Research findings from nonpharmaceutical intervention studies for pandemic influenza and current gaps in the research

Allison E. Aiello, PhD, MS,[a] Rebecca M. Coulborn, MPH,[a] Tomas J. Aragon, DrPH,[b] Michael G. Baker, MBChB, DPH, FAFPHM,[c] Barri B. Burrus, PhD,[d] Benjamin J. Cowling, PhD,[e] Alasdair Duncan, MPH,[c] Wayne Enanoria, PhD, MPH,[b] M. Patricia Fabian, ScD, MS,[f,g] Yu-hui Ferng, MPA,[h] Elaine L. Larson, PhD, RN, FAAN, CIC,[h,i] Gabriel M. Leung, MD, MPH, CCFP, FFPH, FHKCCM, FHKAM,[e] Howard Markel, MD, PhD,[j] Donald K. Milton, MD, DrPH,[k] Arnold S. Monto, MD,[a] Stephen S. Morse, PhD,[i] J. Alexander Navarro, PhD,[j] Sarah Y. Park, MD, FAAP,[l] Patricia Priest, DPhil, MBChB, MPH, FAFPHM,[c] Samuel Stebbins, MD, MPH,[m] Alexandra M. Stern, PhD,[j] Monica Uddin, PhD,[a] Scott F. Wetterhall, MD, MPH,[d] and Charles J. Vukotich Jr, MS[m]

Ann Arbor, Michigan; Berkeley, California; Otago, New Zealand; Research Triangle Park, North Carolina; Hong Kong, People's Republic of China; Lowell, Massachusetts; Boston, Massachusetts; New York, New York; College Park, Maryland; Honolulu, Hawaii; and Pittsburgh, Pennsylvania

In June 2006, the Centers for Disease Control and Prevention released a request for applications to identify, improve, and evaluate the effectiveness of nonpharmaceutical interventions (NPIs)—strategies other than vaccines and antiviral medications—to mitigate the spread of pandemic influenza within communities and across international borders (RFA-CI06-010). These studies have provided major contributions to seasonal and pandemic influenza knowledge. Nonetheless, key concerns were identified related to the acceptability and protective efficacy of NPIs. Large-scale intervention studies conducted over multiple influenza epidemics, as well as smaller studies in controlled laboratory settings, are needed to address the gaps in the research on transmission and mitigation of influenza in the community setting. The current novel influenza A (H1N1) pandemic underscores the importance of influenza research.

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Community mitigation is a collective term for a group of strategies other than vaccines and antiviral medications (ie, nonpharmaceutical interventions) designed to slow or limit the transmission of a pandemic virus.[1] It includes personal protection strategies and interventions for individuals, institutions (eg, schools), and entire communities.[2] Community mitigation research may include studies of the feasibility of effectiveness of, and compliance with protective devices, such as face masks. Research also may include the generation of data to inform mathematical models to estimate influenza attacks rates, along with the development and evaluation of interventions to delay the spread of pandemic influenza by travelers crossing international air, land, and sea borders.

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From the Center for Social Epidemiology and Population Health, Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI[a]; Center for Infectious Diseases & Emergency Readiness, Division of Epidemiology, School of Public Health, University of California, Berkeley, CA[b]; Pandemic Influenza Research Group, University of Otago, New Zealand[c]; Public Health and Social Policy Division, RTI International, Research Triangle Park, NC[d]; Department of Community Medicine and School of Public Health, University of Hong Kong, Hong Kong, People's Republic of China[e]; Work Environment Department, School of Health & Environment, University of Massachusetts, Lowell, MA[f]; Department of Environmental Health, School of Public Health, Harvard University, Boston, MA[g]; School of Nursing[h] and Department of Epidemiology,[i] Mailman School of Public Health, Columbia University, New York, NY; Center for History of Medicine, University of Michigan Medical School, Ann Arbor, MI[j]; Maryland Institute for Applied Environmental Health, Department of Epidemiology and Biostatistics, School of Public Health,University of Maryland, College Park, MD[k]; Disease Outbreak Control Division, Hawaii Department of Health, Honolulu, HI[l]; and Center for Public Health Preparedness, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.[m]

Address correspondence to Allison E. Aiello, PhD, MS, Center for Social Epidemiology and Population Health, 1415 Washington Heights, Ann Arbor, MI 48109. E-mail: aielloa@umich.edu.

Charles J. Vukotich, Jr, MS, Center for Public Health Practice, Graduate School of Public Health, University of Pittsburgh, A711 Crabtree, 130 DeSoto Street, Pittsburgh PA 15261. E-mail: Vukotichc@edc.pitt.edu.

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nonpharmaceutical interventions (NPIs) to mitigate the spread of pandemic influenza within communities and across international borders (RFA-CI06-010).[3] Eleven studies were funded to identify optimal, discrete, or combined NPIs for implementation during an influenza pandemic. The results of these studies have provided valuable contributions to the knowledge of seasonal and pandemic influenza, identified additional gaps in data, and offered important insights into future research on mitigating the current pandemic of novel A (H1N1) influenza. Here we describe the studies, summarize the results, present a synthesis of the research gaps, and define future research needs.

DESCRIPTION OF STUDIES AND FINDINGS

The studies include research using seasonal influenza outbreaks as a model for testing preventive measures for future influenza pandemics, as well as historical research of past pandemics (Table 1). What follows is a summary of the published, accepted, and in-preparation work across all projects.

Assessment of NPI acceptability

Community mitigation of pandemic influenza might be achieved through the use of NPIs, specifically personal protective measures. These measures must gain community acceptance to be effective, however. Studies assessing the acceptability of NPIs have demonstrated that NPI behaviors can be successfully taught to and adopted by a variety of individuals through the use of community health education, interactive classroom teaching, or Internet-based instruction. For example, a study of urban Hispanic households conducted by Columbia University (A) showed that although household members had misunderstandings regarding influenza, their knowledge, attitudes, and practices improved through a community education program.[4] (Note: Here the studies are identified by letter, as listed in Table 1.) In all mask and hand hygiene intervention studies, hand hygiene interventions that generally were perceived as typical daily behavior were more readily accepted than mask wearing. For example, hand sanitizing with alcohol-based preparations, handwashing with soap, covering sneezes/coughs, and hand awareness (ie, touching the face) showed relatively high compliance, whereas compliance with face mask use was low in most studies. These findings mirror predictions from an earlier study of acceptability of NPI interventions led by Stebbins.[5]

Studies also support the need for consistent and coordinated NPI response during pandemics. For example, research conducted by RTI International (B) identified that the acceptability of NPIs depends largely on early planning, consistent and targeted communication during implementation, and clear delineation of responsibilities and lines of authority. Acceptability also requires communication from both traditional (eg, emergency response organizations, public health departments, media) and nontraditional (eg, churches, child care centers, businesses) sources.

Laboratory assessment of face mask efficacy

The efficacy of face masks for preventing transmission of influenza viruses has yet to be fully determined. In a laboratory study conducted by researchers at University of Massachusetts, Lowell (C), influenza virus nucleic acid was present in fine-particle aerosols from influenza patients in both tidal breathing (14%-33%) and coughing (64%).[6] Preliminary results demonstrated that surgical ear-loop face masks limit the generation of droplets $\geq$5.0 μm in diameter containing influenza virus RNA; investigation of fine droplet virus-containing particles is ongoing.

Examination of the efficacy of NPIs for reducing transmission of influenza in the community setting

The studies assessed the effectiveness of multilayered NPIs (ie, the use of multiple NPIs in conjunction with one another) based on CDC's hypothesis that this approach could create multiple barriers to stop the transmission of influenza.[1] Several studies have shown that NPIs can be efficacious for reducing rates of influenza and influenza-like illness (ILI). Results from the University of Hong Kong (D) suggested substantial reductions in household secondary attack ratios when all household members practice frequent handwashing and wear face masks within 36 hours of symptom onset of the index case.[7] Aiello et al,[8] at the University of Michigan (E), reported that hand hygiene with alcohol-based hand sanitizers and mask use among university students was associated with a 50%-65% reduction in the rate of ILI over a 6-week intervention period. Compared with other projects, rates of mask use were relatively high in this study, with averages of 4 hours per day in year 1 and 5 hours per day in year 2, over the 6-week intervention periods. The greater compliance than reported in household studies might have been due to the higher educational level of participants or the fact that they were paid an incentive to participate. In addition, Aiello et al used a unique study design by asking participants to begin mask and hand sanitizer use every day at the beginning of the influenza season, just after the first case of influenza was identified on campus. This design is in contrast with household studies that examined the effect of mask use on secondary transmission when household members may already have been infected before mask implementation.

Table 1. List of projects funded from 2007-2009 under CDC NPI studies for pandemic influenza RFA-CI06-010

Study title	Institution	PI(s); co-PI(s)	Description
(A) Stopping Upper Respiratory Infections and Flu in the Family: the Stuffy Trial	School of Nursing, Columbia University	Elaine L. Larson, RN, PhD, FAAN, CIC	• Tested the effectiveness of alcohol-based hand sanitizer and sanitizer coupled with face masks on reducing the rates of laboratory-confirmed influenza, symptoms of influenza, and viral upper respiratory infection
(B) Community-based nonpharmaceutical intervention for pandemic influenza	RTI International	Scott F. Wetterhall, MD, MPH	• Assessed, implemented, and evaluated community-level NPI strategies to prevent influenza in rural North Carolina communities
(C) Evaluation of masks as a source control NPI	School of Health and Environment, University of Massachusetts Lowell in collaboration with Department of Environmental Health, School of Public Health, Harvard University	Donald K. Milton, MD, DrPH	• Built an exhaled breath sampling device for influenza virus • Measured the number and aerosol size distribution of exhaled influenza virus • Measured the effect of wearing a surgical mask on generation of large- and fine-particle aerosols containing influenza virus
(D) Controlled trial of masks and hand hygiene for reducing influenza transmission	School of Public Health, University of Hong Kong	Gabriel M. Leung, MD, MPH, CCFP, FFPH, FHKCCM, FHKAM and Benjamin J. Cowling, PhD	• Tested the effectiveness of hand hygiene (hand washing and the use of alcohol-based hand sanitizer), and hand hygiene combined with surgical face masks in preventing influenza transmission within households from subjects at an outpatient clinic
(E) Reducing Transmission of Influenza by Face Masks (M-FLU)	Department of Epidemiology, School of Public Health, University of Michigan	Arnold S. Monto, MD and Allison E. Aiello, PhD	• Evaluated face masks and hand hygiene to estimate the reduction in the rate of influenza infection and ILI among students living in university residence halls
(F) Pittsburgh Influenza Prevention Project (PIPP)	Center for Public Health Practice, Graduate School of Public Health, University of Pittsburgh	Donald S. Burke, MD and Sam Stebbins, MD, MPH	• Tested hand hygiene and etiquette, hand sanitizer, and home isolation on the transmission of influenza and other diseases, and absenteeism in K-5 schools
(G) Pandemic influenza control at the borders of island countries and in households	Pandemic Influenza Research Group, University of Otago, New Zealand	Michael G. Baker, MBChB, DPH, FAFPHM, Patricia Priest, MBChB, MPH, DPhil, FAFPHM, Lance Jennings, PhD, Nick Wilson, MBChB, MPH, FAFPHM, and Heath Kelly, MBChB, MPH, FAFPHM	• Assessed the effectiveness of maritime quarantine for preventing entry of the 1918 pandemic into Pacific Island countries • Estimated the reduction in travel volumes and the quarantine duration needed to exclude pandemic influenza from island nations • Analyzed the relationship between influenza hospitalization and levels of household crowding and other potentially modifiable factors among public housing residents • Screened travelers on international flights for seasonal influenza
(H) Bangkok Household Influenza Transmission Study (HITS)	Influenza Division, International Emerging Infections Program, Thailand MOPH-US CDC Collaboration, Bangkok	Mark Simmerman, PhD, RN	• Evaluated handwashing and handwashing plus face mask use in reducing the spread of influenza in households of pediatric hospital-based clinic patients, testing positive for influenza
(I) Surveillance of ILI among international air travelers	Hawaii Department of Health	Sarah Y. Park, MD, FAAP	• Assessing regional capacity and feasibility to implement voluntary risk-based entry screening of air travelers for ILI
(J) Reducing Influenza-Like Illness among University Students: REDI-US Study	Center for Infectious Diseases and Emergency Readiness, School of Public Health, University of California Berkeley	Tomas J. Aragon, MD, DrPH	• Tested the effectiveness of online education of respiratory and cough etiquette, hand hygiene, hand awareness, and face mask use in reducing the occurrence of ILI among university students
(K) History Informing Public Health Preparedness Policy in the 21st Century: A Qualitative Study of Nonpharmaceutical Interventions and Community Experiences during the 1918-1919 Influenza Pandemic	Center for the History of Medicine, University of Michigan	Howard Markel, MD, PhD, Alexandra M. Stern, PhD, and J. Alexander Navarro, PhD	• Examined the role of NPI for epidemic mitigation in 43 cities in the continental United States from the 1918-1919 influenza pandemic • Creating the first historical atlas on the 1918-1919 influenza pandemic in the United States

The University of Pittsburgh (F) found that after implementation of a 5-layer NPI approach, including hand hygiene and cough etiquette, elementary school students had significantly fewer laboratory-confirmed influenza A infections and a significant reduction in total absences compared with a control group.

Assessment of crowding on influenza transmission

Household crowding can be a factor in community influenza transmission. Investigators from the University of Otago, New Zealand (G) assessed the impact of proximity and crowding indices on influenza by using indices that reflect the geographic distribution (density) and ability of dwellings to provide sufficient shelter and services to their residents.[9] Based on the proportion of the New Zealand population residing in public housing (~6% of the total population), the study found that household crowding as assessed according to the Canadian National Occupancy Standard,[10] as well as the presence of children in the home, significantly increased the relative risk of hospitalization for pneumonia or influenza. According to preliminary results from a study by the International Emerging Infections Program in Thailand (H), 92% of all children enrolled as index cases of influenza within the household slept in the same room as their parents.

Estimation of serial intervals of influenza

The University of Hong Kong (D) evaluated the serial interval, the time between successive cases of infectious diseases in the chain of transmission. The mean serial interval between primary and secondary cases of influenza among pairs of individuals within 14 households was 3.6 days.[11] This finding provides insight into the transmission of influenza among household members.

Assessment of school dismissal and social contacts

School dismissal is a significant part of CDC's pandemic planning. But there is concern that students dismissed from schools may congregate elsewhere, undermining efforts aimed at social distancing to mitigate disease transmission. RTI International (B) found that the number of social contacts among adults and children dropped significantly during school holidays. This suggests that students may not increase other social contacts in the event of school dismissal during pandemic influenza.

Estimation of sensitivity of rapid flu tests

Rapid influenza testing might be a valuable tool in a pandemic. Three studies [(A), (E), and (F)] assessed the use of the Quidel QuickVue Influenza A+B Rapid Test in their household- or school-based study populations. Uyeki et al[12] reported that compared with reverse transcriptase-polymerase chain reaction (RT-PCR), the gold standard test, rapid influenza test sensitivity was very low across these 3 studies, with a median of 27%, despite manufacturer claims of 73% sensitivity. A fourth study conducted in doctors' offices, public outpatient clinics, and hospital emergency rooms in Hong Kong (D), found a sensitivity of 68%, which is more consistent with manufacturer's reports. But that study modified the manufacturer's protocol by combining nasal and throat samples for rapid testing. Thus, the increased sensitivity observed in Hong Kong might have been related to the modification in specimen collection. The Hong Kong study also found greater test sensitivity in outpatients with higher levels of viral shedding, as measured by semiquantitative RT-PCR.[13] Taken together, these studies raise questions about the usefulness of rapid tests in field situations and as the diagnostic tool for enrolling participants in influenza and NPI studies.

Assessing transmission of influenza across international borders

During seasonal epidemics and pandemics, influenza is often spread by travelers crossing international borders. Investigators studied the use of NPIs to mitigate the transmission of influenza across international borders. Historical and modeling evidence support the use of NPIs to control the entry of pandemic influenza into island countries.[14] Rapid, large-scale risk-based entry screening of air travelers for ILI using questionnaires and health assessments was conducted successfully at airports in 2 studies, suggesting that this approach may be possible during a real event and might be generalizable to other venues. The Hawaii Department of Health (I) screened 2 flights, and the University of Otago (G) screened 175 of 307 eligible flights (57%). Screened flights included both English-speaking and non-English-speaking passengers. The Otago investigators also attempted to contact, 3 days after arrival, asymptomatic travelers who volunteered their contact details. This approach was successful 75% of the time, but required numerous attempts and considerable resources. The results of these studies will provide further insight into the trade-offs between the time and resources required for health screening in relation to the potential for mitigating disease transmission.

The Otago investigators estimated the reduction in travel volumes and the quarantine duration needed to exclude pandemic influenza from island nations (G). They estimated that a 99% travel volume reduction would be insufficient to achieve this protective threshold, necessitating other interventions. Quarantine (restriction of asymptomatic, exposed contacts of influenza cases) likely will be a key intervention, but careful planning is required to ensure sufficient capacity for up to 9 days.[15] Based on preliminary analyses, the investigators concluded that voluntary travel restrictions alone would be sufficient to protect isolated populations only with very low numbers of visitors.

Development of a historical database

Markel and colleagues at the University of Michigan (K) are compiling *The American Influenza Epidemic of 1918-1919: A Digital Encyclopedia*, supported by their creation of a massive archive of historical material. This resource provides important data for modeling pandemic disease and NPI interventions. It will have future applications for both community mitigation and prevention of transmission across international borders.

Summary of study findings and limitations

The NPI studies had several limitations. Most lacked sufficient statistical power to examine moderate effects in confirmed influenza outcomes due to insufficient sample sizes exacerbated by a mild influenza season during the first funding year, underreporting of disease, and challenges faced by influenza surveillance, including the poor sensitivity of rapid tests. In addition, differences in study designs prevented the combination of data for pooled analyses.

Taken together, the data provide some evidence that face masks, hand hygiene, cough etiquette, reduced crowding, and school closures are effective in reducing the spread of influenza. Nonetheless, further studies with larger sample sizes, common methodologies to allow pooling of data, and study durations that cover multiple influenza seasons are needed to address some of the aforementioned limitations of the studies. In addition, further laboratory studies are needed to address the relative contribution of transmission modalities (ie, small vs large respiratory droplets and contact transmission).

CURRENT DATA GAPS

Currently there are many gaps in the knowledge of seasonal and pandemic influenza and the effectiveness of mitigation practices. The CDC-funded research project investigators and collaborators contributing to this analysis identified gaps in 2 categories: (1) behavioral and social sciences and (2) biological and technological sciences (Table 2). A detailed account of these gaps follows.

Behavioral and social sciences

Little data exist for evaluating differences in NPI use across diverse populations, especially among socioeconomically disadvantaged and minority populations. More research is needed to assess knowledge, attitudes, and preventive practices related to influenza, especially predictors of the willingness to wear masks, receive immunizations, undergo travel screening, practice social distancing, and self-quarantine across heterogeneous racial and ethnic groups. Investigators at the University of Michigan identified stigma, perceived risk, and fear as factors shaping an individual's willingness to comply with mask wearing, social distancing, travel restrictions, and quarantine recommendations among university students.[16] How these factors lead to differences in influenza transmission is unknown.

In historical analyses of the 1918 pandemic in the United States, Markel et al[17] found that NPIs tended to be implemented more consistently and with greater compliance in localities where the lines of authority and communication were transparent and clearly delineated, suggesting the importance of health risk communication and a high level of trust in public officials during a pandemic crisis. Nonetheless, in modern times, how and where people obtain their information, along with its subsequent influence on NPI practice and ultimately disease transmission, are unknown. In addition, there have been few studies on the accuracy and consistency of various sources of information about influenza and the effect of different communication styles at the community level, particularly for vulnerable populations (eg, recent immigrants, non-English-speakers). This information gap underscores the importance of further assessing risk communication strategies and their impact in the context of potential uncertainty, as well as the roles of incentives and psychosocial factors that might influence current NPI compliance and influenza transmission. Gathering these types of data on influenza A (H1N1) and future pandemics is warranted.

Current gaps in research preclude the ability to assert the effectiveness of various mask-wearing protocols, respiratory etiquette, and layered NPIs. The feasibility and acceptability of selective, reactive, or preemptive school and other institutional dismissals across various communities require further evaluation. Furthermore, assessment of the relationships between the quantity and quality of social interactions on influenza transmission rates, the impact of social distancing without dismissals of events and schools, and cost-effective analyses are needed. Large-scale community interventions and research conducted over multiple influenza outbreaks are required to fill these knowledge gaps.

Table 2. Summary of gaps in data

Behavioral and social sciences	Biological and technological sciences
• Knowledge, attitudes, and practices related to use of NPIs across diverse populations • Role of social, demographic, and cultural factors on NPI practice • Decision making dynamics with respect to NPI recommendations • Effective risk communication strategies for enhancing NPI compliance • Extent of barriers to implementation of NPIs • How behavioral and social determinants influence NPI efficacy	• Adequate clinical influenza definitions • Prevalence and impact of asymptomatically influenza-infected persons • Sensitive and specific influenza rapid tests for community-based studies • Relative contributions of influenza virus transmission modalities (ie, large droplet nuclei, small particle droplet nuclei, and contact) to disease spread • Clinical implications of influenza viral load • Prevalence, risk factors, and impact of influenza superspreaders on disease transmission • Impact of environmental crowding and density on influenza transmission • The influence of international travel on transmission of influenza • Sensitive and specific screening tools for identifying influenza-infected travelers at international borders • Efficacy of different types of masks, hand hygiene, and combinations of personal protective measures for reducing transmission of influenza

Biological and technological sciences

There are many biological and technical gaps in our understanding of influenza diagnostics, transmission, and mitigation measures. The many unanswered questions that we describe below have together contributed to difficulties in quantifying the efficacy of NPIs for preventing particular influenza transmission pathways.

Clinical definitions, diagnostics, and surveillance. Studies that assess the accuracy of the clinical definitions of ILI for the purpose of syndrome-based surveillance are needed. Case definitions of influenza vary widely according to the presentation of symptom combinations.[18,19] Little data exist on how case definitions differ by population demographics and molecular characteristics of the virus. Furthermore, little is known about the association between preexisting immunity (humoral- or cell-mediated) and severity of infection, which may influence the prevalence of subclinical or asymptomatic infections in different populations and subgroups or secondary transmission rates among those who contract influenza following vaccination. Rigorous studies comparing rates of asymptomatic influenza virus infection with symptomatic infection are needed.

Further studies are needed to examine the factors accounting for the low sensitivity of rapid influenza diagnostic tests compared with other confirmatory methods,[13] as well as the relationship between viral load and the sensitivity of rapid tests. Surveillance methods providing more accurate influenza rates in individuals not utilizing health care services need identification. The acceptability and use of secure Web-based surveillance systems for monitoring rates of infection and compliance with interventions require assessment.

Laboratory studies of transmission. Studies of influenza using laboratory-adapted surrogate strains, similar to the early work done with rhinovirus, may help uncover transmission pathways, that is, the relative contributions of large and small respiratory droplets and surface contact toward the transmission of influenza viruses.[20] However, the respiratory droplets shed by persons experimentally infected with laboratory strains and by persons naturally infected with wild-type viruses must be fully characterized to ensure that the laboratory infections accurately model the real world. In addition, laboratory studies should consider whether higher viral loads cause increased viral shedding and transmission and whether the dose of infectious particles or the source of these particles vary between individuals. In other words, are there "superspreaders" for influenza strains?

Environmental factors and transmission. Data describing the impact of environmental factors on influenza transmission are limited. The relative influence of contact versus droplet transmission and the roles of surface contamination and humidity in primary or secondary infection are unclear. As Langmuir aptly stated, "what is essential and necessary evidence is the demonstration that the elimination of one or more of the means of spread, keeping the remaining ones constant, radically and consistently reduces the incidence of actual disease."[21] Environmental studies using engineering interventions that do not require individual compliance are likely to yield valuable information on transmission modes, such as ultraviolet light and air-exchange installations.[22-25] Studies that include both personal and environmental virologic sampling are warranted.

Density and crowding. Deficits exist in our understanding of the relationship between population densities and influenza rates. For example, research evaluating the impact on influenza rates of living in close quarters (eg, locked wards, prisons, dormitories, military bases, households) is limited. This underscores the importance of developing standardized crowding indices to examine the impact of household or residence size and composition on influenza transmission.

International travel and border screening. Research into the risk of disease transmission associated with international travel also contains gaps. For example, border screening and quarantine for delaying the spread of influenza across international borders require further assessment. Asymptomatic and incubating travelers present particular obstacles. Studies of screening measures for travelers, including assessment of the utility of infrared thermography scans, design of sensitive and specific screening questionnaires, and assessment of how to combine screening with quarantine and other approaches, are necessary to provide a useful level of border protection.

Personal protection measures. Little data exist on the effectiveness of various types of face masks, hand hygiene, and layered interventions on confirmed influenza outcomes in the community setting. Published experimental data from the hospital setting show that no detectable influenza viral RNA (limit of detection of 250 copies/mL) was detected after 9 influenza cases were asked to cough 5 times into both routine surgical masks and N95 respirators, suggesting that these masks are equally efficacious at preventing transmission of viral RNA among hospital patients.[26] Whether the use of surgical masks limits the generation of fine particles associated with viral aerosols requires further exploration in the community setting (ie, whether influenza is transmitted through the airborne route, not merely through large droplets and by contact spread). Studies are also needed to assess the effects of mask wearing by uninfected individuals at risk for exposure to influenza or other respiratory viruses and the contribution of embedding masks with microbiocides. In addition, research on specific hygiene habits and compliance levels associated with reductions in illness are merited.

DISCUSSION

The studies described here have added much to our understanding of preparedness and mitigation techniques for pandemic influenza. Findings from these studies have provided information on the acceptability and protective aspects of NPIs, as well as on the limitations in implementing these measures on a large scale in varied settings; however, many of the remaining research gaps can be addressed only by laboratory- and community-based studies with common protocols conducted over multiple years, given the consistently variable and unpredictable severity of influenza epidemics and pandemics.[2] Plans have been developed that describe what needs to occur in the event of pandemic influenza, but these plans fall short in detailing how to carry out the recommendations.[27] The 2009 influenza A (H1N1) pandemic may provide an opportunity to assess the effectiveness of NPIs against the spread of this novel influenza A virus in some communities.[28-31] Additional studies also are needed to identify the relative contributions of large droplet, small particle droplet nuclei, and contact transmission of seasonal influenza, the 2009 influenza A (H1N1), and newly emerging strains. Finally, research should include assessments of psychosocial and cultural factors that shape compliance with NPIs, to explore why certain groups accept NPIs while others do not, and whether barriers to compliance are lifted during a global pandemic.

In conclusion, the current influenza A (H1N1) pandemic may provide us with an opportunity to address many research gaps and ultimately create a broad, comprehensive strategy for pandemic mitigation; however, the emergence of this pandemic in 2009 demonstrated that there are still more questions than answers. More research is urgently needed, especially in light of the potential for mutations in influenza A (H1N1). If mutations do occur, or if new pandemic strains emerge in the future, NPIs likely will play a crucial role in mitigating the spread of infection when vaccines are unable to provide sufficient protection.

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