Modeling Community Containment for Pandemic Influenza

A Letter Report

Committee on Modeling Community Containment for Pandemic Influenza
Board on Population Health and Public Health Practice

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Willing is not enough; we must do."
—Goethe

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COMMITTEE ON MODELING COMMUNITY CONTAINMENT FOR PANDEMIC INFLUENZA

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **David R. Challoner**, Vice President for Health Affairs, Emeritus, University of Florida. Appointed by the National Research Council, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Admiral John Agwunobi, M.D., M.B.A., M.P.H.
Assistant Secretary for Health
US Department of Health and Human Services

Dear Dr. Agwunobi:

On behalf of the Institute of Medicine (IOM) Committee on Modeling Community Containment for Pandemic Influenza, I am pleased to report our conclusions and recommendations. The committee was charged with convening a major workshop to review: (1) the quality of existing models about a potential influenza pandemic and their utility for predicting the effects of various community containment policies on disease mitigation; (2) the available science and previous analyses of the efficacy of community mitigation approaches; and (3) the historical record of community interventions utilized during previous influenza pandemics and other relevant outbreaks. The committee was asked to prepare a letter report based primarily on information from the workshop that includes conclusions and recommendations, based upon available evidence, regarding:

- Strengths and weaknesses of the models presented, and strategies to improve predictive ability and usefulness;
- Conclusions that can be drawn from the historical record and available science, gaps in current knowledge, and approaches that would narrow these gaps; and
- Whether community-wide interventions have a role in reducing infection transmission and the community impact of implementing community containment strategies.

The need for this report stems from a concern by scientists and policymakers that the US may soon face a pandemic in which neither vaccines nor sufficient antivirals will be available to protect the public. Some have argued that nonpharmaceutical community containment strategies may help in the absence of sufficient medical interventions. There has been some research—historical and modeling—examining the possible utility of these strategies. The committee was convened to assess the possible utility of these strategies and to formulate conclusions and recommendations for policymakers. While the report's primary and intended purpose is to advise policymakers, the committee hopes this will be useful in educating other stakeholders about pandemic influenza, including current state-of-affairs, state of science, and ongoing considerations for confronting the disease. The committee understood its charge to be to address the utility of community containment strategies during a severe pandemic. Although there is no formally agreed-upon definition of "severe", most influenza experts apply the term to influenza pandemics similar to that of 1918, rather than the pandemics that occurred in 1957 or 1968.

This report is organized into six sections, beginning with a review of key characteristics about the epidemiology of influenza and what it might tell us about the next pandemic influenza. This is followed by a discussion of the mathematical models of containment strategies for pandemic influenza. The third section includes the committee's evaluation of the models for community containment. The fourth section reviews historical analyses of the effectiveness of community containment strategies used in previous pandemic outbreaks. The fifth section assesses the role for community interventions in reducing pandemic influenza virus transmission. Table 1 provides a summary of the committee's conclusions regarding the community interventions and Table 2 provides a listing of the recommendations. These tables can be found at the end of the report.

INFLUENZA EPIDEMIOLOGY

Influenza, an infectious disease that causes an estimated 36,000 or more deaths in the United States during a typical influenza season, has a clinical attack rate that is highest in young children but a case-fatality rate that is highest in the elderly. One measure of infectivity is "R_0", the average number of secondary cases of disease generated by a typical primary case in a susceptible population. Influenza has an R_0 that typically ranges from 1.5–3.[1] The United States' vaccination strategy has long been geared to decreasing individual risk, rather than community transmission, by focusing on the elderly and those with chronic health care conditions that increase the risk for severe illness, hospitalization, or death. Recently, the recommendations for vaccination have expanded to include young children and people over 50 years of age. The incubation period for seasonal influenza is approximately 2 days (range is 1–4 days) and is most communicable beginning 1 day before onset of symptoms and up to five days thereafter. Despite the cumulative toll of influenza in the United States and the rest of the world, there remain key unknowns that are relevant to discussions of pandemic influenza. A significant unknown relates to the mode of transmission of influenza; namely, is the virus is primarily transmitted through droplets, aerosol, or contact with fomites.[2] This uncertainty is significant because it calls into questions some key "tried and true" interventions that are used for protecting against seasonal influenza, as will be described in subsequent sections. There are also unknowns about the virus itself—particularly what changes in the virus are predictive of infectivity, case-fatality, and responsiveness to antiviral drugs. All these uncertainties are magnified when considering pandemic influenza.

Three previous pandemics occurred during the 20th century.[3] The 1918-1919 pandemic (often referred to as the "Spanish influenza") was associated with 500,000 deaths in the United States and over 20 million (and possibly up to 100 million) deaths worldwide. The subsequent pandemics were milder. The 1957 "Asian influenza" was associated with 69,800 deaths in the US and the 1958 "Hong Kong influenza" with approximately 33,800 deaths in the US. The 1918-1919 pandemic was unusual in that significant mortality occurred in young, healthy adults, in addition to groups usually affected by influenza, such as infants, the elderly, and the ill.

As has been said many times, a pandemic of influenza is "long overdue". There is little doubt that the world will experience another pandemic, but there are many uncertainties about this pandemic. For instance, no one knows when the pandemic will occur. It could arrive soon, emerging from mutations and/or reassortment of the currently worrisome H5N1 virus circulating in wildlife in Asia, eastern Europe, and Africa. The currently circulating H5N1 virus could also remain primarily a virus of wildlife and poultry and never become a significant human pathogen. The next pandemic virus might not be

[1] Measles, for example, is much more infectious and has an R_0 of approximately 10.
[2] An inanimate object that can transmit infectious agents from one person to another through contact or touching.
[3] See http://www.hhs.gov/nvpo/pandemics/flu3.htm for more information.

of the AH5N1 type[4] at all. This brings into question the utility and potential effectiveness of the current antiviral drugs currently being stockpiled and the vaccines being developed now for use in a future pandemic.

Other important uncertainties include clinical and epidemiological characteristics, such as the case-fatality rate, infectivity, incubation period, the lag between onset of symptoms and infectivity, serial interval, and the age-specific attack rate. It is unclear where the pandemic will emerge. Many people *assume* the pandemic will start in Asia and that the United States, particularly the less densely populated and less-traveled central region and will experience an important time lag between when the pandemic is recognized overseas and when it hits the United States. It is in the context of these many uncertainties that the committee prepared its conclusions and recommendations.

Information on the workshop that informed much of the committee's discussions can be found at http://www.iom.edu/CMS/3793/37624.aspx. The committee reviewed information from models and from history, as per the charge. The committee also reviewed other "available science", particularly from expert opinion reviews. The committee also heard from a panel of stakeholders at the workshop who provided valuable insights regarding the potential impact of community interventions.

The committee chose to include targeted antiviral prophylaxis and treatment as a community containment strategy. Because a stated goal of community interventions is to delay or dampen the epidemic until a vaccine is available, the committee does not review the effect of vaccine in this report. It is widely assumed, and the committee agrees, that rapid availability of an efficacious vaccine is desirable and most likely to affect the course of a worldwide pandemic.

MODELS OF CONTAINMENT STRATEGIES FOR PANDEMIC INFLUENZA

A number of mathematical models have been developed to evaluate alternative strategies to mitigate the effects of pandemic influenza. This report reviews models that were specifically developed to assess potential community containment strategies of pandemic influenza. First an overview of models and their role in policy decisions is presented. Next is a synopsis of the models presented to the committee at its workshop in October 2006. The report then outlines the strengths and weaknesses of these models and suggests ways to improve their predictive ability.

Role of Models in Policy Decisions

A model is defined as "a simplified or idealized description or conception of a particular system, situation, or process (often in mathematical terms) … that is put forward as a basis for calculations, predictions, and further investigation" (Oxford English Dictionary, 1989). Models represent an idealization of the truth, but in such a manner that they aim to reflect reality. Models serve to organize and synthesize data from a variety of

[4] 1918 virus was AH1N1, 1957 was AH2N2, and 1968 was AH3N2. The seasonal influenza vaccine for 2006 protects against AH1N1 ("New Caledonia"), AH3N2 ("Wisconsin"), and influenza B ("Shanghai").

sources, identify data gaps, and to set priorities for further data acquisition. Modeling can also be used to promote dialogue between scientists, policymakers, and stakeholders about alternatives, uncertainties, assumptions and value judgments that underlie decisions.

Models are regularly used to inform policy decisions in many areas such as military planning, environmental regulation, transportation planning, social programs, and health-care decisions (NRC, 1991; Weinstein et al., 2001). Model-based analyses have appeared with growing frequency in the infectious diseases literature. For example, models have been used to examine the potential clinical impact and cost-effectiveness of interventions to prevent tuberculosis (Brewer et al., 2001), HIV infection (Kahn, 1996, 1998; Owens et al., 1998), and opportunistic infections in HIV-infected individuals (Ioannidis et al., 1996; Bayoumi and Redelmeier, 1998; Rose, 1998; Goldie et al., 2002).

Models exist on a spectrum ranging from very simple to very complex. The choice of model and its complexity, resolution, and descriptive accuracy should be largely driven by the user and its purpose. It is important to realize, however, that even the most complex model is a simplification compared to the real world.

Because all models are based on some extrapolation, some degree of uncertainty is inherent in all models. There are two major sources of uncertainty: parameter uncertainty and model uncertainty. Parameter uncertainty arises from imprecision and variation in the estimation of the input data values that are used in the model. This kind of uncertainty is typically managed via sensitivity analysis which explores how robust the results are in the face of alternative input data values. Model uncertainty arises from the structure of the model itself (e.g., choice of variables; degree of detail; approach to the statics/dynamics of the interactions being simulated, etc.). Model uncertainty can greatly affect model output and is much more difficult to manage. Methods for managing this kind of uncertainty include: comparisons across competing models; and tests of face validity, relying heavily upon expert judgment as to the inherent reasonableness of the model as a representation of reality; tests of predictive validity using independent sources of data. In order to be of use to decision makers, results generated by models should be accompanied by rigorous estimates of parameter and model uncertainty. For these reasons, investments in data and model validation are critical (NRC, 1991).

Above all, models should be viewed as aids to decision-making, rather than substitutes for decision-making. The notion that models can somehow provide the “right” answer is erroneous. Models can be enhanced or improved with additional time and investment, but there is also a cost for obtaining additional data and that trade-off should be weighed (Weinstein et al., 2001). Similarly, a “one-size-fits-all” approach to modeling is not appropriate. Many policy decisions may require more than one modeling technique and models sometimes incorporate a combination of approaches (NRC, 2001).

In short, the value of modeling lies in its ability to focus attention on those uncertain parameters that appear to have the greatest consequences for the outcomes of interest, to help different individuals focus systematically on parts of the larger problem without losing sight of the whole, and to inform consideration of policy alternatives.

Simulation Models of Containment Strategies for Pandemic Influenza

At the workshop held in Washington, DC, on October 25, 2006, the committee heard presentations regarding six models specifically evaluating the role of nonpharmaceutical interventions (NPI) in mitigating a pandemic influenza outbreak.[5] While other models have examined the potential role of vaccines in reducing pandemic influenza spread, those analyses are not the focus of this report.

Both unpublished and published models were presented at the committee's workshop. While the following description summarizes the key design features and findings of these models, it is not intended to be a comprehensive review. The committee's description of these models should not be viewed as agreement with or endorsement of their methods or findings. Furthermore, the results of unpublished models that have not undergone formal peer-review should be interpreted with caution.

Modeling Influenza in Households

The committee first heard from Dr. Larry Wein, who presented an unpublished analysis to assess the effectiveness of nonpharmaceutical interventions during a severe influenza outbreak assuming: (1) no vaccine and a limited supply of antivirals, and (2) that most sick individuals would be cared for at home because hospitals would be too overwhelmed to treat all cases. His model was motivated by the observation that without an understanding of the likely route of transmission (i.e., aerosol, droplet, or contact), it would be difficult to understand how effective certain infection control measures, such as hand washing or face protection, would be in preventing transmission (Wein and Atkinson, 2006).

He estimated the probable route for influenza transmission using historical data on influenza and rhinovirus.[6] He first formulated a simple model of transmission within a household. He then estimated various parameters necessary for his model for rhinovirus transmission, then extrapolated these findings to infer transmission of influenza. His review of the data suggested aerosol transmission as the primary form of transmission for influenza. The model also suggested that droplet transmission was an unlikely mode of transmission, and that contact transmission played a comparatively small role. He then extended this "in-household" model to a simple "between household" model to develop a "hierarchical epidemic model" (Wein and Atkinson, 2006).

His model predicts that short-range aerosol transmission would be the dominant mechanism of transmission for influenza, a finding that implies the importance of face masks (specifically N95 respirators or modified surgical masks) and, to a lesser extent, room ventilation, humidifiers, and social distancing in reducing transmission. His find-

[5] The committee was aware that the MIDAS modelers were specifically commissioned to prepare models that could inform federal policymaking. During preparation for the workshop, three additional relevant models were brought to the committee's attention as possible contributors. The committee is aware that other models of potential relevance are in different stages of development and analysis.
[6] Rhinovirus is the cause of the common cold.

ings further imply that hand washing would have little or no impact in limiting the spread of influenza infection.

Wein's analysis sheds important light on blind spots in current thinking and raises questions about assumptions that were implicit in the other models presented. Specifically, his model highlights the significant uncertainty that surrounds the modes and mechanisms of influenza transmission, suggesting this as an important area for future study. In addition, Wein's analysis forces us to ask whether minimizing influenza transmissions is too narrow an objective, emphasizing the critical importance of further research to address these issues.

MIDAS Models of Targeted Layered Containment

Another group of models presented at the workshop was developed by researchers from the Models of Infectious Disease Agent Study (MIDAS) network, sponsored by National Institute of General Medical Sciences, National Institutes of Health. MIDAS is a collaborative network of scientists involved in research of computational and mathematical models to prepare the nation for outbreaks of infectious diseases. MIDAS was not developed as a response to the threat of pandemic influenza; rather it was conceived as a research project that would further develop and improve the science of modeling infectious disease spread.

One of the MIDAS pandemic influenza projects involved creating simulation models to examine the robustness of community containment strategies in mitigating a pandemic in the United States, assuming a limited supply of antivirals and no vaccine (Berg, 2006). Three MIDAS researchers constructed models to evaluate the effectiveness and robustness of a combination of interventions referred to as "targeted layered containment" (TLC) in mitigating a pandemic influenza outbreak in the United States. TLC includes a combination of interventions that includes: targeted antiviral treatment and isolation of ascertained cases, targeted prophylaxis and quarantine of household contacts of index cases, school closure and keeping children at home for the duration of the closure; social distancing in workplace (e.g., via telecommuting), and social distancing in the community (e.g., cancellation of public events) (Barett et al., 2006). The decision to model this particular combination of interventions was driven by discussions with policymakers who were concerned that, in the likely absence of an effective vaccine and with a limited antiviral supply, none of the interventions used alone would be sufficient to contain an outbreak in the United States. However, they thought that when these interventions were combined or "layered", they might have additive or potentially synergistic effects (Cetron, 2006). Furthermore, because of the time required to increase vaccine production and because of the anticipated limited availability of antivirals, various "social distancing" measures may be the primary interventions for some portion of the epidemic.

The three MIDAS models are referred to in this report as: University of Washington/Hutchinson Cancer Center/Los Alamos National Laboratories model (UW/LANL) (Germann et al., 2006), the Imperial College/University of Pittsburgh model (Imperial/Pitt) (Ferguson et al., 2006), and the Virginia Bioinformatics Institute at Virginia Tech model (VBI) (Eubank, 2005; Lewis et al., 2006). The details of these models are well described in the referenced publications and are therefore not discussed here. Below is a summary of the main similarities and differences between the models and their results. A more detailed comparison of the models can be found in Barett et al. (2006).

All three models are individual-based, stochastic simulation models that simulate a pandemic outbreak in a population of 8.6 million similar to that of Chicago (Barrett et al., 2006). Two models (UW/LANL and Imperial/Pitt) supplemented these analyses with large-scale simulations in the United States (Ferguson et al., 2006; Germann et al., 2006). Each model is based on a social structure where individuals can mix within households, schools, workplace, and the community. Models assumed that transmission could occur in any of these groups, although there were different assumptions about the proportion of transmission occurring in these areas (Barett et al., 2006).

As noted, all three models evaluated the same basic set of interventions known as TLC. The primary outcome measures in the models were influenza illness attack rates and courses of influenza antivirals used. The models examined the sensitivity of these two outcome measures to changes in levels of case ascertainment, compliance with interventions, thresholds for initiating interventions (in terms of the percent of population developing influenza), and transmissibility of the virus (Barett et al., 2006).

Key differences between the models are how the social networks were constructed and the assumptions about how people interact with one another (Barrett et al., 2006). Because of the complexity of the social structure in each model, the committee does not discuss them here. Details regarding construction of the social network in each model are described elsewhere (Eubank et al., 2004; Ferguson et al., 2005, 2006; Germann et al., 2006; Lewis et al., 2006). In general, assumptions about contacts and social networks have implications for the effectiveness of alternative interventions.

Another important difference is that each model makes different assumptions about the degree of transmission occurring in schools and among youth and its role in propagating the epidemic. The Imperial/Pitt model had the most conservative assumptions about the degree of transmission that occurs in schools and therefore has the most conservative predictions about the effects of school closure. The Imperial/Pitt models found that closing schools either as an isolated intervention or coupled with treatment would not reduce overall attack rates, but would flatten the peak and lengthen the epidemic period (Ferguson, 2006). The Sandia National Laboratories model (discussed below), which was not part of the MIDAS group but which did focus on many of the TLC interventions, assumed a high degree of transmission in schools and among children and therefore predicts that school closure is an extremely important intervention and that using it alone can substantially reduce overall attack rates (Glass et al., 2006a,b). The VBI and UW/LANL models fall into the middle of the spectrum, with VBI being more conservative than UW/LANL in assumptions about the importance of school transmission.

Assumptions about the natural history of the disease also varied across the three models. For example, the IMP/Pitt model assumed peak infectiousness to be prior to the onset of symptoms, while infectiousness in the UW/LANL and VBI models was assumed to be flat. The implication of these differences is that the targeted interventions, which rely on case ascertainment (treatment and isolation of sick patients and prophylaxis and quarantine of household contacts), are less effective in the Imperial/Pitt model than the in other two models (Barett et al., 2006).

Beyond uncertainty about the nature of the pandemic virus and its implications for the epidemiology of the disease, other key uncertainties in the MIDAS models include: the proportion of transmission occurring in different settings (home, school, workplace, and community), the lethality and risk groups for severe illness, effectiveness of social distancing measures, population compliance with interventions, the behavior of the population independent of interventions (e.g., people may spontaneously avoid travel or public places), quality and timeliness of case ascertainment, and logistical constraints (Ferguson et al., 2006).

Although the structure of each model is different, the authors report that the results regarding the effectiveness of interventions are qualitatively similar. All three models predict that TLC would be effective, even with modest compliance with interventions, in reducing the transmission of influenza in an immunologically naïve population. The authors conclude that at an R_0 of 2 (similar to that of 1918 epidemic), timely implementation of TLC measures can reduce overall attack rates. Early isolation of sick individuals and closure of schools were key drivers in these findings (Barett et al., 2006).

Sandia National Laboratories

Dr. Robert Glass from Sandia National Laboratories (SNL) presented the results of a model examining the effectiveness of community containment strategies during an outbreak (Glass et al., 2006a,b). Similar to the MIDAS models, this model focuses on social distancing interventions to limit influenza (assuming a limited availability of antivirals and low-efficacy vaccine). Specific interventions examined include: school closure, child/teen social distancing, adult and senior social distancing, home quarantine, targeted antiviral treatment for diagnosed individuals, antiviral prophylaxis of household members, and extended antiviral prophylaxis of persons linked through house, school, work, and neighborhood contact.

In brief, SNL researchers designed a network-based simulation model for the spread of influenza in a stylized community of 10,000 people representative of a small town in the United States. Similar to the MIDAS models (although the details differ), SNL researchers built a social contact network linking individuals to one another in the context of a community. Their network was developed by specifying groups of a certain size where people interact (e.g., schools, houses, clubs, etc.). The spread of influenza was simulated by imposing behavioral rules for these individuals, their contacts, and the disease (Glass et al., 2006b). The rules were then modified to simulate interventions in the community, which were then evaluated for their effectiveness. The simulation model was run using a matrix of containment strategy combinations. The SNL researchers then examined the impact of these containment strategies on overall attack rate and epidemic peak size. Details of the model can be found in Glass et al. (2005, 2006b).

Based on the social network design which assumes a high rate of contact among children and teens, as well as a higher infectiousness among this group, this model results emphasize the importance of interventions targeting this group. Assuming an infectivity similar to that of the moderate 1957–1958 influenza pandemic, this model predicts that closure of all schools (universities excluded) and keeping children at home—in the absence of other interventions—would be effective in significantly lowering the overall attack rate and averting an epidemic in the simulated community. Assuming infectivity similar to that of the severe 1918–1919 pandemic influenza, the model indicates that social distancing interventions for both adults and children are needed in order to reduce the overall attack rate and contain the epidemic. As R_0 increases, the model predicts that an increasing number of social distancing measures would be required to reduce the overall attack rates. They argue that social distancing measures should be applied first, and then followed by targeted strategies focused on diagnosed cases. They also found that pre-pandemic vaccination, assuming 7 percent coverage and 50 percent efficacy, would not reduce influenza transmission and that instead vaccines should be reserved to keep critical people at work. Finally, they found that an influx of individuals from other communities reduces the effectiveness of community containment strategies and increases the duration that strategies must be applied (Glass et al., 2006b).

Beyond assumptions about the virus strain and social network structure, the results depend on a number of key assumptions, some of which may not be realistic in all communities. For example, the model assumes that all mitigation strategies begin after 10 individuals are diagnosed within the community, that adults are able to stay home to care for the sick or watch children following school closure, and that there is high compliance with interventions (90 percent). Several sensitivity analyses were conducted to examine the impact of changes in individual parameters on attack rates, including compliance with interventions, implementation threshold (number of cases diagnosed before intervention measures are implemented), disease manifestations (e.g., period of infectivity; asymptomatic infected vs. symptomatic infected), and infectious contact network. The model results were found to be highly sensitive to a reduction in compliance and changes in the contact network.

RAND Model

Dr. Steven Bankes presented an unpublished model developed by the RAND Corporation that examined the robustness of models of NPIs to reduce the spread of influenza (Bankes et al., 2006). He noted that a major challenge in the quantitative modeling of effectiveness of NPIs is the substantial uncertainty regarding the magnitude of the effects. The RAND researchers sought to identify conclusions that were robust or stable across the range of uncertainty. In particular, they looked for policies that would generate outcomes that meet or exceed an acceptable level of performance in most if not all plausible scenarios. This approach avoids the instability that can result from selecting policies that are optimal in a single specific or "most likely" scenario but could fail under the specific conditions that prevail in an actual future pandemic (Bankes et al., 2006).

The RAND developed a model of the natural history and time course of a hypothetical avian influenza pandemic. The model tracks the flow of individuals as they move in and out of different influenza health states[7] and counts the number of people in each of these states over time. They then developed a corresponding policy model to isolate and analyze the effect of different NPIs on the flow of patients from one health state to another. The policy model allows one to examine the effects of individual and grouped NPIs on outcomes of interest (e.g., morbidity, mortality). The policy and epidemiology models were linked by specifying how certain categories of NPIs (in the policy model)

[7] Health states include susceptible, latent infection, sub-clinical infection, symptomatic illness, diagnosed, dead, and recovered.

would affect the flow of individuals from one health state to another (in the epidemiology model).

The 17 NPIs evaluated in the model include: hand hygiene, respiratory etiquette, surgical masks,[8]* domestic travel restrictions, canceling community events, school closure, workplace closure, voluntary self-isolation, voluntary quarantine, mandatory isolation , limited mandatory quarantine, N95 respirators,* other personal protective equipment (PPE),* surveillance, contact tracing, and rapid diagnosis. They also evaluated a group of NPIs (hand hygiene; respiratory etiquette; surveillance; rapid diagnosis; social support; voluntary self isolation; domestic travel restrictions; surgical masks;* N95 respirators;* other PPE*) designed to reflect the preferences of experts expressed during a meeting on this issue ("Expert Choice") (See section below on "Other Evidence Reviewed" for a description of the expert evaluation process and its outcomes) (Bankes et al., 2006).

In the absence of data about the effectiveness of NPIs in a pandemic scenario, the modelers made educated guesses about the "base case" strengths of these effects and assumed large uncertainty ranges based upon a combination of secondary sources in the literature, personal communication with experts and the results of a conference of experts held in January 2006. They then analyzed how alternative assumptions would affect policy recommendations.

The RAND researchers ran the linked epidemiology and policy effectiveness models 1,000 times while randomly varying all inputs and determined the most effective NPI for each of the 1,000 situations. Of the 1,000 model simulations, in which assumptions were varied over all plausible ranges, the "Experts Choice" package of relatively simple and economically non-disruptive interventions was most effective in 974 simulation (97.4 percent). This suggests that the group of NPIs recommended by the expert panel is a rather robust policy option, even when compared with more aggressive alternatives such as school closure or cancellation of public events (Bankes et al., 2006).

They also found that the choice of NPIs is most important in a moderately severe epidemic, because in mild epidemics many NPIs are viewed as being effective, and in very aggressive epidemics, most are not. However, they found that the relative ranking of the NPIs varies little with changing epidemic scenarios (Bankes et al., 2006).

EVALUATION OF MODELS OF COMMUNITY CONTAINMENT

The committee was asked to evaluate the strengths and weaknesses of the models and to provide suggestions for improving their predictive ability. Rather than providing a critique of each model, the committee comments on the general strengths and limitations of the state of modeling for pandemic influenza and areas where models could be improved to aid policymakers.

In terms of strengths, the committee found that the models were useful in organizing the current state of knowledge about potential responses to influenza pandemic. The models helped articulate alternative strategies, available information, and gaps in knowledge so that policymakers could have a more informed discussion, and also so that improved questions and data could be developed for the next iteration of pandemic planning

[8] * To be applied in ambulatory and hospital settings only.

and modeling efforts. In addition, the models highlighted important areas of uncertainty and topics for future research, as discussed below. Similarly, the models examined a wide range of interventions. Furthermore, the discussions at the workshop served as an important forum for open dialogue among policymakers at various levels, modelers, researchers, and other stakeholders.

As noted, however, it would be a mistake for policymakers to assume that any of these models can provide an exact roadmap of actions to take during the next influenza pandemic. Comments at the workshop suggested that some policymakers might be seeking guidance about which model(s) are 'best' and can be relied upon in forming their strategy. While there are ways to improve the predictive ability of the models and their utility for decision making, the models should serve primarily as a tool to aid in open discussion for making explicit alternative strategies, assumptions, data, and gaps. The committee believes that the models presented at the meeting were helpful in that regard.

The committee identified a number of limitations in the current models and areas for further research. Not all models suffered from these limitations, but the issues outlined below represent common difficulties with the present state of modeling influenza epidemics.

A major limitation of the models is the uncertainty in many of the assumptions. There is little evidence to support many of the key parameters, such as transmissibility of the virus, natural history of the disease and its implications for infectivity, the effectiveness of social distancing interventions, and compliance with interventions (Morse et al., 2006).

Recommendation 1: The committee recommends the development of a research agenda to answer critical research gaps and better inform pandemic influenza planning. A priority topic would be to answer fundamental questions about influenza virus transmission and epidemiology. Prospective epidemiological studies of seasonal influenza should be strongly considered as a supplement to passive surveillance. Observational or randomized studies should also be undertaken to evaluate the effectiveness of certain interventions in community settings. Results of these studies should be incorporated into the various models of pandemic influenza as appropriate.

While more research can help to reduce the uncertainty inherent in certain assumptions, additional effort is needed to quantify and categorize the uncertainty related to the models. As noted, it is important to consider both model and parameter uncertainty. It is insufficient to provide standard errors, whose size can be influenced by replications and the magnitude of simulation sample sizes. It is also insufficient to perform only a few sensitivity analyses on a subset of parameters; these only provide a measure of model sensitivity to individual parameter specifications. The committee believes that the models presented at its October 25, 2006, workshop, sometimes accompanied by standard errors and sometimes accompanied by sensitivity analyses, generally lacked a realistic measure of uncertainty.

Recommendation 2: The committee recommends that modelers develop improved estimates of model and parameter uncertainty.

The models that included school closure as an intervention option lacked nuance in their modeling of this intervention. All of the models designated schools as either "open" or "closed". Practically, however, policymakers might consider a broader range of options. For example, one might consider closing elementary schools but not high schools or instituting only partial closings. Incorporating a measure of probability of closure into the models might also be useful. For example, one might construct a model that could analyze the proportion of schools that would have to close or the proportion of children that would have to stay home to reach 50, 80, or 90 percent of the benefit of a full closing. Further research on the effectiveness of school closures in reducing influenza transmission would be helpful in answering these types of questions.[9] Many of the same questions could be applied to models that examine potential workplace closures.

Recommendation 3: The committee recommends that models examining the potential effectiveness of school and workplace closures on mitigating pandemic influenza include a broader range of closure options in their analyses.

Another limitation of current models is their focus on a narrow set of influenza-related outcome measures, which ignores the broader cost-benefit tradeoffs of alternative intervention strategies. For example, one might weigh the costs associated with a school closure against its benefits. Costs need not necessarily be measured in dollars; costs can also include other benefits forgone (e.g., health benefits). The potential benefits of school closing might take the form of reductions in influenza transmission to the adults living in households that include school-age children. However, the costs or risks associated with extended school closings are largely non-influenza-related and mostly affect the children themselves. For example, some might experience increased exposure to violence in communities or poor nutrition due to lack of free or subsidized school lunches. These costs would not be captured in a model that focuses only on influenza-related outcomes. It would be important to weigh benefits and costs for epidemics of different severity. Indeed, employing a broad range of social interventions may entail a cost greater than the pandemic itself (Ferguson, 2006). To that extent, the models presented could be improved by expanding their focus beyond influenza-related outcomes to include a broader range of outcomes.

Recommendation 4: The committee recommends that future modeling efforts incorporate broader outcome measures, beyond influenza-related outcomes, to include the costs and benefits of intervention strategies.

Finally, the committee believes that the scope of models being considered by policymakers should be expanded. Some policymakers appear to be placing significant emphasis on the three MIDAS models evaluating the effectiveness of TLC, to the exclusion of other potential models that could be informative. While the MIDAS models certainly provide valuable insights, they were all designed with the same set of policy questions, interventions, and outcome measures. Because of the significant constraints placed on the models, it is not surprising that the results of the three models were similar. Other types of models have been developed that could inform policy on pandemic influenza and

[9] See section below in "Historical Analyses" on modeling of French seasonal influenza surveillance data by Ferguson and colleagues for an example of current efforts to evaluate the effectiveness of school closures.

should also be explored. These include, but are not limited to, models at the national level, air-traffic related disease spread models, symptom-based behavioral response models, and multi-agent network models of disease propagation. Much of this additional modeling effort has been supported by other federal agencies such as Air Force Office of Scientific Research, Office of Naval Research, and Defense Advanced Research Projects Agency.

Recommendation 5: The committee recommends that policymakers consider a broader set of models to inform strategies and policies regarding pandemic influenza.

It is important to recognize that policy decisions will have to be made over a sustained period of time. Modeling is an iterative process and emphasis needs to be placed on continuing to improve the existing models. Increased public dialogue among policymakers, modelers, and stakeholders is also necessary for improving the models.

Recommendation 6: The committee recommends that policymakers regularly convene forums for public dialogue on pandemic influenza modeling and analyses, and recommends the development of a standing expert panel to provide ongoing advice regarding models of pandemic influenza.

Methods for Improving Predictive Ability of Models

The committee was also asked to comment on ways to improve the predictive ability of the models and methods for narrowing existing gaps in knowledge. One way to improve predictive ability is to adapt or construct decision-aid models that can incorporate surveillance data in real time and adapt to the actual experiences of an outbreak as it occurs. Current models are based on educated guesses for a range of plausible values based on information from previous pandemics. As a result, they are not able to predict with any certainty the future course of a pandemic and the effectiveness of interventions to reduce transmission. However, this uncertainty can be improved by incorporating information from surveillance during the pandemic (see, for example Wallinga and Teunis, 2004; Cauchemez et al., 2006). By using surveillance information once the pandemic starts, it is possible to narrow the probable values on factors such as transmissibility and antiviral resistance. This information can then be incorporated into the models to obtain more realistic estimates. The committee did not judge any of the models on their ability to adapt to surveillance information. Some models may be more easily linked to surveillance data than others. For example, some very complex models cannot be readjusted to provide real-time feedback during an epidemic, so simple models may be more useful in this regard. For these models to be most useful during a pandemic, efforts should be made to incorporate surveillance information into models.

In addition, in order to gain a better understanding of the clinical, epidemiological, and biological aspects of the pandemic virus, it is important to identify critical data needs, develop and approve research protocols, and put operational plans in place, so that data needed to inform the models can be more easily gathered once a pandemic starts.

Recommendation 7: The committee recommends that steps be taken now to adapt or develop decision-aid models that can be readily linked to surveillance data to provide real-time feedback during an epidemic. Research protocols should be developed, approved, and put in place now to generate the information needed during an outbreak to inform models, and improve their disease sub-models. In addition, existing data on influenza should be compiled, integrated, and made publicly available, and updated in a timely way so that it is available to more of the modeling community.

Other strategies that could improve the predictive ability of models of pandemic influenza include the following:

- Current simulation models of pandemic influenza need to be further developed and validated.
- Existing simulation models could be enhanced by refocusing efforts on their individual strengths (e.g., the VBI model could focus on interventions dependent on transportation, such as mass transit closures).
- Models at different levels of fidelity and scope are needed to support different aspects of the decision making processes, as such, efforts to develop a single one-size-fits-all model are misguided.
- Models could be developed that could be used by the lay public to educate them about the nature of pandemic influenza, factors that support its spread, and why intervention policies are likely to be effective or ineffective.

HISTORICAL ANALYSES

At the October 2006 workshop, several researchers presented historical evidence about the effectiveness of NPIs in previous pandemic influenza outbreaks.

Case Series Analysis of Interventions during the 1918 U.S. Pandemic

Dr. Howard Markel presented preliminary findings from a case series study of 45 cities within the United States circa 1918 that is currently being prepared by Markel and colleagues. Sixteen NPIs were identified: making influenza a reportable disease, isolating sick individuals, quarantine of households with sick individuals, school closure, protective sequestration of children or adults, cancellation of worship services, closure of public gathering places, staggered business hours to decrease congestion on trams, mandatory or recommended use of masks in public, closing or discouraging the use of public transit systems, restrictions on funerals, parties, and wedding, restrictions on door-to-door sales, community-wide curfew measures and business closures, social distancing strategies for those encountering others, public health risk communication measures, and declaration of public health emergency.

Summary analysis of six of these cities was presented at the Institute of Medicine Workshop (Markel and Wantz 2006).[10] From these case studies, Markel concluded that investment in public health infrastructure and the building of public trust by local health officials seemed to have facilitated the implementation of the interventions. He also observed that "fatigue" was an important factor; in other words, communities which had to reinstitute interventions after having lifted them experienced pushback and noncompliance in the second phase of restrictions. Finally, he concluded that the community interventions may have lowered the peak death rate and that proactive and early implementation were associated with flatter epidemic curves, although there were examples of cities that implemented the strategies but still had severe epidemics.

Markel and colleagues had previously analyzed seven communities termed "provisional influenza escape communities", which had reported few cases of influenza during the 1918 pandemic (Markel et al., 2006).That analysis suggests that protective sequestration can protect against infection if it is instituted early and is sustained. The analysis fails to show that other community strategies did or did not protect that community.

Analysis of Timing of Interventions and Epidemic Patterns During the 1918 U.S. pandemic

Dr. Marc Lipsitch presented findings from a retrospective analysis of 17 cities in the United States during the 1918 influenza epidemic that examined two questions (Lipsitch et al., 2006). First, were early interventions associated with different epidemic patterns? Second, did cities that intervened earlier in their epidemics have better outcomes (e.g., reduced epidemic sizes)? In assessing the first question, they examined whether the first peak of the epidemic in the fall of 1918 was reduced in those cities that implemented NPIs early. Assessing the second question was more complicated due to the complex relationship between the timing of interventions and the epidemic size. This is because all cities implemented interventions of only limited duration; no cities implemented interventions for the entire duration of the epidemic. This makes it difficult to assess the impact of specific interventions on epidemic sizes.

The researchers first compiled historical data from newspapers and secondary sources on the timing of interventions. They considered 17 NPIs, ranging from strict isolation to closing schools and canceling public gatherings. Outcome data included weekly excess pneumonia and influenza death rates (as compared to average death rates in the corresponding weeks from 1910–1916), compiled from the public health reports of 1930. They only included cities in the analysis for which they were able to obtain reliable information on timing of interventions, and for which reliable death data could be obtained.

A number of methodological challenges presented themselves in this analysis. For example, defining the time of the intervention is difficult. The definition they used of time was the number of cumulative excess deaths divided by 100,000 from September 1918 onward, until the date at which the intervention happened. Thus, an early interven-

[10] The committee is aware that Markel and colleagues are preparing a statistical analysis of these case studies; however, this analysis was not available for committee review and consideration.

tion defined as one that was implemented when relatively few people had died.[11] Another limitation is that the use of deaths as a proxy for cases assumes a similar case-fatality proportion across cities, when in fact a previous analysis suggests that there was up to a three-fold variation in the case-fatality proportion between cities (McLaughlin, 1920).

Although there are many potentially confounding factors, the researchers found that early interventions were significantly correlated with a lower peak death rate (Spearman p = -.65; p = 0.005). Of all the interventions, early school closure was most closely associated with a lower peak. Theater or church closings were also associated with a flatter epidemic curve. There was a weaker correlation between early interventions and total number of deaths in 1918. There was no relationship between the timing of school closure and the total number of deaths in 1918. There were no associations with the timing of other interventions (e.g., making influenza reportable, isolation) and the epidemic curve.

The authors explored alternative explanations for the finding that early intervention and lower peak were correlated. One possible explanation is that those cities with early interventions are simply proxies for cities where the epidemic started later and where perhaps the virus was less virulent or they had more lead time to prepare their interventions. They discounted this explanation because they found no evidence that the disease became less severe in cities with a later start to the epidemic. In addition, they found that while cities with later epidemics had lower peaks, the intervention effect changes little after adjustments were made for timing.

A second alternative explanation for this finding is that the epidemic size varied across cities for reasons independent of the interventions. For example, differences in timing of the epidemic or case-fatality proportion could mean that the overall size of the death curve was greater in some cities than in others. This could induce a correlation due to a non-causal mechanism. Additional analyses did not support this possible explanation.

Effectiveness of Interventions During 1918 U.S. Pandemic and Effectiveness of School Closures

Dr. Neil Ferguson presented two unpublished analyses using historical data (Bootsma et al., 2006). The first used historical data from the 1918 epidemic to estimate the effectiveness of interventions in 16 US cities. The second analysis uses seasonal influenza data from France to estimate the importance of school-based transmission in propagating seasonal influenza epidemics and the likely impact of school closure on transmission of influenza during a pandemic.

The first analysis is based on two observations about the 1918 pandemic. First, in the fall of 1918, very different epidemic patterns were seen in different cities across the United States. Second, the timing and the nature of interventions varied between these cities. The goal of the analysis was three-fold: (1) to assess the extent to which these two observations were correlated; (2) to determine whether public health interventions provide a plausible quantitative explanation for this variation; (3) to conduct what-if scenarios that examine outcomes in the absence of interventions or if they were imposed earlier.

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[11] “Early” interventions were defined as those interventions implemented below a threshold of 20 cumulative excess deaths per 100,000 people.

In the first part of the analysis, they found that both peak and total mortality were weakly correlated with the timing of the epidemic and the previous year's mortality. Lower peak mortality was correlated with "early" interventions—the same results that Lipsitch and colleagues (2006) found in their analysis. However, they also found that interventions across the country were started within a few days of each other. The date when the epidemic reached the cities varied more. They also found that peak mortality was strongly correlated with the presence of two autumn peaks, but that total mortality was only weakly associated. These findings point to a major theoretical reason to explain why NPIs may have little impact on total mortality; that is, unless interventions are kept in place until there is no longer a threat of reintroduction, the interventions may delay when people get infected without having much impact on the total size of the epidemic (the total number of people infected) (Bootsma et al., 2006).

In the second part of the analysis, they used a simple transmission model to reproduce the pattern of the epidemic curves observed in 16 cities during the 1918 pandemic. The model incorporated city-specific effectiveness of interventions, which were assumed to reduce transmission by a fixed amount for the period in which they were introduced. To obtain a good fit for the model and reproduce patterns seen, they had to add another feature to the model that allowed for spontaneous behavior change of the population. Spontaneous behavior change meant that people reduced social contacts on their own, independent of any interventions, as a function of deaths reported in the previous days or weeks. Spontaneous behavior change was found to be a significant factor in reproducing the epidemic curves (Bootsma et al., 2006).

In the third part of the analysis, they compared the predicted epidemic curve to curves predicted under different scenarios using assumptions. They first modeled what the epidemic curve in each city would have looked like had there been no interventions. Then they modeled the epidemic curve in each city if assuming in addition to no interventions, there was also no spontaneous social distancing. Finally, they modeled the epidemic curve assuming that interventions had been implemented in cities right at the start of the epidemic and maintained throughout the epidemic (Bootsma et al., 2006).

In overlaying the curves, they could determine which cities were most effective. They were able to generally rank order the effectiveness of the interventions by city. They found that the effectiveness of interventions in the top group of cities was quite high, with an estimated 40-45 percent reduction in transmission. All of the cities with the best outcomes had two peaks. They introduced interventions early and then reintroduced interventions after having lifted them. For cities that introduced their interventions "late", the interventions made almost no difference in the height and shape of the epidemic curve; they were virtually the same when overlaid (Bootsma et al., 2006).

They conclude from this exercise that a simple transmission model allowing for city-specific effectiveness of interventions can closely reproduce the various shapes of the epidemic curves observed in the fall of 1918. They also conclude that a reduction in the spontaneous contact rate during periods of high mortality is needed to best reproduce the epidemic curves. Estimated effectiveness of interventions is not well correlated with observed peak mortality. They also found that the timing of interventions is as important as their efficacy. Interventions that are implemented early and for the full duration are the most effective in reducing transmission. This model does not explain much variation in total mortality or the R_0 between cities. Furthermore, they have not disaggregated the types of interventions. They considered closure (e.g., schools, entertainment), masks and case isolation. While speculative, these models suggest that interventions with the highest effectiveness rates, if imposed for the entire duration of a pandemic until a vaccine was available, would be able to significantly reduce attack rates (Bootsma et al., 2006).

The second set of analyses was based on estimating how much seasonal influenza transmission occurs in schools and how important schools might be to the propagation of influenza during a pandemic. They used data from the French Sentinelles network, which was established in 1984 and contains over 1,200 active sentinel practitioners (150 – 200 participating each week) who report detailed information on individual influenza-like illness cases they see. In collaboration with researchers from Paris, they analyzed data on 420 individual annual epidemics (data from 21 years and 20 different geographic regions). Data were stratified by age (over 18 was considered adults) (Bootsma et al., 2006). They also collected data on holiday timing from the French Ministry of Education. The fact that French holidays are staggered across regions and the timing varies from year to year, provides some control for internal temporal effects that might be independent of the timing of the holiday (Bootsma et al., 2006).

They developed a stochastic simulation model of household, school, and community influenza transmission. Household transmission data were derived from previous analyses of transmission rates on households with children and adults (Cauchemez et al., 2006). Children are considered two-times more infectious than adults. The household transmission rate is inversely proportional to household size. School transmission assumes random mixing of children. The school transmission rate is inversely related to school size. Community transmission has two rates: adult to adult transmission and other (child to adult or adult to child transmission) (Bootsma et al., 2006).

A global school closure effect was estimated which shows the impact of school closure on increases in household and community transmission rates. They assumed zero transmission in schools when they were closed, which would shift transmission to the community and household.

Immunity was incorporated into the model. Because influenza is an endemic disease, a certain portion of the population is immune. They assumed that approximately 27 percent of the population would be fully immune at any given time. They developed an age-structured model of immunity assuming that newborn children are completely susceptible and a constant probability that an immune subject becomes susceptible.

The model predicted school closure alone will reduce the baseline attack rate (proportion of the population infected) from 33 percent to 29 percent. The reduction is highly sensitive to assumptions about how much non-school contacts increase when schools are closed. If contacts outside of school increase by 50 percent, school closure does not impact the attack rate. Ferguson and colleagues (2006) assume 16 percent of transmission occurred in schools, 21 percent in workplaces and 50 and 25 increases in household and community contacts, respectively during closure. The authors found that the results of school closure to be similar to those results reported in Ferguson et al. (2006); that is, school closure would cause only a small reduction on overall attack rates, but that it would have a significant impact on peak rates. The model further demonstrates that any transmission reduction achieved by school closure is mainly in children.

John Barry discussed unpublished data relating to morbidity and mortality in army training camps during different waves of the influenza pandemic in 1918-1919.[12] In particular he described the first wave of influenza in the spring of 1918 that was very mild, causing very low mortality, and the second wave in the fall of 1918 that was associated with significantly higher mortality. The third wave, which he did not discuss, in the spring of 1919 was also described as mild.

Army epidemiologists analyzed training camps with respect to the number of soldiers with less than one month service (who would not have been in camp during the mild first wave) and those with more than one month service (many of whom would have been exposed to the first mild wave). The latter group were less likely to experience morbidity and mortality in the more severe second wave than the former group. If one assumes, as Mr. Barry does, that the two waves were due to the same virus, the data suggests that if a future pandemic occurs in similar waves—first mild, second more severe—then there could be benefits from holding off implementing mitigation strategies until the second, more severe wave. The immunity acquired during the first wave is protective against the second wave and there is the opportunity to introduce interventions during the more serious second wave without having to battle the "intervention fatigue" the community might experience following the first wave of disease and intervention. In the discussion, it was pointed out that these conclusions could not be generalized, and that, for example, in the 1957 pandemic, most of the mortality was seen in the first wave.

LESSONS FROM SIMULATION MODELS AND HISTORICAL ANALYSES

Several lessons can be gleaned from the simulation models and historical analyses. The models generally suggest that a combination of targeted antivirals and NPIs can delay and flatten the epidemic peak, but the evidence is less convincing that they can reduce the overall size of the epidemic. Delay of the epidemic peak is critically important because it allows additional time for vaccine development and antiviral production. Lowering the peak of the epidemic is crucial also because it can reduce the burden on healthcare infrastructure by avoiding an extremely large influx of patients. Another important finding is that interventions will likely be most effective if they are initiated early in the epidemic and sustained until the threat of reintroduction of the virus has been eliminated.

Specific concerns about the use of historical data were raised at the workshop. Significant differences in society, health, and healthcare could limit the relevance of information from the 1918 pandemic in preparing for a pandemic in the 21st century. Population density (nationally, locally, in schools, and even in family homes), for example, is very different. The availability of antibiotics to treat secondary infections such as pneumonia could increase survival. That said, the committee believes that the finding from Markel and Wantz (2006) regarding the importance of a strong public health infrastructure in mitigating the epidemic likely remains true today.

[12] The source material is from the National Archives and freely available.

OTHER FORMS OF EVIDENCE REVIEWED

The primary expert opinion review used by the committee was that conducted by RAND (Aledort et al., 2006). The RAND effort involved three components: a staff-prepared literature review to identify possible nonpharmacological public health interventions (NPIs), the solicitation of the opinion of a panel of experts as to the relative merits of the NPIs, and a straw poll regarding the relative effectiveness of the NPIs. The straw-poll vote was to endorse, consider, or dismiss each of the NPIs for use in the United States. RAND grouped the NPIs into four categories: infection control and prevention, patient management, contact management, and community restrictions. A fourth RAND effort related to this evidence review was the modeling described previously.

The conclusions of the RAND expert opinion review were to:

- Strongly encourage the promotion of good hand hygiene and respiratory etiquette in all settings and at all times and to encourage use of hand soap and alcohol-based rubs;
- Develop and disseminate the capability for early rapid viral diagnosis;
- Limit mandatory segregation of individuals, including isolation, quarantine, sheltering, location-based community restrictions, and travel restrictions; and
- Encourage voluntary efforts to reduce social contact, especially including self-isolation of the sick but also self-quarantine of the exposed, and (when feasible) sheltering at home by the well.

The committee also considered a recently released IOM report (IOM, 2006) and other forms of expert guidance, such as from World Health Organization (WHO) or the Centers for Disease Control and Prevention (CDC). The primary evidence base for these guidances derives experience with seasonal influenza (e.g., www.cdc.gov/flu) or from the experience with Severe Acute Respiratory Syndrome (SARS). The general guidance for seasonal influenza, in addition to vaccination and use of antivirals, is to avoid close contact with people who are sick and, for those who are sick, to avoid close contact with others;, stay home from work, school, and errands when sick; practice respiratory etiquette and hand hygiene; avoid touching eyes, nose, and mouth; and engage in general good health habits (http://www.cdc.gov/flu/protect/habits.htm). It is unclear how strong the evidence for these interventions is specifically regarding influenza. Some of the evidence is generally derived from other respiratory illnesses.

THE ROLE FOR AND COMMUNITY IMPACT OF CONTAINMENT STRATEGIES

The committee's task was to review the evidence supporting community-wide interventions for pandemic influenza. The goal of this exercise is to determine whether these interventions have a role in reducing influenza virus transmission. In light of the many uncertainties about how the next pandemic will present and the limitations of modeling and historical analyses, the committee concludes that the lessons from many **sources** of information are needed to frame their discussion regarding whether community interventions have a role in reducing transmission of pandemic influenza infections.

The committee chose to review five sources of evidence:

- simulation models,
- historical analyses,
- expert opinion reviews,
- experience from seasonal influenza, and
- other research (including experience from SARS).

The strengths and weaknesses of the information gleaned from models and historical data have been discussed in previous sections of this report. Expert opinion reviews include summary documents (but not original research) from groups such as RAND, the IOM, the WHO, and other expert bodies. The committee concluded that scientific evidence regarding interventions used in seasonal influenza provides a valuable contribution. Finally, the committee also included other evidence, including information from SARS.

The committee reviewed 20 specific containment strategies, grouped under six general **intervention categories,** in order to answer the question in its charge of whether community-wide interventions have a role in reducing influenza virus transmission. The intervention categories are:

1. infection control and prevention,
2. antiviral prophylaxis and treatment,[13]
3. patient management,
4. contact management,
5. community restrictions, and
6. risk communication.

This section of the report is organized by the six intervention categories. Within each intervention category the committee reviews the evidence by source (models, history, etc.), with an emphasis on whether the use of a specific containment strategy for reducing influenza virus transmission is supported by one or more of the sources of evidence. Because the committee charge was limited to identifying whether community-wide interventions "have a role" in reducing infection transmission, the committee does not provide an overall assessment of the strength (e.g., strong, moderate, weak) of the evidence. Further, no framework exists to weigh the value of evidence from modeling compared to other sources, for example, and the committee had insufficient time to attempt to develop

[13] Although community containment strategies commonly are referred to as a package known as nonpharmaceutical interventions (NPI), use of antiviral drugs is prominent in many of the descriptions of possible interventions that could be used to contain a community-wide outbreak of pandemic influenza. Antiviral treatment or prophylaxis is also considered in some of the computational models developed to study community containment. Thus, the committee includes the use of antiviral drugs as part of community containment strategies. Because a stated goal of community containment strategies is to delay the introduction of an influenza pandemic until vaccine is available, vaccination is not considered one of the containment strategies.

one. However, the committee descriptions of the evidence include caveats and qualifiers where it was able to do so. The inability of the committee to prioritize or otherwise distinguish among the individual community interventions likely will disappoint some readers.

The committee then assesses generally the community impact of implementing the strategy. The committee articulated the community impact in terms of economic costs, social costs, ethical concerns, and feasibility/logistical considerations only for those interventions that are supported by evidence as having a role in reducing influenza virus transmission. Table 1 summarizes the conclusions of the committee and can be found at the end of the text.

Considering Community Impact

Before embarking on a review of the evidence for each of these intervention categories, it is important to articulate a vital caveat. Public health interventions often involve the sacrifice of individual rights and freedoms in the interest of improving the communal good. While imposition of costs on individuals can often be justified, care must be taken to ensure that individual sacrifices are only imposed when necessary to protect the public's health. Balancing benefits and costs is particularly important in the event of a pandemic, where the stress and fear caused by an immediate threat of widespread morbidity and mortality can lead to ill-considered decisions.

Determining whether an intervention should be included in pandemic influenza preparedness planning is more complicated than simply looking at supporting evidence. While each public health intervention is potentially beneficial, many could also create negative secondary effects. Public health interventions could have adverse effects on civil and economic liberties and could raise important questions about ethics and social justice. For example, some hypothesize that school closings could lead to elevated rates of child abuse and domestic violence. Workplace closings will cause a loss of income that could be devastating to families already living at subsistence levels.

Furthermore, NPI tools that might be implemented on a large scale present a number serious implementation challenges that must be considered. An effective NPI strategy must meet the requirements of a population that has a diversity and abundance of needs. Particularly in cases that may require expansive or prolonged measures, governments must be capable of meeting the needs of those who cannot do so independently, including provision of essential goods (e.g., food, water, medical supplies); essential services (e.g., sanitation, energy, communication); special populations' needs (e.g., families, disabled, foreign nationals, prisoners); financial needs; mental health needs; and non-outbreak-related activities need to be considered. Supporting these needs will require substantial governmental and non-governmental coordination. Addressing these needs is important to encourage compliance, but also may require creative, non-traditional or novel innovations in the how services are provided. Assessment and planning on how these key factors would be addressed during implementation, and the impact of these factors on the potential success or failure of an intervention, should be studied.

Recommendation 8: The committee recommends that future assessments of nonpharmaceutical interventions for pandemic influenza include consideration of both their potential public health benefits as well as their potential

negative effects.

In ideal circumstances, the goal should be to only use interventions where the demonstrated benefit outweighs the demonstrated harms. However, in conditions of severe uncertainty, this ratio will often be difficult, or impossible, to determine with any confidence. Furthermore, there is a real risk that in the midst of a crisis, there will be pressure for government to employ public health interventions, even in the absence of proven benefits, and without consideration of secondary effects.[14] Therefore, prior to the emergence of the threat, it is vital that these potential secondary effects be identified, articulated, and publicly debated. Before utilizing an unproven intervention, government officials and the communities they represent should be made aware of the intervention's potential negative effects. Interventions that will create particularly severe consequences should only be undertaken when the scientific evidence supports their utility, or when measures are taken to mitigate these negative effects. Unfortunately, it is beyond the scope of this report to engage in a detailed examination of the negative community impact of public health interventions. However, the committee did articulate community impact in terms of economic costs, social effects, ethical concerns, and feasibility/logistical considerations, as summarized in Table 1 at the end of the text.

Infection Control and Prevention

Strategies in this category include surveillance/case reporting,[15] rapid viral diagnosis, disinfection, hand hygiene, respiratory etiquette, and personal protective equipment (masks).

There is sparse consideration of these strategies in the <u>models</u> reviewed by the committee. The <u>model</u> presented by Wein considered masks, but assumed use of N95 respirators, which are unlikely to be available for community use outside of hospitals.

The UW model from the MIDAS group assumed 60 and 80 percent ascertainment of the 67 percent of influenza infections that are symptomatic and the Pitt/IMP model assumed 90 percent case ascertainment. The interventions the models investigate apply only to ascertained cases. The interventions dependent on case ascertainment are antiviral treatment, targeted antiviral prophylaxis of household contacts, home isolation of cases, and quarantine of household contacts. The models do not discuss the affects of varying case ascertainment in much detail. The Pitt/IMP model shows that if the interval between detection and treatment is short, policies relying on case detection have a larger impact than if the interval is longer.

The RAND <u>model</u>, while preliminary as described above, included hand hygiene, respiratory etiquette, rapid diagnosis, and surveillance in their "expert choice" intervention, which the model predicts will have utility in mitigating virus transmission in com-

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[14] On the other hand, the committee recognizes the potential value of implementing public health interventions that are not strongly based on evidence of effectiveness. A benefit of an intervention could be that government action, whether or not based on scientific evidence, can promote civil order and public trust.

[15] Case reporting is not generally thought of as an intervention, rather it is a way to track the progress of the epidemic and target interventions to those who have influenza. If done in a timely manner, it can impact on surveillance. It is included here due to its presence in material reviewed by the committee.

munities. The RAND model did not predict usefulness for individual interventions and did not include the use of masks outside of the healthcare setting.

Historical analyses that report the use of masks (Markel et al., 2006) by the public during the 1918 pandemic, however, are not useful for supporting or refuting the impact of the intervention on the epidemic given the caveats the committee expressed about historical analyses in previous sections of this report.

Expert opinion reviews include the RAND analysis (Aledort et al., 2006) and a recent IOM report (IOM, 2006). The RAND review endorses the use of surveillance/case reporting, rapid viral diagnosis, hand hygiene, and respiratory etiquette. The RAND review was less supportive of disinfection beyond usual practices, and made no recommendation for masks for the general public. The recent IOM report (2006) hesitated to discourage facemask use by the general public, even though the evidence did not support it, but was concerned that their use could give a false sense of protection that would encourage risk taking and/or decrease attention to other hygiene measures.

Surveillance and case reporting, as well as rapid viral diagnosis are components of health department response to seasonal influenza. Disinfection outside of the healthcare setting has not been shown to impact spread of seasonal influenza. The CDC provides advice regarding hand hygiene and respiratory etiquette during seasonal influenza. There is a paucity of data supporting the effectiveness of these interventions for influenza, but they are recommended based on common sense, common medical practice, and evidence from effectiveness against other respiratory illnesses. People support these interventions because they "can't hurt" and are relatively cost-free.[16]

Several analyses of these strategies during SARS suggests that frequent mask use by the general public in public places, frequent hand washing, and disinfecting living quarters were protective against SARS[17] (Lau et al., 2004). However, the uncertainty about mode of transmission (aerosol versus droplet) for influenza calls into question the relevance of the experience with mask use by the general public during SARS.

Conclusion 1: In summary, evidence suggests a role for surveillance and case reporting, rapid viral diagnosis, hand hygiene, and respiratory etiquette in reducing pandemic influenza virus transmission.

The evidence derives primarily from experience with seasonal influenza and from SARS. Current modeling and historical analyses provide little to no evidence regarding and little support for a role for these measures.

The committee identified the economic cost and logistics of both surveillance/case reporting and rapid viral diagnosis[18] as potential challenges for communities considering these interventions. Capacity will restrict the use of rapid viral diagnosis and masks. Hand hygiene and respiratory etiquette presented the fewest challenges.

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[16] See for example, http://www.globalsecurity.org/security/ops/hsc-scen-3_flu-pandemic-mitigation.htm; http://www.cdc.gov/ncidod/EID/vol12no01/pdfs/05-1371.pdf. Cumulative costs for soap and paper towels or for alcohol-based hand sanitizers could present a burden for small or economically disadvantaged communities, schools, or workplaces.

[17] Important differences between influenza and SARS (SARS has a longer serial interval and the infectivity peaks at a longer period than will likely be true for an influenza pandemic) and uncertainties regarding the mode of transmission of influenza call into question the direct relevance of the SARS experience.

[18] Rapid viral diagnosis would be important during the early phase of a pandemic but unfeasible and unnecessary in the late phases.

Antiviral Prophylaxis and Treatment

The simulation models from the MIDAS consortium included targeted antiviral prophylaxis (TAP) as an intervention. These models assumed that household contacts receive one course of prophylaxis beginning one day after onset of symptoms in the household index case. The UW and IMP/Pitt models suggests that TAP could play a role in mitigation of a pandemic alone or in combination with other community strategies, however the number of doses required could be substantially larger than exist in current stockpiles. The committee has sufficient reservations about using the models for specific guidance, as discussed in previous sections of the report.

Historical analyses have obviously not included the use of antiviral drugs. The RAND expert panel did not review antiviral drugs.

Antiviral drugs have proven effectiveness in treating seasonal influenza by decreasing the duration of illness by one day (for a summary, see (Smith et al., 2006). Effectiveness as a prophylaxis is also demonstrated in households and in health care settings. The amount of drug needed for prophylaxis is significantly more than for treatment. Influenza viruses develop resistance to these drugs.

Conclusion 2: In summary, evidence suggests a role for antiviral prophylaxis and treatment in reducing pandemic influenza virus transmission within households and healthcare settings. Use of these drugs during a pandemic will require monitoring of resistance to the drugs and appropriate modification of this strategy if resistance emerges.

The evidence derives primarily from basic research, as well as experience with seasonal influenza and from modeling. The evidence from modeling does not take resistance into account. Historical analyses obviously provide no evidence regarding and no support for a role for these measures.

The committee identified economic cost and logistics as potential challenges for communities considering using antiviral treatment and prophylaxis. Limited capacity will require prioritization if governmental agencies distribute the drugs. Ethical concerns arise if some individuals, families, or communities can afford to stockpile drugs, while others cannot. Such stockpiling can deplete supplies and lead to inappropriate use (e.g., for those who do not have influenza). Excessive use could lead to resistance and diminish needed supplies. In addition, the drugs have been associated with serious adverse reactions in some. Finally, resistance to antiviral drugs could develop rapidly and this intervention could be rendered useless.

Patient Management

Strategies in this category include isolation of sick individuals and provision of social support services.[19] Social services include things such as providing home food delivery, access to prescription medication, legal and banking services, and coping with loneliness for those sequestered for a long period of time.

[19] Antiviral treatment of a patient confirmed or suspected to have influenza is covered in a separate section.

Two (UW/LANL and VBI) of the MIDAS simulation models include home-isolation of ascertained cases. However, the results provided do not highlight the effect of home-isolation only. The results of the RAND model, as described in previous section, are preliminary but do not identify isolation of sick individuals or provision of social support services as effective interventions when applied individually, but they are part of the "expert choice" package of interventions that they found effective.

Lipsitch's historical analysis does not support the effectiveness of isolating sick individuals. Markel's historical analysis does not separate isolation of sick individuals from other interventions, and therefore is unable to support its effectiveness.

The RAND expert opinion review strongly supported voluntary isolation of sick individuals in the home in an advanced epidemic if health care settings are at capacity. Similarly, the review strongly recommended provision of social support services, although this appeared to be based on opinion and common sense, rather than on data. Provision of social support is thought to increase adherence to isolation and some social distancing recommendations and therefore to increase the effectiveness of those measures.

The CDC recommends that sick individuals suffering from respiratory illnesses including seasonal influenza stay home from work, school, and social gatherings (http://www.cdc.gov/flu/symptoms.htm).

Experience with SARS and from traditional public health approaches to persons with tuberculosis indicates the importance of providing social services in order to improve adherence to recommendations regarding isolation.

Conclusion 3: In summary, the evidence suggests a role for isolation of sick individuals and for providing social support services to those isolated individuals. The evidence base is scant and primarily based on common sense or from other illnesses. Neither modeling nor historical analyses provide support for these interventions.

The committee identified economic costs, social and ethical issues, and logistics as potential challenges for communities considering these interventions.

Contact Management

Contact management refers to activities related to a person who has had contact with someone already ill with influenza. Strategies in this category include contact tracing, voluntary sheltering,[20] and quarantine.[21]

The IMP/Pitt model includes home isolation of household contacts of ascertained cases (a form of quarantine) and concludes it is potentially the most effective "social distancing" measure if adherence is high (Ferguson et al., 2006). The RAND model includes quarantine, but it is not one of the interventions termed "expert choice", which RAND identified as the package of interventions that their model predicts would be most effective during a pandemic. The RAND model does not include any of these strategies in the "expert choice" package of interventions that they found effective in mitigating a pandemic.

[20] Sheltering refers to the voluntary sequestration of healthy persons to avoid exposure.
[21] Antiviral prophylaxis of contacts is covered in a separate section.

Historical analysis documents the use of both voluntary sheltering and quarantine of households with sick individuals during the 1918 pandemic. As described above, Markel and colleagues (2006) are unable to identify specific interventions as influential to the course of the pandemic in any city.

The RAND expert opinion review endorses contact tracing as potentially valuable in the early stages of an epidemic. It more strongly endorses quarantine and particularly voluntary sheltering if the pandemic is advanced in the United States.

Experience from SARS supports the importance of sheltering and quarantine (WHO Writing Group, 2006), but important differences (SARS has a longer serial interval (the mean interval between onset of illness in 2 successive patients in a chain of transmission) and the infectivity peaks at a later period than will likely be true for an influenza pandemic) call into question the relevance of the SARS experience with voluntary sheltering and quarantine.

> **Conclusion 4: In summary, the evidence suggests a role for contact tracing (early in the epidemic) to allow for individual action by the contact, voluntary sheltering, and quarantine in reducing pandemic influenza virus transmission.** The evidence derives from modeling and expert opinion.

The committee identified economic costs, social and ethical issues, and logistics as potential challenges for communities considering these interventions.

Community Restrictions

Strategies in this category include general social distancing, restrictions on public transportation, international travel restrictions out of affected areas, cancellation of group events, and school closures.

Models presented to the committee provide evidence of a possible effect of community restrictions on several parameters (including attack rate), but summary judgment is that at most, the models suggest that community restrictions can dampen and delay the peak of the epidemic, but total mortality might not change. Peak effects can have significant impact on the ability of the health care system to handle the surge in patients requiring hospitalization or needed supplies or medications. Delay of the peak in a community can "buy time" until needed vaccine is available. The models also suggest that the more transmissible the pandemic strain is, the more aggressively (with respect to the speed and breadth of the intervention) the community restrictions would have to be implemented in order to impact the epidemic.

The most controversial community restriction involves school closure with or without restrictions of youth going outside the home for any public gathering. Several models (Ferguson et al., 2006; Germann et al., 2006; Glass et al., 2006b) suggest that school closures or other restrictions on the gathering of children and teenagers could have a significant impact on community influenza (perhaps primarily by dampening the peak attack rate, not the community mortality), however the committee identified (see previous section on the models) several weaknesses in the models which make it difficult to understand how robust the effect of school closures will be. In addition, models do not take into account the natural behavior of people. For example, schools will be naturally de-populated during a pandemic because of influenza-related absences and because parents will keep healthy children home. It is whether or not mandatory school closures would have an effect beyond that which would occur naturally. Partial closures or other means of increasing the distance between children who remain in the school might also be useful.

Historical analyses include the possible effects of community restrictions. These analyses, both the qualitative analyses by Markel and colleagues (2006) and the quantitative analyses by Lipsitch and colleagues (2006) suggest useful effects in some communities of implementing a package of community restrictions. None of the analyses can single out specific community restrictions as particularly or specifically effective.

The expert opinion review by RAND contains no recommendation regarding school or workplace closure or suspending public transportation, but does support cancellation of events on a case-by case basis. The RAND report also supports travel advisories, rather than compulsory travel bans.

Communities experiencing unusually severe seasonal influenza rarely close public events. Schools are occasionally closed in response to severely decreased attendance by students or teachers due to illness.[22] Some evidence from Hong Kong (e.g., Lau et al., 2004) suggests that visits to crowded places did not confer increased risks for SARS, however as discussed elsewhere, many people in Hong Kong wore masks in public and engaged in frequent hand washing, which could have mitigated possible transmission via exposure in public places. As noted elsewhere, differences between SARS and influenza call into question the direct relevance of these interventions for influenza. The CDC included community-wide restrictions in their guidance for response to SARS (http://www.cdc.gov/ncidod/sars/guidance/D/app1.htm). There were also efforts to discourage handshaking during this period.

> **Conclusion 5: In summary, the evidence suggests a role for community restrictions in reducing pandemic influenza virus transmission. The evidence does not allow for differentiating possible effects of specific types of community restrictions, nor does it allow differentiation between voluntary versus mandatory community restrictions. In general, evidence from modeling and from historical analyses confirm what is known for any infectious disease outbreak, that is, early intervention shows more promise than later intervention. The main effect might be to slow the time to peak of the outbreak in a community, which could be important for hospital-based management of ill patients and to allow for delivery of vaccine if available.**

The evidence comes from models, historical analyses, expert opinion (including recommendations for seasonal influenza), and from the SARS experience.

The committee identified economic cost, social implications, ethical issues, and logistics as potential challenges for communities considering these interventions. The committee had the most concerns about the effects of school closures, although all forms of

[22] Yancey County, NC, and Mitchell County, NC, public schools were closed at the direction of local officials for approximately one week in November 2006 in response to an influenza B outbreak (Newsome and Neal, 2006). CDC is analyzing this event for lessons learned applicable to both seasonal influenza and for pandemic influenza.

community restriction will pose substantial challenges. The committee identified "intervention-fatigue" as a factor that could undermine the potential effectiveness of any of these measures.

Risk Communication

Historical analyses illustrate the role that trusted spokespersons can have in influencing a positive course of action to a pandemic influenza (Markel and Wantz, 2006). The RAND expert opinion review, IOM reports on the smallpox vaccination program (IOM, 2005), and countless exercises in emergency management, public health, and disaster preparedness all endorse a role for a key spokesperson during a crisis such as pandemic influenza.

Conclusion 6: In summary, the evidence suggests a critically important role for risk communication, specifically the identification of key and trusted spokespersons, in cultivating an environment conducive to public acceptance of and adherence to community containment strategies for reducing pandemic influenza virus transmission.

CONCLUDING REMARKS

It is important to recognize that pandemic influenza is unlike other problems normally encountered in health care decisions because of the large number of lives at risk and the short period of time in which it will occur. Given the crisis, it is essential that policymakers and communities continue their plans and preparation for this pandemic.

However, there are significant uncertainties regarding the next influenza pandemic. This is complicated by gaps in knowledge about transmission of seasonal influenza and the evidence base for some well-accepted interventions. It is almost impossible to say that any of the community interventions have been proven ineffective. However, it is also almost impossible to say that the interventions, either individually or in combination, will be effective in mitigating an influenza pandemic. There is simply a dearth of strong evidence concerning the efficacy of community containment strategies, which is particularly troublesome given the fact that many of the interventions will carry significant economic, social, ethical, and logistical consequences.

Given this lack of scientific evidence, it is important to look at multiple sources of information to support community containment interventions. As described in previous sections, modeling is an important and useful tool for organizing information and illustrating gaps in knowledge, but the models reviewed by the committee cannot be depended upon to predict effectiveness of community interventions. History teaches us many things, but, like the modeling, can only paint a broad picture that suggests community-wide intervention is possibly better than no intervention. Neither of these two streams of research can be said to support a specific intervention, specific timings of interventions, or to predict the outcome of the interventions with any precision.

Recommendation 9: The committee recommends that communications regarding possible community interventions for pandemic influenza that flow

from the federal government to communities and from community leaders to the public not overstate the level of confidence or certainty in the effectiveness of these measures. The communications should also not overstate the role that modeling or historical analyses play in supporting these interventions.

Recommendation 10: The committee recommends that policy guidance stress that interventions cannot be implemented in isolation. Key accompaniments to the policy guidance include a communication plan, plans for when to trigger the interventions and when to rescind them, and plans to help mitigate the adverse consequences of implementing some of the policies.

Recommendation 11: The committee recommends that any discussion of using these interventions consider not only their potential health benefits, but also their likely ethical, social, economic, and logistical costs.

Ideally, society will only utilize strategies where there is sufficient evidence to determine that the benefits will outweigh the costs. However, as the potential magnitude of the outbreak increases, a society might be willing to accept interventions that will cause secondary effects, even when there is less certainty of potential benefits. Furthermore, since it is a reality that during public health crises the efficacy of interventions may be unknown, and societies will be willing to accept a greater level of uncertainty, it is important to evaluate and openly discuss the potential negative effects of interventions before the stress and immediacy of a traumatic event.

Sincerely,

Adel Mahmoud, M.D., Ph.D.

On behalf of the Committee on Modeling Community Containment for Pandemic Influenza

Table 1: Summary of Committee Conclusions[23]

Category	Interventions for which evidence suggests a role in reducing pandemic influenza virus transmission	Committee comments regarding the impact on communities of implementing the interventions
Infection Control and Prevention	• Surveillance/case reporting • Rapid viral diagnosis • Hand hygiene • Respiratory etiquette	• Economic cost and logistics are concerns for both surveillance/case reporting and rapid viral diagnosis.[24] • Supply will restrict the use of rapid viral diagnosis and masks. • Hand hygiene and respiratory etiquette presented the fewest concerns.
Antiviral use	• Treatment of person ill with influenza • Prophylaxis of household contacts (preventive treatment of people within the household of someone who is ill with influenza)	• Economic cost and logistics as potential concerns for communities considering using antiviral treatment and prophylaxis. • Limited supply will require prioritization if governmental agencies are in charge of distributing the drugs to individuals or households who have not "stockpiled" their own antiviral drugs. Excessive use could lead to resistance. **Use of these drugs during a pandemic will require monitoring of resistance to the drugs and appropriate modification of this strategy if resistance emerges.** • Use for illnesses other than influenza will diminish needed supplies.

[23] Because the committee charge was limited to identifying whether community-wide interventions "have a role" in reducing infection transmission, the committee does not provide an overall assessment of the strength (e.g., strong, moderate, weak) of the evidence. The committee was unable to prioritize or otherwise distinguish among the individual community interventions.

[24] Rapid viral diagnosis would be important during the early phase of a pandemic but unfeasible and unnecessary in the late phases.

Patient Management	• Isolation of sick individuals • Provision of social support services to isolated individuals	• Economic costs, • social and ethical issues, and • logistics.
Contact Management (Managing people who come into contact with someone who is ill with influenza in order possibly to prevent more virus transmission)	• Contact tracing (early in the epidemic) • Individual action by the contact • Voluntary sheltering • Quarantine	• Economic costs, • social and ethical issues, and • logistics.
Community Restrictions	• A package of interventions, including general social distancing, restrictions on public transportation, international travel restrictions of out of affected areas, cancellation of group events, and school closures • The evidence does not allow for differentiating possible adverse effects of specific types of community restrictions, nor does it allow differentiation between voluntary versus mandatory community restrictions • In general, evidence from modeling and from historical analyses suggests that early intervention shows more promise than later intervention • The main effect might be to slow the time to peak of the outbreak in a community, which could be important for hospital-based management of ill patients and to allow for delivery of vaccine if available	• Economic cost, social implications, ethical issues, and logistics as concerns for communities considering these interventions. • The committee had most concerns about the effects of school closures. • The committee identified "intervention-fatigue" as a factor that could undermine the potential effectiveness of any of these measures.
Risk Communication	• Identification of key and trusted spokespersons to cultivate an environment conducive to public acceptance of and adherence to community containment strategies	Effective risk communication will increase the likelihood that recommended community interventions are: • understood, • adhered to, and • maximally effective.

Table 2: List of Committee Recommendations

Recommendation 1: The committee recommends the development of a research agenda to answer critical research gaps and better inform pandemic influenza planning. A priority topic would be to answer fundamental questions about influenza virus transmission and epidemiology. Prospective epidemiological studies of seasonal influenza should be strongly considered as a supplement to passive surveillance. Observational or randomized studies should also be undertaken to evaluate the effectiveness of certain interventions in community settings. Results of these studies should be incorporated into the various models of pandemic influenza as appropriate.

Recommendation 2: The committee recommends that modelers develop improved estimates of model and parameter uncertainty.

Recommendation 3: The committee recommends that models examining the potential effectiveness of school and workplace closures on mitigating pandemic influenza include a broader range of closure options in their analyses.

Recommendation 4: The committee recommends that future modeling efforts incorporate broader outcome measures, beyond influenza-related outcomes, to include the costs and benefits of intervention strategies.

Recommendation 5: The committee recommends that policymakers consider a broader set of models to inform strategies and policies regarding pandemic influenza.

Recommendation 6: The committee recommends that policymakers regularly convene forums for public dialogue on pandemic influenza modeling, and recommends the development of a standing expert panel to provide ongoing advice regarding models of pandemic influenza.

Recommendation 7: The committee recommends that steps be taken now to adapt or develop decision-aid models that can be readily linked to surveillance data to provide real-time feedback during an epidemic. Research protocols should be developed, approved, and put in place now to generate the information needed during an outbreak to inform models, and improve their disease sub-models. In addition, existing data on influenza should be compiled, integrated, and made publicly available, and updated in a timely way so that it is available to more of the modeling community.

Recommendation 8: The committee recommends that future assessments of nonpharmaceutical interventions for pandemic influenza include consideration of both their potential public health benefits as well as their potential negative effects.

Recommendation 9: The committee recommends that communications regarding possible community interventions for pandemic influenza that flow from the federal government to communities and from community leaders to the public not overstate the level of confidence or certainty in the effectiveness of these measures. The communications should also not overstate the role that modeling or historical analyses play in supporting these interventions.

Recommendation 10: The committee recommends that policy guidance stress that interventions cannot be implemented in isolation. Key accompaniments to the policy guidance include a communication plan, plans for when to trigger the interventions and when to rescind them, and plans to help mitigate the adverse consequences of implementing some of the policies.

Recommendation 11: The committee recommends that any discussion of using these interventions consider not only their potential health benefits, but also their likely ethical, social, economic, and logistical costs.

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