on the requirements of the transmission model, an effective contact ‘rate’ (no. of contacts per unit time) or ‘probability’ (expressing the likelihood of making at least one effective contact per unit time) can be defined. Given a base infectivity of the influenza virus, the effective contact rate/probability varies across individuals based on the volume, frequency, and proximity quotients of their contacts. For example, compared to adults, elementary school children may meet a larger number of contacts in playgrounds and classrooms. Besides the fact that children may shed more virus, the transmission risk per contact may be higher since they engage frequently and get in closer proximity (within three to six feet of each other¹³). However, proximity becomes a less strict criterion in closed, cool areas with minimum airflow, such as an aircraft cabin. In another example of variation, a rural, dispersed population may have lower volume and frequency of contacts.

In modeling studies, effective contact properties are purposively fixed for certain groupings of individuals. The parameter values are often estimated from observational data using an equation such as $\beta_i = \gamma_i * \rho_i$ (where β is the effective contact rate, γ is the total number of contacts per unit time, and ρ is the risk of transmission given contact, with i as a subscript referring to the particular population group). The estimates of total contact rates across various groups describe a social network. Other aspects of social network analysis are also important for modeling influenza transmission, as will be discussed later.

Concepts in modeling transmission and control of pandemic influenza: The discussion above sets the stage to discuss concepts that in modeling determine whether an infectious disease will be rapidly controllable after the initial emergence of an outbreak:

- The *basic reproduction number* R_0 is a measure of the base or intrinsic infectivity of any infectious agent such as an influenza virus. It is defined as the number of secondary infections generated by a primary infection in a homogeneous population where everyone is equally susceptible to infection (complexities in defining R_0 in a heterogeneous population are omitted). R_0 is a modeling construct that captures several characteristics of infectivity – the transmission risk per contact, duration of the infectivity period, mode of transmission, etc. – and is difficult to predict in advance of an epidemic. Some estimates of R_0 for past outbreaks are provided in Table 4.
- The *disease generation time* T_g is the mean interval between infection of one person and infection of the people that the individual infects¹⁴ (Ferguson *et al.* 2005 use $T_g=2.6$).
- The *proportion of transmission occurring prior to symptoms* (i.e., asymptotically), θ .

The importance of these constructs in modeling can be seen against modern practice in outbreak control. These public health practices – in the absence of effective vaccine or treatment in the prevention of spread – are credited with containing the spread of SARS. The first actions are active surveillance and then the effective isolation of individuals displaying pre-identified symptoms. The second is the tracing and quarantining of the contacts of the individuals who are displaying symptoms. Success here depends on whether the symptomatic individuals are rapidly identified by authorities (e.g., at airports) or they voluntarily report to a public health facility soon after their symptoms emerge.

Given the importance paid to contact tracing, symptom-based screening, and surveillance in discussions on pandemic influenza, it is useful to review the SARS experience. On the plus side, SARS symptoms preceded the peak infectivity period by a few days. There was little evidence of asymptomatic transmission. This implies that θ was low. The outbreaks also happened to occur in cities with well-functioning public health systems where trust in official communications and measures was high and maintained. In the negatives, the symptom-based entry screening process at Canadian airports was not found cost-effective¹⁵. If θ is low but R_0 is high (see Table 3) in a SARS-like outbreak, it may be preferable to rely on surveillance to detect the cases early and then to quarantine quickly.

Table 3: Estimates of important modeling constructs for infectious disease outbreaks

Disease Outbreak	R_0	θ	Source
Pandemic influenza, 1918, New Zealand	$1.3 < R_0 < 3.1$	n.a.	Sertsov <i>et al.</i> 2006 ¹⁶
Pandemic influenza, 1918, UK (first wave)	$1.7 < R_0 < 2$	n.a.	Ferguson <i>et al.</i> 2006 ³⁷
Pandemic influenza, 1968-69, Hong Kong	1.89	n.a.	Rvachev & Longini 1985 ³¹
Smallpox	$4 < R_0 < 10$	$0 < \theta < 20\%$	Eichner & Dietz 2003 ¹⁷
SARS 2003 Hong Kong	$2 < R_0 < 4$	<11%	Fraser <i>et al.</i> 2004 ¹⁴

The higher is R_0 (and lower is T_g) the quicker do public health authorities need to intervene with screening, case-patient isolation, and enhanced active surveillance of the population. The higher is θ , the lower the cost-effectiveness of symptomatic screening. Authorities may not be able to remove infectives fast enough before they cause secondary cases. If a pandemic influenza outbreak occurs, it may be possible to quickly estimate θ from available data on infected people and their contacts. Estimating R_0 is harder, but together with θ , the parameter would set valuable context for the efficacy of proposed policies. Based on what is known of seasonal influenza as well past influenza pandemics, it is believed that:

- Symptomatic screening will be difficult (initial high fever, headache and respiratory symptoms are shared with a few other diseases, including non-pandemic influenza).
- A person with influenza-like symptoms may not self-isolate for up to a day, during which time they would be infective, given what is known about R_0 and θ .
- Even with screening, many infectives would not be detected and isolated (one study found that up to 83% of infectives entering the UK via air travel may be missed¹⁸).
- R_0 for prior pandemics of influenza was relatively low, lying between 1.5 and 4. Where a future pandemic's R_0 lies in this range has huge bearing on policy efficacy. Certain threshold values for R_0 have been estimated to discuss the efficacy of standard policies. These will be discussed further below when comparing policies.

The efficacy of vaccines in prevention: The US government has allocated 58% of the 2006 pandemic influenza supplemental budget to vaccines (16% on antivirals)¹⁹, perhaps based on success with seasonal influenza. Vaccine efficacy is defined both for reducing susceptibility (VE_s) and in reducing infectiousness (VE_i), both of which prevent an outbreak from growing. Though feasibility and financing problems may prove to be larger obstacles in the developing world's adoption of pharmaceutical policies, the efficacy issue should be considered. A brief overview of the issues in vaccine efficacy is provided below.

The consensus among experts is that a vaccine based on currently circulating avian influenza A (H5N1) strains that have attacked humans will not prevent infection in most susceptible individuals from a mutated, pandemic-capable strain. However, since these vaccines contain antigens matched to the H5N1 pandemic candidate subtype, there may be immunity against a pandemic strain in some individuals, and more widespread immunity against any currently circulating strain (including those the vaccine does not derive from)²⁰. Based on an assumption of partial protection, the vaccines based on current strains are classified as 'pre-pandemic' vaccines. Governments have stocked these in risk-limiting moves. A pre-pandemic vaccine was licensed by the US Food and Drug Administration²¹. Other pre-pandemic vaccines are in stages of development. Without delving into issues of feasibility or ethics (considered later), the following factors modify efficacy:

- Efficacy depends on priorities. Reducing the total number of infections requires vaccination of those most likely to be infectious. Targeting severe health outcomes requires vaccination of those at most risk of severe morbidity or mortality. Optimum policy mixing or a single choice here could depend on the infectivity of the virus, as a study finds²². This is considered later below.
- Efficacy of pre-pandemic vaccines is difficult to determine, and can only be reported as immunogenicity (ability to create an immune response, i.e., matched antibodies). Current studies show immunogenicity is dependent on dose size. This is an issue if antigen supplies are limited and if as reported, the dosage for pre-pandemic vaccines without adjuvant is high, e.g. only a 90 μ g dose reached reasonable immunogenicity in the vaccine licensed by the FDA²³, six times the volume of a standard 15 μ g seasonal influenza dose. For some vaccines, adjuvant reduces the antigen required²⁴. The issue of dosing is considered in more detail later.

Efficacy of chemoprophylaxis: If there will be delay in the availability of an effective vaccine, antiviral prophylaxis has a role. Modeling studies have considered policies of targeted antiviral prophylaxis around an outbreak to prevent its spread. Many countries have stockpiled antiviral doses, including in the developing world. However, there is debate about the efficacy of antivirals in containment, specifically neuraminidase inhibitors. In this context there is confusion over an antiviral formulation's efficacy for primary prevention

(pre-exposure prophylaxis of infection), secondary prevention (post-exposure risk reduction of complication or disease progression), and treatment (therapeutic, to restore health of patients). The quality of evidence varies across these roles for antiviral use in human cases of avian H5N1. Some studies had found oseltamivir – a neuraminidase inhibitor – to be less effective for treatment in such cases, but since these were small-observational rather than clinical trial studies, the WHO has classed the results as weak evidence. Also, it appears that such oseltamivir-resistant avian H5N1 ‘wild type’ viruses may have lower fitness for transmission²⁵, but with more cases of transmission and antiviral use, compensatory mutations may emerge. If sustained drug resistance does appear during post-exposure prophylaxis, antiviral use would have to cease to prevent further selection of a drug-resistant pandemic virus⁵. This would shatter currently favored mixed intervention strategies. Drug resistance in influenza A will need to be continuously monitored. Considering the debate and the evidence, WHO has recently published guidelines²⁶ for *post-exposure* chemoprophylaxis of human cases of avian H5N1:

- Oseltamivir (*Tamiflu*) with zanamivir (*Relenza*) as an alternative is strongly recommended for high risk groups, at a seasonal influenza dosage. Amantadine is strongly not recommended. Both recommendations based on low quality evidence.
- Oseltamivir with zanamivir as alternative is weakly *not* recommended for moderate and low risk groups and *strongly not* recommended for low-risk pregnant women.

There are no clinical studies of antivirals in the primary preventive role for human cases of avian H5N1, or for their efficacy in reducing the infectiousness of exposed individuals. This must be kept in mind when targeted antiviral prophylaxis policies are discussed below. A study²⁷ proposes the relation $R_{av}=R_0/3.6$ where R_{av} obtains with preventive, mass, and prolonged oseltamivir prophylaxis. In the absence of evidence, any reading of the *post-exposure* chemoprophylaxis guidelines above as indicative of efficacy in reducing susceptibility or infectivity with antivirals should be undertaken with caution.

Efficacy of physical prophylaxis: Vaccines and antivirals may theoretically limit both susceptibility and infectiousness, analogous respectively to ex-ante prevention and ex-post mitigation of outbreaks. Similarly, personal protective equipment such as N95 or higher *respirators* (rather than surgical facemasks) could prevent a person getting infected if they are susceptible or from infecting others. The availability of such respirators is likely to be limited for community outbreak control even in industrialized countries. Other equipment, such as gloves, is designed to prevent an uninfected person from coming in contact with fomites and respiratory secretions. During SARS, it was common to see individuals undertake self-protective behavior by wearing facemasks.

However, if influenza is also transmitted in aerosols emitted in sneezes or coughs, i.e. particles of diameter less than 10 μ m (in comparison, large droplets are defined as having a diameter of 50-100 μ m), then surgical masks may not offer effective prophylaxis. Some review studies have indicated that aerosol generation is likely in the average individual with influenza, and this is increased by aerosol-generating procedures in healthcare settings (e.g., endotracheal intubation, open suctioning)¹³. Besides the fear of them slipping through the average facemask, aerosols are a concern since they may stay airborne longer²⁸. However, they may also carry a smaller infectious dose. More research is required on these characteristics, especially as the efficacy of facemasks, which are affordable enough for personal use and local stocking, is of prime importance in community outbreak control. At present this efficacy remains controversial. Some recent laboratory

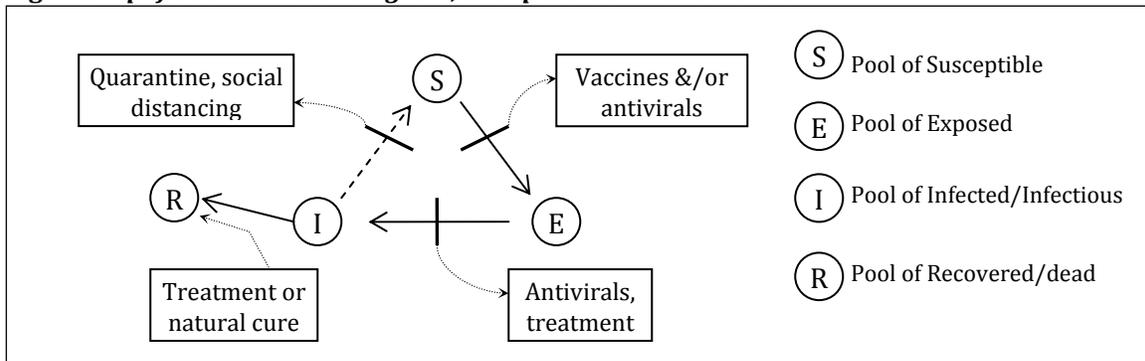
studies using test aerosols of appropriate diameter (but not infectious agents) have shown that facemasks may have protective properties comparable to high end respirators^{29, 30}.

PREDICTING THE COMMUNITY TRANSMISSION OF PANDEMIC INFLUENZA: AN OVERVIEW OF METHODOLOGIES

Epidemiological modeling of future pandemic influenza transmission is complex because the biology of the virus, responses of a population, etc., are difficult to predict beforehand. Non-epidemiological studies from the impact literature use historical data from 20th century pandemics to estimate a flat rate of infections across the entire population during a wave, known as the Gross Attack Rate (GAR). These assume the same risk of infection for every individual, and hence GAR is applied as a fraction of the population. The section below discusses methods for the *epidemiological* modeling of infections in a wave of pandemic flu transmission. Results of the studies are compared in the next section.

Compartment or SIR/SEIR models of pandemic flu transmission: The simplest non-stochastic (deterministic) models of influenza transmission - pandemic or seasonal - are based on SIR (Susceptible, Infected, and Recovered) models of 1920s vintage. By adding the 'exposed' category, SEIR models are the root of *deterministic modeling* of epidemics. Fig. 1 on this page is an unorthodox representation⁵⁹, modified to show some (but not all) impact points of public health interventions. Individuals transition based on predetermined probabilities from being susceptible (S), to exposed (E, i.e., infection is latent), to infectious (I) and then to removed (R, recovered or dead). Other preset parameters are the length of time individuals stay in state E without becoming infectious (latency period), and the time they stay infectious before being removed. The model is specified in differential equations that define the stock of people in the various states after a discrete time step (usually a day). At time zero, a number of seed infections are introduced and the model is run.

Fig. 1: Simplified SEIR model diagram, with potential interventions



For pandemic influenza, the possibility that any infected person contacts a susceptible during a time step is set as the fraction of the population susceptible at that point, multiplied by a fixed decimal: the ‘probability of infection conditional on contact’, analogous to transmission risk as introduced earlier³¹. The method has the assumption of population homogeneity with ‘uniform mixing’. This implies every person is equally at risk of infection and every individual in the population is equally likely to contact someone else.

The simple SEIR models neglect the fact that individuals do not mix uniformly; each person has contact with only a small fraction of a population. Also, the population is not homogenous – some individuals have more contacts and meet them more often. Therefore, while the first real world factor reduces the risk of infection for the average individual, the second may raise it for some individuals, for example, urban citizens vs. those from rural, low population density areas. In reality, risk of infection varies widely across people.

The policy intent of SEIR models is to describe transmission dynamics at the population level by varying attributes of individuals that locate them within compartments (disease state, age, reported case or hospitalization status). These models may predict natural quenching of an epidemic (i.e., due to ‘population/herd immunity’ when the number of susceptibles left falls below a sustaining threshold³²). Public health interventions – such as antiviral prophylaxis – can be introduced, and the effect observed via a change in the probability of transmission per contact across the various infective group members and the remaining susceptible. For capturing more of the variation in risk of infection across individuals, SEIR models have to add compartments without losing mathematical tractability. Several improvements in this vein have been made, which can be discussed by relating them to the effective reproductive number of the epidemic, or R .

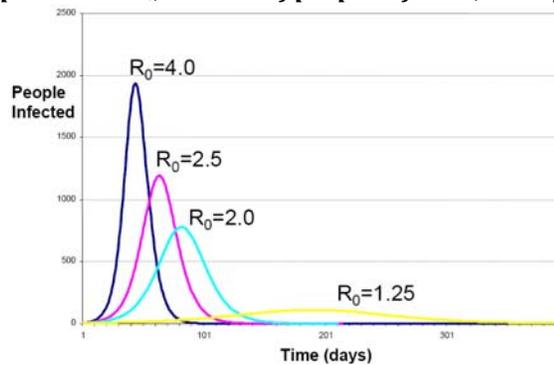
In this context, the basic reproductive number, R_0 , captures the *a priori* infectiousness of a communicable disease in a particular setting. It is defined as the number of secondary infections caused by a single typical infected case in a completely susceptible population, and in the absence of interventions. At the start of an epidemic, it determines how quickly the epidemic will spread. The effective reproductive number, R , is equal to $R_0 * s$ where s is the proportion of the at-risk population still susceptible. Theoretically, if R can be pushed below 1, an epidemic usually dies out due to herd immunity³². Compared to the *a priori* R_0 , R is always lower. Given any initial ‘intrinsic’ R_0 , R for the epidemic depends on T_g , or more generally on factors including:

- The risk of transmission per proximate contact, ρ

- The number of effective contacts an average person has per unit time, β
- Relative duration of the latent and infectivity periods

As briefly discussed previously, R is an important factor³³ in determining how many infections will be suffered in one wave of the epidemic, i.e., the gross attack rate. The widely reported ‘threshold R_0 ’ effects for the efficacy of certain interventions should be seen as model-specific and indicative rather than definitive for policy analysis. Early and pervasive public health communications after an outbreak of pandemic influenza can reduce the average R over any subsequent epidemic wave (which may be prevented entirely by successful outbreak containment). For example, by forcing or urging people to limit contacts, encouraging hand-washing and other personal hygiene, or promoting the use of facemasks. Historically, public health communications became effective enough to modify overall R during subsequent epidemic waves when the authorities were poised to begin them early, and similarly in cities and countries with later outbreaks^{34,56}.

Fig. 2: Theorized relationship between R_0 , number of people infected, and epidemic duration



Source: Risk Management Solutions (2007)

Population heterogeneity and SEIR: In the *no intervention* case, actual R may vary across population groups based on age structure and the types of social mixing situations. The SEIR models can be improved to account for age structure. The importance of age as a determinant of susceptibility to a clinical case of pandemic influenza infection may be due to both behavioral and biological factors. The W-shaped curve relating excess mortality rate in percent during the 1918 pandemic (y-axis) to age groups (x-axis) suggested that deaths were highest in the segments between 15-39 years and lower for higher and lower age groups¹¹. Mortality reflects both the underlying attack rate and the case fatality rate (CFR). There are hypotheses for the higher CFR in younger individuals, which relates to hyper-interaction of the symptoms of avian-derived pandemic influenza viruses and the more robust immune systems as present in younger persons. For this study, the implication of the W-shaped curve for the variation in the attack rate is stressed. The portion of the variation in mortality by age during 1918-19 that is explained by age-differenced attack rates is unknown¹¹. Estimates of age-differenced attack rates using data from later pandemics suggest that a biological factor may be in play, related to the particular influenza A subtype that causes the pandemic. The 1957-58 pandemic with subtype H2N2 displayed a higher attack rate in U.S. children, whereas the 1968-69 influenza pandemic with subtype H3N2 had a similar attack rate across age groups³. In general, younger people shed more viral material¹⁵. As such, the risks of infection for children in schools would be higher.

Behavior also differs across age groups in ways that affects susceptibility. In high population density areas, younger people have contacts more frequently and at closer quarters – e.g., on urban transport, in offices, and on playgrounds. Older people who are homebound and do not have as many contacts have a lower risk of being near an infectious person, but when near such a person, may have a higher risk of getting infected because of weaker immune systems.

In SEIR models, one way to simulate these differences in behavioral and biological factors of susceptibility is to introduce varying transmission probabilities defined in advance for different age compartments. With more computing power available in recent years, such age-structured models have become more common.

When simulating the effectiveness of public health policies, as much heterogeneity in risk of infection is desirable as is reasonable to model. Location is another important source of such variation. Urban areas can be quarantined or social distancing measures imposed, which cut the contact rates in the population. But these are more difficult to impose in rural areas where there are less defined modes of entry and exit and the population is harder to reach with public health communication. Therefore, while in rural areas the average number of effective contacts per person might be low, the public health measures might have low impact. And as occurs for older people, rural people on average may have poorer health status. They may also have poor access to antivirals. In the pandemic influenza case, since the entire country is susceptible to pandemic influenza and rapid transmission via air and road networks is probable, modeling simultaneous SEIR progress in multiple cities that exchange susceptible and infectious people is desirable. However, this requires mainframe computing resources if the time step of a day is considered.

Physical distribution and structure of populations: In comparison with non-spatial SEIR, *stochastic-spatial* models have more success in incorporating population and location heterogeneity. They also have a different intent and modeling philosophy. A stochastic-spatial epidemic model simulates the epidemic process as a series of random events in space and time with the probability of specific events defined by the model parameters. The two event probabilities of interest are the probability of effective contact (c), and probability of transmission on contact (x). The former varies at the individual level based on factors – location in space, and characteristics of that location. The latter varies in reality based on age, public health context, individual behavior, etc., and is usually a constant in analysis as it is difficult to model.

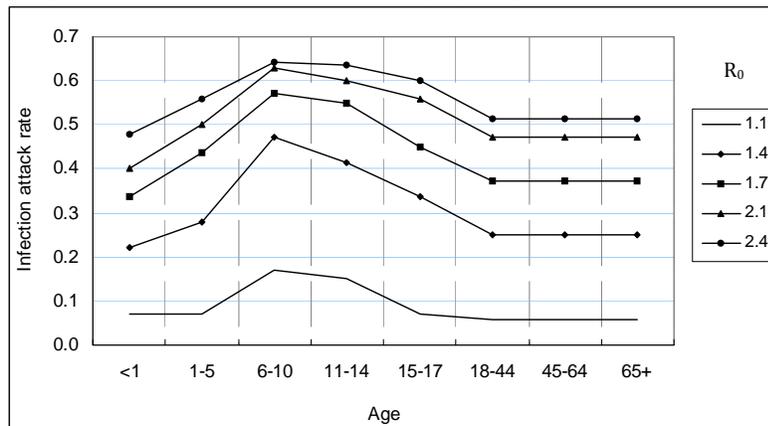
In a recent stochastic-spatial model of pandemic flu spread in rural SE Asia the location contexts are called ‘mixing groups’ (e.g., offices, schools, and households), and for each such context a specific probability of effective contact per day is defined³. The age-distribution of individuals, number of mixing groups and their average sizes, as well as their clustering are set so as to mimic a real population (in this case rural Thailand). Average inter-mixing group distances –important to generate the spread across the simulated space – are based on GIS data. At the time of model generation, 500,000 individuals are distributed according to an algorithm in close contact mixing groups (households, schools, and workplaces), as well as casual/social contact mixing groups (temples, markets, shops). The people have effective contacts based on the assumed average rates for that mixing group context. For example, the authors assume that the probability of two children making at least one effective contact per day in a household mixing group is 0.6³⁵.

For the base case, stochasticity is introduced by conducting Bernoulli trials and generating N uniform $[0, 1]$ numbers for N mixing groups. If the probability for an individual to be infected on a day in that group³⁶ is greater than the random number, then a single infected individual in his/her latent period is ‘introduced’ into each of N mixing groups at model inception. Secondary infections result in each mixing group that has an infected individual. Similar to ‘hierarchical epidemic’ models, this within mixing group dynamic is extended to between-group analysis. The spread to mixing groups without primary introductions is modeled, based on assumptions and distance from infected groups. Each stochastic realization, for a certain R_0 , leads to an overall attack rate.

Such stochastic-spatial models are computationally intensive if populated with millions of individuals, but can evaluate public health interventions such as quarantines and social distancing, ring prophylaxis (where a fixed percentage of people in an x square mile radius around an outbreak are given antivirals), and vaccination. Similar models, but with different assumptions and techniques, have also been constructed for Thailand⁵, the US and UK³⁷, and separately for the US³⁸. Important differences obtain in whether the model is capped at producing an overall attack rate for a level of R_0 and in how higher R_0 is reflected.

Stochastic-spatial models capture population-level effects by describing the intensity of risk at the individual level. They can also be calibrated to a specific magnitude of GAR from prior pandemics (Longini *et al.* chose to calibrate to 33%, based on the first wave of the 1957 and 1968 pandemics) and a relative attack rate pattern across ages (see Fig. 3 below). As suggested above, the stochastic model produces a distribution of age-specific and gross attack rates at different R_0 . By selecting for an overall GAR of 33% and an age-specific attack rate pattern, Longini *et al.* determine the model seeding that reproduces past pandemics as a base case. They test the intervention strategies thereafter at this setting.

Fig. 3: Assumed pattern of attack rates across age groups at different R_0 (Longini *et al.* 2005)



*Pattern is based on US data from 1957-58 (more children infected) and 1968 (similar attack rates across ages) pandemics, mixed with seasonal influenza data from SE Asia (similar to 1957-58 pandemic in the US).

The calibrated stochastic-spatial technique ensures that the locational and demographic heterogeneity of the epidemic area is captured, while the full range of the stochastic results are capped at past experience. This method is good at predicting whether an epidemic that begins randomly somewhere will spread, and evaluating which control options will be successful in limiting its spread. Table 5 provides a comparison of a model like in Longini *et al.* (2005) and the age-structured SEIR model portion from a proposed

World Bank study. The two models differ in the captured heterogeneity in risk of infection and in the intent. Since the pandemic in 1918 had unique features leading to a severe impact, when constructing a model for a high risk Asian country it is important to base it on Asian experience in 1957 and 1968 (as in Longini *et al.* for SE Asia). In general, some parameters are exogenously imposed constants not varied in modeling. Varying parameters allow sensitivity to the modeling assumptions to be tested, necessary given the uncertainty in estimates, e.g., of contact rates. The model should also be portable, with important variables generated endogenously rather than assumed.

Table 4: Comparison of two model archetypes for predicting pandemic influenza transmission

<i>Characteristic</i>	<i>Deterministic SEIR: age-structure</i>	<i>Stochastic –spatial model</i>
Source study	Part of a proposed WB study	Longini <i>et al.</i> (2005)
Contact rates by age	Exogenous constants [#]	Exogenous constants
Attack rates by age	Endogenously derived	Endogenously derived [§]
Contact rates by location	Exogenous constants [#]	Exogenous constants
Attack rates by location	Endogenously derived	Endogenously derived
Whole epidemic R_0	Not modeled	Exogenously varied
Whole epidemic GAR	Endogenously derived	Endogenously derived
Raw data needs	Demographic data, seasonal influenza contact rate estimates	Demographic data, geographic data, contact rate estimates
Attack rates by policy scenario	Proposed to be modeled	Endogenously derived
Primary policy use	Describe population-level dynamics, estimate of no. of infections	Describe individual-level dynamics, test public health measures

[#] Proposed to create separate matrices of child-child, adult-child, etc., *effective* contact rates for cities by seasons.

[§] Calibrated to fit patterns of age-structured attack rates from prior pandemics at various R_0 .

Mathematical or static scenario models of pandemic influenza: Table 4 suggests that existing pandemic flu transmission model archetypes suit different policy questions. If interest is limited to impact analysis of the base case of a pandemic, then complex deterministic or stochastic transmission models are not required. This logic drives recent non-epidemiological impact analyses, with scenarios based on 1918⁸. However, some quasi-epidemiological detail is required if the scenarios are to be more realistic. For resource allocation decisions, the impact estimates should be as contextual as is feasible.

Two studies are briefly discussed that use a mathematical or static scenario-based model to inform domestic policy decisions. Meltzer *et al.*⁹ use a Monte Carlo ‘mathematical simulation’ model to estimate the impact in the US of a pandemic of influenza and scenarios of related key interventions. A similar model is used by Doyle *et al.*³⁹ for France. The GAR⁴⁰ is varied in 5 percentage point increments from 15% to 35%. The total numbers of cases at any GAR are then distributed across age groups in two pattern distribution scenarios:

<i>Age group</i>	<i>Pattern A</i>	<i>Pattern B</i>
	% of all cases	% of all cases
0-19 years old	40	46
20-64 yrs old	53.1	46.7
65+ yrs old	6.8	7.3

Based on upper and lower estimates of age-specific attack rates from 1918, 1928-29, and 1957 influenza epidemics in the U.S (1918 and 1957 were pandemics).

The three age groups also differ in the proportions in each with pre-existing conditions that cause complications once an individual has influenza. These complications are health outcomes such as severe illness and death, and rates of these per age group are distributions with upper/lower limits based on statistics from past influenza epidemics in the US. The result of the study is not a single estimate of the number of clinical illnesses or a dollar figure, but a range for such variables. The authors describe their intent as “altering a number of variables and evaluating how the results affect key (policy) decisions⁴¹.”

In van Genugten *et al.*⁴², researchers using a ‘static’ scenario method to test policies for pandemic influenza in the Netherlands. The GAR was exogenously set at 30%, and an age distribution of the cases was obtained by applying a pattern based on seasonal influenza in the Netherlands. The ‘scenarios’ are separate policy interventions that reduce adverse

health outcomes. Compared to Meltzer *et al.*, the study is static since the parameters for health outcomes are all point estimates from prior Dutch influenza epidemics.

MODELING THE EFFECTIVENESS OF DIFFERENT POLICIES FOR CONTAINING PANDEMIC INFLUENZA

As abstractions of reality, models of future pandemic transmission and its control are selective over the range of included policies and the efficacy for each policy. This is important for model parsimony, but the choices for inclusion and exclusion affect the conclusions. The choice set of policies to include for testing in simulations are those suggested by the modeling of potential bio-terror attacks in the US, the experience with SARS, and public health practice over the latter half of the 20th century. The parameter ranges for the efficacy of vaccination and prophylaxis are either assumed in such modeling, or derived from studies of closely linked disease and epidemic situations. Table 5 presents a categorized menu of control policy choices available for a potential pandemic of influenza. Italicized prevention policies have received more research attention, or have had their effectiveness modeled. These are the only policies considered in detail in the section below.

Table 5: A taxonomy of policies for containment and mitigation of pandemic influenza

Type	Sub-Category	Individual policies (M: mitigation; C: containment)
Nonpharmaceutical	International	<ul style="list-style-type: none"> • International land border quarantines (C) • <i>Air travel restrictions & advisories</i> (C) • Quarantine of ships & other restrictions (C)
	National or central	<ul style="list-style-type: none"> • <i>Inter-city movement restrictions</i> (C, M) • Aspects of quarantine (C, M) • Public communications (C, M)
	Community or local	<ul style="list-style-type: none"> • <i>Case detection and isolation</i> (C, M) • <i>Social distancing</i> (C, M) • <i>Local quarantines</i> (C, M) • Public hygiene and disinfection (C, M) • Local public communication (C, M) • Personal protective equipment (C, M)
Pharmaceutical (or drug-based)	Vaccination	<ul style="list-style-type: none"> • <i>Targeted vaccination policies</i> (M) • <i>Broad-based vaccination policy</i> (C, M)
	Antiviral prophylaxis	<ul style="list-style-type: none"> • <i>Targeted (ring) prophylaxis around an outbreak</i> (C) • <i>Prophylaxis based on contact tracing</i> (C,M) • <i>Mass prophylaxis in the at-risk population</i> (M)

Distinctions between C and M only indicate emphasis, as containment achieves mitigation (lowers the GAR).

Based on results from modeling studies reviewed further below, different configurations of policies from Table 5 are currently proposed for pandemic influenza. These configurations are an example of prospective modeling evidence on effectiveness being used in policymaking. The review of studies follows after an introduction to the field.

In the earliest instance, a group of researchers within the MIDAS (Models of Infectious Disease Agents Study) network in the US proposed a framework for mitigation policies in the US after the emergence of pandemic influenza. The guiding assumptions were of limited antiviral supply with no effective vaccine immediately available, and that interventions must begin rapidly at the *community level* to prevent an uncontrollable spread that overwhelms response. The proposed strategy of ‘targeted layered containment’ (TLC) attempts to benefit from synergies across the combined policies⁴³. The policies considered high priority are: targeted antiviral treatment and isolation of cases, targeted prophylaxis and quarantine of household contacts of index cases, closure of schools and keeping children at home for the duration of the policy, social distancing at the workplace (telecommuting) and in the community (cancelling public events). Since the assumptions on pharmaceutical availability are very relevant for developing countries, this selection of policies from the menu has been influential for modeling and agenda-setting.

The WHO Interim Protocol for community/local control measures¹ sets forward guidelines for the rapid containment of an outbreak of pandemic influenza, differentiating it from the response to current outbreaks of avian influenza. The Interim Protocol samples policies that also appear in TLC above, articulated here for the containment objective. The current version (dated May 2007) takes a geographically based approach where the initial area of the outbreak becomes the main target – the *containment zone* – in which actions are taken to stamp out the infection and prevent its spread. Within the containment zone and in an area around it called the *buffer zone*, surveillance and community mobilization will check and maintain containment. In the buffer zone, any ‘break through’ cases are quickly detected and isolated. The boundaries of the two zones, the duration of the operation, and

the exact choice and intensity of policies are to be driven by local context and the outbreak characteristics. The generally recommended policies in the containment zone follow TLC:

- Antiviral drugs for treatment and prophylaxis
- Restrictions (e.g., screening) on movements within, into, and out of the zone
- Isolation of ill persons, voluntary quarantine for exposed, and social distancing

The sub-section below discusses some modeling studies comparing policy configurations that appear in the TLC or WHO frameworks. Studies with a containment focus influenced the Interim Protocol, but WHO notes these caveats about the models used:

1. Emergence of the pandemic virus is in a localized and circumscribed area
2. The efficient and sustained human transmission of the virus is rapidly detected and reported such that an appropriate containment strategy can begin
3. Availability of minimum drug stockpiles and the ability to rapidly distribute
4. Movement restrictions and other nonpharmaceutical interventions are feasible

Caveats #2-4 involve 'likelihood of use' and feasibility. Most of the studies do note that these issues will be important. However, such realism is difficult to account for in modeling without introducing additional complexity and uncertainty. The comparative studies below allow for the effect of delay in starting policies and find that it reduces the effectiveness for control. This is discussed more specifically below. The models assume baseline efficacy for some policies. Such assumptions on efficacy for a study are noted below. The discussion should be read in light of the prior review of methodologies; the comparative studies all fall in the category of spatial-stochastic models. After the sub-section below, specific studies of a few italicized policies from Table 5 are discussed.

COMPARATIVE MODELING OF POLICIES

1. Longini *et al.* (2005)³: Rural South-East Asia

Policies compared: Various levels of targeted antiviral prophylaxis (TAP), geographically targeted antiviral prophylaxis or 'ring prophylaxis' (GTAP), quarantine, and pre-vaccination; used singly or in combination. The TAP policy is defined here as the treatment of an assumed *percentage* of identified index cases (i.e., the first symptomatic illness in a particular mixing group – mixing groups defined in the previous section), and prophylaxis for *all* their close contacts if the case belongs to a household or preschool group, and some assumed percentage of their contacts if in a workplace or other school group. The antiviral used is oseltamivir, and a single course is administered to the contacts at the same time that therapeutic treatment of the index cases begins (assumed 1 day after symptoms). The GTAP policy is defined on the understanding that identifying index cases spread across 'mixing groups' will be resource intensive. In GTAP, a geographical approach is taken, and once an index case is identified in a locality, an assumed *percentage* of the people in the entire locality are given one course of oseltamivir. Quarantine is also defined at the locality level: once an index case is identified, all infected plus an assumed *percentage* of susceptible restrict their movements to the household or neighborhood. Pre-vaccination occurs before the pandemic and those vaccinated develop some level of immunity. All the italicized *percentage* levels of the policies are referenced in Table 7 below.

Assumed pharmaceutical efficacy: Vaccine efficacy for susceptibility (VE_s) is assumed to be 0.3, and for infectiousness (VE_i), 0.5⁴⁴. These are low values. Oseltamivir efficacy for

susceptibility to infection or primary prevention (AVE_S) is assumed to be 0.3, efficacy for secondary prevention (AVE_D , against disease progression) is assumed to be 0.6, and efficacy in therapy for symptomatic disease is $= 1 - (1 - AVE_S)(1 - AVE_D)$, equal to 0.72. Oseltamivir efficacy for infectiousness (AVE_i) is assumed to be 0.62. The values for antiviral efficacy are derived from prior studies of household infection with seasonal influenza⁴⁵.

Control objective: Containment of cases (i.e., symptomatic infection) at ≤ 1 per 1000.

Table 6: Effectiveness of policies for control in a population of 500,000 (Longini et al.)

Percentage application of policy	Cases per 1000		Containment proportion [#]	
	$R_0 = 1.4$	$R_0 = 1.7$	$R_0 = 1.4$	$R_0 = 1.7$
a. No intervention	211	384	-	-
b. 80% TAP	0.13	149	98%	33%
c. 90% GTAP	0.28	54	95%	59%
d. 80% TAP + 50% pre-vaccination	0.02	0.16	100%	98%
e. 80% TAP + 70% pre-vaccination	0.01	0.04	100%	100%
f. 70% quarantine	0.17	1	98%	57%
g. 80% TAP + 70% quarantine	0.06	0.14	100%	100%
h. 80% TAP + 70% quarantine + 50% pre-vaccination	0.02	0.03	100%	100%

[#] Proportion of simulations with the policy in which cases per 1000 are ≤ 1

Discussion: The results in Table 6 show a dependence on the value of R_0 , especially for the effectiveness of TAP, GTAP, and quarantine. As R_0 increases from 1.4 to 1.7, the required courses of antiviral in TAP (not shown) increases 78 times. Mixed strategies are more robust (**d-e, g-h**). The authors expect initial R_0 for an emergent influenza strain to be below 2, which implies a role for antivirals at their assumed efficacy (the results are moderately sensitive to the assumed AVE_S value, as may be expected). This finding has led to recognition in the policy sphere of ‘threshold R_0 ’ effects for policy effectiveness, i.e., with a more infectious viral strain, containment may be very difficult. As R_0 may increase during transmission as the viral strain gains fitness through mutation, the authors suggest early intervention is very important. This insight is valuable.

A caveat is placed on the results. The dependence on R_0 is in part a model artifact. Longini *et al.* calibrate the baseline model at $R_0=1.4$, which fits the historically observed overall 33% attack rate, and further to an age-specific attack rate pattern as in Fig. 3. They then generate the other R_0 levels (e.g., $R_0=1.7$) by increasing the transmission probability ρ per contact, fixed across all age groups and contexts. Recall the equation discussed above for the effective contact rate, $\beta = \gamma * \rho$ (where γ is the total number of contacts, and ρ is the transmission probability per contact). In the Longini *et al.* model, higher R_0 mechanically generates more cases from the channel of ρ . Hence, single effect policies which only impact ρ fare poorly from increases in R_0 , but mixed policies (ρ and γ) are robust.

In a real epidemic, there would be differences, but deviation from the results in Table 6 is uncertain. Targeted antiviral use may raise awareness and lower willingness to mingle, hence affecting γ , besides the effects on ρ ⁴⁶. Additionally, public communication, low cost yet not modeled, could cut R levels by encouraging personal protective behavior.

2. **Ferguson et al. (2005)**⁵: Thailand plus 100-km wide zone of contiguous border nations

Policies compared: The policies considered are similar to Longini *et al.* Social targeting of antivirals (TAP variant) is considered for a percentage of pupils or colleagues in an assumed proportion of the schools/workplaces with index cases. So is GTAP (here called ring prophylaxis), except it is defined as the prophylaxis of the entire population within a ring of a certain radius (5, 10 or 15km) centered on each index case. A drug-sparing variant of ring prophylaxis is considered, where only the nearest 10-50,000 people within 10km of an index case are given a course of antivirals. For nonpharmaceutical measures, they consider social distancing (school and workplace closure), but allow that these might have unforeseen effects by increasing household and random contact rates by 100% and 50% respectively. They also consider an area quarantine policy. Specific definitions of the two latter policies are given along with Table 7 below, which shows the results for selected values of the policy implementation levels. In this study the authors exclude vaccination.

Assumed pharmaceutical efficacy: Ferguson *et al.* (2005) assume oseltamivir efficacy for susceptibility to infection to be 30%, and efficacy for secondary prevention at 65%. Oseltamivir efficacy for infectiousness is assumed to be 60%. Over the entire course of treatment, oseltamivir reduces total infectiousness by a maximum of 28%. The assumptions reference work on resistance to oseltamivir, and other studies.

Control objective: Containment: increasing the probability of eliminating a large epidemic. The 'large' criteria is likely to be geographical, i.e., a country-wide epidemic.

Table 7: Effectiveness of policies for control in a population of 85 million (Ferguson *et al.* 2005)

Percentage application of policy	Av. no. of courses (10^6)		Prob. of elimination (%)	
	$R_0 = 1.5$	$R_0 = 1.7$	$R_0 = 1.5$	$R_0 = 1.7$
1. 90% TAP + 90% GTAP [‡] in 90% of cases	≈1.8	≈2	≈92%	0%
2. Drug-sparing GTAP*	≈1.2	≈1.6	≈95%	≈75%
3. Drug-sparing GTAP*, 80% quarantine**	≈0.75	≈1.25	100%	≈92%
4. Drug-sparing GTAP*, social distancing#, 80% quarantine	≈0.75	≈1.4	100%	≈99%
5. 90% GTAP [‡] & 80% quarantine, but with a 3 million courses limit	-	-	≈92%	≈80%
6. Drug-sparing GTAP* & 80% quarantine, but with a 1 million courses limit	-	-	≈90%	≈60%

[‡] Within a 5km radius of an index case * 50,000 courses (people) within a 10km radius of an index case

80% reduction of movement in and out of a zone defined by merging the 5km rings around index cases

** 21-day closure of 90% of schools and 50% of workplaces within 5km of an index case

Discussion: Table 7 presents a comparison of outcome measures for selected levels of implementation (mostly the median) for policies at levels of R_0 . In their paper, the authors represent outcomes graphically, and allow for 95% confidence limits for results at a particular R_0 and level of implementation. Therefore the \approx sign in Table 7 represents approximation for discussion purposes.

The threshold effects of R_0 on policy effectiveness seen in the Longini *et al.*³ study have intensified. A pure targeted antiviral policy (TAP and GTAP) does not provide containment at higher R_0 . Mixed pharmaceutical plus nonpharmaceutical policies (e.g., 4 in Table 7) achieve full elimination at lower R_0 , and up to 90% at $R_0=1.9$, a trend similar to Longini *et al.* Containment with TAP+GTAP fails at lower levels of R_0 if delays in policy initiation grow from 0 to 4 days (not shown in Table 7). It is not clear why a drug-sparing

GTAP policy alone performs better than TAP+GTAP. Even at 10,000 courses per index case (lower than the 50,000 courses case in Table 7), the containment performance is comparable to TAP plus a 5km GTAP policy. The results may reflect the choice of initial outbreak seeding: a sparsely populated rural area, where a prophylaxis policy of 10,000 courses buys more coverage than ring prophylaxis of radii 5-10km.

The authors show that a low stockpile of antivirals could be significant constraint for outbreak containment at higher levels of R_0 in a large population. For a modeled Thai population of about 85 million – without considering the neighboring countries' border areas – a stockpile of 3 million+ provides reasonable prevention if mixed strategies are considered. The authors find the results dependent on the assumptions of antiviral efficacy. Low sensitivity (e.g., picking up less than 40% of infection) of case detection impacts containment, while low specificity (false positives) wastes drugs and logistical capacity.

3. **Ferguson *et al.* (2006)**³⁷: The United States and Great Britain (GB)

Policies compared: The policies compared here derive from Ferguson *et al.* (2005), but with assumed implementation level and efficacy suited to the context of a country at risk of secondary outbreaks after initial occurrences elsewhere globally; and where subsequent internal spread is likely to be rapid⁴⁷. Social targeting of antivirals (TAP variant) is considered for a percentage of schoolmates or work colleagues of the index cases. GTAP is excluded, but a pre-vaccination policy is introduced. Here various nonpharmaceutical measures are key. The possibility that outbreaks will occur in the developing world means that entry restrictions (air and border control) may delay and/or limit the outbreaks in the US and GB. Various types of movement restrictions are considered – reactive (RMR, where a 20km exclusion zone is established around every index case and movement in and out is stopped), and blanket (BMR, where journeys over 20-50km from the home are stopped). They consider social distancing (school and workplace closure), but allow that these might increase household contact rates by 100%. They also consider a quarantine policy for households with index cases, with a 50% compliance rate. Early case detection and treatment is evaluated, but note that the assumption is that *only 50%* of symptomatic illnesses are reported or targeted (across policies **5-25** in Table 8). Results for the US at select implementation levels of various policies (and related specifics) are shown in Table 8.

Assumed pharmaceutical efficacy: Assumed oseltamivir efficacy is as in Ferguson *et al.* (2005), except reduction in total infectiousness – given time delays in detection and treatment – is capped at 25%. For a pre-pandemic vaccine, assumed efficacy for reducing susceptibility to infection is 30%, efficacy for secondary prevention is 50%, and efficacy for reducing infectiousness is 30%. For an assumed *pandemic* vaccine, these values are 70%, 50%, and 30%. A single dose is assumed sufficient, and vaccine coverage is set at 90%.

Control objective: Mitigation. Outbreaks in the US/GB are considered inevitable and mitigation policies begin with a delay from the global emergence. Policies are compared on the delay in the US/GB epidemic peak and the reduction in total cases that they achieve.

Table 8: Effectiveness of policies for control in the US pop. of 300 million (Ferguson et al. 2006)

Percentage application/effectiveness of policy	Delay in US peak (days)		Cum. attack rate %	
	$R_0=1.7$	$R_0=2.0$	$R_0=1.7$	$R_0=2.0$
1. No intervention	0	0	27%	34%
<i>Entry control and movement restriction</i>				
2. 90% effective border control [‡]	≈15	≈10	-	-
3. 99.9% effective border control [‡] + air restrictions*	≈50	≈42	-	-
4. 99.9% effective border control [‡] , BMR 20km**	≈60	≈52	-	-
<i>Case detection, treatment, and isolation</i>				
5. Same day treatment for all reported cases***	-	-	≈25%	≈31%
6. As 5 but 90% receive, and with 2 day delay***	-	-	≈25%	≈31%
7. As 6 but same day treatment***	-	-	≈22%	≈29%
8. Same day case isolation, 70% of cases [#]	-	-	≈21%	≈28%
9. Same day case isolation, 90% of cases [#]	-	-	≈18%	≈25%
<i>Household policies & prophylaxis policies</i>				
10. Antiviral treatment for 90% cases + prophylaxis for their household contacts [¶]	8	6	17%	22%
11. As 10 plus prophylaxis of school/work contacts	18	26	7.6%	13%
12. 14-day quarantine for households with a case ^{¶¶}	4	2	24%	30%
13. Combination of 10 and 12	10	8	15%	20%
<i>Social distancing policies (school/workplace)</i>				
14. 100% reactive school & 10% workplace closure [§]	13	9	24%	32%
15. As 14 but with 50% workplace closure	16	11	23%	31%
16. Mass vaccination from day 30 of world outbreak beginning with 0-16 y/o ^{‡‡}			0%	1%
17. As 16 , but with start from day 60 of world outbreak ^{‡‡}			19%	31%
18. Random vaccination from day 60 of world outbreak ^{‡‡}			4%	16%
19. As 17 , but beginning with those over 60 y/o ^{‡‡}			21%	31%
<i>Profiled mixed strategies (as in Ferguson et al. 2006)</i>				
20. Household quarantine ^{¶¶} + 100% reactive school closure [§]			21%	29%
21. As 20 , plus 50% next day case treatment			19%	27%
22. 100% reactive school closure plus 90% next day case treatment			22%	30%
23. As 22 plus household prophylaxis as in 10			13%	20%
24. As 23 , plus <i>pre-vaccination</i> of 20% of population, prioritizing 0-16 y/o			7%	14%
25. As 23 , plus 80% prophylaxis of school/work contacts, plus 99% effective border controls			1%	10%

[‡] Targeted at inbound intl. travelers (air and land) * Full closure of domestic air traffic

** Journeys over 20km from home are banned *** Delay between symptom onset and antiviral treatment

Assumed to cause 90% reduction in contacts ¶ Prophylaxis with delay of 1 day since symptoms of the case

¶¶ With 50% compliance § Only a % of schools/workplaces closed that have a detected case (reactive)

‡‡ Mass vaccination at the rate of 1% of the population per day since inception of policy

Discussion: The authors try policies for the prevention of a large caseload in the US given that outbreaks are *inevitable* (a specific critique of this follows further below). All policies **2-25** are sensitive to R_0 and policies **5-9** and **16-19** are sensitive to time delays. Even prompt and pervasive case detection (policy **9**) or treatment (policy **6**) does not offer substantial containment. An approximate 18% attack rate in the former will still be a major health event for the US. An intensive antiviral prophylaxis policy (**11**) will substantially contain the attack rate, but will require a stockpile sufficient to cover 72% of the population at $R_0=1.7$ (not shown in Table 8)⁴⁸. Based on the delayed availability of a *pandemic* vaccine (and assumed efficacy as noted above), substantial containment can be achieved if a mass vaccination program begins reasonably quickly and is targeted at children (policy **16**). However, the 30-day timeline (since a circulating pandemic virus strain is identified) for the

production and mass deployment of a pandemic vaccine is unlikely. A random vaccination policy (**18**), beginning after 60 days since the start of the world outbreak performs better than age-specific vaccination policies. These results assume a single dose is sufficient. If two doses – as some vaccines require – must be administered one month apart, then a pandemic vaccine must be ready for distribution at 30 days.

These results point to the need for mixed strategies. The mixed strategies here do not involve a pandemic vaccine policy. Of all the potential combinations (the authors provide about 30 mixed strategies in the online Supplementary Materials), they picked six for discussion, which are reproduced in Table 8. Of these, two strategies offer substantial protection (**24** and **25**). A *pre-pandemic* vaccine (efficacy as noted on the previous page) in combination with household prophylaxis and treatment of cases can be effective (strategy **24**). The effectiveness was enhanced by social distancing, which is singly ineffective. A more intensive prophylaxis policy with entry controls can be very successful, and would only require an antiviral stockpile to cover 11% of the population at $R_0=1.7$ (strategy **25**).

The authors note several caveats about their model and assumptions which are omitted here. Given that the policy case relates to the US (and GB), the objective of the two governments may be to prevent any outbreaks at all. Therefore, the policy of border (entry) controls is of particular significance – a policy included in the best mixed strategy (**25**). This policy has high economic and social costs, and it is reasonable to expect it will be invoked only given carefully considered need. In the modeling for Ferguson *et al.* (2006), this need is not carefully considered. While strategy **25** has an attack rate reduction outcome, this is not associated with pure border control or movement restriction policies **2-4**. Part of the reason lies in the model seeding assumption, via which infectives arrive in the US (and GB). The authors model the epidemic in the Rest of the World (ROW) as a homogeneous SEIR (deterministic model), implying rapid and universal spread. From the incidence of infections per day in the ROW, the authors sample a proportion as the number of ‘imported infections per day’ into the US, dependent on the intensity and nature of air traffic. Border controls in the Ferguson *et al.* (2006) model arbitrarily begin with some delay and act to reduce the proportion of imported infections by 90-99.9%; eventually compensated for by an increase in world prevalence. The result is a delay in the epidemic peak in the US (pushing of the epidemic curve to the right), but outbreaks do inevitably begin in the US. The onus for limiting them thereafter is on some form of mixed strategy.

In the context of the results above, consider that the objective in the US is *containment*, not just mitigation. In other words, assume it may be possible to eliminate the possibility of imported outbreaks. Separately, assume that limiting the import of infectives has larger policy benefits beyond delaying a peak. If true, these have implications for policy in countries at risk of secondary outbreaks of pandemic influenza.

For the former possibility, note that international spread may not be instantaneous or homogeneous in terms of the risks posed for importing infectives into a country. Some regions may be seen at high risk of pandemic influenza outbreaks (e.g., rural SE Asia). A global influenza transmission model based on air-traffic – as admitted by Ferguson *et al.* (2006, Supplementary Information) – would better predict the risk of importing infectives. A city’s risk would derive from the intensity of its connections and links to cities at high risk of outbreaks. Given this heterogeneity in the ROW pandemic transmission, and the learning

from SARS, a blanket ban on flights from certain regions, incrementally updated based on new information⁴⁹, could indefinitely delay importation of infectives. An airport-based quarantine and antiviral prophylaxis policy (as planned at airports like LAX⁵⁰), could supplement this, targeting any initially asymptomatic travelers detected en route and those they potentially exposed. It can be recalled that of the 29 SARS cases in the US (plus 137 suspect and 19 probable), all imported, there were no reports of secondary transmission⁵¹. 'Intelligent border controls' may *contain* the US epidemic, i.e., minimize the attack rate.

Second, even if an intelligent border control policy, supplemented by airport-based quarantine/prophylaxis plus movement restrictions only delays the outbreaks, this delay is valuable for pandemic vaccine policies. This is considered explicitly in Germann *et al.* below. The delay may also help healthcare facilities better prepare for the surge in demand that is associated with the peak (if the peak itself cannot be reduced). This is a crucial consideration in actual prevention of severe illness and mortality. In Table 8, 99.9% effective border control (policy **3**) – given a homogenous SEIR transmission model for ROW – obtained a delay of 50 days in the US peak. In the context of a heterogeneous ROW transmission scenario, this delay may be larger and applied to the first instance of secondary cases rather than the peak. Even a 50 day window is valuable for the development and deployment of a pandemic vaccine, for which manufacturers no longer solely rely on egg-based production. As available, this vaccine may be administered to passengers, airport and healthcare workers, and other potential exposures, which may minimize the in-country case attack rate (see policy **18** in Table 8).

4. Germann *et al.* (2006)³⁸: The United States

Policies compared: The policies compared here are similar to Longini *et al.* and Ferguson *et al.* (2006). The model derives from the former. For an assumed percentage of true index cases (excludes false positives), social targeting of antivirals (TAP variant) is considered at different levels for their preschool, school, and work contacts, as relevant. It is assumed a fixed 60% of cases and their contacts can always be targeted with antiviral, the constraint being stockpile size. Social distancing is considered – mainly the closure of schools, including preschool and play groups. In addition, movement restrictions are considered. The authors consider a 'dynamic mass vaccination' policy which uses both pre-pandemic and pandemic vaccines as they become available, with distribution schemes either random across the eligible population or prioritizing children. A one-dose policy allows the vaccination of twice as many people, assumed sufficient for achieving efficacy levels for a pre-pandemic vaccine. A two-dose policy confers maximum protection for a well-matched pandemic vaccine. Specifics are given with Table 9 below.

Assumed pharmaceutical efficacy: Oseltamivir efficacy and pre-pandemic vaccine efficacy are as in Longini *et al.* For an assumed *pandemic* vaccine, $VE_S=0.7$ (0.5 for those older than 65), and $VE_I=0.8$, more optimistic than Ferguson *et al.* (2006). Two doses of the pandemic vaccine and one dose for the pre-pandemic vaccine are assumed to be required.

Control objective: Mitigation, as in Ferguson *et al.* (2006), with flavors of containment. In their discussion, the authors suggest policies to slow the spread within the US (delay the epidemic peak) such that mitigation policies can reduce total morbidity.

Table 9: Effectiveness of policies for control in a US pop. of 281 million (Germann et al. 2006)

Policy/Mixed strategy	Illnesses : cumulative incidence per 100	
	$R_0=1.6$	$R_0=1.9$
1. No intervention	32.6	43.5
2. TAP with unlimited stockpile*	0.06 (2.8 mn.)	4.3 (182 mn.)
3. Dynamic vaccination: one dose, random [†]	0.7	17.7
4. Dynamic vaccination: one dose, child-first [†]	0.04	2.8
5. Dynamic vaccination: two doses, random [†]	3.2	33.8
6. Dynamic vaccination: two doses, child-first [†]	0.9	25.1
7. School closure [¶]	1.0	29.3
8. Local social distancing [¶]	25.1	39.2
9. Travel restrictions [§]	32.8	44.0
10. Local social distancing and travel restrictions [¶]	19.6	39.3
11. TAP*, school closure**, & social distancing**	0.02 (0.6 mn.)	0.07 (1.6 mn.)
12. Dynamic one dose random vaccination [†] , social distancing [¶] , travel restrictions ^{¶§} , & school closure**	0.04	0.2
13. TAP*, dynamic one dose random vaccination [†] , social distancing [¶] , travel restrictions ^{¶§} , & school closure**	0.02 (0.3 mn.)	0.03 (0.7 mn.)
14. Dynamic one dose child-first vaccination [†] , social distancing [¶] , travel restrictions ^{¶§} , & school closure**	0.02	0.2

* For 60% cases. Policy begins 7 days after pandemic alert (brackets: antiviral supply needed, in millions)

[†] 10 mn. doses per wk. for 25 wks., timed so individuals develop immunity on the date of first US index case.

[¶] Intervention starting 7 days after pandemic alert ** Intervention starting 14 days after pandemic alert.

[§] Reduction in long-distance travel to 10% of normal frequency, occurs during entire simulated epidemic

Discussion: Table 9 above closely follows the results as reported in the study. Given comparable vaccine *efficacy* to Ferguson *et al.* (2006), the *effectiveness* of dynamic vaccination policy is very high, lowering cumulative incidence (analogous to the attack rate in this context) to 0.04% at $R_0=1.6$. The best vaccination policy (**4** in Table 9) prioritizes children and is antigen saving by using only one dose. The distribution is timed such that a proportion of the population has some immunity before the first US case. This proportion depends on the number of weeks by which the vaccination program precedes a global outbreak. In comparison, Ferguson *et al.* (2006) model pre-pandemic vaccine administered to a fixed 20% of the population while prioritizing children, which in combination with other interventions can lower attack rates to as low as 1% at $R_0=1.7$ (not shown in Table 8).

The threshold effects of the basic reproductive number R_0 are very intense in their study for the increase from 1.6 to 1.9 (results for $R_0>1.9$ not shown in Table 9 imply single policies will fail). But even at higher levels of R_0 , combination strategies with a dynamic vaccination policy perform very well, and also limit the need for large antiviral stockpiles.

The authors consider the potential feasibility issues for TAP carefully and find that the policy – though successful at lower levels of R_0 – requires many onerous assumptions of policy preparedness and is vulnerable to uncertainty. School closure and other social distancing are considered, but do not generate sufficient benefits given the social cost. However, a TAP policy in combination with social distancing (strategy **11**) is valuable for containing the attack rate, such that a larger proportion of the population remains eligible until the point a well-matched pandemic vaccine becomes available (strategy **13**). Such a mixed strategy reduces the overall caseload dramatically. This combination was as

suggested by the critique of Ferguson *et al.* (2006) above. Germann *et al.* do not model border control policies for achieving the delay useful to deploy a pandemic vaccine.

The combination strategies generate benefits in their model due to the nature of the ‘dynamic vaccination policy’. Here more efficacious vaccines for larger proportions of the population become viable (both due to an antigen sparing single dose regimen and because less people are symptomatic due to TAP/social distancing). This process is realistic, as the incrementally available information on the circulating human influenza A strains is currently used to update the seasonal vaccines. In their model, a pre-pandemic vaccine (based on precursor strains) could be available up to 2 months before the global outbreak, and a better matched vaccine up to 2 months later. The details were not provided of the initiation point within this timeframe for the two vaccine types for the dynamic vaccination related policies/strategies in Table 9 (3-6, 12-14). Despite this unknown and connected uncertainties in the efficacy of a pandemic vaccine, or in the dose dependent delay between vaccination and full efficacy, or in the actually feasible dosage to achieve significant population coverage; Table 9 encourages a vaccination using mixed strategy.

STUDIES OF THE EFFECTIVENESS OF SPECIFIC POLICIES

1. **Vaccination policies:** *Distribution and dose size choices*

The discussion of vaccination policies in the comparative studies above introduced two issues in choosing an appropriate policy: type of targeting (distribution) and the size of the vaccine dose. The former issue emerges from a debate on allocation policies for a vaccine (pre-pandemic or pandemic) based on the assumption that antigen production ramps up slowly after a candidate strain is identified. Targeted distribution in this context may prioritize the most infectious individuals (children, e.g., policy **16** and **17** Table 8) to limit total sickness, or those most likely to face serious health complications up to death as a result of sickness (older people, e.g., policy **19** in Table 8). Separately, the issue of dose size also relates to a shortage of antigen, but with a different flavor. This issue has emerged from the realization that even given planned increase in global vaccine production capacity (currently at 350 million doses of trivalent seasonal influenza vaccine²⁴), antigen supplies will be lower than required to cover significant proportions of population in countries at risk of initial outbreaks. In this context, studies have compared the effectiveness of a vaccination policy that uses a smaller dose – sacrificing some efficacy for higher coverage of the population – to a policy using the maximum dose for smaller coverage. Both distribution/targeting and dose size issues are considered below.

Choices in targeted distribution: In the US, the National Vaccine Advisory Committee and the Advisory Committee on Immunization Policy (NVAC/ACIP) recommend a scheme that puts highest priority on high-risk individuals 0-64, vaccine and health-care workers (HCW), government leaders, and pregnant women. The next tier of priority applies those above 65, moderate risk individuals, and infants⁵². Healthy individuals aged 2-64 receive lowest priority. This plan is evaluated by Meltzer *et al.* as discussed further below.

Bansal *et al.* (2006)²² evaluate four targeted vaccination policies for pandemic influenza: a mortality-based variant that targets infants, adults, and HCW; a morbidity-based variant that targets school-aged children and school staff; a mixed strategy that

targets groups with high attack rates (children) and high mortality rates (infants and adults); and a contact-based variant that removes a fraction of the most connected individuals in the modeled social network. The authors use epidemic contact network analysis to model the spread of pandemic influenza, varying the transmissibility of the viral strain by varying ρ (the transmission probability per contact). The model is based on demographic and social network data from Vancouver (Canada). Approximate results based on the graphical depiction in their paper are shown in Table 10 for discussion.

Table 10: Effectiveness of different targeted vaccination policies (Bansal *et al.* 2006)

Targeting policy	Proportion effectively vaccinated*, % (Fraction of available vaccines given to the group, %)					Attack rate, % (Mortality rate, %) at $\rho=0.15^{\S}$
	Infants	Children	Adults	Elderly	HCW	
No vaccine	-	-	-	-	-	≈ 62 (≈ 0.35)
Mortality-based	≈ 75 (≈ 25)	-	≈ 50 (75)	-	≈ 40	≈ 50 (≈ 0.26)
Morbidity-based	-	≈ 50 (≈ 95)	≈ 2 (≈ 5)	≈ 2	-	≈ 38 (≈ 0.25)
Mixed	≈ 10 (≈ 5)	≈ 25 (≈ 45)	≈ 10 (50)	-	≈ 20	≈ 40 (≈ 0.25)
Contact-based	-	≈ 40 (≈ 80)	≈ 2 (≈ 8)	≈ 5 (≈ 10)	≈ 100 (≈ 2)	≈ 20 (≈ 0.22)

* Product of the implemented coverage level (% of each group's size) and the group-specific vaccine efficacy

\S Transmission probability for human influenza A per contact, assumed linearly related to R_0

The authors model the results of vaccination as full protection, and those 'effectively vaccinated' (see note to Table 10) are removed from the epidemic network. Therefore, the contact-based policy, which is very effective for limiting mortality and morbidity at $\rho=0.15$, should be disregarded as it is very model specific. The morbidity-based policy is effective on both counts at lower transmissibility. At higher levels of ρ not shown in Table 10, the mortality-based or mixed vaccination policies are more effective to limit mortality.

Overall, this study reiterates the insight that effectiveness depends on the intent of vaccination policy (limiting morbidity or mortality) as well as the base infectiousness of the pandemic viral strain. Morbidity-based policies are in essence transmission-limiting, as children and others in school settings could be most at risk of infection as well as most infectious for reasons previously described. As a result, the policy could lead to herd immunity that unambiguously lowers eventual mortality. The child-prioritizing vaccine policies incorporating some delay in Ferguson *et al.* (policy **16** in Table 8) and Germann *et al.* were effective and robust to infectivity. However, when delays in the start of the policy are introduced in the model in Bansal *et al.*, prioritizing children has higher value (in terms of limiting the attack rate) only if compensated by low to moderate levels of ρ (<0.11). Multiple reintroductions of the pandemic also favor a mortality-based policy in Bansal *et al.* Their results are specific to the particular urban setting (Vancouver), and prone to model and parameter uncertainty (e.g., over the value of ρ). Therefore, the choice of mortality-based vs. children-based policies should be driven by context, as well as early estimates of R_0 in a pandemic. Also, these insights on targeting do not reference feasibility issues that relate to the overall antigen availability. This is considered next.

Choices in vaccination dose size: Riley *et al.* (2007)²⁴ evaluate the effectiveness of an antigen-conserving vaccination policy that covers a larger share of the population but at a lower level of protection. They use clinical trial data on efficacy for three pre-pandemic vaccines (including one licensed by the US government). The clinical trial data provides a range of dose sizes that produced some immunogenic response, specified from minimum to maximum antigen volume. As an example, for the US government licensed vaccine this

range was 7.5-90 μg ²³. The model is mathematical, relating the attack rate to the protection offered by a vaccine and to R_0 (for a homogenous population). In their most involved model variant (a 'leaky' policy), they assume that the vaccines could offer partial protection in some individuals even with the maximum dose, i.e., the population is heterogeneous in the efficacy of the vaccine. In this variant, the model is calibrated to a predicted attack rate (73%) at $R_0=1.8$; derived from the simple, homogenous form of the model⁵³.

For all three vaccines, increasing population coverage with the minimum dose leads to lower infection attack rates. As an example, assume that for one of the vaccines, an adjuvanted influenza A (H5N1) vaccine, there is a stockpile such that the maximum dose allows coverage of 20 out of 300 million Americans and yields an attack rate of 67.6%. Then the authors find that for a heterogeneous population using the minimum dose is optimum, producing an absolute reduction in the attack rate of 8.9 percentage points. Even if healthcare workers are prioritized (up to 45% reservation of the same stockpile) the minimum dosing policy would still be superior, reducing the attack rate by 4.8 percentage points. The insights are as usual subject to the caution that the clinical trials involved poorly matched pre-pandemic vaccines, and that the dependence on R_0 in the involved model variant is a source of uncertainty. These caveats are discussed in a related review note⁵⁴.

2. **Community policies:** *Case isolation & contact tracing, social distancing, quarantines*

Community-level nonpharmaceutical interventions (NPIs) figure across the containment and mitigation focused studies above. These form the core of the WHO *Interim Protocol*, aimed at developing countries, as well as the DHHS/CDC⁷ plan, where different NPIs are recommended based on expected severity. Since it is difficult to predict the severity in advance, the prioritization may be difficult to implement. There are two reasons to consider NPIs in further detail. First, community-level policies are likely to be of importance in resource-poor settings. Second, the comparative studies produced a dichotomy that goes beyond containment vs. mitigation focus. Generally, social distancing and quarantines were effective and robust to an increase in R_0 for containment in SE Asia (see policy **f** in Table 6, and compare policy **4** to **1** in Table 7), but not for mitigation in the US (e.g., review policies **7-10** in Table 9 at $R_0=1.6$, and then across $R_0:1.6-1.9$). This counters the logic that policies successful at containment should also mitigate successfully. If there are factors beyond methodology (e.g., different objectives or core assumptions) that make community-level policies ineffective in some contexts, it should interest policymakers. This issue can be examined with recent studies that specifically analyze these policies, beginning with analyses of historical data on community-level nonpharmaceutical policies.

Historical evidence: A WHO review⁵⁵ surveyed the accounts from the 1918 pandemic (when almost all control policies were nonpharmaceutical) and found public health officials of the period skeptical on the success of quarantines or case isolation. Early case detection and isolation supplemented by movement restrictions had more impact on attack rates in closed settings (e.g., military barracks and college dormitories). Social distancing, especially school closure, may have more value, as suggested by studies of seasonal influenza epidemics in Israel and France⁵⁵. However, in some contexts school closure or holidays can lead to children becoming more mobile in the community, thus leading to higher transmission. The WHO review provides some evidence for this from US cities during the 1918 pandemic. In this case, school closure without additional household restrictions on

children may not be as effective. In general, the WHO review concludes that North American and Australian data from the 1918 pandemic indicate that community level nonpharmaceutical measures were not ‘demonstrably’ useful historically.

Recent studies of NPIs during the 1918 pandemic have examined the evidence. Hatchett *et al.* (2007)⁵⁶ analyze data from 17 cities that implemented some form of NPIs and varied in their peak or overall mortality rates during the fall 1918 pandemic wave. The most common NPI configurations included social distancing and case isolation. The authors found that school, theatre, and church closures were most effective. By statistically analyzing the difference in pandemic outcomes given the policies employed, the authors conclude that timing of the interventions was a key explanatory factor for peak mortality, but not overall mortality. In other words, city governments who initiated interventions sooner after an outbreak began in their jurisdiction were able to ‘flatten’ the epidemic curve, and also limit the total deaths⁵⁷ (a proxy for the infection attack rate). Again, this points to how the demonstration effect of prior outbreaks allows cities with later outbreaks to time their interventions better and achieve overall reductions in R .

The reduction in overall mortality could have been much larger if the effective interventions had continued for a longer period. As it happened, cities with effective community interventions protected their citizens from the first wave, but this kept a larger number susceptible. When the interventions were lifted prematurely (usually after mortality rates began to decline), the cities experienced a second wave as infectious individuals restarted an epidemic. In comparison, second waves were relatively smaller in cities with poor policy implementation in the first wave, even if such cities may have had larger overall mortality. Epidemiologically, the cities with effective but prematurely lifted interventions did not reduce R to a low enough level to achieve substantial herd immunity. These insights are corroborated by Bootsma *et al.* (2007)³⁴, who fit the 1918 data to an SEIR model and test similar hypotheses. Bootsma *et al.* conclude that transitory community-level policies have the potential to reduce attack rates (and hence mortality) by 30-40%, but higher reductions require sustaining the social distancing and movement restriction policies for longer durations, imposing greater social and economic costs.

Besides the insights on timing and length of policies, both studies make a point not considered before about individual reactions. The 1918 data indicates that rising mortality rates caused people to react by reducing risky behavior. This manifested most visibly as lower rates of social contact, and possibly as greater personal hygiene or mask-wearing. Such ‘prevalence-elastic’ behavior has been theorized before for other diseases. In statistical analysis, such reactive behavior plus indirect effects from family members reducing contacts to stay at home to care for the sick boosts the effectiveness of social distancing policies. But, in realistic epidemic settings, the results of over-dependence on reactive behavior may be difficult to predict. Poor information availability – especially on mortality which is the most observable indicator but occurs with a lag to transmission – may mean that private reactive behavior is too little and too late. Prompt and trustworthy public health communication is required to reinforce the positive factors, as seen during SARS.

Prospective modeling: Carrat *et al.* (2006)⁵⁸ using French data on effective contact rates in an influenza epidemic, simulate community transmission of pandemic influenza and find local nonpharmaceutical policies more effective compared to antiviral prophylaxis. A

policy of contact tracing and confinement implemented for 70% of reported cases worked well to limit the attack rate, as did general school and workplace closure started after a threshold of infections was reached. These results are in tune with the insights from the historical studies, but confound those from Ferguson *et al.* (2006).

It is likely that during a pandemic substantial number of secondary infections may occur in households, where the index cases acquire the disease in community transmission. Wu *et al.* (2006)²⁷ compare the effect on the overall attack rate of community-level policies that reduce such within- and between-household transmission. The model used is a 'stochastic SEIR' simulation, which lacks a spatial component unlike the other comparative studies. Wu *et al.* make the claim that rapid spread will make this issue less relevant⁴⁷.

Table 11: Effectiveness of different NPIs/mixed strategies in a pop. of 1 mn. (Wu *et al.* 2006)

Policy/mixed strategy	$R_0=1.8, \theta=30\%$	
	Attack rate %	Peak Q*
<i>No intervention</i>	74%	0
Q: <i>Quarantine</i> - segregation within their own homes of a complying household contacts of suspected case	49%	9.6%
QI: <i>Q + Isolation</i> (<i>I</i> , complying symptomatic individuals are removed from their household to a separate facility)	43%	7.1%
QA: <i>Q + Antivirals</i> (<i>A</i> , complying symptomatic household members take 2 doses of antiviral and symptom-free members take 1)	44%	0.5%**
QIA: <i>Q + I + A</i> for all complying individuals, as appropriate	40%	6.2%
QIAC: <i>Q + I + A + Contact tracing</i> (<i>C</i> , symptomatic and isolated individuals name people they may have infected, and those are notified and asked to take precautionary measures <i>Q</i> and <i>A</i>)	34%	≈13.5%

* Peak % of the population living in conditions of household quarantine ** 3.9 doses per person in the population

The authors find a significant role in mitigation for NPIs at moderate levels of compliance even without TAP. At similar compliance levels in Ferguson *et al.* (2006), quarantine had lower relative effectiveness (policy **12**, Table 8). Antiviral prophylaxis reduces the number of people in quarantine, thus reducing the social and ethical burden. However, for the baseline simulation (Table 11) at 50% compliance for the policies and $R_0=1.8$, the antiviral stockpile required is quite large. The proportion of presymptomatic or asymptomatic transmission, θ , was assumed to be 30% in the baseline simulation⁶⁰.

The major contribution of their study is highlighting aspects of feasibility for community-level policies. First, they explicitly compare their assumptions to those in the studies by Germann *et al.* and Ferguson *et al.* (2006). While Wu *et al.* assume 67% of cases will show symptoms and be reported (vs. 50% in Ferguson *et al.* and 60% in Germann *et al.*), they conservatively assume a 50% compliance with subsequent policy interventions. The other two studies mostly model higher levels of implementation with their reported cases. Wu *et al.* rule out contact tracing as infeasible in large networks (even if effective as **QIAC**), though Germann *et al.* allow that TAP for 60-100% of contacts outside the household will be feasible in early stages of a US epidemic. Second, Wu *et al.* consider compliance more carefully. For policies that confer immediate benefits to the individual (**QA**, as well as **QI** since guaranteed access to antiviral is assumed in case isolation) compliance may be higher, while lower for quarantine policy. Compliance with isolation would be affected by the characteristics of the index case and household structure. Third, with the peak quarantine rate as an outcome, the authors discuss feasibility in terms of the demands various policies place on authorities to ensure essential supplies for the restricted population. Finally, they

point out that strategies involving a case isolation policy assume too easily that facilities to effectively isolate individuals will be available, especially when urban transmission occurs on a significant scale. If antivirals are available and useful, they may be considered in lieu of isolation (i.e., *QA* vs. *QI*). Where antiviral stockpiles are limited, the use of large-scale case isolation may be needed – a contingency to be planned and prepared for.

Discussion: The results above indicate NPIs have a role in *mitigation* at moderate R_0 and θ , even without TAP or vaccination in tandem. The timing requirements are not more onerous than for drug-based strategies, but the duration NPIs have to continue to minimize the GAR – based on historical experience – may have significant societal costs. The dichotomy in NPI effectiveness seen in the modeling studies across SE Asia and the US may be due to model-related factors. The early use of NPI intervention, limited seeding, and the lack of reintroductions in the SE Asian models may explain the observed effectiveness of NPI in containment. In contrast, given some delay in intervention start, multiple infection seeds, reintroduction risk, and widespread transmission as in the US models, a persistent decline in susceptibility and infectiousness through vaccination and/or TAP is preferred (as **11** in Table 9). However, pharmaceutical policies are resource and capacity intensive, and may be overkill in conditions of moderate R_0 if a strategy of cooperative international air travel restriction mixed with border control/airport quarantine is probable. In this case, for countries at secondary risk, the policy objective resembles early containment. This implies that the choice of stringent, layered NPIs at airports and *reactive* NPIs in communities (as **15** in Table 8) could minimize the attack rate. This strategy has *a priori* lower social cost if a smaller epidemic size is assumed since widespread school and workplace closure are avoided and unfeasible contact tracing during sustained urban transmission is not required. However, in situations of higher infectivity (R_0), the primary benefit of NPIs will be to delay peak transmission such that a well-matched vaccination policy becomes viable. However, vaccination contains the assumption of adequate antigen stocks in resource-poor settings.

3. International air travel restrictions and advisories

The reduction in the volume of and entry-points for incoming infectives would eliminate multiple outbreak seeding; increasing the probability of waging containment battles at airports and high risk communities rather than a large-scale mitigation war. This could be achieved with entry and travel controls, which could also delay an epidemic peak in a country. Depending on the delay, this would enhance the viability and timeliness of other control policies from NPI to vaccination. For pandemic influenza – given higher θ than SARS – symptom-based entry screening is not expected to be an effective preventive measure¹⁸. Instead, the cancellation of flights to and from certain (or all) cities worldwide could be considered by each airport. Retrospective modeling of the 1968-69 pandemic³¹ suggested a role of the international air network in the spread of influenza. Recent work by Brownstein *et al.* (2006)⁶¹ analyzed the ‘natural experiment’ of the post 9-11 shutdown in US air traffic, and found it connected with a delay in the seasonal influenza peak in 2002.

However, control in an actual pandemic situation with higher transmissibility and susceptibility compared to interpandemic influenza needs to be evaluated. The success of international air travel restrictions (IATR) for pandemic control depends on a proactive WHO role, the nature of the initial outbreaks, the identification of highly connected cities that may exchange infectives (which may be isolated from each other), further analysis of the SARS experience, and some voluntary self-restriction by travelers who expect to have been exposed to infection. There is considerable uncertainty if IATR will be effective. Modeling studies have attempted to bring greater predictability to the issue.

The comparative modeling studies did not model IATR or entry controls in great detail. Full border controls – 99.9% effective in reducing imported infectives – in Ferguson *et al.* (2006) only delay the epidemic peak. As noted previously, if most countries cooperate on air travel restrictions and information on outbreaks is widely and immediately shared, the global circulation of infectives may be lower. In other words, the global prevalence of pandemic influenza need not be ever rising to diminish the effect of border controls. Germann *et al.* make a simpler assumption that while international air travel will be the dominant mode of infection seeding in most countries, achieving ‘impenetrable’ borders will be prohibitively expensive. However, such considerations did not prevent studies from evaluating NPIs or drug policies that affect many persons or require significant resources.

Two recent studies^{62,63} model international air travel within a highly connected or nodal set (105-155) of major global cities using real flight data and demographics, and attempt to simulate the global spread of pandemic influenza. They introduce similar IATR policies in similar model settings, but obtain differing results. Both models use a stochastic SEIR model for the epidemic in each city, with the proportions of people in various states in a city affected by the number of travelers entering and departing each city. The proportion of the air passengers in the various disease states traveling between two connected cities is identical to the proportion of people in the states in the city of origin. Sequential travel bans – considered more realistic than a simultaneous global shutdown of the air network – begin in each city after a threshold of cases is recorded. This threshold is higher for the first city to have a major outbreak. This framework is biased such that epidemics in each city in the modeled network are near inevitable (containment is not an objective), but the peak in each city may be delayed by the sequential flight bans. This effect manifests in the city imposing restrictions, but also in cities connected to it yet to reach their intervention threshold.

Cooper *et al.* (2006)⁶² set the threshold at 1,000 symptomatic cases for the originating city, and 100 for each city thereafter. Even when 99.9% of air traffic was suspended, there was no containment (loosely defined as the low probability of an epidemic in at least some cities), and delays in peaks were small and insignificant for the viability of other control policies. This result was robust to assumptions about the originating city in their model, the timing of the first outbreak, the initial susceptibility of populations, and infectiousness (only at very low R_0 values was there significant delay).

Epstein *et al.* (2007)⁶³ use a flat threshold of 1,000 cases for their baseline modeling of sequential flight bans. The results obtained are slightly less bleak on the effectiveness of IATR – a 95% reduction in flight volume would produce a delay of two to three weeks at $R_0 = 1.7$, and hence a reduction in the total global cases after 6 months. At the baseline, there is little or a worsening effect with IATR, depending on the timing of the first outbreak⁶⁴, on total cases over the entire pandemic. The results are sensitive to the originating city (delays are larger with Hong Kong than London). The authors model the use of a vaccination policy in tandem with IATR and find that the mixed strategy greatly boosts the effect on the attack rate. Adding a policy of 0.1% daily vaccination – which can be applied to larger number of people thanks to the delay in epidemic peaks achieved by IATR – would reduce the number of cases in urban areas of the US from 102 million to 57 million. This insight follows discussion previously in the context of the studies by Ferguson *et al.* (2006) and Germann *et al.* The 2-3 weeks delay in itself would also allow many more cities to get ready with NPIs.

These results are not encouraging for IATR proponents looking for containment of a global pandemic, i.e., major reduction in the overall number of cases. It is uncertain whether 95% reduction in travel volumes could be achieved with sequential restrictions, but this

would at least generate delays sufficient for other policies. Epstein *et al.* have already considered that the threshold for intervention would reduce, as cities further down the timeline react faster. This factor did not change their conclusions in a major way. But, future research with stochastic SEIR/air travel models could address some lacunae.

First, the two studies assume that in the no-intervention scenario the air travel network remains stable in flight and passenger volume until sequential IATR begins, which implies significant circulation of infectives and the spread of pandemic influenza. However, flights cancellations may begin earlier in cities other than the originating city, before their 100/1000 cases are recorded. This is because flight cancellations at one airport affect airline operations, which means disruptions can spread to other airports, especially major hubs⁶⁵. This effect may bring down global *flight volume* much earlier than predicted by the IATR timeline. When flight bans are imposed, they enhance the airline-related ripple effect. The amount of early reductions in flight volume will depend on the location of the first outbreaks and the associated airlines. Second, effects deriving from individual volition can bring down *passenger volume*, e.g., decisions not to fly at all based on assumed risk of infection on flights or at airports. Due to such prevalence-elastic behavior, many trips except for repatriating visitors may be cancelled, especially in countries near an outbreak zone. This would boost the effectiveness of sequential restrictions in a similar way.

Third, further research is required on the benefit of passenger- and airport-based interventions that are dependent on a global information criterion and begin much earlier rather than indicated by a case-rate threshold in the city an airport serves. The decision triggers in the US pandemic plan are an example of such early policy activation⁷. The effective contact rate of passengers may be easily modified with in-flight risk communication, airport-based interventions (issue of PPE, antivirals), etc., that could begin very soon after the first outbreak is reported anywhere in the world. Though asymptomatic and symptomatic transmission may still occur on a flight, and later with community contacts (in the absence of passenger quarantines), the compartmentalization of passengers – in the language of uniform mixing SEIR models – may mean R_0 should decline in cities further down a timeline that benefit from more information. Such passenger- or airport-focused interventions that follow the principles of ‘targeted layered containment’ would improve with better global outbreak surveillance, WHO coordination, and airline participation. By reducing travel volume, IATR would boost the effectiveness of these policies. As a result, the chances would be higher that more cities contain their epidemics and that the delays in peaks in others are longer.

4. **Therapeutic use of antivirals with global redistribution of stockpiles**

Colizza *et al.* (2007)⁸⁰ investigate a global mitigation strategy for pandemic influenza involving the therapeutic (rather than preventive or prophylactic) use of antivirals. Their international model links 3,100 urban areas across 220 countries in an airline network, and they use a stochastic SEIR model to simulate the epidemic within each of those urban areas. Effects due to seasonality in influenza epidemics are factored in for parameters on infectiousness. Based on the results in other studies^{62,81} they discount the possibility of IATR obtaining significant delays in pandemic peaks or reductions in overall attack rates. As a result, they focus their modeling of interventions on antivirals.

Assumed pharmaceutical efficacy: Neuraminidase inhibitor antiviral efficacy for reducing infectiousness (AVE_i) is 0.62, as in Longini *et al.* Further, Colizza *et al.* assume that

the average length of the infectious period for treated and infectious individuals is reduced by one day. Given the proportion p_{AV} of symptomatic individuals who can be feasibly identified and treated per day, the overall reduction in the infectiousness of treated individuals ranges from 30-50%. With baseline values, they approximate the following relation: $R_{av}=R_0/1.3$, where R_{av} obtains based on the unrealistic expectation of timely and widespread therapeutic use of neuraminidase inhibitors from the start of the pandemic. This reduction is lower than in $R_{av}=R_0/3.6$, proposed for the prophylactic use of antivirals of similar base efficacy²⁷.

Policies: The authors consider two scenarios for an antiviral policy. In the first ‘maximal coverage’ scenario, every urban area has sufficient antiviral stockpiles to treat cases according the prevailing treatment protocol p_{AV} . The second, realistic ‘limited supplies’ scenario has two flavors. The *uncooperative* flavor of this scenario has a limited number of rich (‘prepared’) countries with stockpiles sufficient to treat 10% of their own populations with antivirals, and two other frontline countries – Vietnam and Thailand for this study – receive some stockpiles as well (up to 10% of the population). In the *cooperative* flavor of the limited supplies scenario, the prepared countries donate from one-tenth (cooperative strategy I) to one-fifth (cooperative strategy II) of their antivirals into a global stockpile for international use as needed. In this cooperative world, symptomatic cases receive treatment as per the p_{AV} as long as the global or country stockpile has drugs. Results for effectiveness in containment (Table 12) and mitigation (Table 13) are below.

Table 12: Probability of a global pandemic one year after seeding in Hanoi in October

Antiviral policy scenario ($p_{AV} = 50\%$)	$R_0 = 1.5$		$R_0 = 1.9$		$R_0 = 2.3$	
	No outbreak	Outbreaks in >100 countries*	No outbreak	Outbreaks in >100 countries*	No outbreak	Outbreaks in >100 countries*
Maximal coverage	≈66%	0%	≈40%	≈60%	≈30%	≈70%
Limited coverage, uncooperative	≈66%	≈16%	≈40%	≈60%	≈30%	≈70%
Limited coverage, cooperative –I, II	≈66%	0%	≈40%	≈60%	≈30%	≈70%

* Probabilities not shown for global outbreaks in the ranges: 2-10, 11-50, 51-100 countries.

Table 13: Average cases per 1000 globally after seeding in Hanoi in October (Colizza et al. 2007)

Antiviral policy scenario ($p_{AV} = 50\%$)	$R_0 = 1.5$	$R_0 = 1.9$	$R_0 = 2.3$
Maximal coverage	0.01	35	184
Limited coverage, uncooperative	16	222	397
Limited coverage, cooperative -I	0.01	126	305
Limited coverage, cooperative -II	0.01	97	287

Discussion: Containment success is poor across the distribution scenarios for any R_0 greater than 1.5. If sufficient stockpiles of antivirals are available (2-6% of the global population) and a cooperative strategy is maintained with timely redistribution of the stockpiles of prepared countries, then mitigation even at a R_0 of 1.9 is possible. Based on details not shown in Tables 12-13, the cooperative system results in delays of the peak of the global pandemic for as much as a year for R_0 between 1.5-1.9, which is sufficient for the development of a well-matched pandemic vaccine. The amount of redistribution of antiviral stocks involved is modest, reducing the availability of stockpiles in the prepared countries to 8-9% of the population from the prior 10%.

COST AND COST-EFFECTIVENESS OF POLICIES

Direct costs: The direct cost of vaccine and antigen production/procurement and distribution for the overall health sector could be estimated for different stockpile and coverage scenarios, though rigorous studies of these costs are yet to be initiated. The affordability of large-scale vaccination and antiviral prophylaxis policies remains out of the reach of many developing nations. These costs and potential financing mechanisms require urgent research given the conclusions from the studies reviewed so far.

For NPIs, it is unclear what the direct costs should include: social, economic, and resource costs will all be incurred. For the purposes of this review, the economic costs of NPIs due to reduced demand or due to workforce disruptions (absenteeism and productivity loss due to telecommuting where this occurs) will be considered *indirect* costs. Direct costs to the local and central public health systems of enforcing case isolation, contact tracing, movement restrictions and social distancing may be very large if these continue for long and occur in large cities. As noted by Wu *et al.*, when a quarantine policy is selectively enforced for the households of cases and their contacts, the local authorities may have to ensure a supply of essential supplies for the quarantine to be ethical. Also, the disruption to the normal routine of people has a social cost which is difficult to compute. Such cost issues are a prime factor leading the DHHS/CDC plan to be circumspect about the recommended NPIs at different forecast levels of severity⁶⁶. NPIs would be instituted in an actual pandemic regardless of such recommendations. The DHHS/CDC plan institutes centralized coordination which can reduce social costs. However, severity is difficult to predict in a way meaningful to public health plan activation, and the cost of any mistakes in terms of an inefficiently contained/mitigated epidemic with higher illnesses and deaths would be worse. Hence, the results of the modeling studies reviewed so far on the effectiveness of policies at different levels of transmissibility and feasibility are appropriate starting points for taking decisions based on the local context.

Indirect costs: The indirect costs emerge from disruptions of domestic economic activity from the NPIs in the intervention scenario, as well as the reduction in international travel and business due to IATR. The costs of IATR were estimated by Epstein *et al.* for the US and found to be lower than previously assumed. The per annum cost of major IATR is in the vicinity of 0.8% of GNP, vs. a potential reduction in the overall caseload reduction of about 45 million cases in urban areas in their model. Whether this loss in GDP is low from a policy standpoint is a cost-effectiveness question. Such questions are controversial where it answers would require analysts to value the mitigated morbidity and mortality and the long-term economic benefits therein. The latter estimates are available from other studies⁸ which have been reviewed extensively elsewhere. Costs of NPI related reduction in demand in a city with social distancing or quarantines have been estimated as well in prospective economic modeling. The experience from SARS, where there was a quarterly reduction in the demand for services and in travel/hospitality industries in the affected cities (Hong Kong, Taipei, Beijing) are the basis for such estimates. Some of the estimates from outbreaks in locations where social distancing and/or quarantines were instituted are reported in Table 14.

Table 14: Disease outbreaks: estimates of business losses due to local disruption

Location (Year)	Length of disruption	Sectors Affected	Estimated Loss	Disease
Surat, India (1994)	Two-three weeks	Local demand (during the festival season)	US\$ 260 mn. ⁶⁷	Pneumonic plague (1391 cases*, 52-68 deaths)
Beijing, PRC (2003)	Nine months (April-Dec)	Decline in domestic tourists (87%) and cancellation of Labor Day holiday (13%)	US\$ 2.8 bn. ⁶⁸ (7.5% of 2002 Beijing GDP)	SARS (2521 cases, 190 deaths)
Taiwan (2003)	Two months (May-June)	Tourism revenue (domestic and international)	US \$350 mn. ⁶⁹	SARS (346 cases, 37 deaths)
Hong Kong, PRC (2003)	Three months (March-May)	Local demand (metric: total retail sales)	-6.1% in March, -15.1% in April, & -11.1% in May, year on year ⁷⁰	SARS (1755 cases, 398 deaths)

* Probable cases for Gujarat state.

While the effects on the local economy dissipate in subsequent financial periods as demand picks up and workers report back, in the shortest term the possibility of severe losses to the local business sector can ‘stay the hand’ of city governments, imposing unnecessary added risk of epidemic escalation⁷¹. This is crucial for effectiveness, since studies have repeatedly stressed timeliness and completeness for all control policies.

Cost-effectiveness studies: Meltzer *et al.* (1999)⁹ estimated the net returns to vaccination policies in the US – targeted (mortality-based) or mass vaccination – using an assumed range for cost of vaccine per person. Vaccine efficacy was defined in terms of reductions in the health outcomes (death, types of healthcare utilization) in the vaccinated group. A high scenario of vaccine efficacy reduced death in those vaccinated by 60-75% (higher in the younger age groups) from baseline, and hospitalization from 50-55%. Benefits of vaccination were estimated as the avoided costs of excess mortality, accounting for 83% of economic losses in the no-intervention scenario, as well as the avoided costs of excess healthcare utilization (17% of losses). This approach did not include avoided costs due to demand or supply disruptions discussed above. The former costs were estimated using the present value of lost earnings, varied by age group, while the costs of hospitalization varied depending on the severity of symptoms, and were aggregated from the numbers of individuals with different health outcomes from the baseline scenario. The following discussion should be read in light of the review of their ‘mathematical scenario’ methodology in a previous section.

If maximizing calculable net returns is an objective (other objectives: minimizing the total case attack rate, minimizing risk for death) then the following results apply. Since the largest amount of losses in their model emerged from deaths, a policy aiming to reduce total cases/deaths would produce the largest returns – e.g. a policy aiming at 60% coverage of the US population (320 million doses of vaccine to be produced and delivered in a 2-3 month period). Given resource constraints for such coverage, especially if a well-matched vaccine requires two doses, certain targeting policies are considered. Vaccinating those at high risk of complications – e.g., comorbidities – in the 0-64 age group (a priority under the new NVAC/ACIP plan) would generate higher returns regardless of the cost of vaccine compared to vaccinating those 65+ at *any* risk (also priority under NVAC/ACIP), or those 0-64 not at high risk (lowest priority under NVAC/ACIP).

The results in van Genugten *et al.* (2003)⁴² are presented at a higher level of generalization. They find no relative benefits in terms of deaths and hospitalizations of

targeted vaccination (for those 65+ and healthcare workers) compared to mass vaccination. Given the higher resource need of mass vaccination, this argues implicitly for targeted vaccination, though the prioritized target group differs from Meltzer *et al.* Results in both studies are highly sensitive to the assumed variation across age groups in attack rates and the proportion at risk for complications. It is uncertain what patterns and risks would obtain in a real pandemic. The challenge of identifying the high risk proportion in the absence of relevant health records in some countries (or even the population distribution of comorbidities) will complicate wider replication of the analysis in the Meltzer *et al.* study.

ETHICAL DIMENSIONS OF PANDEMIC CONTROL POLICIES

Ethical dimensions of pharmaceutical policies: When drug stocks are limited and a particular control objective is identified, a decision usually follows to target some particular group: contacts of cases, healthcare workers, older individuals, or those most infectious. These decisions are made based on the local context and using both prospective modeling of efficacy and the actual feasibility. As a result of such targeting, some individuals are invariably left at higher risk of illness or death. In healthcare settings, triage is not uncommon, but the ethical implications are complex. In the resolution of these issues, several operative principles are in circulation. So far in this review, the following principles have appeared in the context of drug-based policies:

- 'Save the most lives' – a policy that reduces the GAR and hence the total deaths
- 'Save those most at risk' – a policy that targets those most likeliest to die or be severely sick, without necessarily considering the impact on the GAR
- Maximize the protection of productive life years – implicit when benefits of avoided mortalities are calculated using the present value of lost future income. This calculation usually benefits those younger with more years of work left.

For a particular drug-distribution policy, the connection to the principles above depends on the arguments made. As an example, some of the NVAC/ACIP vaccine priorities – vaccine workers and HCW – could be construed as 'save the most lives' as they aim to keep vaccine production lines and healthcare centers open, eventually raising total mitigation. Other views on the same priorities resemble 'saves those most at risk' (HCW again, plus people with two or more risk conditions, pregnant women, and older persons). After reviewing the NVAC/ACIP priorities, Emanuel *et al.* (2006)⁷² propose a 'life-cycle principle' which prioritizes younger individuals over older cohorts, as they have more life stages to pass through. Vaccine and HCW workers are still the top tier of the priorities. An investment variant of the life-cycle principle prioritizes young adults and those in college over children, as they have made more developed life plans. The intent is to save the most 'years of life stages' across the whole population.

A recent WHO consultation on ethical issues raised concerns that prioritizing HCW in a situation of a *severe* pandemic – where it could be assumed that their role has been limited compared to household members – would lead to requests for prioritization from other professions who also consider themselves indispensable⁷³. In a moderate pandemic, the WHO consultation recommendations for vaccination resemble NVAC/ACIP.

Though some age-based prioritization may be considered unavoidable due to projected antigen shortages for vaccination policies, further research is needed on the priorities that match different social objectives of vaccination (and antivirals). Meltzer *et al.*

provided an early example of such research. This is required since the effectiveness of targeted distribution policies remain prone to assumptions about the transmissibility of the pandemic strain. For example, in Bansal *et al.* for the objective of limiting the GAR, i.e., 'save most lives', the preference shifts when transmissibility and delays were considered, from a morbidity-based policy that prioritized children to one that was mortality-based and prioritized adults. It may well be ethical to base priorities closely on the available information on age-based mortalities of candidate strains, as well as further modeling of potential effects of transmissibility on vaccination policies.

Ethical dimensions of surveillance and NPIs: As already discussed, isolating cases and quarantining households, and potentially social contacts via tracing, poses profound issues of law and ethics. If the policy is not well explained, voluntary cooperation may be ill-informed and less ethical. The treatment of those in quarantine or isolation must be humane and meet minimum standards of hygiene, comfort and material availability, albeit with due considerations for the outbreak as an emergency situation. For social distancing, quarantine and other NPIs to be ethical and legally sanctioned, they must be evidence-based, documented, and well communicated to the public. Especially for isolation and quarantine, the appropriate legal authority of those declaring and implementing the policy (at separate levels) should be established in all countries⁷⁴. Even where legal provisions for quarantine under medical emergency are well developed, as in the US, a review has found lacunae⁷⁴. This indicates that the issue may require attention in other countries as well. Minor incidents of social unrest witnessed in China during the SARS controls⁷⁵ would have been ameliorated with better communication and trust between authorities and the population. Any policy which is unethical at the individual level and/or inequitable in the risks imposed on different groups in the population cannot be called effective.

Ethical dimensions of international pandemic control: The border entry controls and IATR in the situation of worldwide pandemic influenza outbreaks are the rights of individual nations, as well as a potential recommendation from the WHO. However, given that free movement of people and goods is also a basic right, over-zealous or excessively long duration restrictions against movements from a particular country are challenges to the system. Preemptive travel and import restrictions based on disease risk impose a cost on the targeted country, and while warranted in the situation of pandemic influenza, they require careful consideration. These issues have been tackled in a recent paper⁷⁶.

Ethical dimensions of international cooperation: The current system of international cooperation in public health – between governments, private firms, NGOs, the UN agencies and multilateral institutions – functions under the aegis of the WHO and treats prevention and mitigation of diseases of international concern as a global public good. Recently, government and WHO interests in a portion of the system seem to have diverged to the detriment of the effectiveness of future pandemic control. This divergence has ethical dimensions rooted in the sharing of responsibility in and benefits from cooperation.

Alongside early revelation of an outbreak, the biological information on communicable disease strains is critical for the WHO crafting an adequate international response. Under the existing plan for free sharing of disease-related samples (such as seasonal influenza), the WHO has urged countries to make these available to it directly or to its collaborating centers, such that the causative agent can be analyzed and vaccine manufacturers can focus their work. Particularly for the H5N1 avian influenza virus, the WHO established the H5 Reference Laboratory Network, and countries – even if they have

the local laboratory capacity to genetically sequence the virus and provide the sequence information electronically – have been urged to contribute human and avian samples.

The WHO views the free sharing of samples as a ‘collective responsibility’⁷⁷. The recently released best practices⁷⁸, by asking for the open posting by collaborating centers of all the genetic sequence data on the viruses, has given such information the status of an international public good. However, some governments have shown in their actions that they view the viral samples (or both the samples and related sequencing information) as ‘national’ public goods, which are to be protected from use by other governments or foreign commercial concerns without a defined contract. There are three factors that are driving this dissonance. First, the divergence of the H5N1 viruses into genetically and antigenically distinct clades – like the Indonesian strain – has given specificity to the viral information that is valuable for vaccine development. Additionally, governments – through both national and international law – have sovereignty over the viral information collected under their jurisdiction, which means that both the WHO and other foreign parties can be excluded⁷⁹.

Second, the governments in developing countries have had some justification in questioning the free sharing of sample and sequence information under an ‘international public good’ system, given the current lack of an accepted global vaccine plan, backed by adequate financing and logistical details. It is a fact that the preponderance of vaccine manufacturing capacity is in the industrialized world, and national pandemic plans ask for securing stockpiles to cover domestic populations first. In such a situation, even if governments honor their international collective responsibility and share information, they cannot be assured that in the use of the information, the information has characteristics of being ‘non-rival’ in consumption, i.e., affordable global availability of adequate vaccine doses to cover at-risk populations. In fact, global manufacturing capacity for such vaccines, and the technologies involved, remain in the private sector, which would not undertake the massive investments in producing capacity without a compelling commercial logic.

Third, in nationalizing the information, governments stand to make large revenues when they sign privileged commercial contracts. Most developing countries do not have the production capacities or technology to capitalize on the specificity of the viral strain. However, in exclusive revenue-sharing contracts with foreign pharmaceutical companies, both funds as well as technical know-how can be procured, which benefits domestic health security. In contrast, there is a government’s net-loss view of the world where other commercial concerns will sell the country a vaccine based on the local strain.

The WHO has been sympathetic to the country governments’ concerns, while insisting on the continuing free transfer of sample and genetic sequence information. However, if governments proceed to view viral information as a national good, this may create a major challenge for the response against a potential pandemic of influenza. Some governments have indicated they would honor the global sharing of information if WHO collaborating centers and foreign countries sign Material Transfer Agreements (MTA) that would prevent release of the data for commercial use. However, given that vaccine production capacity remains privatized; such MTAs would be tantamount to crippling the creation of a multi-sourced and robust global influenza vaccine strategy.

Three policy efforts would secure a system of ethical and cooperative international sharing of disease information. First, further urgency is needed for the development of candidate H5N1 vaccines with true cross-protection across the strains currently circulating. Second, an internationally brokered and financially comprehensive plan is needed that sets

agreed-upon pricing and logistical details for adequate doses of a well-matched pandemic vaccine – whatever the national origin of the base strain – for all of the populations at risk. Three, as a part of the international plan for vaccine pricing and logistics, countries that provided the majority of the sequencing and sample data for the candidate vaccine strain could be recompensed with a side-payment of royalties from doses sold in the industrialized world. These potential models of cooperative efforts require urgent research into their feasibility and implementation such that the world is better prepared for a pandemic of influenza.

CONCLUSION

The studies reviewed in this paper indicate that with adequate preparedness planning and execution it is possible to contain pandemic influenza outbreaks where they occur for viral strains of moderate infectiousness. For viral strains of higher infectiousness, containment may be difficult, but it may be possible to mitigate the effects of the spread of pandemic influenza within a country and/or internationally with a combination of policies suited to the origins and nature of the initial outbreak. Unfortunately, it is very difficult to know in advance how infectious the pandemic-capable viral strain will be; i.e. the basic reproductive number can only be estimated with a lag.

Public health authorities at the start of a pandemic influenza outbreak will attempt to prevent its spread (avoid an epidemic) and will try to isolate and treat the index cases. This is generally referred to as containment. When containment has failed, authorities at the local and national level, even in uninfected countries, will take steps that would prevent rapid and uncontrollable spread, reduce the morbidity and mortality rate of an unavoidable epidemic, and suppress the peak daily rate of cases. Both containment and mitigation policies reduce the overall attack rate, and reduce and delay the peak rate of cases per day. However, by definition, containment begins earlier than mitigation on the time curve of an epidemic and hence has a larger effect on the overall attack rate.

The delay in the peak case rate obtains time for a coordinated international effort to isolate the pandemic strain for vaccine production purposes. However, even if creating a well-matched vaccine is the cornerstone of lasting protection against the particular pandemic-capable strain of influenza, global funding and distribution plans for such a vaccine remain poorly defined at this point. Stamping out the outbreak in local communities via containment operations, and strictly monitoring and preventing the international communication of the disease is the most preferred course of action¹.

Given the emphasis on timely and efficient containment operations, resource-poor countries at a risk of initial outbreaks may have to invest in containment measures that can address a wide range of scenarios of infectiousness. The need for resources towards such preparedness – keeping in mind the opportunity cost of national and multilateral funds – would lessen if planning focuses on control policies of proven effectiveness. Even if true effectiveness can only be estimated in the field in an actual epidemic due to the unpredictable behavior of individuals and social entities, it is possible to model robust strategies (mix of control policies) that have containment power over a greater range of

outbreak scenarios. The more robust is the strategy to pandemic influenza infectiousness, the lower is strain on government capacity, and the greater the possibility of containment at source. At the margin, the probability of containment in resource-poor countries grows if there is a global redistribution – especially of pharmaceutical stockpiles – that matches resources to the risk of preliminary outbreaks. Currently, resources are concentrated in countries at risk of secondary outbreaks, deriving from the focus in such countries on mitigation – rather than containment of initial outbreaks – of pandemic influenza in their society during an ‘inevitable’ global pandemic.

The modeling studies reviewed in this study indicate a variety of effective control policies and strategies, as well as their variants suited to particular feasibility, cost and ethical standards. These results (summarized below) are a first cut at winnowing the field of potential interventions for containment and mitigation. They are cross-referenced to the known science on theoretical or laboratory efficacy of particular policies. These results indicate the likelihood of containment success in ‘frontline risk’ countries, given specific resource availability and level of infectiousness; as well as mitigation success in ‘secondary’ risk countries, given the assumption of inevitable international transmission through air travel networks. However, from the analysis of the modeling results on interventions in the U.S. and U.K. after a global pandemic starts, as well as the results from modeled containment strategies in S.E. Asia, there is a basis for arguing that the emphasis in the secondary risk countries could shift from mitigation towards containment. This follows since a mitigation-focused strategy in developed countries presupposes that initial outbreak containment in these countries will necessarily fail. This is paradoxical if containment success at similar infectiousness of the virus is likely in developing countries with lower public health resources, based on results using similar modeling methodologies.

Such a shift in emphasis could have major implications for global risk management for diseases of international concern such as pandemic influenza or a SARS-like disease. For example, if international air travel reduction (as a function of globally coordinated policy as well as due to self-restraint of travelers) combined with airport/border control has a strong chance of reducing the entry of infectives into the U.S., then the minimum required size of the U.S. stockpile of antivirals and pre-pandemic vaccines would reduce. This is a reflection of the shift in emphasis from community-level *mitigation* across urban areas towards specific, risk-based *containment* at the level of airport/border areas as well as the traced contacts of international travelers. Given the reduction in the minimum stockpile size in the U.S., the balance could be efficiently and quickly redistributed. This could contain the spread in frontline countries (e.g., in S.E. Asia) for a greater range of infectiousness, reducing the overall global risk of the current wave of the pandemic as well as reducing the possibility of large subsequent outbreaks. This shift in emphasis could reduce the overall global burden of deaths and illness compared to a scenario where the resource-rich countries retain the preponderance of resources in a strategy of ‘hope for the best, prepare for the worst’.

Summary of modeling results for containment of outbreaks in frontline countries

Nonpharmaceutical interventions (NPIs) such as quarantine of infected individuals, social distancing measures including the closure of schools and offices, etc., are effective in containing the overall size of an outbreak within a country such as Thailand for viral strains of moderate infectiousness (R_0 less than 1.4)³. When NPIs are combined with a policy of

targeted antiviral prophylaxis (TAP) of a proportion of the index cases and their contacts, containment can be achieved for viral strains with R_0 as high as 1.7³. The policies of TAP or pre-vaccination (with a poorly matched vaccine) are resource intensive given the available laboratory estimates of efficacy of the associated pharmaceuticals. Prophylaxis of a certain number of the population within a ring of a certain radius around an index case or outbreak (drug-sparing geographical TAP: GTAP) can achieve a containment probability of 90% when combined with NPIs, for R_0 as high as 1.9⁵. In a modeled Thai population of 85 million, a feasible strategy combining GTAP using a maximum stockpile of 3 million doses of antivirals mixed with quarantine policies achieves containment for R_0 as high as 1.7⁵. The required stockpile of pharmaceuticals, the effectiveness of policies, and the feasibility of containment are all sensitive to infectiousness as proxied by R_0 . In a model⁵, the seeding of the initial outbreak in a sparsely populated rural area can improve the estimated effectiveness of interventions, and reduce cost in terms of resources and economic disruption (e.g., of NPIs).

Summary of modeling results for international containment (travel networks)

Are restrictions in the free movement of international air travel passengers after an outbreak likely to reduce the possibility of a large global pandemic of influenza and delay the peak of a country epidemic? If the policy of sequential travel bans is considered – more realistic than the simultaneous global shutdown of the air travel network – then the results of modeling studies are mixed. In one study (Cooper *et al.* 2006) evaluating a sequential travel ban policy triggered by 1,000 symptomatic cases in the originating city and 100 cases in each city thereafter, the global pandemic was not contained even when 99.9% of air traffic was suspended⁶². This result was robust to assumptions about the originating city, the timing of the outbreak, initial susceptibility and infectiousness (only for very low R_0 was there a delay in the peak of the epidemic). However, another study (Epstein *et al.* 2007), using a flat threshold of 1,000 cases per city to trigger sequential air travel bans found that a 95% reduction in travel volume would produce a delay of two to three weeks in the country epidemics at $R_0=1.7$ ⁶³. The total global cases would be reduced over the course of a six-month global pandemic timeline. The results were sensitive to the assumption of the originating city. The latter study also found that adding a policy of daily vaccination of 0.1% of the population would reduce the number of cases, e.g., from 102 million at the baseline in the U.S. to 57 million with the air travel restrictions and vaccination. The two to three week delay would also allow more communities and local governments prepare NPIs.

Summary of modeling results for mitigation in secondary risk countries

Suppose the spread of pandemic influenza is inevitable to countries at secondary risk such as the U.S. and the U.K.: i.e., international air travel restrictions (IATRs) do not contain the pandemic, and community transmission in cities of the secondary-risk countries is also inevitable (which assumes airport-based quarantines and controls, and passenger contact tracing as seen for SARS fail, presumably due to reasons such as asymptomatic transmission). In this situation, which policies or combinations of policies (strategies) will reduce the overall attack rate, and reduce and delay the peak rate of cases per day?

One modeling study (Ferguson *et al.* 2006)³⁷ finds that U.S. strategies combining NPIs with targeted antiviral policy are less effective in reducing the overall attack rate, compared to frontline countries above. Pervasive antiviral prophylaxis for 90% of cases, their household, school, and work contacts – involving prompt contact tracing and

treatment within 1 day of symptoms of the case patient – substantially reduces the attack rate even at high levels of infectiousness ($R_0=2$). However, such a policy is unfeasible even in well-prepared countries in conditions of sustained community transmission. A child-first pre-vaccination strategy prioritizing 0-16 year olds with a pre-pandemic vaccine (i.e., offering lower efficacy) in combination with antiviral prophylaxis for 90% cases and close contacts is effective in mitigating the U.S. pandemic. This effectiveness rises if NPIs are added to the strategy. In this study, pre-vaccination policies become more feasible and effective since vaccines can be better matched to the circulating strain and subsequently rapidly produced, with the increase in the delays in importation of the pandemic from abroad (e.g., via 99% effective border controls in the U.S.).

Another modeling study of the U.S. (Germann *et al.* 2006)³⁸ evaluates pre-vaccination policies – termed ‘dynamic’ vaccination in the study – that ramp up to cover most of the susceptible population (i.e., those still uninfected) such that there is substantial protection conferred at the point a pandemic begins to spread within the country. They find a child-first pre-vaccination policy is effective in reducing the overall attack rate even at infectiousness as high as $R_0=1.9$. Dose requirements for the pre-pandemic vaccine can dramatically influence the effectiveness of the policy since they change the size of the covered population for fixed resource availability of antigen. Therefore, a pre-pandemic vaccine requiring two doses is substantially less effective than one requiring a single dose. Given a dosage requirement, the effectiveness of the pre-vaccination policy rises dramatically when combined in a strategy adding TAP and NPIs. For example, a strategy combining random – as compared to child-first – pre-vaccination and NPIs nearly eliminates projected disease incidence in their model even at $R_0=1.9$. The authors observe that delivering a strategy combining NPIs (and/or TAP) and vaccination could be onerous for local governments, even if there are large synergies in terms of delaying the spread of the disease within the country such that more individuals are eligible for the vaccine.

The recommendations of the two modeling studies above that consider mixed strategies are contradicted by studies that consider NPIs in isolation. Of these, Wu *et al.* (2006)²⁷ also assess the feasibility of these NPIs in terms of the demands on local governments and the social and economic burden imposed (via the proxy of the size of peak quarantined population). The study finds that NPIs – even with conservative assumptions on the proportion of cases reported, and compliance with subsequent case isolation or local quarantines – can halve the overall attack rate at $R_0=1.8$. This result is obtained with the assumption of 30% asymptomatic transmission of pandemic influenza, usually a burden on receiving benefits from contact tracing and early isolation of cases. The use of antivirals can be considered to achieve similar mitigation results – if large stockpiles are available – in lieu of isolation of cases and contacts.

Global Policy Implications

Current policy orientation in secondary risk countries remains focused on mitigation, with the objective to lower the overall attack rate while achieving delays in the peak of the epidemic such that a well-matched vaccine strategy could become feasible and local health systems are not overwhelmed. In countries where resources allow it, the strategy emphasizes antiviral prophylaxis for cases and contacts during community transmission alongside nonpharmaceutical measures as appropriate. The efficacy of

antivirals for a future pandemic strain may vary from the known parameters today, and a well-matched vaccine will only be ready with a lag since the beginning of a global pandemic. Additionally, pharmaceutical policies are resource-intensive, which implies only certain countries will be able to use them.

The current distribution of global resources indicates that risk-reduction strategies that emphasize non-pharmaceutical measures alongside techniques to reduce international spread would be valuable from the perspective of secondary risk countries (the majority of countries). However, modeling of NPIs has shown varying effectiveness according to modeled context and historical evidence from the 1918 pandemic. Globally, NPIs have a role in *mitigation* at moderate R_0 and θ , even without antiviral prophylaxis or vaccination in tandem. The timing requirements for NPIs are not more onerous than for drug-based strategies, but they may have significant societal costs. The NPI effectiveness seen in the studies for S.E. Asia is higher than in studies for the U.S., possibly due to model-related factors. The early use of NPI intervention, limited seeding, and the lack of reintroductions in the S.E. Asian models may explain the observed difference. In contrast, for U.S.-specific models, given likely delays in starting interventions, reintroduction risk alongside multiple infection seeds, a persistent decline in susceptibility and infectiousness through pre-vaccination with a pre-pandemic vaccine and/or antiviral prophylaxis is preferred.

However, pharmaceutical policies are resource and capacity intensive, and may be overkill in conditions of moderate R_0 if a strategy of cooperative IATRs mixed with border control/airport quarantine in secondary risk countries is probable and effective in reducing infection seeds. Also, if containment in frontline countries following the WHO Interim Protocol¹ is progressively successful, and more countries cooperate as seen in a recent study⁸⁰ to share antiviral stockpiles, the reintroduction risk globally would fall. In this situation, for countries at secondary risk the policy objective will resemble early containment. This implies that the choice of stringent, layered NPIs at airports and reactive NPIs in communities could minimize the attack rate in secondary risk countries, and be less costly from a social perspective. Backward induction from this insight implies that if international cooperation can be ensured, the pharmaceutical-focused strategy in certain countries should be recalculated.

In situations of higher infectivity (R_0), the primary benefit of NPIs will be to delay peak transmission such that a well-matched vaccination policy becomes viable. However, any such vaccination policy that succeeds internationally will require a plan for the distribution of antigen stocks to resource-poor settings to mitigate the risk of future outbreaks as well as to meet current ethical standards. Early estimation of the infectiousness of the pandemic strain and timely and complete sharing of viral data will be essential in setting international priorities and control strategies.

Note: For specifics on the particular dose and distribution choices for vaccination strategies, see the main text. Also see the main text for details on ethical considerations of particular policies as well as international cooperation on viral data; as well as cost-effectiveness studies of particular control strategies.



Cited References and Notes

- ¹ World Health Organization 2007a "Interim protocol: Rapid operations to contain the initial emergence of pandemic influenza" Geneva: WHO
- ² CDC 2004 "Influenza viruses" Online: www.cdc.gov/flu/avian/gen-info/flu-viruses.htm (6/27/07)
- ³ Longini *et al.* 2005 "Containing pandemic influenza at source" *Science* **309**(12):1083-1087
- ⁴ Risk Management Solutions 2007 "Analytical methods for modeling pandemic flu" Presentation at The World Bank, Washington D.C., April 25, 2007
- ⁵ Ferguson *et al.* 2005 "Strategies for containing an emerging influenza pandemic in Southeast Asia" *Nature* **437**(8):209-214
- ⁶ World Health Organization 2007b "Communicable disease surveillance and response: avian influenza data" Online at: www.wpro.who.int/sites/csr/data/data_Graphs.htm (6/27/07)
- ⁷ Centers for Disease Control 2007 "Interim pre-pandemic planning guidance: community strategy for pandemic influenza mitigation in the United States" Atlanta: CDC
- ⁸ McKibbin *et al.* 2006 "Global macroeconomic consequences of pandemic influenza" Sydney: Lowy Institute for International Policy
- ⁹ Meltzer *et al.* 1999 "The economic impact of pandemic influenza in the United States: priorities for intervention" *Em Inf Dis* **5**(5):659-671
- ¹⁰ Taubenberger *et al.* 2005 "Characterization of the 1918 influenza virus polymerase genes" *Nature* **437**:889-893; Gibbs *et al.* 2006 "Was the 1918 pandemic caused by a bird flu?" *Nature* **440**:E8
- ¹¹ Murray *et al.* 2006 "Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918-1920 pandemic: a quantitative analysis" *Lancet* **368**: 2211-2218
- ¹² Afkhami, A. 2003 "Compromised constitutions: the Iranian experience with the 1918 influenza pandemic" *Bull Hist Med* **77**:367:392
- ¹³ Centers for Disease Control 2006 "Interim guidance on planning for the use of surgical masks and respirators in health care setting during an influenza pandemic" Atlanta: CDC
- ¹⁴ Fraser *et al.* 2004 "Factors that make an infectious disease outbreak controllable" *PNAS* **101**(16):6146-6151
- ¹⁵ Bell *et al.* (WHO Writing Group) 2006a "Nonpharmaceutical interventions for pandemic flu, international measures" *Em Inf Dis* **12**(1):81-87
- ¹⁶ Sertsov *et al.* 2006 "Key transmission parameters of an institutional outbreak during the 1918 influenza pandemic estimated by mathematical modeling" *Th Bio & Med Modelling* **3**:38
- ¹⁷ Eichner *et al.* 2004 "Transmission potential of smallpox: estimates based on detailed data from an outbreak" *Am J Epidemiol* **158**:110-117
- ¹⁸ Pitman *et al.* 2005 "Entry screening for severe acute respiratory syndrome (SARS) or influenza: policy evaluation" *BMJ* **331**:1242-1243
- ¹⁹ Dept. of Health & Human Services 2006 "Pandemic planning update III" Washington DC: DHHS
- ²⁰ World Health Organization 2007c "Questions and answers on pandemic influenza vaccine" Online at: www.who.int/immunization/newsroom/PI_QAs/en/print.html (6/27/07)
- ²¹ Food & Drug Administration 2007 "FDA approves first U.S. vaccine for humans against the avian influenza virus H5N1" Online at: www.fda.gov/bbs/topics/NEWS/2007/NEW01611.html (6/27/07)
- ²² Bansal *et al.* 2006 "Comparative analysis of influenza vaccination programs" *PLoS Med* **3**(10):e387
- ²³ Treanor *et al.* 2006 "Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine" *NEJM* **354**(13):1343-1351
- ²⁴ Riley *et al.* 2007 "Optimizing the dose of pre-pandemic influenza vaccines to reduce the infection attack rate" *PLoS Med* **4**(6):e218
- ²⁵ Ong *et al.* 2007 "John F. Enders lecture 2006: antivirals for influenza" *J of Inf Dis* **196**(2)
- ²⁶ World Health Organization 2006a "Rapid advice guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus" Geneva: WHO
- ²⁷ Wu *et al.* 2006 "Reducing the impact of the next influenza pandemic using household-based public health interventions" *PLoS Med* **3**(9):e361
- ²⁸ Tellier, R. 2006 "Review of aerosol transmission of influenza A virus" *Em Inf Dis* **12**(11):1657-1662
- ²⁹ Li *et al.* 2006 "In vivo protective performance of N95 respirator and surgical facemask" *Am J Industrial Med* **49**:1056-1065

- 30 Toner, E. 2007 "CBN report: surgical masks may provide significant aerosol protection". Online at www.upmc-cbn.org/report_archive/2007/02_February_2007/cbnreport_02152007.html (6/27/07)
- 31 Rvachev *et al.* 1985 "A mathematical model for the global spread of influenza" *Math Bios* **75**(3)
- 32 Stated in another way, herd immunity/effects are the double whammy results of containment policies: antiviral prophylaxis, vaccination, social distancing, etc. People not directly targeted by the intervention are also protected because chains in transmission are broken. For example, vaccinating a high-risk individual also reduces the infectiousness of their close contacts.
- 33 The other is mortality: the more lethal the virus the less an epidemic can spread. Severe complications from the disease – by rendering a person bed-ridden – can do the same.
- 34 Bootsma *et al.* 2007 "The effect of public health measures on the 1918 influenza pandemic in U.S. cities" *PNAS* **104**(18):7588-7593
- 35 Longini *et al.* derived these probabilities based on prior studies of mixing groups from Thailand. If the distribution algorithm has assigned n individuals to that household group, then the average number of effective contacts per infected introduction = $c(n-1)$, where c : 'mixing group specific probability of effective contact per day' age stratified in a household, e.g., child-child, adult-child.
- 36 The probability of infection for a susceptible per day is $p=cx$ (x : per contact transmissibility). For no intervention, a school child is exposed to a number of child and adult infectives in her household, I_{hc} and I_{ha} ; her neighborhood cluster, I_{nc} and I_{na} ; her school I_{es} ; and the two social groups she mixes in, I_{s1} and I_{s2} ; with corresponding transmission probabilities for each contact of p_{hcc} (child to child), p_{hac} (adult to child), p_{ncc} , p_{nac} , p_{es} , p_{s1} & p_{s2} , respectively. The probability P the child becomes infected on the day = $1 - (1 - p_{hcc})^{I_{hc}}(1 - p_{hac})^{I_{ha}}(1 - p_{ncc})^{I_{nc}}(1 - p_{nac})^{I_{na}}(1 - p_{es})^{I_{es}}(1 - p_{s1})^{I_{s1}}(1 - p_{s2})^{I_{s2}}$
- 37 Ferguson *et al.* 2006 "Strategies for mitigating an influenza pandemic" *Nature* **442**(27):448-452
- 38 Germann *et al.* 2006 "Mitigation strategies for pandemic influenza in the United States" *PNAS* **103**(15):5935-5940
- 39 Doyle *et al.* 2006 "Influenza pandemic preparedness in France: modelling the impact of interventions" *J. Epidemiol. Community Health* **60**:399-404
- 40 They use GAR not in the sense of infections (exposures) but the number of clinical cases caused by pandemic flu per unit population during a wave.
- 41 Example – if influenza-related death rates among 20-64 yr olds range between 0.06-0.15 per 1000 persons given a GAR of 15%, does it make economic 'sense' (return a positive net present value) to vaccinate everybody in this age group? They use two scenarios of base vaccine efficacy.
- 42 van Genugten *et al.* 2003 "Pandemic influenza and healthcare demand in the Netherlands: scenario analysis" *Em Inf Dis* **9**(5)
- 43 Institute of Medicine 2006 *Modeling Community Containment for Pandemic Influenza - A Letter Report* Washington DC: The National Academies Press
- 44 If $\rho_{\cdot 0}$ and $\rho_{\cdot 1}$ denote the transmission probability to unvaccinated and vaccinated susceptibles, respectively, where the dot in the subscript can denote any vaccine status or an average across the population, then in $VE_s=(1 - \rho_{\cdot 0}/\rho_{\cdot 1})$, VE_s represents the proportionate reduction in the transmission probability given a specified exposure to infection. Analogously, if $\rho_{0 \cdot}$ and $\rho_{1 \cdot}$ denote the transmission probability from unvaccinated and vaccinated exposed to susceptibles, respectively, where the dot in the subscript can denote unvaccinated susceptibles or an average across the population, then in $VE_i=(1 - \rho_{0 \cdot}/\rho_{1 \cdot})$, VE_i represents the proportionate reduction in the infectiousness of the vaccinated. See: Halloran *et al.* 1999 "Design and interpretation of vaccine field studies" *Ep Rev Vaccines* **21**(73)
- 45 Longini *et al.* 2004 "Containing pandemic influenza with antiviral agents" *Am J of Epidemiol* **159**(7)
- 46 See discussion of such effects in the context of vaccines in Halloran *et al.* 1999
- 47 The assumed rapid spread within a country depends on internal connectivity. In a large country such as the US with sparsely populated areas, but more domestic long- and short-distance travel, differences in attack rates across locations may be equalized as rapidly as 1-2 weeks after the first outbreak, as per Wu *et al.* (references therein). This may not follow in other country contexts.
- 48 This requirement may inflate if the possibility of false positives in case identification – given that symptomatic diagnosis of influenza viral infection is often inaccurate – is considered.

- ⁴⁹ The international quality and currency of outbreak information has improved, based on changes since SARS. The WHO official and rumor surveillance networks, along with the resources of the CDC could ensure that the delays in receiving information may be minor.
- ⁵⁰ Oldham, J. 2005 "LAX plans for bird flu quarantines", The LA Times, October 18
- ⁵¹ CDC 2003 "Revised U.S. surveillance case definition for Severe Acute Respiratory Syndrome (SARS) and update on SARS Cases - United States and Worldwide, December 2003", *MMWR* **52**(49)
- ⁵² Dept. of Health and Human Services 2005 *HHS Pandemic Influenza Plan* Washington DC: DHHS
- ⁵³ The simplest model in Riley *et al.* (2007) is: $a=(1 - p_v*c)(1 - e^{-R_0*a})$ where a is the attack rate, c is the proportion of the population vaccinated, and p_v is the proportion of c who receive complete protection. The first part of the equation describes the initial proportion susceptible and the latter is the overall probability of infection. If p_v is 39% with two 10 μ g doses, then if 20 out of 300 million people in the US are vaccinated, the initially susceptible proportion = $1 - (20/300)*0.39$, and the attack rate drops from the no-vaccination baseline of 73% (at $R_0=1.8$) to 69.5%.
- ⁵⁴ Fraser, C. 2007 "Influenza pandemic vaccines: spread them thin?" *PLoS Med* **4**(6):e228
- ⁵⁵ Bell *et al.* (WHO Writing Group) 2006b "Nonpharmaceutical interventions for pandemic flu, national and community measures" *Em Inf Dis* **12**(1):88-94
- ⁵⁶ Hatchett *et al.* 2007 "Public health interventions and epidemic intensity during the 1918 influenza pandemic" *PNAS* **104**(18):7582-7587
- ⁵⁷ In Hatchett *et al.*, 'timing' of policies could explain only 50% of the variation in total excess mortality across their sample of cities, an indicator closely tied to the CFR. Unknown factors that could account for variation in CFR may include: differences in general public health (which may also tie with observed differences in mortality in Afkhami 2003), varying levels of bacteria in the environment, etc. The authors rule out antigenic variation in the viruses across waves as a factor.
- ⁵⁸ Carrat *et al.* 2006 "A 'small-world-like' model for comparing interventions aimed at preventing and controlling influenza pandemics" *BMC Med* **4**(26)
- ⁵⁹ See Wu *et al.* for a more involved graphical depiction of a stochastic SEIR model.
- ⁶⁰ Wu *et al.* reviewed the available studies on θ and found the range to be 0-50% (based on Rvachev *et al.*). Their assumed value is then slightly above the median.
- ⁶¹ Brownstein *et al.* 2006 "Empirical evidence for the effect of airline travel on inter-regional influenza spread in the United States" *PLoS Med* **3**:e401; Viboud *et al.* 2006 "Air travel and the spread of influenza: important caveats" *PLoS Med* **3**(11):e503
- ⁶² Cooper *et al.* 2006 "Delaying the international spread of pandemic influenza" *PLoS Med* **3**(6): e212
- ⁶³ Epstein *et al.* 2007 "Controlling pandemic flu: the value of international air travel restrictions" *PLoS One* **2**(5):e401
- ⁶⁴ Epstein *et al.* conclude that pandemics that originate in January in Hong Kong could, due to effective international air travel restrictions, lead to a peak in the temperate Northern hemisphere in September. Therefore, the delay of epidemic introduction would push major transmission into the influenza high season, leading to more cases. This assumes that pandemic influenza A would demonstrate similar seasonality in their infectivity as interpandemic strains. This effect would be reversed for a July start to the pandemic in the tropics, which would cause a peak in spring.
- ⁶⁵ Jani, M. 2005 "Modeling the large scale disruptions of an airline network" *J Trans Engg* **131**(4): 249-260. For more on the hub-and-spoke nature of the international network in the context of communicable disease spread, see Colizza *et al.* 2006 "The role of the airline transportation network in the prediction and predictability of global epidemics" *PNAS* **103**(7):2015-2020
- ⁶⁶ Pandemics of severity category 1-5, based on their CFR. See CDC 2007, Table A, pp. 12
- ⁶⁷ Susarla, A. 1996 "Plague in Surat, India" Unpublished. Clark University Gr. School of Geography.
- ⁶⁸ Hai *et al.* 2004 "The short-term impact of SARS on the Chinese economy" *Asian Econ Papers* **3**(1):57-61
- ⁶⁹ Lee *et al.* 2005 "The impact of the SARS epidemic in Taiwan: implications for human resources, labour markets, and unemployment in the service sector", Working Paper Series, Judge Business School, University of Cambridge
- ⁷⁰ Siu *et al.* 2004 "Economic impact of SARS: the case of Hong Kong" *Asian Econ Papers* **3**(1):62-83

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- ⁷¹ Brahmabhatt, M., Dutta, A. 2008 "On SARS type economic effects during infectious disease outbreaks," Policy Research Working Paper #4466, The World Bank: Washington, DC.
- ⁷² Emanuel *et al.* 2006 "Who should get influenza vaccine when not all can?" *Science* **312**:854-8555; also see *Letters* in the same issue critiquing Emanuel *et al.* (from Frey, H., and Galvani *et al.*)
- ⁷³ World Health Organization 2006b "Global consultation on addressing ethical issues in pandemic influenza planning: summary of discussions" Geneva: WHO
- ⁷⁴ Gostin, L. 2006 "Public health strategies for pandemic influenza: ethics and the law" *JAMA* **295**(14):1700-1703
- ⁷⁵ Huang, Y. 2004 "The SARS epidemic and its aftermath in China: a political perspective" in *Learning from SARS: Preparing for the Next Disease Outbreak* Washington DC: National Academies Press
- ⁷⁶ Fidler, D. 2004 "SARS: political pathology of the first post-Westphalian pathogen" in *Learning from SARS: Preparing for the Next Disease Outbreak* Washington DC: National Academies Press
- ⁷⁷ World Health Organization 2006c "Avian and pandemic influenza: developments, response and follow-up, and application of the International Health Regulations" Geneva: WHO
- ⁷⁸ World Health Organization 2007d "Best practice for sharing influenza viruses and sequence data" Report by the WHO Secretariat to the Executive Board, Geneva: WHO
- ⁷⁹ For a true or 'pure' public good, it would be necessary that it possess a 'non-excludable' nature, i.e., it would be too expensive to exclude anyone from using it; and is 'non-rival' in consumption, i.e., use by one person would not diminish its availability for another.
- ⁸⁰ Colizza *et al.* 2007 "Modeling the worldwide spread of pandemic influenza: baseline case and containment interventions" *PLoS Med* **4**(1):e13
- ⁸¹ Flahault *et al.* 2006 "Strategies for containing a global influenza pandemic" *Vaccine* **24**(44-46):6751:6755