



**NBSB** NATIONAL BIODEFENSE SCIENCE BOARD

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**H1N1 COUNTERMEASURES STRATEGY AND DECISION-MAKING:  
REPORT WITH RECOMMENDATIONS**

**FROM THE  
NATIONAL BIODEFENSE SCIENCE BOARD**

**FOR THE  
SECRETARY  
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**JULY 17, 2009**

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## INTRODUCTION

The National Biodefense Science Board (NBSB) was asked by RADM William C. Vanderwagen, M.D., Assistant Secretary for Preparedness and Response (ASPR), to work with the other U.S. Department of Health and Human Services Advisory Committees to clarify its potential role in advising on H1N1 countermeasure issues, and to provide clarity in responsibilities for: the Advisory Committee on Immunization Practices (ACIP), the Vaccines and Related Biological Products Advisory Committee (VRBPAC), and the National Vaccine Advisory Committee (NVAC). The NBSB was also asked to provide insight on decision pathways and critical data needed to inform decision-making around the issues of H1N1 novel influenza.

## EXECUTIVE SUMMARY

The Pandemic Influenza Working Group (PIWG) of the National Biodefense Science Board (NBSB) convened a group of experts, government scientists, and stakeholders in Bethesda, Maryland, on June 18 and 19, 2009, to identify key areas around which the United States (U.S.) Department of Health and Human Services (HHS) should focus its decision-making on countermeasures for novel H1N1 influenza virus. Presentations from government, industry representatives, and invited experts on vaccines, diagnostic methods, and antivirals identified relevant challenges, considerations, progress, and projections.

To improve the process of identifying key decision points and preparing to make these decisions, the working group felt it was critical to develop a Report to: clarify the key assumptions, and identify the specific goals and principles for a response. Specific contemporary responses take advantage of the foundation of preparedness efforts undertaken during the last five years; however, these responses must be adapted to the specific epidemiology, circumstances, and existing resources of the current pandemic.

The National Biodefense Science Board held an urgent public teleconference on July 17, 2009, to consider and discuss the Report from the Pandemic Influenza Working Group of the NBSB. Following discussion by the members and public, the NBSB voted on, and unanimously approved the 'H1N1 Countermeasures Strategy and Decision Making: Report with Recommendations,' to the Secretary of HHS for prompt action, with timing appropriate to the current pandemic situation.

In brief, the key findings of the meeting and subsequent deliberations include the following:

### *H1N1 Vaccine*

- Based on available data, the NBSB recommends that HHS set a goal of having several tens of millions of doses of unadjuvanted monovalent A/H1N1 vaccine available for clinical use not later than September 15, 2009. To achieve this, HHS should pursue a simplified testing program to achieve that goal. Additional studies may be

appropriate for additional supplies in subsequent months, but time of availability seems to be the dominant criterion for vaccine decision making.

- Decades of experience with A/H1N1 influenza viruses provide a basis for selecting initial antigen quantities and dosing. If the US goal is vaccine availability on the shelf in September 2009, 15-mcg unadjuvanted subunit vaccine and live attenuated intranasal vaccine for children may be a rational approach.
- If the second wave is delayed or production is slower than expected, mix-and-match studies of vaccine plus separate adjuvant may yield information that may stretch the available vaccine supply.

#### *Antiviral & Other Therapeutic Agents*

- H1N1 strains appear to be sensitive to neuraminidase inhibitors, which are effective in reducing symptoms and progression in early stage disease, and for post-exposure prophylaxis in asymptomatic exposed patients.
- If the H1N1 vaccine is not available at the time of an early wave of disease, the use of antiviral drugs for post-exposure prophylaxis should be considered, but was not extensively discussed at the conference.
- Evidence for effectiveness of antivirals in advanced disease is less robust; there will be no approved parenteral formulation of any influenza antiviral available that could be used by fall 2009.
- Novel antiviral drugs effective against resistant strains and advanced disease will not be available for the existing pandemic, but should be developed vigorously for future pandemics.
- HHS should reassess its current and anticipated supply of approved antiviral products and other therapeutic agents (e.g., antibiotics, seasonal influenza vaccine, pneumococcal vaccines) where surge demand might overwhelm normal supply.

#### *Diagnostics*

- Public health laboratories are not equipped to meet the clinical diagnostic needs posed by the present pandemic. Assays with clinical utility should be more widely distributed among clinical-care laboratories.
- Existing rapid diagnostic tests have unacceptably low sensitivity to rule out H1N1 infection in individual patients.
- Clinical criteria will likely be the primary diagnostic tool used in the upcoming fall outbreak.
- Better diagnostic tests should be developed.
- HHS should reassess its current and anticipated supply of laboratory reagents, and their availability to clinical-care laboratories.

## **H1N1 Vaccine**

### Key Assumptions

- Novel H1N1 viruses will continue to circulate.
- A second wave is likely to occur, as soon as fall 2009. Best estimates suggest that infection rates will be 2-3 times higher than expected with seasonal influenza. The second wave could peak in October, but we must anticipate onset as early as September.
- Attack rates will continue to be highest in children and young adults.
- Hospitalizations and deaths will continue to be concentrated among children and younger adults with underlying medical conditions.
- Children will continue to act as an amplifier to community spread of the virus.
- Severity will continue to be similar to or somewhat greater than the current wave, but the number of cases will be substantially larger.
- Catastrophic disruption of societal function, as anticipated in some planning scenarios for a severe pandemic, is unlikely.
- Waiting for a full characterization of the immunologic properties of candidate vaccines with extensive studies, and doing studies in series would result in the H1N1 vaccine not being available until late fall.
- Having vaccine only after the peak may be worse than having no vaccine at all: it incurs all of the risk and cost with no potential benefit.
- Licensed vaccines, or vaccines similar to licensed products, will be most acceptable at the beginning of the next epidemic wave.
- Safety of the vaccines, both real and perceived, will shape risk-benefit calculations and acceptance. This will be true for both public health officials applying a collective perspective, and for individuals deciding whether to be vaccinated.
- Decisions about vaccine formulation must be made rapidly on the basis of available data. Strategies can and should be changed as more data become available, but we cannot wait beyond mid-August if vaccine is to be in supply by mid-September.
- The Biomedical Advanced Research & Development Authority (BARDA) strategic goal of being able to produce vaccine for all 300 million Americans within 6 months of declaration of a pandemic is an appropriate goal for capacity. However, it **is not the same** as the strategic goal for dealing with a specific pandemic.

*N.B., It is crucial for government officials to iteratively check that assumptions remain correct and revise assumptions and strategy as additional data become available.*

### Goals and Principles

- A critical goal is to have some monovalent novel H1N1 vaccine available by mid-September 2009, should it be needed. This goal can take advantage of the decades of experience with other H1N1 subunit vaccines, typically at a 15-mcg dose.

- Begin with the goal of targeting a small amount of the vaccine to a small group where it will do the most good. To the extent possible, this should be driven by sound epidemiologic data.
- This likely means focusing on infants, toddlers, school-age children, pregnant women, and adults with risk factors applicable to novel H1N1 virus.
- Manufacturing of vaccine for additional cohorts of the US population and the world should proceed, but without interfering with the goals listed above.
- Safety monitoring must be in place before novel H1N1 vaccination begins, and have the sensitivity, power, and speed to detect signals and determine causal relations in a timely manner to aid policy and communication.
- HHS should remind States and local health departments that durable record-keeping of who receives the vaccine (preferably in electronic format) is an essential component of local implementation plans.
- HHS should consider recommending school-based immunization delivery for children for logistical simplicity.
- Decision-making should remain flexible, based on clearly articulated principles and scientific evidence, and should be transparent.

## Implications

- A pathway to licensing egg-grown subunit vaccine and perhaps live attenuated influenza vaccine (LAIV) by September should be identified.
- It may be possible to harness clinical-trial data on LAIV administered as nasal drops to increase the available supply.
- The minimum early data set needed for decisions by the Advisory Committee on Immunization Practices (ACIP) should be identified (e.g., risk factors for infection, age-stratified immunogenicity response to vaccination). The primary set of studies should be designed to provide these data. These might include:
  - Immunogenicity and safety of one dose of 15 mcg unadjuvanted vaccine. These studies should include explicit substudies among infants, children and pregnant women. Two dose studies may be needed for infants and children.
  - Immunogenicity and safety of LAIV in its standard age range.
- More detailed studies to determine an optimal dose, the potential need for multiple doses by age strata, and the effect of adjuvants are also important. However, these studies should not delay early licensure of a traditional-process product.
- Alignment of the strategic goals with the process can be improved. This may require close coordination among government leaders of the National Vaccine Program Office (NVPO), Centers for Disease Control and Prevention (CDC), Biomedical Advanced Research and Development Authority (BARDA), National Institutes of Health (NIH), and Food and Drug Administration (FDA).
- Epidemiologic data, modeling, and early evidence of vaccine safety and immunogenicity will inform ACIP recommendations, but it will be necessary to make decisions before all of the data are available. Modifications will be made if indicated by evolving knowledge.

## **Antiviral & Other Therapeutic Agents**

### Key Assumptions

- There is substantial evidence that antivirals against influenza ameliorate symptoms, speed return to work, decrease secondary pneumonia, antibiotic use, hospitalizations and mortality.
- The quality of the evidence is of lower quality for more severe disease. Although randomized trials do not address hospitalized patients and prevention of mortality, existing observational studies are well designed, show consistent benefits, and are consistent with our understanding of influenza pathogenesis. The consensus of expert opinion is that antiviral drugs are likely to offer substantial benefit to patients at risk for or with severe disease.
- Antivirals must be used early for patients with uncomplicated disease (e.g., within 48 hours of symptom onset, but the earlier the better). For severe disease, delayed treatment may confer benefit.
- Emergence of resistance to existing agents must be anticipated, particularly with oseltamivir. At the least, co-circulation of oseltamivir-resistant seasonal H274Y H1N1 and resistance to adamantines for novel H1N1, influenza A/H3N2, and influenza B will complicate treatment decisions.
- If novel H1N1 becomes widely oseltamivir-resistant within the next few months, healthcare providers will have few treatment options. This is likely to lead to increased morbidity and mortality.
- Intravenous zanamivir could be the best option in the short term for oseltamivir-resistant novel H1N1 for hospitalized and severely ill patients. The future of development for this drug by its sponsor remains uncertain.
- Under the draft FDA guidelines for antiviral agents, it is unlikely that any antiviral for influenza can meet the requirements for approval for the indication of severe disease.
- Incentives exist for antiviral development, including NIH and BARDA assistance for early and advanced development. However, it is unlikely that any candidate influenza antiviral agent will be approved in the next 12 months.
- Antibody-based treatments are unlikely to be available in a useful way before the second wave of novel H1N1 develops in the northern hemisphere.

### Goals and Principles

- All treatment approaches must be considered, including: alternate routes of administration and doses for existing drugs, combination therapy, new agents in existing classes, and new classes of antivirals.
- Treatments that could modify the immunologic cascade and clinical impact of influenza are also attractive. At present, there do not appear to be any such attractive candidates for immunologic or anti-inflammatory treatment, with the possible exception of celecoxib.
- High barriers exist, including the need for an achievable pathway to approval.

## Implications

- Antiviral treatment approaches must be developed and available for:
  - Oseltamivir-resistant virus.
  - Use in persons with severe disease.
  - Use in pregnant women, young children and infants.
- Regulations and/or incentives must be improved that will ensure pharmacokinetic and safety testing in pregnant women and children early in the development process.
- The development of FDA's draft guidance is an important first step; fundamental issues remain to be resolved.
- A reasonable pathway to approval for antivirals in severe disease must be developed. Scientific and methodologic barriers will need to be overcome; appropriate endpoints and surrogate markers need to be developed. An FDA workshop may be an effective way to achieve this goal.
- If intravenous zanamivir is not further developed by the manufacturer, the US Government should give strong consideration to purchasing the rights and pursuing development under an alternate pathway.
- HHS should reassess its current and anticipated supply of approved antiviral products.
- HHS should reassess the current and anticipated supply of other therapeutic agents (e.g., antibiotics, seasonal influenza vaccine, pneumococcal vaccines) where surge demand might overwhelm normal supply.

## **Diagnostics**

### Key Assumptions

- Public health and clinical laboratories play an important role to detect and quantify viral circulation in the community, identify outbreaks, provide samples to detect viral drift and to detect drug resistance.
- Public health laboratories primary role is to inform community level action.
- Clinical laboratories inform infection control, appropriate choice of treatment and use of limited resources, and allow prophylaxis among contacts.
- Laboratory resources and capacity both in the public health sector and clinical sector are limited. They are likely to again be rapidly overwhelmed as they were in May and June 2009.
- Co-circulation of novel H1N1 and seasonal influenza viruses, as well as other respiratory viruses, will occur.

### Goals and Principles

- It is essential to increase the capacity, throughput, and efficiency of high-quality diagnostics for pandemic response, and sustain those improvements over the course of decades.
- Public health laboratories should not function for clinical needs. Therefore, diagnostic capacity in the clinical arena needs to be strengthened to guide individual care. However, data from clinical laboratories are also essential to public health. They can detect outbreaks, define clinical illness and provide clues to the efficacy of vaccines and antivirals.
- Improved platforms for detection and typing of influenza viruses should be rapidly developed and deployed. These can improve throughput in public health laboratories and bring greater capacity to the clinical arena.
- It will be critical to have effective surveillance for neuraminidase inhibitor (NAI)-resistant seasonal influenza viruses, as well as possibly NAI-resistant novel H1N1 viruses.

### Implications

- The capacity of public health laboratories should be augmented above current levels. This expansion of capacity needs to be sustained after the current pandemic passes, for multiple biosecurity reasons.
- Assays with clinical utility should be more widely distributed among clinical-care laboratories.
- Accurate molecular (e.g., nucleic acid amplification-based) diagnostics need to be available for the management of hospitalized patients.

- Improving diagnostic capacity for hospitalized patients contributes to public-health readiness, because it improves containment, efficient use of resources and unburdens public health laboratories.
- The capacity for resistance testing needs to be dramatically increased. Optimally this should be available both at the state public health laboratory and for management of patients requiring treatment.
- Programs to share diagnostic reagents and perform cross validation are critical.
- Barriers to increasing capacity, such as restrictions that arise for licensed tests or the desire to achieve licensure, should be identified. These barriers will need to be resolved or eliminated. Examples include:
  - Restrictions on migrating the CDC protocol for typing of influenza and confirming novel H1N1 onto high-throughput platforms.
  - Restrictions on divulging sub-typing information that is produced by existing platforms, if that was not in the license.
  - Restrictions on sample type (e.g., CDC data submitted for the Emergency Use Authorization [EUA] did not include nasal washes, therefore some public health laboratories did not accept these specimens, despite overwhelming data in the literature that nasal-wash specimens outperform other specimens covered in the EUA).
- The impact of improved diagnostic availability on infection control, optimal use of antiviral stockpiles, slowing of resistance and appropriate use of antibiotics require further study. Mechanisms to fund these studies are needed.
- HHS should reassess its current and anticipated supply of laboratory reagents, and their availability to clinical-care laboratories.

## **Appendices:**

**Appendix A:** Pandemic Influenza Working Group Roster

**Appendix B:** H1N1 Countermeasures Strategy and Decision Making Forum – Detailed Report

**Appendix C:** Forum - Agenda

**Appendix D:** Forum - List of Participants

**APPENDIX A**

**H1N1 COUNTERMEASURES STRATEGY AND DECISION-MAKING  
FORUM**

**PANDEMIC INFLUENZA WORKING GROUP ROSTER**

**PANDEMIC INFLUENZA WORKING GROUP (PIWG)  
NATIONAL BIODEFENSE SCIENCE BOARD**

**JULY 2009**

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