

COMMENTS ON 2004S-0212 - Pandemic Influenza Preparedness Plan
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Marc Lipsitch, D.Phil. Associate Professor Departments of Epidemiology and Immunology and Infectious Diseases Harvard School of Public Health 677 Huntington Avenue Boston, MA 02115 (617) 432 4559 mlipsitc@hsph.harvard.edu	Christina Mills M.D./D.Sc. Candidate Harvard Medical School and Department of Epidemiology Harvard School of Public Health 677 Huntington Avenue Boston, MA 02115 (617) 432 1476 cmills@hsph.harvard.edu
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We wish to submit the following comments on the Pandemic Influenza Response and Preparedness Plan.

1. OVERALL COMMENTS. The document overall is comprehensive, is well thought-out, and generally reflects up-to-date science. In particular, we support the Plan's emphasis on providing a safe and effective vaccine for an emerging strain as fast as possible. The plan makes note of research whose findings can be expected to help speed this process, and we believe that this research deserves very high priority, in light of the high probability of another pandemic in the coming decades and the near certainty that the pandemic will have significant impact in the US.

For vaccine production technologies as well as other control, communication and epidemiologic activities, it will be critical to engage in "practice" and test runs during interpandemic years to ensure that they are as effective as possible during the disruptions that will likely result during a pandemic.

Our major concern is that, given the nonspecificity of influenza symptoms and the ability to transmit before symptom onset, most "traditional" public health measures, including those that were successful in containing SARS, will have limited utility [1,2]. While the Plan acknowledges this risk, *we believe the Plan could be improved by further consideration of measures that can be taken if indeed control by isolation, quarantine, and related measures are impractical prior to vaccine availability.* Many of our suggestions below (2-4) address the data needs and possible interventions available during this period.

2. PREPAREDNESS FOR RAPID EPIDEMIOLOGIC DATA GATHERING AT THE OUTSET OF THE PANDEMIC BY DEVELOPMENT AND TESTING OF STUDY PROTOCOLS. With the emergence of a new pandemic strain, several basic epidemiologic quantities (in addition to the reproductive number, see below) will be

unknown, and knowledge of these quantities will be important to the scientifically based design of control measures. Baseline estimates will be needed as early as possible, and continuous monitoring will be required as many of these quantities will change over time. Specifically, these quantities include:

- (a) The case-fatality proportion in various risk groups
- (b) The clinical risk factors for hospitalization, mortality and other severe outcomes
- (c) The time course of viral shedding relative to time of infection
- (d) The time course of symptoms relative to time of infection and to viral shedding
- (e) The effectiveness of the vaccine (once available) in various demographic groups, both in preventing infection (shedding) and in preventing illness and severe illness.
- (f) The proportion of infections that are susceptible to antiviral agents by laboratory criteria (this is a number that is particularly prone to change).
- (g) The proportion of hospitalized cases in which evidence of bacterial superinfection is present as an exacerbating factor
- (h) The effectiveness of nonspecific therapies, such as steroids, in treatment of severe cases.

As in the case of the surveillance indicators described above, it will be difficult to gather these data in the context of a pandemic. **Protocols, questionnaires and (where required) information systems should be developed in advance and tested/rehearsed in interpandemic years wherever possible to facilitate the estimation of these quantities, which characterize a novel strain and inform the design of control measures.**

3. EXPANDED SURVEILLANCE DURING A PANDEMIC. *Monitoring the effectiveness of control measures* is an important objective of surveillance that is largely overlooked in Annex 4 and the plan as a whole. Throughout the pandemic, and especially in the period prior to widespread vaccine availability, decisionmakers and the public will need to know the extent of ongoing transmission and the effectiveness of containment measures. An overall measure of the effectiveness of containment is the instantaneous estimate of the reproductive number of the infection. The reproductive number at a given time, represented as $R(t)$, is the average number of secondary cases infected by each primary case infected at time t . This number must be held steadily below one for the spread of the virus to decline; while this objective may or may not be possible for pandemic influenza without a vaccine, the level of $R(t)$ is perhaps the best single measure of the effectiveness of control measures at a given time.

Fortunately, methods for calculating this quantity in real time have been described in a recent publication [3,4]. Existing surveillance systems should incorporate this method, or a variant of it, to provide decisionmakers with data to monitor containment activities.

In addition to this overall measure of effectiveness, there are a number of process measures that may be relevant to monitoring the impact of particular interventions. These depend on the type of intervention, but include such indicators as:

- (a) The mean (and distribution) of time from identification of a case to isolation of that case (if isolation is used)
- (b) The mean (and distribution) of time from identification of a case to antiviral prophylaxis and/or quarantine of contacts (if targeted prophylaxis and/or quarantine is used)
- (c) The number and proportion of travelers testing positive for influenza (if border controls are used)
- (d) The effectiveness of antiviral medications for prevention of defined endpoints.
- (e) The number of individuals quarantined, the number and fraction of these who go on to develop disease (if quarantine is used).

The gathering of such data, as shown by the SARS experience, is difficult; indeed, Singapore was the only country for which these data were available in nearly real time in a comprehensive way. **Thus we recommend the advance development of specific plans for rapidly gathering, analyzing, and communicating indicators of epidemic progress and of the effectiveness of control measures. Protocols should be developed despite the fact that these plans are not easily “practiced” in nonpandemic years (unlike those in 2 above).**

4. SPECIFIC PLANS FOR TRIGGERING INTERVENTIONS TO REDUCE CONTACT BY “INCREASED SOCIAL DISTANCE.” In the event of a pandemic that causes widespread disease before vaccines are available in adequate quantities, there may be a need to implement “social distance” interventions, including school closings, encouragement of telecommuting, cancellation of large gatherings, etc. This general class of interventions is mentioned very briefly in Annexes 8 and 12. The value of such interventions in previous pandemics is said to be limited (Annex 8), but few specifics are given. We suspect that these measures (as well as those recommended elsewhere in the Plan and in these comments) may be important, even if they have limited effectiveness, in “buying time” before vaccines become available. **It is important, during the interpandemic period, to develop principles for when “social distance” interventions should be implemented. Specific means of assessing the usefulness of these and other interventions should be developed (see point 2 above) so that they can be maintained with public support if appropriate, or discontinued if ineffective and disruptive. Plans should also be made to determine who will bear the costs of reduced work attendance, unavailability of childcare, and other likely consequences of such interventions.**

5. PLANS FOR INTERNATIONAL COOPERATION IN TREATMENT AND USE OF LIMITED ANTIVIRAL MEDICATIONS TO CONTAIN EARLY HUMAN-TO-HUMAN SPREAD. If human-to-human transmission of a new strain with pandemic potential is detected, it may be possible to contain this transmission by intensive interventions in the first population in which this transmission occurs, before spread becomes widespread (phase 0, level 3) [5]. This intervention may occur overseas, and may involve use of antiviral medicines that are being stockpiled in the United States for an eventual pandemic. **Plans for appropriate use of stockpiled antiviral medications as a preventive measure should be developed.**

6. ADVANCE PLANNING FOR COMMUNICATION AND LOGISTICS TO PREVENT AND TREAT SEQUELAE OF INFLUENZA INFECTION. The impact of an influenza pandemic is likely to be felt not only as an increase in both mild and severe respiratory infections, but also as an increase in complications and deaths from ischemic heart disease, diabetes, stroke, and other conditions [6], as well as in secondary bacterial pneumonias, including many in which the bacteria may go undetected [7]. These considerations emphasize the need to plan measures to alleviate these consequences.

(a) In a pandemic setting, especially before an appropriate influenza vaccine is available, pneumococcal polysaccharide vaccine may be indicated not only for existing risk groups, but for healthy children (≥ 2 years) and adults. While the plan justifiably emphasizes pre-pandemic vaccination of existing risk groups, broader vaccine coverage may require vaccine supplies that exceed those currently available. Moreover, given that children under 2 are considered a high-risk group for severe complications of influenza, and that the pneumococcal conjugate vaccine (but not the polysaccharide vaccine) is effective in this age group, it will be important to improve immunization coverage with the 7-valent pneumococcal conjugate vaccine, currently at 68%, the lowest of any childhood vaccine (http://www2a.cdc.gov/nip/coverage/nis/nis_iap.asp?fmt=v&rpt=tab02_antigen_iap&qtr=Q1/2003-Q4/2003). **Thus stockpiling of pneumococcal polysaccharide vaccine should be considered. In addition to the Plan's recommendation for improved coverage of the polysaccharide vaccine in adults, efforts to improve coverage of the conjugate vaccine in infants should be enhanced.**

(b) Much of the morbidity caused by pandemic influenza will involve comorbidities, including asthma, diabetes, and cardiovascular disease. Plans should be in place to educate the public and the medical community about these elevated risks and to deal with increases in demand for treatment of these and other related outcomes, as well as with "traditional" influenza pathology. Educating the public about modifiable risk factors for influenza disease, most importantly smoking, may also be valuable in the setting of elevated concern that will surround a pandemic. **Plans should be developed to prevent and treat the likely complications of influenza, and to encourage avoidance of risk behaviors such as smoking in the context of a pandemic. In addition, given the**

nonspecificity of influenza symptoms, plans should be developed for cohorting of patients with known or suspected influenza.

7. RESEARCH ON THE USE OF VACCINES IN TRANSMISSION RISK GROUPS (E.G. SCHOOLCHILDREN). The Plan makes a strong recommendation that first priority for vaccination, when vaccines are available, should be given to individuals at high risk for severe disease and their close contacts. There is considerable evidence – though not, as noted in the Plan, in the setting of a pandemic – that the vaccination of schoolchildren may be as effective as, or more effective than, vaccination of elderly and other high-risk populations in reducing total mortality. This effect occurs because of schoolchildren’s important role in transmitting and amplifying infection. Further research on this strategy is urgently needed. An ethical approach during interpandemic years might be to design community-randomized studies in which high-risk individuals are vaccinated in all communities, but schoolchildren are also vaccinated in a randomized subset of communities, and attack rates in all age groups compared. **It is important in the interpandemic period to refine our understanding of the usefulness of vaccines in various age groups and to consider seriously the possibility of vaccination to block transmission, rather than only to protect the most vulnerable.**

8. RAPID DIAGNOSTICS. The importance of specific influenza diagnosis will be increased during a pandemic, for many reasons: epidemiologic tracking, isolation of influenza-infected individuals, etc. The plan makes little or no mention of the role of diagnostic kits. **Further consideration should be given to ensuring adequate supplies, so that (for example) hospitals can accurately monitor which patients are infected and prevent nosocomial spread.**

9. LEGAL ISSUES FOR VACCINE PRODUCTION. The Plan does not make reference to the issue of providing legal protection for vaccine manufacturers. **Given the prominence of this issue in the response to Swine Influenza, it should be included in the plan.**

REFERENCES

- 1 Ferguson NM, Fraser C, Donnelly CA, Ghani AC, Anderson RM (2004) Public health. Public health risk from the avian H5N1 influenza epidemic. *Science* 304: 968-969.
- 2 Fraser C, Riley S, Anderson RM, Ferguson NM (2004) Factors that make an infectious disease outbreak controllable. *Proc Natl Acad Sci U S A* 101: 6146-6151.
- 3 Wallinga J, Teunis P (2004) Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *Am J Epidemiol* 160: 509-516.
- 4 Lipsitch M, Bergstrom CT (2004) Invited commentary: real-time tracking of control measures for emerging infections. *Am J Epidemiol* 160: 517-519; discussion 520.
- 5 Enserink M (2004) Influenza: girding for disaster. Looking the pandemic in the eye. *Science* 306: 392-394.
- 6 Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, et al. (2004) Influenza and the winter increase in mortality in the United States, 1959-1999. *Am J Epidemiol* 160: 492-502.
- 7 Madhi SA, Klugman KP (2004) A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat Med* 10: 811-813.