



NBSB NATIONAL BIODEFENSE SCIENCE BOARD

**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

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

National Biodefense Science Board (NBSB) Pandemic Influenza Working Group Roster

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APPENDIX B

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

DETAILED REPORT

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

JULY 2009

**H1N1 COUNTERMEASURES STRATEGY AND DECISION MAKING FORUM
HOSTED BY THE PANDEMIC INFLUENZA WORKING GROUP
NATIONAL BIODEFENSE SCIENCE BOARD
June 18–19, 2009**

DETAILED REPORT

June 18, 2009

INTRODUCTION TO DAY ONE

The Pandemic Influenza Working Group (PIWG) of the National Biodefense Science Board (NBSB) convened a group of stakeholders from government agencies and industry, invited experts, and representatives from other Department of Health and Human Services (HHS) advisory groups, in Bethesda, MD, on June 18–19, 2009. The goal was to identify key areas around which HHS should focus its decision-making process as it develops its countermeasures strategy for the novel H1N1 influenza virus.

GOALS

Andrew Pavia, M.D., PIWG chair, explained that the goals of the meeting were: to determine what decisions HHS must make immediately to address H1N1 influenza vaccines, antivirals, and diagnostics; identify the areas of pandemic influenza planning that did not meet expectations; and determine efforts that must come up to speed quickly. The first day's focus would be on the development of H1N1 vaccines, a complex topic that involves potentially high risk but also substantial benefits. Decisions about vaccines should be made carefully and transparently, said Dr. Pavia, with attention to the evolving science, and with flexibility to change course as needed.

WELCOME

RADM William C. Vanderwagen, M.D., Assistant Secretary for Preparedness and Response (ASPR), said the meeting participants brought with them broad experience to inform the deliberations and ensure that decision-makers keep in mind the historical context in which they are working. He noted that the NBSB was created as part of the Pandemic and All-Hazards Preparedness Act (PAHPA) and has brought to ASPR and HHS insights that might not have been recognized among those working entirely within government confines. RADM Vanderwagen said Federal decision-making will affect not only the 300 million Americans who depend on the government to support the public health system but also people all around the world. He said the global impact of U.S. policy was particularly clear during a recent meeting of the Global Health Security Action Group.

RADM Vanderwagen called on the participants for insight on decision pathways and the critical data needed to inform decision-making for this summer and fall. He hoped the discussion would also inform discussions planned for early July in Mexico among ministers of health from around the world on how they can work together to address global public health concerns.

RADM Vanderwagen noted that preparedness is a broad enterprise with a wide variety of partners. For example, the National Institutes of Health (NIH) works on discovery research; the Biomedical Advanced Research and Development Authority (BARDA) translates that research into products to counter threats, e.g., a novel virus; the Food and Drug Administration (FDA) ensures the products are safe and effective; and the Centers for Disease Control and Prevention (CDC) conducts epidemiologic and scientific studies and facilitates implementation through distribution of products. Successful implementation, however, all comes down to State and local colleagues: Will they be able to use the tools we develop? How can we support them? How can we encourage them to take advantage of the tools available? Ultimately, their communities, families, and friends receive the countermeasures we develop. Therefore, no single Federal agency acts alone, nor does the Federal government act alone as one entity. Rather, partnership reaches all the way down to the level of the individual patient.

RADM Vanderwagen displayed the decision tree his office is using to facilitate its efforts. Among the issues to consider for H1N1 influenza, he said, is the availability of a vaccine and how a vaccine would be used—both of which are affected by the severity, spread, and timing of the disease, as well as special populations or target groups affected by the disease. The potential use of adjuvants should also be considered. RADM Vanderwagen reiterated the need for outside experts to provide input on the decision-making process. Specifically, the meeting participants should explore what we know about the science of countermeasures (vaccines, diagnostics, and therapeutics) and how to use them. No timeline has yet been identified, but it is believed that we are experiencing the first wave of H1N1 influenza now and anticipate a second wave in the fall. If a vaccine is to be used, many of the questions about what to use, when, and for who must be answered within the next 90 days.

RADM Vanderwagen said the effort represents a worthy challenge, in which public health and preparedness experts must come together to create tools that will ensure resilience, should there be a severe resurgence in the fall. He emphasized that the health and well-being of society at large are the central concerns as the United States gears up to address not only the threat of H1N1 virus, but also the fall hurricane season. He thanked the participants for their time and input.

NOVEL H1N1 VACCINE STRATEGY

H1N1 Vaccine Strategy—Robin Robinson, Ph.D., BARDA

Dr. Robinson said a convergence of events led to the development of the National Strategy for Pandemic Influenza: the H5N1 virus reemerged, and surprising results from clinical studies showed that the H5 vaccine developed would not protect 90% of the people. Hurricane Katrina exposed significant gaps in disaster response planning and capacity. Having only one manufacturer to produce seasonal influenza vaccine (for the 2004–2005 season) demonstrated what a vaccine shortage would be like. With all of these events happening in the early part of the decade, and 29 years after the 1976 swine influenza epidemic, Congress passed PAHPA and established BARDA to develop

countermeasures. The Federal effort was energized with a new plan, funding, and a critical mass of people dedicated to addressing the potential for a pandemic.

The National Strategy describes two critical goals for use of vaccines for pandemic influenza:

- Goal #1: Establish and maintain a dynamic prepandemic influenza vaccine stockpile available for 20 million persons (2 doses/person).
- Goal #2: Provide pandemic vaccine to all U.S. citizens within 6 months of a pandemic declaration (600 million doses).

With new manufacturers in the market and more vaccines available, there are more choices. BARDA is seeking input from experts within and outside of government on what kind of vaccine options to pursue, how much vaccine will be needed, and when it will be needed. It also seeks more information on the capabilities of manufacturers, government agencies, and State and local governments to address pandemic influenza.

Dr. Robinson mapped out the overlapping steps of virus identification, vaccine development, manufacturing, and administration for H1N1 virus that began in late April. The CDC and other laboratories around the world received isolates of the virus, made reference strains, and provided the reference strains to manufacturers, which began production of vaccines for clinical trials. Some manufacturers have now begun commercial production. In recent years, vaccine manufacturers have developed adjuvants, and current clinical trials must also evaluate the safety and efficacy of adjuvants for an H1N1 vaccine.

Dr. Robinson stressed the importance of clinical studies to guide decision-making, especially in light of the lessons learned from the 1976 swine influenza vaccine. While there is current experience with H5N1 vaccine, it is not yet known what kind of vaccine is needed for H1N1, how much vaccine is needed, and whether adjuvants can or will be used. Among other questions to answer is what level of immunity any proposed vaccine will offer (how broad and how deep), and whether a single dose might offer enough immunity to protect some people. The NIH is studying the effects of a vaccine that mixes the antigen from one manufacturer with the adjuvant from another. It is yet unknown how seasonal influenza vaccine might interact with an H1N1 vaccine.

Using the 2005 National Strategy for Pandemic Influenza as the guide for an H1N1 vaccine strategy, Dr. Robinson said HHS moved quickly to secure the components of a vaccine from five manufacturers, especially antigen, which is in short supply around the world. BARDA, in collaboration with FDA, categorized manufacturers into five tiers. Tier 1 manufacturers already provide a licensed seasonal influenza vaccine in the United States. Tier 2 manufacturers are those close to licensure of a product or completing phase 3 trials of vaccine, with or without adjuvant; many of the Tier 2 manufacturers have developed an H5N1 vaccine, and many use cell-based manufacturing techniques. Dr. Robinson said that adjuvants have been purchased and would go to the Strategic National Stockpile (SNS) as a bulk product. The SNS would also have to purchase needles and

syringes to administer vaccines. Potency and antigen assays are available, thanks to years of focus by BARDA, which will help move the process forward. Manufacturers are working on purified antigens.

The CDC leads the Federal effort in administering vaccine and is empowering State and local governments to be part of the decision-making process. Dr. Robinson said recent meetings have been productive and suggest that efforts are getting closer to meeting the potential public health needs.

Previous planning assumptions set a total production goal of 100 million doses of vaccine for a pandemic. Now, however, the expectation is to produce 600 million doses. Dr. Robinson said the key question is, “What do you want and when?” The production capacity for 2009 is much different than in 2005, so BARDA has had to adjust its vaccine distribution planning. The strategic approach for H5N1 vaccine included some flexibility; going forward, as clinical studies provide more information, it will be important to be able to make changes.

The FDA may consider licensing vaccines that do not include adjuvants as the virus strain changes. Adjuvants that do not achieve licenses would need to be approved by the FDA under and emergency use authorization (EUA); pending information on how they would be used, who would receive them, and how they mitigate morbidity and mortality. The FDA has created templates and “pre-EUA” packages to speed up the process.

The key decision points for the Federal vaccine enterprise continue to be: what type of vaccine will be used, whether vaccines will include thimerosal as a preservative, whether adjuvant will be used, and how adverse event safety monitoring will be undertaken after immunization.

Dr. Robinson described three production options: Plan A—vaccine with no adjuvant; Plan B—vaccine with one adjuvant; and Plan A/B—use of vaccine with and without adjuvant, as available. He noted that planning assumes a resurgence of H1N1 on September 15, with the first vaccine available in October. According to projections, manufacturers could provide 150 million doses of a vaccine with no adjuvant (Plan A) in October, and 80 million doses per month from November through March. With Plan B, 312 million doses of adjuvanted vaccine would be available in October, 160 million doses in November, and 120 million doses in December. Dr. Robinson said such a large supply could overwhelm the system under the current planning assumptions, so it would be necessary to revise the strategy.

The combination plan (Plan A/B) would allot some antigen-only vaccine for special populations, such as children, early in the season. Others could receive adjuvanted vaccine if they give informed consent. The amount of vaccine available would be similar to that in Plan B.

Vaccine may take the form of a nasal spray, prefilled syringes, or 10-dose vials of antigen and 10-dose vials of adjuvant that could be combined manually. The total vaccine output by manufacturer is projected as follows:

- Novartis: 45.7%
- Sanofi Pasteur (vial plus syringe): 26.4%
- CSL: 18.7%
- MedImmune (nasal spray): 5.8%
- GlaxoSmithKline (GSK): 3.4%

Dr. Robinson outlined the distribution options, which are subject to change along with production schedules. CDC has identified McKesson as its prime wholesale distributor, and up to four more distributors could be involved. Dr. Robinson said the system allows for quick distribution, but if seasonal influenza vaccine is also being distributed, the carrier system will be worn down, even if the distribution system is seamless and no logistical problems arise. Delivery through point-of-delivery systems (PODS), State and local health departments, and private providers are all under consideration as the system gears up to delivery 40,000–90,000 parcels per day. The President wants the vaccination effort done safely and quickly.

Dr. Robinson said the current pandemic influenza strategy prioritized critical workers, children, and pregnant women as the first tier of vaccine recipients. He reminded the group that the World Health Organization declared a pandemic of H1N1 influenza on June 11, 2009.

Discussion (paraphrased)¹

Tim Gallagher: Do you anticipate an increased demand for seasonal influenza vaccine?

Dr. Robinson: We've taken that into account, and the amount of seasonal vaccine may reflect an increased demand.

Kathy Neuzil, M.D., M.P.H.: I would like to see this strategy applied to seasonal influenza. I think the theme of today is that we can't look at H1N1 in isolation but rather should look at how it intersects with seasonal influenza in terms of immunogenicity, distribution, antigenicity, etc.

Dr. Robinson: We are working with manufacturers, talking with CDC and others, engaging in meetings like this and others, but the clock is ticking, and we need to decide soon. Some manufacturers have not finished production of their seasonal influenza vaccine yet, but it's not interfering now. It would take another level of coordination, but it's worth discussing further.

Dr. Neuzil: The Advisory Committee on Immunization Practices (ACIP) has worked hard to evaluate risk groups and has included more people in its seasonal influenza vaccine recommendations. This will be the first year of full implementation of our recommendations for pediatric patients. It's important to be careful about messaging, especially if there are different target groups. There is potential for confusion—there's

¹ This and subsequent discussions paraphrase the questions and comments of the participants. This document does not represent a verbatim transcript.

always confusion about vaccines. Our compromise with the American Academy of Pediatrics was to recommend that children get two doses of seasonal influenza vaccine in the first year that they are vaccinated. Does H1N1 vaccine count toward that? Should they get two doses of seasonal vaccine also? You can see how the decision on H1N1 will affect our implementation.

Dr. Pavia: Given the data needed to make recommendations, and what's been done in clinical trials so far, the concept of priming patients for seasonal influenza and novel H1N1 adds another level of complexity.

[Unidentified]: Can we reach the goal of 600 million doses?

Dr. Robinson: We have been able to cobble together with the manufacturers the capacity to get that.

[Unidentified]: When does the six-month clock start? October?

Dr. Robinson: May. That's our assumption. On May 22, the Secretary put the pandemic influenza money toward vaccine development.

[Unidentified]: Is it possible to get more product before October?

Dr. Robinson: Maybe we could have some in July, but what amount of antigen should it contain? How much adjuvant? We could make blind decisions, but we want science informing us where possible.

Update: Domestic and International Surveillance Update and Plans—CAPT Anthony Fiore, M.D., M.P.H., CDC

CAPT Fiore said he could provide some information from early U.S. surveillance data. We have illness and we are seeing outbreaks, he said, although there has not been much media attention in recent weeks. In the United States, 17,855 cases of H1N1 influenza have been confirmed and 45 deaths have resulted. The figures are rising. Around the world, there have been approximately 36,000 cases in 76 countries. Clearly, the H1N1 virus is persisting and will continue to circulate.

Surveillance information comes from various sources, including: swabs taken at doctors' offices, hospital-based surveillance, State and territorial epidemiologists (who report weekly), pediatric mortality statistics, and sentinel providers' systems (which look for influenza-like illness (ILI)).

Virologic surveillance involves about 165 public health and hospital laboratories. They get reagents from CDC and report daily on virus changes and antiviral susceptibility. The 2008–2009 influenza season followed typical patterns until the outbreak of H1N1 in April. CDC saw a late surge in acute respiratory disease, mostly due to novel H1N1. Because more people were tested later in the influenza season, CDC found that the typical influenza season appeared to last into May, which is longer than previously thought.

Morbidity surveillance relies on several systems, including the ILI Surveillance Network (ILINet, also called the sentinel providers' system), which now provides daily reports on people who present with acute respiratory infection. It includes 2,400 health care providers and about 16 million visits per year. Reports identify the percentage of patients

who come to a health care provider with symptoms and the diagnosis is not necessarily laboratory-confirmed.

BioSense collects information electronically from emergency departments (EDs), pharmacies, and laboratories. It provides a good sense of patient visits to EDs, use of antivirals, and use of commercial testing. The Behavioral Risk Factor Surveillance System (BRFSS) helps identify what's going on in a community. It gathers State-level data based on telephone surveys in which participants are asked about ILI in the past few weeks or months.

ILINet data can show patterns of disease over time. It can illustrate regional patterns, such as the spike in H1N1 underway in the New Jersey/New York region. CAPT Fiore believes that spike will plateau this week, and some spikes in other parts of the country have resolved.

BRFSS is useful for getting a community-level picture of the spread of illness. It captures people who may not seek health care, which is important information in determining the severity of disease. In some cases, illness is confirmed neither clinically nor by a laboratory test, but it tracks well with past experience and can be used as a model to identify novel H1N1. Surveillance data on severe disease comes from death certificates, pediatric mortality reporting, and reports of severe infections among hospitalized patients, for example.

The goals of surveillance and epidemiologic study from June through September 2009 are as follows:

- Identify continued circulation of novel H1N1 and cocirculation with seasonal influenza (both of which are now confirmed).
- Monitor:
 - genetic and antigenic variability
 - antiviral sensitivity
 - severity of illness
 - transmission characteristics.
- Estimate effects of interventions.

International surveillance comes from well-established platforms at established sites, such as the Global Disease Detection Program (GDD) and the International Emerging Infections Program. These programs operate with CDC staff and funding in partnership with the Global Aids Program for additional laboratory support. For the past five years, in an effort to bolster pandemic preparedness, CDC has established influenza programs in 32 countries to conduct surveillance of severe acute respiratory illness (SARI) surveillance, improve laboratory capacity, and provide reagents. The Southern Hemisphere Initiative is coordinated by CDC and the U.S. Agency for International Development and partners with the Pan American Health Organization to enhance surveillance through Department of Defense (DoD) Laboratories. In addition, the GDD coordinates with WHO offices for surveillance, and the Global Influenza Surveillance

Network provides additional virus surveillance. CAPT Fiore described additional morbidity surveillance efforts through these programs to identify ILI and SARI with laboratory confirmation. Population-based surveillance and community surveys provide still more information.

The WHO Global Surveillance Global Influenza Surveillance Network is likely to be a key source of information in the next few months, said CAPT Fiore. It involves four WHO Collaborating Centres and the CDC in surveillance that includes Australia and Japan. The Centers collect specimens, isolate and characterize the virus, then ship the samples to other laboratories for more sensitive testing. CAPT Fiore said relatively few participating countries (25 of 126) are located in the Southern Hemisphere, but he expects to see both seasonal and H1N1 virus circulation in the tropical areas of the Northern Hemisphere.

A fair amount of CDC staff is stationed in areas in which H1N1 circulation is anticipated. Information is coming in from the Southern Hemisphere. In Australia, 1,400 cases of influenza have been tested, of which about one third represent novel H1N1. The rest are seasonal influenza, mostly H3N2. Surveillance in Central and South America have been reinvigorated with funding and staff, said CAPT Fiore. Peru has established outpatient surveillance similar to ILINet but on a smaller scale, with a focus on severe disease in Lima. Field staff in South America can provide weekly or biweekly information that points to unusual clusters of disease.

CAPT Fiore summarized what we know so far in those areas where H1N1 is circulating:

- Will the pandemic virus continue to circulate? Yes.
- Will it cocirculate with other influenza viruses? Preliminarily, yes.
- Is the virus changing? Viral surveillance plans are in place to evaluate this question.
- Are epidemiologic parameters changing (e.g., attack rate, incubation period)? It will be difficult to obtain representative data in most countries, but ongoing outbreaks in the United States will also provide data.
- Are clinical manifestations changing (e.g., severity, secondary infections)? It will be difficult to determine given different health care parameters, but getting viruses from unusual or severe cases is feasible.
- Are community mitigation interventions working? It may be possible to assess this question in several countries (e.g., from Chile's school closings), but it is unlikely that laboratory-confirmed outcomes data will be available.

CDC is working to increase funding for reporting and field staff. It faces challenges in obtaining representative samples of the virus from other countries. In countries with less surveillance in place, CDC faces challenges in interpreting the data it receives.

Discussion

CAPT Aubrey Miller, M.D., M.P.H.: Is there surveillance data from Canada?

CAPT Fiore: We have reports of severe illness, including among native tribal people in Manitoba, some of whom have confirmed H1N1. There have been reports of severe disease in the United States in the past few weeks, often in referral centers, so we don't know if those are clusters or they are cases being reported by tertiary care centers.

John Modlin, M.D.: What's the age distribution?

CAPT Fiore: Most cases have occurred in older school children, and the most severe cases have occurred in young children. The most striking finding is that few cases occur in those over age 50 years. In the most severe cases, about 60–70% of people had an underlying condition, such as pregnancy, asthma, or heart disease, but 30% had no underlying illness. So, this virus can cause severe illness in a healthy young person.

[Unidentified]: The death rate does not seem high. How does it compare to normal seasonal influenza? Is more severe disease occurring in the younger population?

Dr. Pavia: Let's put that question on hold for now; it involves extrapolation and modeling.

CAPT Fiore: We've seen about 6–7 deaths in pregnant women and about 40 pregnant women in need of hospitalization. What I do know is that the rate of death and severe infection in the elderly is strikingly low. From our surveillance, I think the incidence in younger people is probably not that different from seasonal influenza, but I'm not sure if we have accurate data about the denominator.

[Unidentified]: We publish weekly epidemiologic records and some clinical information from Mexico, based on laboratory confirmation. Among those hospitals, the case-fatality ratio is higher among those over 20 years than it is for young kids, and there's an extremely low frequency in those over 50 years. What U.S. program captures severe pneumonia cases?

CAPT Fiore: The Emerging Infections Program (EIP). We have good surveillance of hospitalization. In the early weeks of the outbreak, there were few cases of influenza in the States where we had surveillance projects. I think that's changing as we get EIP data. We reinstated that and increased its funding. The new National Vaccine Surveillance Network also has that capability.

[Unidentified]: You need to get surveillance on teens and young adults.

CAPT Fiore: The EIP will be useful there.

John Grabenstein, R.Ph., Ph.D.: When will there be serosurveys to evaluate the impact of the first wave? That informs the urgency of the vaccine program. Where are we in the number of infections?

Dr. Pavia: We calculated the cumulative incidence, and there's a 10-fold difference between States. The answer depends on where you look.

CAPT Fiore: We have some serodata and we'll be getting more over the next few months. Laboratory studies and development of sero-assays are challenging and labor-intensive.

Jacqueline Katz, Ph.D.: Work is ongoing and we hope to get serum in the next few weeks. There is one large serosurvey underway in Mexico, but trying to discriminate between novel H1N1 and seasonal influenza is very complicated.

Modeling and Impact of Interventions—Neil Ferguson, MRC Centre for Outbreak Analysis and Modelling

Mr. Ferguson presented modeling results based on data predating the current novel H1N1 influenza. In modeling the spread of pandemic influenza in the United States, Mr. Ferguson and others worked from the assumption that the disease would start outside the United States but in this case, the United States was among the first countries affected. The models did not account for the affect of seasonality, and Mr. Ferguson said the spread of H1N1 has been relatively slow because of the timing.

On the basis of data from past pandemics, Mr. Ferguson estimated that a national, unmitigated pandemic would infect about one third of the population in the first one or two waves. He anticipated a seroconversion rate of about 50–60%. Models suggest that by the fall of 2009, about 100 million Americans will be sick, but most will have mild illness, even if the pandemic is severe. The pandemic is likely to be concentrated and not expected to be synchronized with seasonal influenza. The peak attack rate would be about 1,500 cases per 100,000 people per day. However, perceptions of peak attack rates at the county level may be higher. Some localities may see absentee rates as much as 30% higher than the national average, and those events may be significant enough to cause disruption.

Planning for H5N1 focused on containing the outbreak in the early stages and slowing the international spread of disease. Neither effort is relevant to the current situation. Novel H1N1 virus caused nonspecific symptoms and by the time it was detected containment was not possible. Objectives for controlling the pandemic now focus on mitigation efforts to minimize morbidity and mortality, spread of disease, disruption to society, and economic impact. However, we have more tools to address pandemic influenza and a better understanding of the antivirals, rapid production of vaccine, and mitigation techniques. The emphasis of U.S. pandemic planning is on targeted mitigation and, if the pandemic proves severe, suppression until a vaccine is available.

Combining multiple interventions yields an impact that is larger than the sum of its parts. Each intervention blocks a portion of the disease and provides layers of protection by targeting different groups. The key issue for the United States is the population's relatively low tolerance to impose disruptive measures of mitigation if the perceived severity of the disease is low. Modeling can explore the effects of combining interventions.

Extrapolating from data on seasonal influenza demonstrates that vaccines offer high protection (when highly matched to the virus), but data are limited on predicting the impact of vaccination on reducing the spread of disease. Early data from clinical trials of new vaccines may be available in July or August, but those studies will not show how much the vaccine protects against infection, severe disease, or breakthrough disease. Other data needed includes the number of doses required and whether adjuvants broaden the immune response to H1N1, protect against drift, or boost response after one dose. If the first vaccine is not available until October, how many people would already be

infected? Another key question is whether vaccinating children first will protect the rest of the population.

Other mitigation options include use of antivirals to treat infection, although they are only effective in reducing disease transmission if given early—for example, within 24 hours of the first symptoms. Prophylactic use of antivirals can be very effective in reducing transmission, but supplies are insufficient in the United States. At the peak of the pandemic, school closures could reduce transmission by 40%, but they are disruptive and may not have as large an impact on the total numbers affected. Combining interventions may rise in importance if the health care system is overwhelmed.

Key current issues include the severity of the pandemic, the potential health impact, and the impact on the overall health care system. Interventions must be seen as justified and tolerated by the community. The speed of disease spread and the number of people infected so far are important issues. Understanding the real-world effects of interventions is crucial.

Judging the appropriate response to a pandemic requires decision-makers to balance the cost of interventions against the economic impact of the pandemic. Around the world, a wide range of policies is in place, and some countries choose to do relatively little in response. The United Kingdom has undertaken an intensive containment effort that includes prophylaxis.

The challenge of assessing the severity of the disease lies in the fact that the numerator is uncertain and the denominator is not clear at all. Surveillance is worse in the United Kingdom, Mr. Ferguson said: 20 cases in which patients were hospitalized were reported by chance, not through systematic surveillance. Some U.S. States have more systematic surveillance in place, but the CDC estimate of 45–85 deaths to date is a minimum. The lag between disease onset and death can lead to underestimating the severity of disease.

Very little data exists on case-fatality rates for seasonal influenza and previous pandemics. The age groups affected by seasonal influenza may be different from those affected by pandemic influenza, and while the absolute numbers for morbidity and mortality in people ages 18–50 years could be low, it could also be much higher than expected. The severity of the pandemic in the fall may differ from its current severity.

On the basis of data from Mexico, transmissibility of H1N1 virus is faster than the spread of seasonal influenza but slower than seen in previous pandemics, which may reflect seasonality or suggest that the virus is not fully adapted to humans. Mr. Ferguson said it is difficult to model the spread of the disease in the United States, as the data do not account for variable case ascertainment. Household transmission data, however, may be more reliable. Secondary attack rates indicate levels of spread comparable to seasonal influenza but low for a pandemic. Mr. Ferguson projected a virus doubling time as short as two days in the fall (currently, it's about seven days). In households, children are two-fold more susceptible to the virus than adults, and children under age 5 years are even more susceptible.

Also on the basis of data from Mexico, children appear to be at highest risk of infection but the illness is nearly always mild. U.S. and U.K. data also show that children are principally affected. The pattern of severe disease, Mr. Ferguson noted, is complex. Adults ages 20–50 years, especially those with asthma or chronic obstructive pulmonary disorder, may be at higher risk. The challenge is whether to target those with the highest rates of infection or those at the highest risk of severe disease.

In the United Kingdom, everyone with a confirmed case of H1N1 influenza is treated and household contacts of people with confirmed H1N1 influenza receive prophylaxis with TamiFlu. When disease is treated within three days of onset, about 20% fewer cases occur. Households that received prophylaxis within three days of the index case had dramatically lower attack rates (no cases in 42 household contacts). Among those who received prophylaxis more than three days after the onset of disease, the index case saw an attack of 13%. Therefore, early prophylaxis appears to be very effective.

The Southern Hemisphere is now entering its typical influenza season, so more rapid spread is anticipated. It is expected that the pandemic will spread more rapidly in the Northern Hemisphere when influenza season begins here. More surveillance and field data are needed to better understand what's going on.

Predictions are hampered now because of the lack of data on the total number of people affected and the real impact of seasonality on the disease. Mr. Ferguson estimated that 3 million people in the United States have been infected so far, and he suggested that may be about 5% of the number of infections expected for the year. The critical questions will be how quickly the disease will spread and how long the pandemic will last.

In terms of research priorities, Mr. Ferguson said serologic surveys are key to understanding the prevalence of disease. Cohort studies are needed because they provide unique insights into transmissibility. Community cohort studies can be undertaken with intensive monitoring and biological sampling. Web cohorts can provide a sample size larger than a community. Both approaches can demonstrate the severity of disease and transmission over time. Mr. Ferguson hoped that CDC would provide surveillance reports weekly throughout the summer and fall. Finally, mechanisms are needed to monitor the effectiveness of interventions.

In summary, Mr. Ferguson said to expect that about one third of the population will be sick over a concentrated period of about 8–12 weeks in the fall. Local epidemics will seem to be more “peaky” than national averages suggest, especially if sick people stay home. Combining interventions has a high impact, but consideration must be given to what interventions people will tolerate. Decisions must be made about intervention without much data, because the severity of the disease will only be well measured in retrospect. The current virus is not seasonal influenza—animal models indicate it is a different pathogen, and the virus may not be fully adapted to humans. The incubation period may be longer than seasonal influenza and may evolve over months. Precautionary efforts should seek to put mechanisms in place now for severe disease, but

strategies may need to change. Mr. Ferguson concluded that he hoped to have real-time analysis with modeling to enhance situational awareness.

Discussion

Dr. Pavia: We have been able to understand a lot quickly, but uncertainty looms large about severity, transmissibility, mortality, and which groups are at highest risk. Which of those parameters most influences our decision-making processes, and can we focus our resources on that?

Kathryn Edwards, M.D.: According to CDC surveillance studies of hospitalized patients, only 20% of people with confirmed influenza actually get the diagnosis, so we underappreciate hospitalization due to seasonal influenza. In the Southern Hemisphere, where you see cocirculation of H1N1 and H3N2—is that a sign that we need to protect against both? Or would we expect that if the virus becomes more virulent, H1N1 would take over and the seasonal influenza strain lessen?

CAPT Fiore: Others could answer that question better. The main goal of surveillance is to identify patterns, like the replacement phenomenon. We think there will be cocirculation in the fall so that's our working assumption.

Mr. Ferguson: It's a mixed picture in the Southern Hemisphere. We see rapid depression of seasonal influenza strains in Chile and Argentina, but it's more mixed in Australia, where we see more H3N2 and influenza B. In past pandemics, new influenza subtypes have replaced existing subtypes, but data are not sufficient to tell us the time scale over which that happens. Also, we're not talking about a truly novel subtype.

Mr. Gallagher: In Manitoba, for example, we're not seeing evidence of more susceptibility. The spread may be related to the isolation of the community and lack of medical care. We're not seeing the same rates in the neighboring province with a high native population.

Patrick Scannon, M.D., Ph.D.: Is the virus changing? I read a report about a variant in Brazil.

Mr. Ferguson: We looked at the sequencing, and it's identical to others we've identified.

Dr. Katz: While there were some amino acid substitutions, the strain is consistent. I think the media misinterpreted the findings in that case.

Gregory Poland, M.D.: Regarding decision-making at the Defense Health Board, Mr. Ferguson made a point about macro-modeling and local or micro-modeling. The same may be true in the military. We have people deployed and moving around, we have combat troops—how will we make decisions about use of vaccine among them? It's different at the micro level than at the civilian population level; it's a difficult decision for them and their stateside beneficiaries. There are special considerations for DoD compared with the general population. No one has looked at micro-modeling for special subgroups.

Mr. Ferguson: There has been some modeling on the spread of influenza in army camps. But I don't think it's really a modeling issue—I think it's more capability. If there were an epidemic in a camp, what would the operational capacity cost be? Can you tolerate that cost? That might inform prioritization.

Bruce Gellin, M.D., M.P.H.: We have ongoing studies in the United States, but what are we *not* looking at that we should be looking at?

CAPT Fiore: Serologic studies to determine what's going on in mild illness or asymptomatic people. We have collected data from New York City and Chicago that can help us learn about the effect of school closures, household transmission, and use of antibiotics, but we still need to churn through that.

Mr. Ferguson: We have lots of detailed data from the States from the past few weeks, and we're working with CDC to look at school closings and transmission. The phone survey will provide valuable information on those with mild disease. More work could be done, such as using a web cohort or automatic data collection efforts, which are used in Europe. I'd like to see someone take ownership of that effort. It would take maybe half a million dollars to set up.

Dr. Pavia: I've seen some demonstrations.

Walter Dowdle, Ph.D.: H1N1 is not a novel subtype, but in 1976 and 1978 there was existing priming in the population, and there was considerable infection experience. Is that built into models?

Mr. Ferguson: There are uncertainties about the vaccine impact. We have modeled that, especially containment, with one versus two doses. The biology people have more expertise. It's plausible that adults, especially older adults, have some priming but it's not clear whether that would be true in kids if you used adjuvants. That's not a modeling question: it requires data to answer.

Dr. Dowdle: Does priming indicate some protection, such as a rapid response to vaccine or less severe disease? Is this an interpandemic event?

Mr. Ferguson: We've considered that. The 1957 pandemic was truly novel, and it is similar to novel H1N1. Age-specific attack rates vary by pandemic. Attack rates could be two to three times higher than seasonal influenza. Even a bad year of seasonal influenza has only a 10% attack rate, and it's concentrated in kids and the elderly. I think we should be planning for an event three times as bad as a bad seasonal influenza year in terms of clinical disease.

Terry Adirim, M.D., M.P.H.: Has there been any thought about triggers for de-escalation of mitigation strategies?

Dr. Robinson: Part of our planning has been to include exit ramps. The next one would be in September. On the basis of clinical data and surveillance, would we buy more antigen and adjuvant?

Dr. Pavia: After this meeting, you should look more closely at CAPT Fiore's data to determine the likelihood of an exit point at which we don't vaccinate. But that's not terribly relevant right now.

James James, M.D., Dr.P.H., M.H.A.: Considering the wave nature of pandemics, when you model, how do you handle background immunity or herd immunity? How does that translate into vaccine-sparing policies?

Mr. Ferguson: It's relatively easy with models; they allow for different susceptibility for different age groups and can take into account background immunity. With an epidemic, we run various scenarios and evaluate what the current situation implies about immunity in the fall. However, we need more data to validate those projections. We could have 3 million to 20 million people infected by September. We need serologic data to resolve some questions.

Fred Hayden, M.D.: How do existing population susceptibility patterns affect your projections of background immunity? If you look at age patterns using attack rates to

date, if there were no changes in viral antigenicity and given background immunity, could there be less impact?

Mr. Ferguson: How much seasonal influenza spread impedes the spread of the pandemic and how much background immunity slows spread are difficult to untangle. Looking at South America, if only a small percentage is infected by September, we could see explosive spread in September. That should be a planning assumption. If later data show that lots of people are already infected, that could affect decision-making.

Dr. Hayden: Is there a drift variant of H3N2?

Dr. Katz: We don't have data, but I have heard that the WHO Collaborating Centers are looking at it and characterizing strains of H3N2.

Dr. Modlin: Children have higher attack rates, and some of the most serious disease is occurring in young children, including those zero to six months old. That group is not currently targeted for vaccine. That group is difficult to surveil and has a high rate of respiratory disease. They will not have maternal antibodies. We should think about surveillance in this special population, because we may recommend extending vaccine to the very young.

Dr. Pavia: The National Vaccine Surveillance Network might capture that, and there may be some surveillance in certain cities. I don't expect us to answer all the questions we've raised. We should be thinking about which of those questions will influence decision-makers, such as severity of disease and age-specific risk groups.

NIH Clinical Trials—Linda Lambert, Ph.D., National Institute of Allergy and Infectious Diseases, NIH

The clinical trial infrastructure supporting a substantial part of the H1N1 response falls under the purview of the Division of Microbiology and Infectious Diseases at NIH/NIAID, Dr. Lambert explained. The cornerstone of this clinical research capacity is the Vaccine Treatment and Evaluation Units (VTEUs), a consortium of individual contractors that were initially awarded in the 1960s, and offers a ready resource to conduct clinical studies. NIH awarded eight new prime contracts in 2007, with several subcontractors. There is a broad range of capabilities—from phase 1 through phase 4 clinical trials—and the capacity to evaluate different doses and formulations of vaccines, immunotherapeutics, and conduct surveillance studies. The VTEUs reach a wide range of populations, including healthy adults, the elderly, and pediatric and special populations. The contractors also have access to immunocompromised and pregnant patients, for example.

Dr. Lambert commented that the lessons learned from NIH's H5N1 influenza vaccine clinical trials were enormous. As soon as the H1N1 outbreak occurred, NIH immediately began discussions with FDA, CDC and BARDA. FDA led the discussions with manufacturers about core elements for clinical trials, submitting proposals, and providing feedback. BARDA's role is to address vaccine supply issues, and NIH would identify areas for clinical support needed from the U.S. Government. NIH did not want to duplicate manufacturers' efforts; rather, NIH support should be complementary and collaborative, focusing on areas in which NIH could leverage the VTEU infrastructure. NIH identified three key areas of support for H1N1 clinical trials:

- **Assist licensed vaccine manufacturers in generating clinical data needed for licensure.** For example, NIH may be able to speed up availability of data in populations within a company's license and can generate data in groups for which H1N1 vaccines may be used under an emergency use authorization (EUA). The agency can also assist with generating data from special populations, such as infants under six months of age, pregnant women, and immunocompromised subjects. NIH is investigating trial capacity within this area of support.
- **Generate clinical data to help inform policy decisions and/or address gaps.** NIH-supported efforts can be used to develop data that may help inform real-world scenarios for possible large scale vaccination programs. These include studies assessing whether shorter dosing intervals result in comparable immune responses (presuming two doses are needed), evaluating coadministration of live, attenuated vaccine (TIV) and H1N1 vaccines and priming and boosting with different adjuvants. NIH supported assays can be used to compare immunological responses to different H1N1 vaccines using a standard approach.
- **Generate data on mixing stockpiled vaccine antigen and adjuvants from different manufacturers.** Dr. Lambert said it has not yet been confirmed which H1N1 products would be used in these types of mixing studies, but that the flexible capacity of the VTEUs would enable multiple options. NIH had been planning to conduct such studies for H5N1 vaccines and that experience has indicated that significant preclinical data may be required prior to initiation of these types of clinical trials.

NIH is currently negotiating with FDA, other global regulatory groups, and manufacturers about the scope of the clinical trials that would be done by the NIH. The status of NIH future activities rests on the manufacturers' plans. NIH has contacted manufacturers about the availability of vaccine, documents used for regulatory filing, and access to clinical samples for evaluation in a standard assay. NIH is working with VTEU sites and investigators on access to target populations and expansion of ongoing studies. NIH hopes to finalize its protocols in the next two weeks and submit them to FDA.

NIH will need serologic samples from H1N1 human cases to serve as a positive control for ongoing H1N1 immunologic assay development. VTEUs have already initiated a protocol to collect these specimens and assess clinical outcomes, sequencing of isolated viruses, shedding, humoral and cell response, etc. The VTEUs also have started a protocol to assess safety and immunogenicity of trivalent inactivated influenza vaccines (TIV) in pregnant women in their second and third trimester. Dr. Lambert noted that a follow-up study of TIV is planned with all of the TIV vaccines for the coming fall.

Manufacturers' Vaccine Development Plans

GlaxoSmithKline—Bruce Innis, M.D.

The H1N1 vaccine that GSK proposes to manufacture is monovalent and incorporates a vaccine strain recommended by WHO. The standard dose is 3.75 micrograms of hemagglutination administered twice, 21 days apart. The antigen comes in a 10-dose vial

with a thimerosal preservative and is mixed before injection with AS03, a tocopherol based emulsion adjuvant system also presented a 10-dose vial. The adjuvant is manufactured in Belgium and the United States; the antigen is manufactured in Dresden (D) and Quebec (Q); the processes differ depending on the location.

GSK's Dresden-manufactured H5N1 vaccine is approved in the European Union (EU), Australia, Singapore, Malaysia, and Hong Kong. GSK plans to submit the Q-H5N1/AS03 vaccine for approval in Canada and the United States in 2009. The company has clinical data from 3,500 adults, ages 18–93 years, and a safety summary from approximately 9,900 adults, including completed studies with the Dresden vaccine. GSK believes the data are sufficient to support use of the H1N1/AS03 vaccine under an EUA and eventually licensure.

Clinical data suggest that the Dresden- and Quebec-manufactured H5N1 antigens plus adjuvant have equivalent immunogenicity. Current plans permit GSK to initiate clinical trials of a Dresden-produced H1N1 pandemic vaccine several weeks before trials of the Quebec product. Dr. Innis noted that early data from the Dresden vaccine can guide emergency use of the Quebec product. The H5N1 vaccine is highly immunogenic in children and adults and even in the elderly, despite prior TIV vaccination. These responses greatly exceed the thresholds for seroconversion mandated by CBER in its guidance.

The correlates of immunity against pandemic influenza A are unknown. Therefore, GSK has investigated the effect of its adjuvant on cell-mediated as well as humoral immunity. The company's evidence shows that the adjuvanted H5N1 vaccine generates better T and B cell memory than unadjuvanted vaccine.

Immunization with the H5N1 vaccine is protective. In ferrets administered a range of doses of adjuvanted vaccine or control vaccine on days 0 and 21 and challenged 4 weeks later, all the controls died, and 22/23 animals receiving the adjuvanted vaccine survived. Moreover, the adjuvanted vaccine reduced the amount of virus in the subjects' lung tissue by at least 3.5 logs compared with controls. Immunity elicited by the H5N1 vaccine protects against severe disease and is likely to reduce virus shedding, potentially reducing virus transmission.

Although two doses of vaccine are required, the GSK H5N1/AS03 vaccine can be administered as two injections in separate extremities at a single visit and still achieve protection. This approach saves both time and antigen.

Vaccine with the AS03 adjuvant is a new product, and GSK has made unparalleled efforts prelicensure to evaluate its safety. The company has compiled safety data from adults in eight completed trials of H5N1/AS03 vaccine manufactured in Quebec or Dresden. Subjects were followed for 6 months after vaccination. Rates of medically attended and serious adverse events were comparable between the vaccine and controls. The total number of adverse events with adjuvanted vaccine is slightly higher than the total for controls because of increased reports of reactogenicity during the days

immediately following vaccination. These events were predominantly mild and transient. There was no escalation with the second dose, and compliance in receiving the second dose was above 95%.

GSK agreed with CBER to query the data for a list of 120 immune-mediated diseases, called adverse events of special interest (AESIs). There were 16 AESIs in the H5 group and one among the controls ($p > 0.2$).

GSK ran the same query on a pooled database of 11,721 subjects enrolled in five clinical trials of TIV conducted by GSK since 2004. Comparing the data demonstrates that the events reported more than once in the H5 group also appear in the TIV control group. These data provide no evidence for an association of any single event or of this class of events with the H5N1/AS03 vaccine.

GSK's safety summary supports a favorable risk-benefit profile for AS03-adjuvanted influenza vaccines and additional trial data are forthcoming. GSK has investigated two reports of asymptomatic autoimmune hepatitis. In case 1 (a child) the condition existed before vaccination and is in remission following treatment. In case 2 (an adult), the condition resolved spontaneously, and experts have cast doubt on the diagnosis.

Since September 2008, GSK has been following a cohort of 43,000 elderly subjects vaccinated with TIV/AS03 or control, and their safety data are being reviewed by an Independent Data Monitoring Committee. GSK recently expanded the pooling of safety data to include recipients of any influenza vaccine with AS03. Results from this analysis of 20,500 adults exposed to AS03 will become available in July.

The planned clinical development of H1N1 vaccine with AS03 includes at least 13 trials of D- or Q-H1N1 vaccine in the United States and Canada or in Europe, with over 5,000 children and adults exposed to adjuvanted vaccine. The trials performed under an investigational new drug application (IND) are all randomized, blinded trials using antigen-only vaccine as a control. The adjuvanted vaccine will be evaluated simultaneously in children and adults. The trials will evaluate the benefit of the adjuvant in terms of dose-sparing, efficacy, and immunogenicity compared with antigen-only vaccine, and the two-dose, one-visit schedule. The possibility of interference between TIV and the pandemic vaccine will be evaluated when these products are coadministered or given sequentially. GSK will assess whether AS03 can overcome interference and will also confirm the equivalent immunogenicity between D and Q products. GSK will rapidly expand the safety database for this new vaccine. By December, the Company anticipates that 4,340 subjects will have been exposed to H1N1/AS03 in a GSK trial.

Because the use of a novel adjuvant raises questions that can be addressed best by long-term follow up, GSK is discussing with HHS the need for a large, simple safety study involving, for instance, 40,000 persons who would be followed for up to two years after vaccination.

If a potency reagent is available in early August, the product could be ready for clinical trials in early September, and the first data would be available in November. Pilot data from GSK's smaller trials in Europe, including interim analyses after administration of dose 1 (in a 2-dose schedule), could be available somewhat earlier, in October.

Novartis Vaccines and Diagnostic—Rino Rappuoli, Ph.D.

Dr. Rappuoli said Novartis has been working on pandemic influenza since 1999. The company plans to begin trials of an H1N1 vaccine with and without adjuvant in late July or early August. Studies will include about 4,000 children and adults ranging in age from six months to over 65 years. Data analysis should be completed by October or November, but preliminary data may be available sooner. Data from influenza cell culture trials in Europe may be available in September.

Novartis' adjuvant, Mf59, has been licensed for use in Europe since 1997 as part of a seasonal influenza vaccine, and 45 million commercial doses have been distributed. It provides protection against drifted strains. Data comes from 120 studies involving more than 200,000 subjects, including a database of pediatric patients.

After one dose, Mf59 stimulates strong response from helper B cells and T cells. Boosting with Mf59 induces a protective immune response against all H5N1 isolates in seven days.

H5N1-plus-Mf59 prepandemic vaccine increases antibody production when compared to unadjuvanted vaccine and so reduces the amount of antigen needed. It also demonstrates cross-reactivity against most H5N1 subclades that have caused human disease, and Novartis has seen cross-coverage when Mf59 is combined with seasonal influenza vaccine. After a primary vaccine is administered, a booster dose can be given 6-8 years later and demonstrate protection in 7 days. The prepandemic vaccine has a favorable safety profile and a growing clinical database that includes children as young as six months.

The combined safety data for Mf59 provided to FDA include 25,000 cases compared with normal influenza vaccine. Adverse events are all local reactions that resolve quickly. Novartis is currently conducting a 3-year trial in Italy of 150,000 elderly people. The pharmacovigilance database from that study includes spontaneous reports after 40 million doses and has revealed no safety signals for selected adverse events.

Novartis is producing a cell-culture based H1N1 vaccine at its facility in Germany and is working with HHS to build a plant in North Carolina. With the addition of the North Carolina plant, Novartis will have the capacity to produce 150 million doses. Novartis is planning to have commercial production of prepandemic vaccine, adjuvant, and seasonal influenza vaccine in 2012.

Novartis' influenza cell culture (Optaflu) demonstrated efficacy of 84% against vaccine-like virus strains when compared with placebo. Adjuvanted influenza cell culture H5N1

vaccine is both antigen- and adjuvant-dose-sparing. Novartis has limited capacity to produce this product, but it can still be available quickly.

Dr. Rappuoli concluded that Novartis has had an ongoing partnership with HHS to develop an H5N1 vaccine. It is working to develop a novel H1N1 vaccine for current pandemic in adjuvanted and unadjuvanted formulations, with potential use of Mf59 potential for dose sparing and cross-protection.

MedImmune, LLC—Raburn Mallory, Ph.D.

Dr. Mallory explained that the FluMist A (H1N1) is a monovalent live attenuated 6:2 reassortant vaccine. It will be delivered intranasally via a unit-dose AccuSpray device at 0.2 mL per dose (0.1 mL in each nostril). It contains no preservative or adjuvants. The vaccine dose is fixed on the basis of clinical efficacy studies conducted with MedImmune's trivalent seasonal influenza vaccine, FluMist, at $10^{6.5-7.5}$ FFU (fluorescent focus units). Lower doses resulted in lower efficacy in one study, and higher doses are constrained by sporadic fever rates and the manufacturing process. While no correlate of protection (e.g., seroprotective hemagglutination inhibition assay [HAI] titers) has been identified, vaccination generates a broad immune response including cellular, humoral and mucosal responses.

MedImmune conducts an annual study to incorporate new influenza strains into FluMist and the FluMist A (H1N1) studies are based on this design. Two concurrent, placebo-controlled, clinical studies are planned to evaluate the attenuation of the new influenza A (H1N1) vaccine; one in adults ages 18–49 years (n = 300 subjects) and one in children ages 2–17 years (n = 300 subjects). The subjects in the studies will receive two doses approximately one month apart. Investigators will evaluate fever rates and serum immune responses after each dose and also look at solicited symptoms and adverse events.

Initiating the studies depends on selection of the final master virus seed, which Dr. Mallory expected to occur shortly. The clinical studies will begin in August and initial safety data will be available about 1 month after the first patients are enrolled. The annual strain change procedure that MedImmune usually follows with CBER would allow for vaccine approval based on this safety data. Immunology data could be available beginning in October, which may be late in terms of the planned distribution of the vaccine.

Sanofi Pasteur—James Matthews, Ph.D.

Dr. Matthews said Sanofi Pasteur is doing parallel work on H1N1 vaccine in Europe and the United States. The company has been working on a clinical development plan for the United States since the end of April. It is currently negotiating with CBER on proposed trial designs. CBER has asked the company to expand the number of subjects in the clinical trials (from 1,500 to 3,100 children and adults), limit the number of formulations tested, and place less emphasis on the adjuvanted formulations. Sanofi Pasteur's proposed protocol would have provided some data by mid-October, but accommodating CBER's requests will affect the timeline of studies and availability of data. The company has proposed to drop one of its non-adjuvanted formulas from its studies; also, it may not

study children ages 10–17 years, as CBER believes data from other age groups can be extrapolated for this age group. CBER has proposed longer safety follow-up monitoring and more complicated laboratory testing for safety assessment, as well as intensive follow up for any adults who receive the adjuvant. Dr. Matthews predicted that the final trial design will represent a hybrid of the various proposals.

Sanofi Pasteur is focused on a timeline that will produce clinical data quickly so that vaccine could be available as early as January 2010. Trials would begin as early as mid-August and include a placebo group. Timelines are based on commercial production schedules. One key assumption is that vaccine will be formulated on the basis of comparability data. The company does not expect to have fully calibrated reagents until the end of August or early September.

The current plan is to produce the needed material for clinical study in the next few weeks, file an IND in July, and begin enrolling patients in August. The 21-day HAI serology results would be available in mid-October, and booster data in November and December. Data on adjuvanted vaccine would be available in early 2010.

CSL Limited—Jillian Bennet

Ms. Bennet said CSL licensed an influenza vaccine in the United States in 2007 and is currently fulfilling FDA postmarket study requirements for that product (Afluria). CSL is the only influenza vaccine manufacturer in the Southern Hemisphere. Its product is an egg-derived, classical, inactivated vaccine. In the United States, Afluria is available in a thimerosal-free prefilled syringe and in a multidose vial. The antigen is manufactured in Australia, and CSL has fill-and-finish capacity in Australia and Germany. The company has applied for FDA approval to open a fill-and-finish plant in the United States.

CSL is on track to meet the forecast requirements for seasonal influenza vaccine in the United States. For its H1N1 vaccine, CSL is doing strain evaluation. The seed lot has been selected, and the company is inoculating its first load of eggs. CSL has the capacity to produce excess antigen that could be shipped to the United States after it meets the needs of Australians and others in the Southern Hemisphere. Regarding reagent viability, Ms. Bennet said CSL would like to talk with FDA about an early-release protocol similar to that described by Dr. Matthews.

CSL has completed manufacture of its required antigen for the Northern Hemisphere; production of extra antigen would occur in June and July. The company is in a good position to make additional H1N1 antigen, though the projections for producing more antigen assume that CSL will receive approval to begin operations in a U.S. fill-and-finish plant.

CSL is planning two trials of H1N1 vaccine. The company is located in the epicenter of the influenza pandemic in Australia, where it is currently winter and the middle of the typical influenza season. In the United States, pending FDA approval, CSL would begin trials under an IND in pediatric and adult populations (including evaluation of a thimerosal-free vaccine in children ages 6 months to 3 years). The study would compare

a placebo against vaccine in three formulations (7.5 mcg, 15 mcg, or 30 mcg). The vaccine would be given in two doses, 21 days apart. Safety would be assessed 21 days after each dose, with monthly assessment for up to 6 months. The study would monitor for serious adverse events of new-onset chronic disease. CSL is determining whether it could prospectively review immunogenicity and safety data after each dose. Ms. Bennet wondered whether a placebo should be used in pediatric populations, which might impede recruitment, and whether using a licensed seasonal influenza vaccine instead of placebo would be an acceptable alternative.

Ms. Bennet compared the planned CSL studies in the United States and Australia. In Australia, enrollment would stratify adults ages 18–64 years in an attempt to identify people who were exposed to the 1957 epidemic. The Australian study is only exploring two vaccine formulations (15 mcg and 30 mcg doses). The Australian study will look at both hemagglutination inhibition (HI) and microneutralization (MN) titers, while the U.S. study would look only at the former. Monthly follow-up would be more intensive in the United States. The Australian study would not be conducted under an IND, but the data would be provided to the FDA.

In Australia, adult patient enrollment would begin in July and pediatric enrollment in August; in the United States, enrollment for both children and adults would begin in August. Interim analysis following the first dose could begin in September in Australia and in October in the United States. Ms. Bennet hoped analysis following the second dose could be concurrent in both countries. She added that pediatric recruitment takes a long time and she anticipated that pediatric data from either the United States or Australia would not be available until late November to mid-December.

Discussion

Dr. Neuzil: What I'm hearing is that five companies are working on vaccines, and they are testing multiple doses or multiple combinations of antigen and adjuvant in multiple age groups. We could end up with many different vaccines, and that complicates policy issues. How will decisions about licensing be made? Do we have a definition of success? Will the focus be on individual response, like the correlation with HAI antibody, or on population responses? Could there be a lower threshold to cover more people, or do we need a consistent approach to ensure more reliable coverage? We also have to consider distribution issues.

Dr. Pavia: I'm hearing that licensing should take into account public health as well as individual concerns, which is different from what we usually do.

Bob Belshe, M.D.: Two companies are addressing the epidemiology of priming by previous H1 infection. That will tell us at what age you only need one dose and what that dose should be. Kids ages 10–17 years were initially proposed for study but are now out of the Sanofi Pasteur study, but I disagree. That could be a critical age group. Kids under 9 years probably are not primed, but those over 10 might be. Sanofi and CSL should put that age group back in their studies and consider the age at which priming might occur. The only vaccine for which we know the dose is live vaccine, but there are few plans to acquire that. We could vaccinate children and adults, then challenge them with live vaccine as a surrogate to get efficacy data quickly. All the plans seem too late for a fall

epidemic. We need to accelerate so we can have at least first-dose data by the end of August.

Dr. Edwards: I'm struck by the similarities with the development of multiple pertussis vaccines. It's important that we establish some sort of standard of serologic response so that we can understand comparability of the vaccine in different age groups and across different products. Maybe FDA or NIH should lead that effort. Also, there are so many plans. Can we work together to learn more from each other, for example by mapping out all the studies on a spreadsheet and streamlining wherever possible? I'm hearing that a large burden of disease will fall on those under the age of 18. We can't shortchange them; they must be included in studies. We have lots of experience with TIV in young people and with live vaccine; when we compared them in younger children, live vaccine looked good. We need to know vaccines are safe. Do we need to evaluate H1N1 to see if wheezing signals occur in adults before children? The inactive-live combination that Dr. Belshe suggested may be a good approach. I think that if we have data from egg-based vaccine, we can look at that in infants under 6 months. In the context of TIV, it's an enormous problem. We've been demonstrating the impact of seasonal vaccine and recommending that all children be immunized with TIV. How can we do those studies in addition? Maybe some are quadrivalent, compared with trivalent or univalent. That has to be as important a part as H1N1.

Dr. Pavia: Are all of the manufacturers studying coadministration with seasonal influenza vaccine?

[Unidentified]: We've been asked.

Ms. Bennet: We have, too, but in the initial studies, we're not sure what dose to combine. We will probably address that in the next stage.

Dr. Pavia: To deal with the complexity of these studies, consider involving the people who will analyze the data early on. I don't think that's the usual path. Usually VRBPAC and ACIP are not involved in study design. Could that smooth the process?

Dr. Modlin: VRBPAC analyzes data that FDA brings to it; FDA analyzes what the manufacturer provides. We are not part of the process early. I share the concerns of others that there are lots of options, but we have a likely pandemic possibly coming soon. We should identify the most important questions to answer quickly and focus on them, such as the populations most likely to be affected most severely. I'd like us to prioritize the questions.

Dr. Pavia: Yes—we should consider that.

Wellington Sun, M.D.: My views do not necessarily reflect the views of CBER, but we've had ongoing discussion in the vaccine office about the options. The approach we took was to look at the potential urgency and identify the most efficient way to get clinical data that policymakers need to make decisions on vaccine. So, we may have many formulas that work. From the agency's perspective, I think we'll apply the standards outlined in our guidance: HAI level, seroconversion rates, and protection rates. The studies are not large enough to allow for comparison of all the available vaccine. At some point, we will have to prioritize the vaccines, and ACIP and VRBPAC will be helpful there.

Why did we drop ages 10–17 from the Sanofi studies? If this group is at high risk, we need to revisit that decision, but our thought was that we could extrapolate from adults

and from younger kids. Regarding the progression of data for decision-making, adaptive design of clinical studies may not be viable for some clinical trials, but results of a trial from one company using antigen only could apply to immunogenicity for another trial. The need for some mechanism to organize data for policy development is not a regulatory issue. We have wrestled with the timing issues, and we're trying to abbreviate the timelines. We welcome your ideas to fix that issue. Finally, is the context of TIV—that's why we're concerned about concurrent vaccine. We hope to get information from coadministration studies.

Dr. Pavia: What's the most important thing to fix?

Dr. Neuzil: Given concerns about coadministration or sequential administration, when do you anticipate administering the seasonal vaccine?

Dr. Innis: That's less of a problem than you might imagine. About 90% of seasonal vaccine will be released in September, and novel H1N1 will probably not be ready by then. If it's coming from BARDA, it will be later. We can talk about abbreviated release protocols, but vaccine trials should represent the commercial product that will be used in the whole population. There will be very limited data on which to base licensure of novel H1N1 vaccine if unadjuvanted or an Emergency Use Authorization if adjuvanted—the earliest post-dose-1 data would be out in October, and that could lead to distribution of formulated and filled product from the National Stockpile as late as December and January. So, there probably won't be much coadministration. As for sequential administration, data show there can be interference. Subjects with a history of prior TIV vaccination who got unadjuvanted H5N1 vaccine in the clinical trial for licensure, as described by the CBER reviewer to the VRBPAC, did not respond well at all.

Dr. Rappuoli: There are some data on H5N1 with adjuvant coadministered with seasonal vaccine that showed no interference, but we don't know yet about H1N1.

Dr. Innis: I think adjuvant abates some of the interference.

Dr. Mallory: Data for our seasonal influenza vaccine will go to FDA in July. I think early administration of seasonal vaccine is the best strategy.

Dr. Belshe: Novartis has a product online already. You should just put that in a few adults and look for antibodies. That would be very helpful in deciding what to do with the first batches of vaccine. For live vaccine, we need a little safety data on post-dose-1 in adults and kids. I'm distressed about data not being available until October. We need it now.

Dr. Pavia: Do we have the capacity to run assays for all the trials in a way that provides data FDA can use?

Dr. Innis: Manufacturers who are licensed in Europe do annual registration studies in about 100 individuals, and even with no delays, it still takes about 30 days, with a 1-dose vaccination schedule, to get data you can share. We can't go faster and we're limited. GSK will be doing a small but early H1N1 vaccine study in adults designed like an annual registration trial to provide pilot data as rapidly as possible, in Belgium.

Dr. Matthews: We do serology studies internally in the United States. It depends on the size of the study, so that's why we kept it fairly small. With 3,000 subjects, it would be difficult to handle lots of samples.

Dr. Mallory: MedImmune will also be performing serology in-house. If the live vaccine is held to the same standard for immunogenicity that CBER has proposed for inactivated vaccines (TIV), it is unlikely to meet that standard.

Ms. Bennet: Serology depends on the availability of reagents. We have a lab in the U.S. that validates, but that depends on providing reagents. We are frustrated in Australia by WHO's decision to debate a containment level before we could work with seeds.

Theodore Tsai, M.D., M.P.H.: With the release of a cell-culture-based vaccine lot, we're going to clinical trials, with and without adjuvant, in Germany, and we expect to see results in September.

Dr. Edwards: It's not clear that HAI is the best assay. More functional assays may be needed.

Gerald Quinnan Jr., M.D.: I have not been involved in the discussions that occurred regarding this issue previously. However, it is worth noting that this is an extraordinary time and extraordinary measures may be needed. In concert with this theme I raise the question whether we should consider moving now to replace the H1N1 component in the trivalent vaccine with the novel H1N1 component. It is highly likely that people of most ages will respond well to 15 mcg doses of the novel antigen, and it is not clear why there need to be clinical trials before proceeding to use that dose. Moreover, inclusion of the novel antigen in the trivalent vaccine will increase the likelihood that people who need the trivalent vaccine will get vaccinated against the novel strain, and that vaccine with the novel strain will be available to them early in the season. If subsequent clinical trials demonstrate a need for a second dose in some of those people, we could develop a recommendation to do that. If that's feasible, it should be considered.

Industry representatives (all): It's too late to reformulate seasonal vaccine with the novel H1N1 strain.

Dr. Pavia: What's the difficulty with HI assays?

Dr. Katz: It's not that they don't work, but comparing them with MN assays and looking for a cross-reactive response—the MN assays gave higher titers and demonstrated greater seroconversion compared with HI. There may be receptor-binding differences that underestimate the antibody. I encourage manufacturers to use a functional assay like MN. All the manufacturers have well-validated assays for seasonal vaccine and H5N1, but it's difficult to compare between groups because they all have their own assays. So WHO developed a standard human antibody for H5N1, and there's already a discussion about the need for one for H1N1 to better understand the similarities and differences.

Ms. Bennet: When FDA approached us, they asked if we would keep sera samples from our studies so someone could analyze all the sera.

Dr. Pavia: Is there any plan to do that?

Dr. Robinson: All the samples will go to NIH for comparability studies.

Dr. Hayden: I support Dr. Belshe. Look at the antibody responses early on, as early as 7 days, to examine effects of priming. The efforts to develop WHO reference antibody for H5N1 serologic testing took over a year; we can't wait that long. What information do we have from HAI and MN in persons with natural pandemic H1N1 infection? These data are needed to help understand responses to candidate vaccines.

Dr. Katz: There are ongoing studies, and we're waiting for convalescent serum. If we encouraged follow-up serology, we would have to find a way to get follow-up sera from infected people.

Dr. Scannon: Is the only manufacturing process egg-based, or are there also cell-based processes?

Dr. Rappuoli: We have cell-based manufacturing in Germany. Can we produce fast enough for the U.S.? There will be data available sooner, but are we going to wait until all the data are in to decide, or do we want minimal data quickly?

Dr. Robinson: The tier 1 and tier 2 manufacturers are already licensed. The tier 3 manufacturers are near licensing, and that group includes cell-based products. The availability and amount of product are important issues. When we had just one manufacturer, we got locked out. Capacity is important, too. Two million doses is a small amount.

Dr. Neuzil: Getting some data faster is good if we can define how we will judge that data, which will be easy if the results are very positive or negative but much harder if they are in-between. With an imperfect assay, it's possible that titers may be lower, so the percentage of the population that would respond could be lower. What's the simplest approach—e.g., 15 mcg without adjuvant: what's the success rate with that?

Patricia Quinlisk, M.D. M.P.H.: When will the disease come back and how bad will it be? If it returns and it's very serious, we could be accepting a vaccine with low efficacy. If H1N1 vaccine is not available until later in the season, when would we do school-based vaccination? Should we start earlier? Do we want a longer time-lag? We usually wait until October or November.

Eric Rose, M.D.: We're all nervous about the fall and worried about the lack of vaccine. Is it possible to surge or repurpose our antivirals, e.g., use them for family members? Maybe just for 4 weeks?

Dr. Pavia: Hold that thought for our antiviral discussion tomorrow.

[Unidentified]: We face an awkward situation in the fall. We'll be pushing seasonal vaccine and expecting H1N1 outbreaks, and we will have to tell people the vaccine we're giving them will not protect against H1N1. We need a comprehensive strategy that includes messaging and anticipates this awkward situation.

Dr. Pavia: Here are my takeaways: The plan for developing vaccine is complicated and will involve multiple products that are different, so there's a plea for clarifying goals and endpoints and perhaps involving more analysts in the planning stages. Everyone is nervous about timelines and much can go wrong. It's important to identify who can be protected with one dose. There are concerns about the effect of the disease and vaccine on young people. We should use early data to adapt studies as we go, maintaining flexibility.

Swine Influenza Vaccine Version 2.0: Decision-Making Revisited—Walter Dowdle, Ph.D.

During the 1957 H2N2 pandemic, risk assessment was agonizing, said Dr. Dowdle. On the basis of findings in the spring from the Far East, H2N2 was seen to be a fast-moving disease with a high attack rate and against which the population had no immunity. The ghost of the 1918 pandemic loomed large and was the subject of most discussion about H2N2. Although H2N2 looked more like the 1889 pandemic, people thought it might change, and that held things up a bit. The Surgeon General departed from previous thinking and suggested alerting but not alarming the public. The major advisory bodies at the time were the Association of State and Territorial Health Officials (ASTHO), the

American Medical Association (AMA), and the Armed Forces Epidemiology Board (AFEB). The Surgeon General endorsed ASTHO's recommendation to vaccinate providers of essential services and, for the first time, those people who have a special medical risk. He refused to designate who was considered a provider of essential services because the issue was so controversial; instead, he left that determination to individual States. The decision to prioritize certain providers turned out to be highly controversial and did not go over well.

The Surgeon General requested funds for diagnosis, surveillance, and public information, but none for research or vaccine. Vaccine production and distribution through States were to be the responsibility of the private sector. The production of 49 million doses of vaccine coincided with the peak of the mortality curve in October and November. Considerable vaccine went unused. By the time vaccine was available, people felt as if they had either had the disease or not.

The 1968 H3N2 pandemic risk assessment was based on findings from the Far East. The disease was described as a major antigenic drift from H2 but later determined to be a shift to H3N2. It was not seen as a major event, and that affected the attitude toward risk management. Vaccine recommendations were consistent with the 1962 high-risk recommendations from the Surgeon General's Advisory Committee on Influenza. Production of 21 million doses of the vaccine coincided with the peak of the autumn mortality curve. The impact of the vaccine was questionable, said Dr. Dowdle.

In 1977, H1N1 reemerged as a pseudo-pandemic. It affected primarily people under 25 years of age, based on findings from the USSR. Vaccine recommendations were based on limited NIH trials. The vaccine was first available in fall of 1978, but 1978 represented a turning point in U.S. influenza immunization policy—influenza became a major immunization initiative.

The 2009 H1N1 virus situation is very different from past experiences. In the past, far fewer people were involved in decision-making. The role of public health has expanded since 1969, with increasing expectations of public health providers, more WHO involvement, more awareness of global implications, and more tools for intervention and prevention. These changes evolved against a backdrop of planning for the worst-case scenario of H5N1 and the memory of the 1976 swine influenza epidemic. While H5N1 planning has been very helpful, we now have to change gears and deal with reality, not projections.

During the 1976 swine influenza campaign, ACIP could give no assurance that a pandemic would or would not occur. A preemptive strategy was developed, driven by the 1957 and 1968 experiences and by the end of the year, 40 million had been vaccinated. An increase in Guillain-Barré syndrome (GBS) was detected by December. The vaccination program ended when the real risk of GBS outweighed the theoretical risk of swine influenza.

The lessons from the 1976 campaign are as follows:

- Risk assessment based on what might happen is more difficult than on what is happening.
- Balancing management risks and benefits is even more difficult when both are uncertain.
- Influenza vaccine field trials of more than 7,000 volunteers in 1976 were not enough to detect the GBS that occurred at 5 million doses.
- Prevention and intervention risks must be factored into any management decision. Provisions must be in place to modify risk-management decisions if the risk assessment changes (in either direction).
- Take care in determining what the President is asked to say. Certain messages can put decision-makers in a position from which there is no retreat. If the President recommends vaccine for all Americans, manufacturers must produce enough for everyone, even if not all people are willing to accept the vaccine.
- Keep in mind the importance of maintaining the credibility of public health organizations.
- Keep in mind Murphy's law: Everything that can go wrong will. That "law" came into play in 1957 and in 1976. No matter how good your planning is, someone will say the vaccine causes death or accelerates disease. Timelines may be off and disruptions may occur.

Dr. Dowdle summarized the lessons of past pandemics. Risk assessment, he said, is—or should be—a scientific process, but risk management is a political process based on public perceptions of risk and the willingness to pay to reduce that risk. It is notable that two Congressional representatives from Georgia are opposed to any appropriations for swine influenza, and would rather spend money on F22s.

Regarding 2009 H1N1 risk assessment, Dr. Dowdle said that although we always want more data, we have to make decisions with what we have. Considerable data are available on potential treatments, risk by age, mortality, underlying medical conditions, hospitalization, etc., and we are learning more daily. We are in good shape compared with previous years.

Antigenic designations are not based on HI but on common epitopes. Current observations about lower morbidity in older people correlate with the premise that priming has occurred. H1N1 is similar to an interpandemic strain in that circulation is occurring in a population with extensive current (since 1977) and past (before 1957) subtype infection experience.

In terms of H1N1 risk management, Dr. Dowdle noted that considerable data are already available to provide reasonable confidence in management recommendations and decisions. Sound management options are based on sound risk/benefit analyses of the data on hand, not on theories the virus might increase in virulence, might reassort, or might mutate in the coming months. Dr. Dowdle emphasized that decisions must be made based on the data in hand. Decision-making on pandemic influenza responses should plan on contingencies but act on the data.

Discussion

Dr. Pavia: Between the morbidity and mortality we saw in the spring, when we had warm weather, what we might expect in the fall, and which of those two scenarios would you use for risk assessment?

Dr. Dowdle: Modeling is a major help in decision-making, so use the data available and factor in all those components. The summer pattern is not going to be the fall pattern, but you have data from past epidemics on fall/winter patterns, so you know what happens then.

Brian Murphy, M.D.: When do you think we'll get hit—early September? October? That affects vaccine production.

Dr. Dowdle: Look at past experiences and available data.

Mr. Ferguson: In 1957 and in 1918, there was a marked increase in September and the pandemic peaked in October. I think that's what you should plan on.

[Unidentified]: Schools open early in Louisiana.

Dr. Dowdle: In 1957, seeding began in the summer, in June.

Lawrence Schonberger, M.D., M.P.H.: The virus is still here, it has not left. Is there a precedent for that?

Dr. Dowdle: In 1957, it never left, but kept occurring. Also in 1968, it started a little later, but it never left. So are these first and second waves or split epidemics?

[Unidentified]: In thinking about swine influenza, should we not be worried about GBS?

Dr. Dowdle: In 1976, there were field trials of the vaccine, but not to detect adverse events, just to look at immunologic response. That was not a major issue, and it was thought that the GBS risk was small compared with need for H1N1 vaccine.

Dr. Edwards: Are sera still available from the people who got GBS? Were they ever reevaluated?

Dr. Schonberger: No. There was one study after the outbreak that looked at possible HLA associations to see if any HLA type might be a risk factor. The study matched vaccinated GBS cases with vaccinated people without GBS and unvaccinated GBS cases with unvaccinated people without GBS to look for risk factors of GBS other than the receipt of the A/New Jersey/76 influenza vaccine. That study showed no clear association between GBS and HLA. The comparison of case with control subject pairs for history of previous influenza vaccination, however, showed a statistically significant odds ratio of (0.23) suggesting protection against swine flu vaccine-related GBS if the recipient had a history of a previous influenza vaccination. With regard to leftover sera from this study, we have looked and can't find any.

Recently a study by Nachamkin and colleagues was published that involved the use of some saved swine flu vaccines that after thawing were used to inject into mice. Test results of the sera in these mice were then compared with test results of the sera in other mice injected with other seasonal influenza vaccines not associated with GBS. One key hypothesis suggested in a report of the Institute of Medicine (IOM) was that the swine flu vaccines might have been contaminated somehow with *Campylobacter jejuni*, a known trigger of GBS; Nachamkin's study showed that no antibodies against *Campylobacter* antigens were elicited in swine flu vaccine inoculated mice, indicating that this agent did not play a role in the swine flu vaccines' triggering of GBS. However, each of the influenza vaccines (swine flu vaccines and the subsequent seasonal vaccines)

led to production of anti-ganglioside antibodies (anti-GM1) in the inoculated mice. Unfortunately, the Nachamkin study did not quantify the levels of GM1 antibodies induced by the different vaccines. Anti-ganglioside antibodies have been shown in other studies to be associated in humans with GBS. In large part because the technique used in the Nachamkin study detected the presence, but not the amount, of anti-GM1 antibodies, there's still work to be done to determine whether these anti-GM1 antibodies are associated in the mouse model specifically with the 1976 swine flu vaccines that had a higher risk of triggering GBS.

The A/New Jersey/76 (H1N1) vaccine was unique among influenza vaccines in its relatively high risk of triggering GBS in 1976, and no one knows why. The same paper by Nachamkin and colleagues offered a speculative hypothesis, based on earlier work, that the 1976 vaccines' triggering of GBS may have been related to their low content of neuraminidase. This low level of neuraminidase in the 1976 swine flu vaccines was reported in the scientific literature by Dr. Alan Kendal, Ph.D.

Unfortunately, we don't have published levels of neuraminidase for other influenza vaccines; neuraminidase levels are not routinely checked. Neuraminidase mediates the removal of sialic acid on hemagglutinin. A low level of neuraminidase might have allowed for sufficient sialic acid to remain bound to hemagglutinin to mimic an epitope on nerves. Given this hypothesis, it may be reassuring that the new 2009 (H1N1) influenza virus has a substantially different neuraminidase than the A/New Jersey/76 (H1N1) virus, the former was derived from birds the latter from swine. In addition, the hemagglutinin from the 2009 virus demonstrates antigenic drift differences from that present in the 1976 virus, although I learned today that the 1976 vaccine may provide some cross-protection against the new 2009 (H1N1) influenza virus, a potentially unexpected benefit from the 1976 swine flu vaccination campaign.

Dr. Pavia: I think we need to consider the importance of understanding the risk and the public's willingness to accept a vaccine, which ties in to our communication of risks and benefits.

Vaccine Safety and Use of Adjuvants

Vaccine Safety Monitoring—Dan Salmon, Ph.D., M.P.H., National Vaccine Program Office (NVPO)

Dr. Salmon emphasized the importance of H1N1 vaccine safety monitoring in the context of lessons learned from the 1976 mass vaccination campaign, the use of new vaccine(s) and potentially a new adjuvant, limited pre-use data, the fact that some special populations may be given the vaccine early in the campaign, and the need to maintain public trust and confidence (at a time when controversies around vaccines in general are arising).

The goal of safety monitoring is to identify quickly any adverse events following vaccination to determine whether they are caused by the vaccine and to address any spurious associations. If the adverse event is caused by the vaccine, it is important to ascertain the rate of the event and identify subpopulations at increased risk. It is also

important to distinguish adverse events from conditions that would have occurred without immunization given the normal background rates. To illustrate his point, Dr. Salmon referred to spontaneous abortions. Given the current background rate of approximately 15% of clinically recognized pregnancies resulting in a spontaneous abortion (miscarriage), it is likely that with 50% vaccine coverage of all pregnant women, there would be about 1,200 spontaneous abortions within 24 hours of vaccination due entirely to chance. In the event of mass vaccination, an otherwise random event will not be seen as random, especially if and when adverse events occur in clusters.

The following infrastructure are in place to support vaccine safety monitoring:

- VAERS is a passive surveillance system operated by the CDC and FDA that accepts reports from any source. Its limitations include likely underreporting and incomplete data. VAERS can be helpful in detecting signals or generating hypotheses but can not assess causality. It's a national database that can look at vaccine-specific events and subpopulations.
- VSD is a large database of information from eight managed care organizations, operated by CDC, that includes exposure data (including vaccine histories), lot numbers, and complete patient medical records. It is useful for testing hypotheses but is limited by the small numbers of patients represented (3% of the U.S. population).
- CDC's Clinical Immunization Safety Assessment (CISA) Network is used to investigate pathophysiological mechanisms and biological risks for adverse reactions. It incorporates VAERS data and can be used to develop clinical guidance.
- The DoD uses a number of systems, including VAERS, that involve both passive and active surveillance. The Military Vaccine Reporting System provides an option that allows a health care provider to follow up on the report.
- The Department of Veterans Affairs (VA) monitors events through its Adverse Events Reporting System and conducts active surveillance of influenza and pneumococcal vaccines in collaboration with FDA. It is developing rapid-cycle analysis techniques.

The NVPO's summary document, *Comprehensive Review of Federal Vaccine Safety Programs and Public Health Activities*, is available online at <http://www.hhs.gov/nvpo/nvac/documents/vaccine-safety-review.pdf>.

The challenges of safety monitoring for H1N1 include the number of uncertainties about the formula, dosages, use of adjuvant, distribution, and prioritization. Will those vaccinated first be captured under current surveillance systems? What other mechanisms are available for surveillance?

Dr. Salmon said the key challenges of evaluating the data include linking exposure and outcomes data, particularly if the vaccine is not delivered through the health care system. The database of the Centers for Medicare and Medicaid Services (CMS) could be useful if it can identify who was vaccinated. When pregnant women are vaccinated, it may be

difficult to link the woman's exposure with the child's outcome. It's likely there will be more than one vaccine. Background rates of other conditions are difficult to pin down. Finally, there must be a mechanism or planning to link State plans and data with Federal monitoring efforts.

A subcommittee of the National Vaccine Advisory Committee (NVAC) has been charged to review current Federal plans for safety monitoring for a novel (H1N1) vaccine and provide feedback on the adequacy, strengths, weaknesses, and considerations for enhancement. Dr. Salmon stressed the need to get feedback quickly.

Vaccine Safety: Basic Research—Charles Hackett, Ph.D., NIAID

Dr. Hackett informed the NBSB Panel that a high priority for NIAID is conducting basic research relevant to vaccine safety, and it is increasing its research portfolio to that effect. The objectives of the immunological group on vaccine safety and efficacy research are as follows:

- Maximize efficacy and minimize side effects
 - Determine the immunological basis for adjuvant activity
 - Mechanisms of toxicity vs. immunogenicity
 - Extrapolation from animal models
 - Role of formulation and delivery systems
 - T & B cell memory induction and maintenance (an important part of efficacy)
 - Immunogen design and production
 - Critical epitopes—T and B cells; NIAID is awarding grant funding to map both T- and B-cell epitopes and send them to the NIAID Immune Epitope Database
 - Potential mechanisms for cross-protection
 - Innate immune stimulæ in live attenuated vs. inactivated vaccines
 - Potential for adjuvants to expand vaccine supply and make vaccines more efficient
- Diversity of response across human populations
 - Immunologically interesting groups, such as those who do not respond to antigen-only vaccine

Ongoing research programs include the following:

- Immune Function and Biodefense in Children, Elderly, and Immunocompromised (This program includes pregnant women; it is in the early stages, and enrollment has been slow.)
- Population Genetics Analysis Program (This program includes several studies on adverse events with smallpox vaccine.)
- Atopic Dermatitis and Vaccinia Network
- Adjuvant Discovery
- Adjuvant Development (The discovery and development programs have been asked to identify potential adjuvant safety issues.)

How do the findings of basic biological research apply to making a vaccine? Dr. Hackett said there is no profile of normal human immune responses. Among the many diverse populations, measuring immune parameters is difficult, and assays are needed that spare samples. Therefore, NIAID is awarding funds to establish a consortium around the Protection of Human Health by Immunology and Vaccines. The grant would include funding to develop sample-sparing assays.

In December 2008, NIAID and FDA held a joint workshop on biological and regulatory issues around adjuvants. The goal was to assess the scientific knowledge base, facilitate development of a research agenda, and identify approaches to enhance nonclinical safety assessment. The transcript is available online at <http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm095698.htm>.

Essentially all successful vaccines have either naturally occurring or an added adjuvant. Adjuvant activates antigen-presenting cells, which stimulates uptake and increases migration, and causes local inflammation. Adjuvants stimulate interactions at the innate-adaptive interface that initiates an adaptive immune response. Adjuvant also appears to be one of multiple signals that co-triggers antigen-dependent activation of human B cells. One way adjuvant works to increase the breadth of antibody responses is to increase the number and breadth of T helper cells. Also, there may be an additional signal in B-cell receptor-mediated responses that activates more broadly than in the absence of added adjuvants. Adjuvants have both qualitative and quantitative effects on adaptive immune response. B cells are becoming better understood in humans, but many gaps remain.

Influenza has its own adjuvant activity, mostly by internal components. Innate receptors evolved to detect microbial motifs:

- Viral single-strand RNA recognized by toll-like receptor (TLR-7) and RIG-1
- Viral ribonucleoprotein plus other virion components trigger cellular inflammasomes

Influenza endogenous adjuvants are present in whole virion and to varying amounts in split vaccines; they are probably linked to the reactogenicity often observed.

The goal of our adjuvant research program is to replace the toxicity-causing components with less-hazardous, quality-controlled, exogenous adjuvants. Endogenous adjuvants may not be ideal triggers for vaccine immune responses. The innate immune system not only triggers adaptive immunity but also triggers the antiviral response. Dr. Hackett said he would like to see more focus on adjuvants helping adaptive immune response and separating it from innate immune defenses. It is feasible to replace viral immunostimulatory components with defined, tested adjuvants and still meet goals. Cell-mediated immunity, e.g., cytotoxicity of cells, is a good question that should be looked at, said Dr. Hackett.

In terms of vaccine safety, research is needed on the ability to reduce or eliminate the need for nonprotein viral components, eliminate manufacturing variability of endogenous adjuvant activity, and facilitate the meta-analysis of adjuvant function and safety. Meta-analysis could compare adjuvants across platforms and demonstrate alternative uses (e.g., ALDARA (imiquimod) used to treat warts may have potential as a vaccine adjuvant).

In the U.S., seasonal live attenuated vaccine and inactivated trivalent vaccine have endogenous adjuvants only. In Europe, some vaccines have added exogenous adjuvant. At present, it is not possible to look at a human profile and measure precisely what responses adjuvant triggers. The effort to create a consortium of organizations to identify normal human immune response is intended to address that barrier. Dr. Hackett concluded that NIAID hopes to have some platforms and databases on which to address some questions about safety in clinical data.

Discussion

Dr. Pavia: I'm gratified to see the investments in basic research on safety for the future; will any of that investment be useful this fall?

Dr. Hackett: We have nothing like a chip or gene that can help you identify whom not to vaccinate, but there are investigators looking at special populations and generating data. You could get preliminary information from them on special populations.

Dr. Pavia: If Dr. Salmon asked, could you identify the top 10 conditions for which we need baseline rates on, e.g., diseases or adverse events?

Dr. Hackett: That's a good question. We are always concerned that when you trigger B cells could they respond to existing antigens as auto-antigens? That's one priority. For special populations, we are concerned about people who have had transplants and people with autoimmune disease or primary immune deficiency. Those are some groups to look at, but we can't have that data by this fall.

Dr. Schonberger: How do we get key information, such as denominators? It's unclear to me how this vaccine will be distributed (mass campaign? private sector?). In 1976, we had available to us the results of the National Center for Health Statistics (NCHS), Health Interview Survey, Weekly report to identify the proportion of people receiving vaccine each week. I think such surveys should be conducted during the upcoming fall campaign. In 1976-77, we also had the National Influenza Immunization Program (NIIP) weekly and monthly data to evaluate how much vaccine was administered each week as well as each month by age group. In an important re-analysis of the GBS data conducted in Minnesota and Michigan by Dr. Safranek and colleagues published in 1991, the NIIP data worked well in Minnesota, so they were used to determine denominators in Minnesota. In Michigan, on the other hand, the NIIP data on vaccine administration seemed delayed, so the NCHS data were used instead for denominators. Setting up several mechanisms for determining unvaccinated and vaccinated population denominators over time in the fall could be very important for evaluating potential adverse reactions.

The risk of swine flu vaccine-related GBS was not equivalent in all ages. People under 25 years were much less likely to get GBS after swine flu vaccination than older recipients. Those ages 25-44 had a higher than average risk. Among unvaccinated

persons, we normally see higher rates of GBS as people age. In children, we didn't see a statistically significant risk of swine flu vaccine-associated GBS, but we also administered relatively little vaccine to children, about 2% of the total doses. The key points are that to best evaluate adverse responses to vaccinations, you need good denominators and need to obtain follow up information on numerators; that is, the suspected reported adverse reactions. GBS was seen and reported to CDC by physicians, but to identify and establish the association and to determine the magnitude of the risk, a follow-up investigation was critically important. Thus, a system to monitor adverse reactions needs to be able to recognize signals for a possible problem that can trigger a response to potentially get more detailed information.

Dr. Pavia: Yes. That's a critical problem that Dr. Salmon identified.

Dr. Edwards: We're part of the Clinical Immunization Safety Assessment (CISA) Network. We're trying to identify what information to collect from adverse events, how to save the information, what aspects would be interesting to scientists, and how we address issues with patients.

Dr. Schonberger: The size of the GBS problem after influenza vaccinations is so small in absolute numbers that if there were an outbreak of influenza for which you used vaccine and it was effective, the adverse event would be unfortunate but likely accepted by the public (even though the public is less tolerant of problems we create as opposed to problems caused by natural events). The 1976 swine flu vaccinations caused about 25 GBS deaths. With current H1N1, there have been 45 deaths already, and it's likely that these latter influenza virus-related deaths have been underreported.

Vaccinating in the absence of disease is what made GBS a big issue back in 1976. What concerns me is listening to the anticipated schedule today for the availability of vaccine against the pandemic strain; there's a good chance we will be vaccinating after the peak of the outbreak, so we could recreate a 1976 -like problem of sustaining adverse vaccine responses without obtaining much of the vaccines' benefits.

Dr. Hayden: I don't know what the predictive value of existing anti-ganglioside antibody panels for GBS might be, but we should look at it. Different types of GBS and associated provocative factors likely have different patterns. Adjuvant in vaccine might potentially be related. As for baseline rates of GBS, there's an opportunity to get better prospective data as we roll out seasonal vaccine, especially with our current systems. Regarding the association of influenza and GBS, a recent French study shows an association between natural influenza infection and the risk of GBS. Consequently, an effective vaccine might diminish the risk of GBS.

Arnold Monto, M.D.: There's a French study that claims influenza causes GBS. But you get blamed for the vaccine; no one is worried about what the disease does.

Gus Birkhead, M.D., M.P.H.: Given the historical context, we need to address GBS. The potential for the issue of adverse events to blow up is very large. Vaccine safety is an even bigger issue now; there are children not getting vaccinated for measles or haemophilus influenza type b, despite the risk of death. Could the record of adjuvant use in Europe be informative in terms of signals? They must have experience, having dispensed 45 million doses.

Dr. Pavia: There is a list of adverse events.

Dr. Sun: There are some age-related phenomena in immunogenicity and safety. What do we know about the effects of adjuvant by age groups? We struggle with what kinds of signals to look for. We arbitrarily decided to follow subjects who get adjuvant for one year. What data do we have?

Dr. Hackett: Development of the innate immune system is an area of increasing importance for the “hygiene hypothesis” related to the increased prevalence of asthma. That’s the belief that infants and very young children need to be exposed to certain ligands for normal development—that the immune system may be trainable—but it’s just a hypothesis now. The short answer is that we need to profile the innate immune response in children. There’s a cohort of kids in an inner-city study. We need to understand how the immune system develops: some develop better systems with age and some don’t. There’s a belief that the immune system’s set point changes over time, but we need more data.

Dr. Grabenstein: Regarding baseline rates, one lesson from 1976 was that heart attack as a false alarm was important, and it recurred with smallpox in 2003. Also, in some recent vaccines for adolescents, there are issues about seizures.

Dr. Rappuoli: In 1976, the equivalent amount of vaccine was used in Japan and there was no GBS. We’ve delivered more than 45 million doses of vaccine and have data from passive surveillance. We analyzed our data on GBS after about 30 million doses with our vaccine and compared against normal (non-adjuvanted). We saw no sign of increased risk of GBS. In trials, we now look for autoimmune disease. We just had a study of 30,000 and saw no signs. Also, the observational study in Italy of 150,000 people that’s been going on for 2 years has shown no increase in autoimmune disease.

Dr. Salmon: Clearly, we need to look at GBS but must be careful not to focus too much on GBS at the expense of other things. It could be a red herring.

[GSK representative]: No one is talking about pharmacovigilance or the diversity of pharmacovigilance systems. What we’ve heard from European regulators is how they will work with mass vaccination. I’m concerned about redundancy, but there’s no plan for coordination. Pharmacovigilance is always reacting to the previous emergency. GBS and autoimmune disease are important, but for background rates it would be helpful to have a system to identify those regardless of an emergency. We should coordinate activities in pharmacovigilance and systems to identify background rates of disease.

[Unidentified]: There is discussion about GBS surveillance within existing systems, and efforts are underway.

Dr. Salmon: HHS, DoD, and VA are working on a plan. They will describe their activities and the NVAC subcommittee will look at them. Background rates are hard to define. When you pull charts and compare records from VSD information, the diagnosis is not always correct. It’s very difficult to get background rates now.

Adjuvanted Vaccine

Dose Sparing and Cross-Protection—John Treanor, M.D.

Dr. Treanor outlined the information needed to determine whether response to H1N1 should include use of adjuvanted vaccines:

- What is the dose response to plain and unadjuvanted vaccine? Are high doses needed to get a response?

- How much antibody protection is needed?
- How large is the target population?
- How much product is needed and what's the manufacturing capacity?
- What is the impact of dose-sparing on overall coverage? (It's probably not linear.)
- Given that oil-in-water emulsion adjuvant stimulates antibody that recognizes viruses from other clades, does it provide cross-protection? If so, how much cross-protection is needed?

Clinical trials once vaccine is available could answer some of these questions quickly. Data from healthy adults suggest that those with healthy immune systems may be primed and a diluted vaccine could be effective. As seen with H5 vaccine, however, the vaccine could result in little antibody despite high doses. It takes about 90 mcg of H5 antigen to reach high titers in half the people who receive the vaccine, but some people reach high titers with low doses—and some don't, even with high doses. Could you identify people who achieve high titers with low-dose vaccine early on?

With the 1977 unadjuvanted vaccine, even kids had good responses to low doses. Those who had previous priming had a substantial response to low doses. The questions to consider are how much protection is afforded by a vaccine without adjuvant and how much protection does adjuvant add?

In inactivated avian influenza assays, oil-in-water adjuvant showed substantial dose sparing and enhanced response to a single dose. Adjuvant was associated with more local pain and inflammation, but not much else. The effect with H1N1 is similar and dramatic. In seasonal vaccine, however, adjuvant did not substantially increase antibody, and it showed a modest benefit in older adults only. We must evaluate whether the effect of adjuvants would look more like those seen with seasonal influenza or H5N1.

The relationship between the amount of antibody and protection against disease is not known. Sometimes we are willing to make tradeoffs, such as providing less protection in an effort to cover more people. We are looking for the lowest dose we can use to generate an acceptable immune response without knowing what that response is. When you look at levels of antibody that reduce attack rates by 50%, you see that formula variations impact the findings. You could have no protection until you get to a higher level of antibody or more protection at a low level or some combination of both.

Regarding the target population, age-related incidence and morbidity data as the pandemic evolves will define the target. Within target age groups, some people may have risk factors for more severe disease. The size of the target population and its unique features will affect decision-making. While it is important to know the age distribution of disease, Dr. Treanor emphasized that there is little to be saved by not immunizing those over 50 years.

Manufacturing capacity depends on what types of vaccines are used and whether current U.S. supply, in current forms, would be used. Both national and global vaccine supply needs must be taken into account.

It is unclear how using dose-sparing adjuvant would affect overall coverage. Other issues that could limit the usefulness of adjuvant are the production process and availability of components; distribution, storage, and administration logistics; requirements for special formulations; and public perception of the safety of adjuvants.

With H5 vaccine, adjuvants enhance the antibody generated that reacts with other H5 clades. Such cross-protection could be evaluated in clinical trials. It is not known whether antibody titers against a variant can directly translate to protection. Antigenic drift may affect the impact of adjuvants.

When adjuvant does yield a high titer, Dr. Treanor said, it looks as though the result is to raise the antibody titer by the same degree across the board. When older people who have received multiple seasonal influenza vaccines are compared with children naive to vaccine, there appears to be a higher ratio of antibodies to variants.

Dr. Treanor concluded that the factors to consider are whether the available safety database for adjuvants is adequate to enable their use in target populations with confidence; whether available immunogenicity data support the use of adjuvants either for their dose-sparing or cross-protection qualities; and whether adjuvanted vaccine is both desirable and necessary.

Regulatory Implications—Wellington Sun, M.D., CBER

Dr. Wellington Sun provided an overview of CBER's current thinking about H1N1. Notably, H1N1 is considered a strain change and, therefore, manufacturers who already have a licensed vaccine product in the U.S. may use their H1N1 vaccine in all populations approved under current labeling. For populations not covered by the existing labeling, use of the product requires an EUA. CBER requested that all the manufacturers' clinical trials follow a similar design, and all have been asked to evaluate products in all age groups. CBER is working closely with BARDA and NIH to fill gaps in information, such as the anticipated lack of data on pregnant women and infants up to 6 months. The guidance developed by FDA is based on a worst-case scenario and will change as the science evolves.

The final product formulations will be determined by the results of clinical trials. Preclinical toxicity studies are underway and could be helpful if a decision is made to combine antigens and adjuvants from different manufacturers.

Dr. Sun described the criteria for an EUA and noted that H1N1 meets all of them. It is possible that vaccine could be used under an EUA for special populations, and that could include a lot of people.

At present, FDA believes evidence is sufficient to recommend evaluating adjuvants in clinical trials and to consider for use under an EUA. Ultimately, use of adjuvants is a policy decision. FDA recognizes that a coordinated effort may be needed to help health care providers understand the options when faced with a variety of products.

Dr. Sun pointed out that FDA does not have primary responsibility for liability concerns. In general, however, the Public Readiness and Emergency Preparedness (PREP) act provides liability protection and compensation mechanisms for products used under an EUA.

Discussion

Dr. Pavia: What would be the impact of adjuvants on attenuating disease in the fall? Also, what are the international implications if the U.S. uses one-tenth of the global vaccine supply? What are the ethical and legal implications of using a product that may carry a higher risk to the individual but is thought to better benefit society?

Mr. Ferguson: The timing of the epidemic and the vaccination window are key. We expect to see it peak in October, so it's a narrow window. What the U.S. uses affects the rest of the world, and there's a meeting on that topic going on in Seattle right now.

Gary Noble, M.D., M.P.H.: All these points have been made, but I think they bear reiterating:

- It's best not to have the President out there as a spokesperson for vaccine policy.
- Let data drive decisions where you can.
- Keep the steps open to change.
- It is unlikely there will be enough clinical data for decision-making. There are arguments for using adjuvant to extend vaccine and possibly for dampening interference from seasonal vaccine, but there will be real or perceived side effects. If a rapid response is needed, chances are you won't have data.
- Be prepared to address communication and public confidence—e.g., use some term other than “oil-in-water.”

[Unidentified]: Other countries are thinking more about dose-sparing and adjuvants than we are. We had the experience of 1976 and clinical trials show that the priming will be there for many in our population. There are thoughts at WHO that the U.S. will use all the antigen because it will not use adjuvant, and the world needs dose-sparing. But the real issue is when the vaccine will be available. If clinical trials are finished after the event, it doesn't matter, and evaluating the risks and benefits of a monovalent vaccine will not help. The important lesson of 1976 was that we must be flexible. Maybe we should be thinking about priming the rest of the population that was not primed by the first and second wave. We're going to see lots of disease in fall. It's going to be a tremendous job to explain why we're giving seasonal vaccine that doesn't protect against H1N1 and then trying to give H1N1 when seasonal influenza is peaking.

Dr. Pavia: Dr. Robinson showed a model of a hybrid approach of using adjuvant for some people.

Dr. Treanor: That sounds complicated, but it's a good idea otherwise. Tailoring the vaccine for the target population sounds good, but implementation is a problem. We have trouble using vaccine in anything other than simple strategies.

Robert Field, J.D., Ph.D., M.P.H.: Public health ethics differ from clinical bioethics. Mainly, public health is about populations—what's good for large numbers—so it is the principle of utilitarianism. Clinical bioethics focus on autonomy, such as the doctor-patient relationship and the right to die. If we're talking about protecting a population, utilitarian concerns come into play. If the goal is to protect the safety of the population, look at what gets the most vaccine out there. If the goal is to protect vulnerable populations, then more specific issues come into play.

Keep in mind the importance of communication. Vaccine is such a hot topic, as we see with the focus on exemptions, autism, etc. Consider economic, social, and other effects if key people can't function. Let your decision-making flow from your ultimate goals.

Brooke Courtney, J.D., M.P.H.: Liability is always an issue, but there are strong legal tools and protections available, such as EUAs and the PREP act (as long as compensation funds have money). Liability is important, but we shouldn't let liability be too large a concern with moving forward on these difficult decisions and paralyze our planning efforts. If there is mass vaccination, one thing we tend to overlook is that it will largely be coordinated at the State and local levels, which are already stretched to the max to provide daily services and otherwise respond to the pandemic.

You may assume that if medical countermeasures are available, the public health system will easily and quickly be able to get them where they need to go, but that will be extraordinarily difficult, even with good planning; on top of mass vaccination, there are the issues of receiving and storing Strategic National Stockpile assets, use and allocation of antivirals, etc. Even though many health departments have significantly improved their response capabilities since 2001 and are very well prepared, these are very challenging issues, especially with the budget and staffing challenges that most health departments are currently facing.

We need to consider how decisions about adjuvants might impact local public health providers. If the timing is right, a better vaccine using less antigen means more people could get vaccinated. Fewer people would potentially get sick, so the surge in health care could be lower. Having more vaccine available potentially could mitigate difficult vaccine allocation decisions at the local level. It's hard to develop allocation plans on paper but even more difficult to implement them at the local provider levels. So, a shortage of vaccine means more challenging allocation issues at the local level.

On the other hand, using adjuvant in a hybrid approach would seriously complicate local decision-making. There's also the complexity of EUAs at the local level. If you go that route, be sure to get information out as early as possible to public health professionals and health care providers. If an EUA requires forms, such as instruction sheets to hand out to the public, that's a big deal—even things that might seem simple, like the logistics of making copies, can be a big challenge for health departments. Whatever is decided, make sure State and local public health providers get clear, consistent, early guidance

from Federal partners. During the response, they won't necessarily have time to comprehensively evaluate, study, research, or consult.

Dr. Pavia: We have not been thinking about local providers as much. From a local perspective, is it more feasible to have a simple schedule, with no prioritization, and vaccine arriving all at once or to distribute vaccine to multiple providers over a longer period of time?

Ms. Courtney: Both are challenging. With mass vaccination in a short time, there will be staffing issues, and localities will not be able to get help from other areas. And with the longer time frame, you'll be dealing with more difficult allocation decisions. I don't know which scenario is ideal—it's challenging either way.

Dr. Dowdle: We have not heard yet about interacting with the public. What are their expectations, and what do we expect from them? How do we keep in touch and manage? That was a major concern in 1976—we were out of touch. Also, the 40 million doses we delivered did not go uniformly across the country; some states had no uptake. Will there be a dialogue with the public to see what they want? Many people now don't intend to get their kids vaccinated for H1N1.

Dr. Neuzil: I agree with Dr. Dowdle; I hope it's part of our effort. I understand that using adjuvant would give us more total vaccine, but would it give us a vaccine any sooner? Sooner is more important. Will an unadjuvanted vaccine be available in September? CBER is looking at novel H1N1 as a strain change, so with the trials underway, could we get a licensed H1N1 vaccine without adjuvant fairly quickly?

Dr. Sun: For seasonal strain changes, no clinical data are needed from those already licensed and producing.

Dr. Neuzil: So are the trials required for licensure or not?

Dr. Sun: We hope the dose-ranging studies will provide information to guide formulation.

Dr. Pavia: Can Dr. Robinson clarify how the timelines for production with and without adjuvant translate to release times?

Dr. Robinson: It doesn't matter; they start at the same time and both are based on clinical data. Once you say you have sufficient data, it will take about 3–4 weeks to get everything out with no glitches.

Martin Meltzer, Ph.D.: In the simplest model, we could have 10 million doses of unadjuvanted vaccine in week 1, or 40–50 million doses with adjuvant. Using adjuvant, more vaccine would be available earlier and there would be more available for the world. The PREP act allows use of adjuvant and limits liability, but lawyers always require paperwork and that slows down clinical use. How much paperwork would be associated with adjuvanted vs. unadjuvanted vaccine? And would local health departments prefer the easier paperwork, especially with two doses?

Dr. Sun: An EUA requires a fact sheet for recipients; it doesn't require a signature. That's the only real paperwork. It may be necessary to have someone to answer questions [at the local health department].

CAPT Miller: An EUA is product-specific. At issue is risk vs. benefits for using certain products under an EUA, which is continually evolving. The nature of the situation dictates the amount of latitude available. FDA can make the conditions of the EUA more or less stringent. If you're dealing with approved products used in different ways, that's

easier. Using products that are not currently approved or not well understood, like a new adjuvanted vaccine, is more problematic and we have to balance the risks and benefits. The CDC and NIH are also play a part in the EUA oversight and approval process. The agency can look at conditions it thinks are needed to make the product more safe and efficacious. We have required safety sheets in some cases.

Dr. Rappuoli: We can make some decisions earlier, like formulations. We may not need to wait for the second-dose data to do the analysis. We could produce lots of vaccine earlier if we use adjuvants. Regarding strain drift, we don't know if it will happen or how much adjuvant will do if it does. With H5N1 and seasonal vaccine, we know we could cover multiple clades with adjuvant.

We do know that there is little effect of adjuvant in seasonal vaccine on older people, but there is an effect for younger people. Adjuvant increases immune response after one dose, possibly providing earlier protection. Unpublished data have been submitted to FDA on the quality of the immune response. Adjuvant increases recognized epitopes, so the quality of the immune response is different (better). With adjuvant, you get a good response in one dose.

Stephen Redd, M.D.: There is a plan for community engagement and recent experience at CDC. We did a public engagement process for community mitigation guidance and prioritization for vaccination. Those were intensive engagements. The scenarios discussed were related to more severe H5N1. In this case, we have real-life scenarios and public perception is likely to evolve over time.

Dr. Quinlisk: From a State health department perspective, we may be giving seasonal influenza vaccine, the first dose of H1N1 vaccine, and a second dose of H1N1 vaccine, treating people sick with H1N1, and tracking adverse events. We can't handle that with our current capacity, but, if this treatment plan is supposed to work, we need to do all of that.

Dr. Pavia: To sum up, we've heard about the advantages of adjuvants for priming, mass vaccination, and broader immune response as well as the potential liabilities that come from paperwork, uncertainty, and political fallout. We need to think about how we can make the decision-making process easier when the decision has to be made.

HHS Decision Planning—Bruce Gellin, M.D., M.P.H., NVPO

Dr. Gellin said decision planning is all about setting expectations. We need to think what data elements will go into decision-making. No single group is responsible for making these decisions and we need to think about the roles of other Federal advisory bodies in advising on these issues, especially adjuvant. Every government is wrestling with the question of what to do once a vaccine is available.

Decision Process—George Korch Jr., Ph.D., ASPR

Dr. Korch stressed the importance of having a strong decision-making process and the difficulty of balancing multiple factors in making decisions about complex public health concerns. In 1978, Neustadt and Feinburg said the failures with the 1976 swine influenza vaccine stemmed from:

- overconfidence in theories based on meager evidence,
- conviction fueled by a personal agenda,
- zeal by health professionals to make their lay superiors do the right thing,
- failure to address uncertainties or allow for reconsideration,
- insufficient questioning of the scientific logic, and
- insensitivity to media relations, public perception, and long-term credibility of institutions.

Current decision-making must consider at least two scenarios: 1) a rapid epidemic for which limited information is available from the Southern Hemisphere, for which there is no real information on variants, and against which it may be possible to use novel adjuvants under an EUA; and 2) a mild epidemic for which there is not enough vaccine to cover the entire population but against which vaccination of high-risk populations could be initiated.

Dr. Korch identified all the parties that both contribute to and benefit from the decision-making process, noting that all are equal. He asked participants to consider whether a vaccine program is a foregone conclusion, given the following challenges:

- It will cost a lot.
- It will disrupt the medical and public health infrastructure.
- It will have significant political costs if it is seen as wasteful or untimely.
- It will have a long-term impact on vaccine programs if adverse events occur.

In addition, there are uncertainties about the availability of vaccine and whether the vaccine will match the strain. Moreover, Dr. Korch asked whether the decision to use vaccine will be made in advance of the event. It is imperative that the decision-making process be transparent and vetted; relies on the best available evidence; allows for flexibility; ensures that rules are in place for starting and stopping a vaccination campaign; and makes certain that vaccination meets the needs of the end-user.

The elements of a decision plan are as follows:

- Identify all the sequential output decisions.
- Identify critical data needs and inputs for those decisions.
- Identify stopping rules, if needed.
- Evaluate other factors that mitigate or exacerbate the vaccine plan.
- List key assumptions.
- Enunciate decisions that may be made “at-risk” and their cost/benefit impacts.

Among the important variables are the need for patient tracking, a coordinated startup with State and local governments, and clear communication. If the decision is made to vaccinate, the overall objective should be defined:

- Reduce number of overall deaths to seasonal or below levels

- Reduce number of deaths in young age group to seasonal or below level
- Reduce proportion of severe cases to ameliorate surge in hospitalized cases
- Reduce transmission rate in general population
- Protect critical infrastructure
- Comprehensive control of infection in population

The decision tree under consideration by ASPR identifies probabilities at each node as well as the expected values, risks, and effect on the overall strategy. CDC coordinates a lot of the data elements. The relationship of risks to benefits varies depending on the scenario, so biologic and epidemiologic data are critical.

Dr. Korch identified a number of questions about the decision-making process that must be considered:

- Is it a reasonable approach to address the decision?
- Are there important decision points left out?
- Is there a different sequencing or priority of decision points?
- Are there assumptions or mitigating factors that must be additionally identified?
- What additional questions need to be posed?
- Are there other “decisions at risk” that must be posed?
- What is the minimal set of decision nodes that produce a reasoned and defensible outcome?
- What are the appropriate data requirements for each node?
- Are the data required achievable in the time scale needed?
- How much parsimony is tolerable for the data requirements?
- What is the preferred decision methodology for this level of complexity?

He then posed a series of broader questions:

- What alternative decision schema would the NBSB propose?
- What is the best method to define risk vs. benefit for the decision-maker?
- What is the reality of having the data that we believe we need?
- What should be the acceptable (defensible) level of risk to proceed on a decision?
- If you were the President or the Secretary, what would you want to see, know, or have to make this decision?
- How sensitive will the decision process be to different scenarios?
- How engaged will the NBSB want to be during the process leading up to a decision, and thereafter?

Dr. Korch noted that the decision tree he presented informs those at the highest levels, and some elements are the same as for the pandemic influenza strategy. He added that vaccine is not the only mitigation tool and BARDA has looked exhaustively at other tools that might mitigate or exacerbate the vaccine strategy.

Federal Advisory Committees: NVAC—Gus Birkhead, M.D., M.P.H.

Dr. Birkhead explained that NVAC's responsibility is laid out in statute and covers everything from research through funding. He detailed some of NVAC's recent accomplishments, most notably the initiation of a review of the entire Federal vaccine safety system, including mechanisms for monitoring H1N1.

NVAC believes its role in addressing H1N1 is to focus on implementation of vaccine programs by acting as a conduit for stakeholder input, helping with coordination among the other Federal advisory groups, and focusing on vaccine safety. It will hold monthly teleconferences throughout the summer to get updates from Federal and other partners on planning and implementation. NVAC is working with NVPO and the CDC Immunization Safety Office on its vaccine safety assessment.

At its meeting earlier in June, NVAC reached consensus on several issues related to H1N1:

- Accelerate the urgency of planning efforts, because State and local planning efforts are already behind.
- Public health providers need more resources:
 - State and local health departments lost 10,000 workers last year and expect similar staff cuts this year.
 - The pandemic response will be simultaneous and require tracking, treatment, and addressing the concerns of the “worried well,” but pandemic influenza funding for State and local health departments ended in 2008, and other preparedness funding has declined.
 - While Congress has proposed \$350 million in supplemental funding for pandemic influenza response, conservative estimates of the cost of simply administering vaccine are far higher. (At \$15 per dose for administration, the total would \$9 billion.)
- Vaccine safety is critical.

Implementation considerations include the need to involve State and local public health providers in planning assumptions, such as prioritization of target populations. States need to define their role in actual distribution vs. central distributions, and they will need more resources if they are to distribute 15,000 packets per day. Implementation plans should take into account additional clinic procedures if a vaccine is used under an EUA (forms, signatures, counseling, questions), as well as requirements for accounting and measurement. Communication strategies should include risk communication that conveys the risks and benefits; strategies should also be flexible enough to facilitate communication of new risks as they are identified. Adverse event monitoring also should be considered.

Dr. Birkhead said VSD is the key database for determining causal associations between adverse events and vaccination, but it may be of limited use because exposure information will be lacking if vaccine is not administered by health care providers and billed through one of the eight participating managed care organizations. One approach would be to link VSD with public health databases. VSD may also be hampered by the

use of products from up to five different manufacturers, plus seasonal vaccine. Active surveillance is needed, especially for high-priority groups.

Discussion

Dr. Pavia: We probably have a vaccine, and we think we want to use it. So, we need to identify the target groups, priorities, doses, how it will be administered, contraindications, coadministration with seasonal vaccine, etc. I want to hear from the other Federal advisory groups: What information do you need to make a decision? Do you have that information? How can we inform the decision process?

Dr. Neuzil: At ACIP, we're 15 members, selected for our diverse expertise and representation, and we make recommendations to the director of CDC and to the HHS Assistant Secretary for Health. Our charter addresses vaccine licensed for the civilian population and maybe also for vaccines that are not yet licensed. So that's why it's important to understand if the H1N1 vaccine will be licensed or not. Under what circumstances does ACIP make decisions on unlicensed vaccines? Who decides what we should address? It's in our charge to make recommendations on current seasonal vaccine, and we have. Nothing that I've heard so far would make me reassess our recommendation for the 2009–2010 seasonal vaccine. It's important to understand that despite logistical and communication challenges of coadministration or sequential vaccine, nothing makes me think that the benefit for seasonal vaccine is not there.

Dr. Pavia: Have we set a goal? Reduce the number of deaths? Minimize disruption? Who sets that goal?

CAPT Fiore: The overarching goal so far has been to reduce deaths, hospitalization, and complications of seasonal influenza, and I expect the goal will be the same for pandemic influenza. We have relatively few deaths now, so we may need to reassess and look at severe illness and hospitalization or societal disruption. I think ACIP would contribute to goal-setting.

Also, as influenza vaccination progresses, we've expanded the groups for whom we recommend vaccines greatly in the past 10 years; now, 84% of people are affected by annual influenza vaccine recommendations. ACIP goes beyond listed indications, e.g., recommending that pregnant women get influenza vaccine. It is an unusual Federal advisory group. It has ongoing work groups that meet throughout the year, including one on H1N1. The groups have other liaisons and ad hoc experts. ACIP has made decisions despite gaps in data by relying on expertise, and the group is comfortable talking in public forum about its concerns.

Dr. Schonberger: Who deals with questions related to what's available when? If you treated the new pandemic virus-related antigen like regular seasonal vaccine—15 mcg, no adjuvant, injected—and used it under an EUA, that could be ready quickly (without doing formal, time-consuming, clinical trials). But the lines that the manufacturers are pursuing mean there will be delays. Who evaluates that issue? If we decide to do clinical trials on adjuvants, that's a decision that leads to a later vaccine.

Dr. Pavia: If we leave aside the question of adjuvants, I'm uncomfortable making a decision about using one dose for all. We need at least some dose-response studies.

Dr. Edwards: I think Dr. Schonberger makes sense. We may have to decide whether we will go forward with just a few answers, otherwise it may be too late and we'll be spending money on vaccine we may not need. We need to find out quickly what happens with one dose. I'm worried that the trials will miss the mark.

Dr. Schonberger: Maybe there's a precedent. In 1977, we did not call it a pandemic; we just slipped the antigen into the regular seasonal vaccine.

Dr. Dowdle: There was small, simple field trial, but no consideration of a new subtype, and it was very quietly done.

Dr. Quinnan: Dr. Treanor gave data on clinical trials in 1977 from the Russian influenza vaccine that showed very good responses in people who had been alive in 1957. However, that data reflects responses of people who had had multiple natural exposures to H1N1 strains that were nearly identical to the 1977 H1N1 strain. It is important to recognize that similar, very potent responses were observed in the same age groups among people vaccinated in 1976 with the A/New Jersey H1N1 strain, since that strain was very different from the strains that circulated prior to 1957. Those results indicate that we should see the same degree of cross strain priming in people vaccinated now with the novel H1N1 strain based on prior exposure to previously circulating H1N1 viruses. Moreover, the cross priming should be evident in people who were alive before 1957 and in people who have been exposed to circulating H1N1 strains over the past 30 years.

Dr. Murphy: Some respond well to one dose per data on the 1976 trials—about 80-90%. Despite the uncertainty about the number of doses and ability to respond, I think we can make a decision early.

Dr. Pavia: That's all good for people over 50, but that's not the target group.

Dr. Murphy: The viruses circulating in the 1940s and 1950s were priming the population for the virus that circulated in the 1980s. Everybody over a certain age has H1N1 priming.

Dr. Field: This is politically sensitive. Is there a procedure for getting public input and perceptions?

CAPT Fiore: We have one public member [on ACIP] and we have public comment time during meetings. Also, CDC sponsors public engagement.

Dr. Redd: The public engagement process is good for value decisions but not for technical decisions.

Dr. Gellin: We went through the prioritization process for pandemic influenza planning. There is a way to formalize the input, and we see it as a data point.

Dr. Modlin: I'm a veteran of the swine influenza outbreak. We studied the vaccine at Boston's children's hospital and we found the vaccine poorly immunogenic in children, even at two doses.

Dr. Meltzer: In terms of setting a goal, keep in mind that the valuation of a vaccine changes, and you can't transfer that value to others. I don't think seasonal vaccine valuations are comparable in the public's mind to H1N1. As for the data we need to make decisions, e.g., the case-fatality rate, I don't think it's that simple. Public comment is important, but people say one thing and do another. Whether to use one or two doses is important for logistics, etc., but to the public it's a side issue. Regarding the decision process, you need to get down to a few key points. There will never be enough data, but if you start too early, you will be back in 1976.

[Unidentified]: I think the most critical issue is the timing of the arrival of vaccine. We need to see what it takes to get vaccine earlier. We need to consider other approaches to get “good-enough” data. We may still be studying the vaccine here while people in Europe are getting vaccine. I anticipate major outbreaks this fall. If we can’t have vaccine, we need a good plan for using the antivirals in the Strategic National Stockpile.

Dr. Pavia: When will vaccine be ready in Europe?

Dr. Innis: It has not been absolutely determined by the European Authorities that they will issue a license with no clinical data. In Europe, GSK is planning limited trials, and we could have pilot data by October. The first vaccine lots could be released by October based on that data, September without clinical data if necessary.

Dr. Rappuoli: In theory, without trials we could go earlier.

Dr. Mallory: We are licensed in the U.S. If we have extra [vaccine], we will talk with the EU.

Dr. Matthews: We expect to do larger clinical studies over a longer time frame.

Dr. Rose: Are we contemplating mass vaccination with a mild outbreak? I don’t think we have enough information to deploy. We need to figure out what problem to solve first.

Dr. Korch: The decision tree that I showed you includes probability values. It’s an expensive decision, so you need to evaluate all the aspects.

Dr. Rose: The rate-limiting factor is time. I don’t think licensing will be there by September, but there’s still the issue of production. Can you preplan? Can you produce lots of antigen and have adjuvant on hand to uses as needed?

Dr. Katz: We have some sera from adults 25–65 years and we saw some strong rises for those who had vaccine in 1957, some protection. We also see cross-reactivity. We have not studied infants or young children who had seasonal influenza vaccine.

Dr. James: We at least need to be ready to decide.

Mr. Ferguson: We need to include the dose. Even partial protection is some protection.

Jennifer Nuzzo: Many decisions have to be made. Whoever is responsible should identify the target objective for vaccination. The vaccine strategy should match the objectives.

Dr. Pavia: The consistent concern is that if we don’t give vaccine early, it will likely to be too late. The worries about delays are related to regulatory hurdles, money, etc. It’s important to adopt a strategy early. Early use of the vaccine may be the clinical trial. There is a greater probability that older people are primed, and we need minimal data on that.

Dr. Scannon: Manufacturers’ capacity, with or without adjuvant, is a variable that we should map out on the decision tree. It affects our ability to reach goals.

Dr. Korch: Lots of things were left out of that decision tree. There’s a lot more to say about community-level issues, for example. It’s just a device, a way to consider the issues. The *gestalt* may be the answer.

Dr. Dowdle: I’m getting a sinking feeling of *deja vu*. We may be opening up a public nightmare by overreaching, overpromising. To do the job right, we need to think about how we can make a vaccine available and the smallest group we can vaccinate. You can always expand the target groups. But if you wait until the data are perfect, there will never be enough.

[Unidentified]: The most scarce resource is time. Does HHS want vaccine in September? If so, we can move forward without an immediate declaration and add data as we go.

Dr. Robinson: We can have vaccine in September at a very high cost. If you want vaccine by September 15, you need to make a decision on production by August 15. What data do you need?

Dr. Pavia: I worry that the public wants a vaccine immediately but won't get sequential vaccines. We need to work backward, because that affects whether we use adjuvant.

Dr. Neuzil: Let's go back to our deliberation on target groups. That's our starting point.

Dr. Hatchett: The diagram on prioritization was for a severe pandemic, and this one is different. We can make some assessments on the need to prioritize in a severe pandemic, based on general risk and the potential for social disorder, but this pandemic lends itself to some analysis of risk by group. When targeting groups, context is important. If community mitigation focuses on preventing transmission by children, be mindful of the need for consistency with the vaccine strategy. We've looked at a strategy of prioritizing depending on supplies. It's all contextual.

Dr. Pavia: Do we want to start rethinking our goals, maybe focusing less on minimizing disruption from a severe pandemic and more on preventing transmission?

Dr. Meltzer: People are mixing goals with risks and benefits from different perspectives. Perspective is key. For example, reducing transmission is a high-level goal, but parents get vaccines to protect their kids, and they don't care about transmission. With targeting, it's not just to get the highest returns, but people in the group need to know that. Production and delivery of vaccine is one strategic decision, and start time is a different one. Valuation can change rapidly. What is your goal? Communicate it simply, and don't move the goal posts.

Mr. Ferguson: Traditional risk groups may be less at risk. It's more difficult to understand. What we can say is that this pandemic is driven by children. We will be doing modeling in the next few weeks and hope to have more concrete findings on the benefit of targeting children first. We may be able to buy time by vaccinating children early. That's likely, and we can model it. But if we target adults first and let the epidemic hit kids, the pandemic will be over by the time we get to kids.

Dr. Quinlisk: We have primed the public to expect children to be hit because of all the media attention. People think kids will get sick, even if they are not the most seriously hit or the ones who are dying. Adults may have some immunity. Add in the start of school as a possible transmission risk. If we have kids transmitting the disease and critical workers line up for vaccine before them, that's a huge perception problem.

Dr. Pavia: We're back to our comfort zone, talking about risk groups. We need to focus on what the vaccine formulation will be, who will provide input, and what kind of information is needed to make decisions. We're probably going to see that children and young adults are amplifiers and also probably at highest risk. Does that help with the formulation question? If we target them, we need a vaccine as soon as possible, so should we use adjuvant or not? What data are needed? Who weighs in?

Dr. Quinlisk: If we target children, it makes sense to have a vaccine available before school starts, before that's the easiest opportunity for the disease to spread. Maybe it should be required for school entry.

Dr. Adirim: There are 75 million children in the U.S. If there's not enough vaccine for all, you may not get what you want. Do you prioritize among children?

CAPT Fiore: The allocation guidance we developed with the community holds up well, and it's partly based on public engagement efforts. Children and pregnant women are in tier 1. Health care workers are a big chunk of the first tier too, so I think that holds up also. So, the public has weighed in, even though it's not necessarily the same scenario.

Dr. Adirim: So could you use the guidance in vaccinating kids?

CAPT Fiore: Remember that in the South, school starts really early, like August. As to whether this conversation helps with decision-making, in terms of pregnant women and young kids, they may be less likely to accept a vaccine that doesn't look like the others.

Dr. Dowdle: I was thinking about a smaller target group for the first pass. Giving vaccine to healthcare providers who care for those at highest risk—that's very defensible. Then you expand targets as you see more availability of vaccine.

Dr. Pavia: If you focus on infants, toddlers, and those at high risk over 5 years old, you get lots of those at highest risk in a small group.

Dr. Neuzil: We need to focus on what we have to decide now—can there be vaccine ready for what we are seeing?—not the decision that people start a vaccination program. We need to make decisions that prepare us for action in September. This issue is important, but we don't know where we'll be in September.

Dr. Robinson: If we started making vaccine on August 15, we could have around 60 million doses by September 15, or, at best, 20% more. That would be an unadjuvanted, 15-mcg formula.

Dr. Pavia: So the data we have is that vaccines are being manufactured and the next question is the formulation—whether we use adjuvant or not. Do we have enough data to decide that?

Dr. Modlin: I think we should act on these assumptions today:

- We will see H1N1 infection this fall.
- We will likely have a narrow window in which to make decisions.
- We have good reasons to believe that illness could come early (based on biology and epidemiology).
- We expect high attack rates in certain age groups.
- The disease will be at least as virulent as seasonal influenza.
- We anticipate considerable morbidity and mortality.

To act on those assumptions, we need some simple information that could come from simple studies in small numbers of patients about safety and immunogenicity of an unadjuvanted dose, perhaps at 15 mcg. Parallel studies could be undertaken of adjuvanted vaccine, and I think the manufacturers are going that way. We need to know the effect of coadministration with seasonal vaccine, both simultaneous and sequential, because we're not sure what will be available when and we have concerns about a blunting effect. We need to know the effect on special populations. I think we agree children are the highest priority because they are at high risk and because of their role in transmitting disease in the community. We should think more about conducting limited studies in infants up to 6 months; that's difficult, but they may be at highest risk. If we

see hospitalization and death in this group and we have no EUA for a vaccine, that would be a mistake.

Dr. Pavia: I think Dr. Modlin has brought great clarity to the discussion. So, if we agree on those key assumptions, let's look at the clinical trials planned and the timelines. The questions are addressed, but the timelines may be slow. Someone needs to look at the timelines critically and figure out how to get that information much faster.

Dr. Modlin: We need to be prepared to pull the trigger based on limited data.

Dr. Meltzer: I think Dr. Neuzil put it well: What's the decision we need to make today? Dr. Modlin identified the tests we need to get the data for September or later. Have we decided how many doses to buy or when? If that's still open, it's relatively easy to solve the other questions. You have the stock, do you use it?

Dr. Pavia: I think the decision to purchase has been made.

Dr. Robinson: We are doing it in a stepwise approach. If we have the appropriations, we will buy more.

Dr. Pavia: So now we're talking about go or no-go. We can get data and decide later whether vaccine is licensed or used under an EUA. Is time more important than licensure status?

Stephen Cantrill, M.D.: We have not decided to go with a vaccine program, but we have to bring in State and local partners. They can't ramp up in two weeks. Our thinking process has to be shared. At the least we need to put them on notice about what could happen.

Dr. Gellin: Yes—they are not all present, but I think they know the calendar is coming. CDC is engaging with States, talking about the assumptions. They know they need to get contracts in place, etc. We are focusing on vaccine mostly, but we recognize the importance of implementation. What's the earliest we can protect people? The formulations for earliest, single-dose protection coincide with the easiest administration route.

Dr. Pavia: It sounds like we want the minimum data set to learn if one-dose antigen-only vaccine could be available.

[Unidentified]: Only if those data are available by August 15.

Dr. Innis: If you need vaccine in September, you must decide now on the basis of existing data. There's no way you'll have information in August so that Dr. Robinson can get product for distribution in September. Is that crazy? I don't think so. We have learned a lot about adjuvanted H5N1 vaccines; GSK has limited safety and immunogenicity data for children and the profile is similar to that in adults. We know you can give children as young as 3 years of age low doses of antigen and fractionated doses of adjuvant and they respond. You can create immunological memory, so that with a second dose or perhaps upon exposure to virus, they fire up an intense anamnestic response. To be prepared for September, you have to decide now, and you have to consider whether parents will want to have their children vaccinated with the products you make available. When Dr. Modlin tested vaccine in little kids in 1976, it didn't work well.

Dr. Modlin: I agree. I think we're being too timid about adjuvants. I'm reassured by the European data, although I'm concerned about the lack of data in young children. Our most important responsibility is providing a vaccine that is effective and safe. We need adjuvant early, so we need to study adjuvants in parallel in all age groups. That's a high priority.

Dr. Belshe: It's not unreasonable to pick a default dose—say, 15 mcg with no adjuvant—and use it for adults. For children, we could use live vaccine and we know the dose. For those not eligible, we could study alternatives. That approach gets you a long way. CDC showed that if you vaccinate 70% of kids with live attenuated vaccine, you reduce community burden by 99%. We should consider more creative use of two vaccine types.

Dr. Robinson: I agree with the use of the FluMist product, but the manufacturer has a small capacity. They are struggling to get enough. They expect to have about 6.4 million doses by the end of August. The limitations are not in the capacity to produce the bulk product but are inherent in the production of the delivery device.

Dr. Belshe: You could use live vaccine as drops. NIH has conducted several studies with drops.

Dr. Tsai: Novartis' adjuvant has been studied in children. One study in Finland included children 6–36 months, and it found that a single dose led to seroprotective responses to the H3N2 strain. Some adults responded similarly to adjuvanted H9N2 vaccine. There is evidence that in people naive to antigen, the adjuvant promotes good response after one dose.

Dr. Pavia: In closing, I want to summarize what I've heard today. We have some assumptions we're getting comfortable with:

- There will be significant disease this fall, mild to moderate at least.
- We are not locking into a vaccination program, but we need to work on our assumptions.
- Children are likely to be heavily affected and also an amplifier of disease.
- A late decision and late vaccine may be worse than no vaccine. Some options may lead to a safe vaccine at a point when it's useless. We must abandon that approach and move back to an early vaccine strategy.
- Some decisions will be made with limited data and some with no data.

**H1N1 COUNTERMEASURES STRATEGY AND DECISION MAKING FORUM
HOSTED BY THE PANDEMIC INFLUENZA WORKING GROUP
NATIONAL BIODEFENSE SCIENCE BOARD
June 18–19, 2009**

DETAILED REPORT

INTRODUCTION TO DAY TWO

Dr. Pavia explained that the second day would focus on defining the strategic goals for using diagnostics and antivirals against novel H1N1 influenza. He asked participants to think about strategies from the public health perspective and the clinician's perspective.

DIAGNOSTICS

Dr. Pavia said the quality of diagnostic data is key to all the scientific pillars of pandemic response: surveillance, diagnosis, mitigation, antivirals, vaccine, management of complications, and communication. Planners assumed the pandemic would begin outside the country, clinicians would do broad testing to identify its entrance into the United States, it would spread rapidly, and public health authorities would know who was affected. In reality, public health laboratories were swamped. The Centers for Disease Control and Prevention (CDC) bore most of the burden and did a good job getting diagnostic tools to labs, but local labs were not designed for such high throughput efforts and were hampered by low staffing and big financial cutbacks. The health care system has limited capacity in diagnostic testing for influenza: many institutions don't stock diagnostic tests, and many clinicians don't see the value in them. Novel H1N1 spread rapidly with the seasonal influenza virus.

The public health system must now monitor the severity of disease. Local resources have been taxed, and there is extensive confusion about diagnostic testing.

Diagnostics play a role in public health. They can detect novel viruses and distinguish them from seasonal and other respiratory disease—which the new diagnostics did reasonably well for H1N1. They can be used to obtain virus for characterization. The contribution of diagnostics to providing accurate surveillance data is arguable. In the case of H1N1, it has been difficult to define the overall burden of disease, and surrogates may be needed to improve accuracy. Diagnostics can also bolster surveillance that identifies who is at risk for severe disease or death.

H1N1 was initially detected by a device developed under a contract with CDC—a direct result of Federal investment—and confirmed using the FDA-cleared CDC five-target influenza assay. Two cases were identified as a result of an ongoing study with the Department of Defense's (DoD) Global Emerging Infections Surveillance and Response System. If we hadn't been looking for pandemic influenza, Dr. Pavia said, it would have taken additional weeks to identify H1N1.

While it has been difficult to determine the overall incidence of the disease, Dr. Pavia said we could certainly improve the accuracy of reporting of patients who were treated

for influenza-like illness (ILI), hospitalized, or died. CDC is working on methods to improve the accuracy of surveillance for these cases and for those who do not seek treatment. Determining the denominator—that is, all the people infected—is much more difficult. We want diagnostics that can turn ILI surveillance into combined ILI and biologic surveillance, said Dr. Pavia.

Data on the incidence of hospitalization by age and by State show that hospitalization is highest in the very young and declines by age. It's not clear why cumulative incidence varies by State. Dr. Pavia wondered if there is bias in the diagnoses. Expanding clinical diagnostic testing at sentinel sites can provide more complete and accurate data, but it's expensive and may not be rapid enough to affect management. Dr. Pavia said his hospital provides daily counts to unit managers and clinicians, which is informative but may not offer much value in making treatment decisions. Dr. Pavia pointed out that in his hospital system, the number of diagnostic tests performed peaked before the virus arrived and early in the outbreak the system had no antivirals to treat H1N1.

Point-of-care (POC) testing generally has good positive predictive value (PPV) and poor negative predictive value (NPV). Dr. Pavia asked whether it's more important to have a high PPV so you can isolate patients or a high NPV to spare the use of drugs. In most cases, a POC test must be CLIA-waived. Questions remain about whether the turnaround time of a POC test justifies the expense and affects patient management. In the long term, does POC testing affect the use of antivirals (for better or worse) or does it lead to overuse of antibiotics? Dr. Pavia described the case of a Salt Lake City woman who died of hemorrhagic pneumonia after contracting H1N1; she tested negative for H1N1 despite exposure.

Dr. Pavia challenged the participants to consider the ideal strategic goals for public health diagnostic testing, and to consider the goals for secondary and tertiary care centers. If diagnostics are important, should strategies encourage development and deployment, e.g., by this fall? How do we ensure diagnostic tests are accessible and affordable - and that they meet quality expectations?

Influenza Diagnostic Preparedness and Response—Dan Jernigan, M.D., M.P.H., National Center for Immunization and Respiratory Diseases, CDC

Dr. Jernigan described some lessons learned, noting that some of the pandemic influenza planning was right on, while some was far off the mark. Public health authorities expected that the virus would be H5N1 and that it would be severe, virulent, and easily transmitted. They anticipated high fatalities and believed the pandemic would originate in Southeast Asia and hit other countries first. Dr. Jernigan said the flexibility put in place for surveillance efforts and the broad views provided us with early information.

In 2007, CDC determined an internal strategy for diagnostic preparedness that included developing new diagnostic tests and improving diagnostic capacity. It awarded a 10-year contract to develop the Influenza Reagent Resource (IRR), which would facilitate distribution of reagent for manufacturers and others. The IRR is now fully functional and

provides virus to developers and researchers, PCR reagents for assays, WHO reference kits, proficiency testing, surge capacity, and an online storefront for access to reagents.

CDC anticipated there would be lots of test requests early, and better preparation was needed. Diagnostic testing needs differ before a pandemic, at the outset, and during the pandemic. Before a pandemic, the prevalence of disease is low, PPV of testing is low, and diagnostics have high sensitivity and specificity. The crisis level is low but vigilance is critical. The negative implications of false-positive tests are a factor.

As the virus is identified, the prevalence early on is still likely to be low and the virus may occur with seasonal influenza. The PPV of testing is still low and the test should distinguish seasonal from novel influenza. Early detection is critical and the crisis level is high. During a pandemic, prevalence is high, PPV is high (as determined by clinical and lab diagnosis), and the focus of testing is on clinical diagnosis and management. Broad surveillance is still needed.

Diagnostic development efforts can be categorized by short-, medium-, and long-term needs. In the short term, we need diagnostics that improve our capacity to detect an unusual virus. Public labs need sensitive, specific assays. We need to improve subtyping of known influenza strains and the flexibility to detect unsubtypable strains. In the medium term, POC tests for clinics and emergency departments (ED)s, and lab tests for hospitals are needed.

In the long term, we need an improved simple influenza test for CLIA-waived or non-medical settings, a more automated approach to testing, tests to detect antiviral resistance, and rapid antibody tests. Dr. Jernigan said development of diagnostic tests is not as far along as CDC would like.

CDC and FDA partnered with Applied Biosystems for a relatively cheap, fast trial that set the platform for rapid validation of sequences for new assays. The five-target assay has high sensitivity and high specificity. In April, 37 labs were qualified to use the diagnostic device, and now 95 labs are qualified. CDC plans to continue rolling out the device to support surge capacity.

The Mesoscale diagnostic POC test detects antigen by means of a nasal swab that goes into a cartridge that is inserted into a machine. It was being tested at a Naval Health Research Center (NHRC) in San Diego and picked up an unsubtypable strain. It works in about 15 minutes and allows the user to identify influenza A that has not been seen previously. Dr. Jernigan described the use of the Mesoscale device to detect the first case of the pandemic and subsequent confirmation by a Wisconsin State public health lab. The case was reported to WHO. Surveillance was enhanced in Southern California and then expanded nationally when H1N1 was identified in Mexico.

Detection was also enhanced by use of the PCR testing kits that were manufactured under an EUA and shipped within 2.5 weeks of identifying the virus. They were distributed to

95 laboratories in the United States, 15 DoD laboratories internationally, and 250 other laboratories internationally. More than 600 genes have been sequenced.

The enhanced virologic surveillance demonstrated that seasonal influenza continues to occur longer than public health officials thought. Dr. Jernigan pointed out that even poor surveillance efforts can provide useful data if they are consistent.

Initially, testing was recommended for any suspicion of H1N1, but the rapid increase in test requests and increased number of worried-well in clinics led to a change. Also, the number of people with mild disease who might not otherwise seek care confuses the situation. Later recommendations focused on those who were hospitalized or at high risk, so the surveillance results change. Furthermore, recommendations varied by jurisdiction, and there was uncertainty about the performance of rapid tests and direct fluorescent antibody (DFA) testing.

Dr. Jernigan said rapid tests are popular with doctors and they have a place, because positive results mean something. Recent data show rapid tests for seasonal influenza have an average sensitivity of 27% (ranging from 19% to 32%) and average specificity of 97% (range: 96–99%). A DoD Global Emerging Infections Surveillance and Response System (GEIS) site used nasal wash specimens from clinics and compared rapid lab tests with PCR; it found sensitivities ranging from 12% for novel H1N1 to 40% for influenza A, but 99% specificity for novel H1N1, influenza A, and influenza B. Dr. Jernigan said PCR seems to be emerging as the de facto standard.

Dr. Jernigan reiterated the CDC's projections for the course of the disease. PCR kits continue to be distributed globally, which is expensive. The so-called swine primers have been submitted for FDA approval so they can become part of the assay. The PCR protocol has been published, which will allow people to make their own assays.

Dr. Jernigan outlined some of the successes of the planning and response, including the insistence on focusing more broadly than H5N1 for diagnostic tests and the investment in public health labs' diagnostic and development capacity (although more is still needed).

The challenges include the following:

- Pandemic H1N1 subtyping capability is largely limited to public health laboratories.
- Many laboratories are unable to handle a surge.
- PCR reagents were in short supply early in the outbreak.
- Clinicians do not have accessible tests for diagnosing pandemic H1N1.
- Increased number of laboratory-developed tests and new technologies may assist diagnosis, but are difficult to validate.
- Rapid antigen detection tests remain with some uncertainty in performance.
- Engagement of CDC with diagnostic companies for accelerated assay development could be improved.
- Upcoming season may have H1, pandemic H1, H3, and B at once, making for a

complex diagnostic and treatment landscape. (In addition, seasonal influenza may be resistant to oseltamivir.)

- Antiviral resistance testing and serology are not easy to get.

Dr. Jernigan listed the following areas for focus for the CDC:

- Maintain IRR and support for PCR testing at qualified U.S. laboratories and international laboratories.
- Enhance virologic surveillance in Southern Hemisphere and Tropics to monitor genetic, antigenic, and susceptibility changes.
- Improve surge capacity.
- Facilitate development and field evaluation of tests for improving clinician access to pandemic H1N1 diagnostics.
- Collaborate with partners to revise clinician testing guidance.

FDA Perspective: Diagnostics for Influenza Pandemics—Sally Hojvat, Ph.D., FDA

Dr. Hojvat described FDA's mission and goals for pandemic influenza preparedness. She said the streamlined effort to get new diagnostics out to public health labs illustrated the benefits of collaborations with CDC and NIH over the years.

To facilitate product development that would address pandemic needs, FDA is active with commercial entities in trying to move forward with diagnostic tests useful to public health labs and in encouraging those who already have testing platforms in labs to work on an H1N1. FDA seeks to anticipate potential shortages. Dr. Hojvat pointed out that when the H1N1 outbreak occurred, rapid tests were in short supply and FDA worked with U.S. port authorities to get large quantities from overseas producers shipped as quickly as possible.

FDA ensures product safety and efficacy by making sure that performance is established in a consistent manner, but validation of the many available tests remains an open question. FDA does not monitor manufacturing processes until products are cleared. Some cleared diagnostic tests have poor performance but good manufacturing processes (GMP). FDA does monitor adverse events (AEs) for cleared products.

Dr. Hojvat described the various pathways to clearance for an in vitro diagnostic device for influenza. Because it would be a Class-I device, manufacturers would not have to conduct a huge clinical trial but would have to demonstrate the product is safe, effective, and substantially equivalent to existing devices. Unfortunately, sensitivity has never been very good with rapid tests, so the bar for demonstrating equivalence is low. Dr. Hojvat said FDA is using its RNA test to try to set a baseline of about 90% sensitivity for rapid tests. For H1N1, FDA has been using EUA as a pathway to clearance.

Dr. Hojvat described the use of EUA, emphasizing that it is not a substitute for approval, license, or clearance. It requires no informed consent and no IRB approval, and manufacturers don't have to demonstrate GMP or register the product. Every EUA requires that the HHS Secretary has declared an emergency; after that, FDA will consider

each product on a case-by-case basis and may establish conditions to restrict use of the product. FDA consults with NIH and CDC before approval of an EUA. Dr. Hojvat summarized the four statutory criteria for consideration of an EUA.

A request for an EUA can come from any source, and FDA encourages submitting data for pre-EUA consideration when feasible. With data in hand, FDA would be able to move more quickly once an emergency is declared. The EUA expires when the emergency ends, and the product can no longer be used unless it's licensed. FDA encourages manufacturers and other applicants to be prepared to apply for licensure or consider a parallel clearance process for its EUA submission.

Requests for EUAs are prioritized on the basis of several factors, such as the following:

- Seriousness of the clinical condition
- Incidence of the clinical condition
- Effect use of the product may have on ensuring national security
- Availability of product in government stockpiles
- Feasibility of use of product in a large population
- Request of another government agency
- Availability of a similar product
- Adequacy of supporting non-clinical and clinical information
- Quantity of product available

Dr. Hojvat described the information that FDA requests for an EUA; she stressed that if a test has been validated in a lab, all of the requested information should be available.

FDA has approved only two EUAs for H1N1 to date: the CDC PCR kits and the five-target panel. It is currently reviewing about six formal requests and multiple unofficial inquiries, all involving nucleic acid-based diagnostics. None of the requests include true POC rapid diagnostic devices. For EUA denials, FDA is working with the submitting party on products that might be useful in the fall and cleared either through an EUA or the 510k clearance process. EUA approval requires input from NIH and CDC.

FDA's short- and long-term strategy for diagnostics involves the following:

- Continuing to work closely with CDC, NIH, and HHS on preparation/testing needs strategy for upcoming influenza season.
- Making information required for EUA authorization widely available and establishing a standard template for validation of all H1N1 diagnostics.
- Rapidly granting EUA authorization for diagnostics that support public health needs. Prioritizing review of existing/new diagnostics if virus reassortment occurs.
- Encouraging submission of 510(k)s as H1N1 becomes a "seasonal H1N1."

Influenza Diagnostics: Algorithm & Identification Capabilities within DoD—COL Dan Harms, Center for Clinical Laboratory Medicine

COL Harms noted that the military health system has the same goals for surveillance and diagnostic testing as CDC does for the general public: detect introduction of a novel influenza into the United States or overseas DoD locations and monitor changes in the pandemic virus, including development of antiviral resistance. Laboratory planning should take into account that influenza, other than H1 and H3 subtypes, have the potential to become pandemic and that shortages of supplies and staff may occur. COL Harms noted that supply shortages did occur with the initial outbreak.

The military health system is following current CDC guidance for case definitions and testing guidance. As demonstrated at the initial outbreak, testing everyone can overwhelm State public health labs and DoD labs. COL Harms stated it would be beneficial if the CDC recommendations, on who to test once the presence of novel influenza virus infections in a geographic region, were firmly established and more consistently followed/implemented (would tend to alleviate laboratory overload caused by a desire to test/diagnose every case).

The military system emphasizes the use of rapid diagnostic tests. The tests should be capable of differentiating type A and B, and should support the local command's pandemic influenza response plan. Hospitals must amend or establish Clinical Laboratory Improvement Program (CLIP) laboratory certificates as required (CLIP is DoD's CLIA-equivalent program). Medical staff should be aware of the test's sensitivity, specificity, PPV, and NPV.

COL Harms explained the flow of testing for suspected cases of H1N1. Generally, for a positive rapid test result—or a negative test result in a high-risk person for whom there is a high index of clinical suspicion that a H1N1 infection is present—a PCR test is performed. Alternatively, within the Army's Medical Command, a specimen from a patient with a negative rapid test result for whom there is a high index of clinical suspicion that a H1N1 infection is present is first referred for viral culture. Specimens from Flu A positive cultures are subsequently referred for a PCR test. Positive PCR results trigger consultation with the CDC.

The military health system was more prepared to diagnose H5N1 (due to DoD laboratory participation in the CDC's Laboratory Response Network), not H1N1, and only had two sites capable of performing the CDC five-target influenza assay when the H1N1 outbreak occurred (i.e., the U.S. Air Force School of Aerospace Medicine (USAFSAM) in San Antonio, TX, and the Naval Health Research Center (NHRC) in San Diego, CA). Army medical centers, in general, had no influenza subtyping diagnostics at the time of the H1N1 outbreak. Specimens for H1N1 RT-PCR testing are currently sent to the nearest reference laboratory, which may be either a State public health lab or a DoD lab, and specimen referral follows the reference lab's guidance.

DoD has routine influenza surveillance capability through USAFSAM and NHRC; the Air Force Surgeon General oversees DoD's formal influenza surveillance program.

USAFSAM collects specimens from sentinel sites at 43 military installations and 9 allied countries. Specimens from each site are analyzed and subtyped weekly, and some are sent to CDC for further analysis. NHRC conducts population-based febrile respiratory illness surveillance at eight training sites and 20 shipboard sites and along the Mexican border. USAFSAM and NHRC were instrumental in identifying the first U.S. cases of H1N1.

USAFSAM was able to purchase additional PCR platforms quickly in early May, which doubled its testing capacity. The Army Medical Command (MEDCOM) had a stockpile of rapid antigen test kits that were stored at three sites that were distributed in response to the H1N1 outbreak. MEDCOM also had previously sent centrally procured nucleic acid extraction kits and PCR enzymes directly to medical center labs. DoD is now seeking to replenish its rapid antigen test diagnostics resources and is looking at whether to address shortages with viral transport media and viral culture cells.

By the end of June, the Army's Medical Command is expected to award a contract to increase PCR diagnostics instruments. A PCR instrument was also moved to the Walter Reed Army Institute of Research's CLIP-registered lab. The Navy also bought more PCR diagnostics instruments, which will be located in deployable units.

COL Harms said that, ideally, public health and DoD medical center laboratories would have high throughput PCR testing capability for typing/subtyping influenza viruses, and all DoD hospitals have a pandemic-influenza-specific POC rapid antigen test that is sufficiently sensitive. Once the presence of novel influenza virus infections within a population/community is firmly established, testing emphasis should shift to detection of novel influenza virus infections in new communities/geographic locations.

Discussion²

Dr. Pavia: It sounds like DoD tripled its throughput capacity. The strategy seems to be limited, though, so are you going to revise your strategy with the higher capacity? What would you do with increased capacity?

COL Harms: We see that State public health labs will be clogged with requests. Having our own system protects us. But how DoD can assist State public health labs is currently under discussion. Many DoD labs are members of the CDC's Laboratory Response Network, and that includes assisting other member laboratories during a surge. The H5 assay went out under the Laboratory Response Network (LRN), so all those labs had the H5 capability. The CDC five-target assay posed a problem: Texas asked for assistance from USAFSAM, but it was not an LRN assay, so that impeded providing the requested assistance. When DoD labs applied for admission to the LRN, whether we could provide assistance without a Stafford Act declaration of emergency or Economy Act request was evidently not addressed. We're looking at the rules and what we can do, particularly whether there are workarounds to provide surge testing assistance to civilian/non-DoD laboratories without reimbursement.

² This and subsequent discussions paraphrase the questions and comments of the participants. This document does not represent a verbatim transcript.

Dr. Jernigan: Many public health labs have multiple machines. Applied Biosystems loans machines for limited times. But we're limited in how we can use them. It's not an influenza-only platform, and we want to be able to use them. Getting more machines requires more qualifications and also more proven protocols, which we're working on. We also want to improve throughput with the existing platform. With a new platform, we can't distribute reagents. There are limitations of FDA clearance; you could apply for an EUA, but then you have time limits, data issues, etc.

Dr. Pavia: I read the PCR protocol. It lists five platforms for which performance has been explored, and some of those have high throughput.

COL Harms: [There's not enough time during an EUA.] – incomplete answer

Dr. Hojvat: We're waiting for CDC data on lifecycle, but we've gone to commercial companies to get their reagents for H1N1. That would increase clinical labs' [capacity]. Another opportunity is the reference labs. We're working with Quest on an EUA, and with some others as well, to persuade them that EUA submission is not too burdensome, and what they've done already in house should be 90% of the information needed to validate.

Dr. Pavia: What would clinicians do?

Dr. Cantrill: We have a huge problem with the number of worried well coming to the ED. Before I test, I ask how the result will affect my work. If it won't, is there a public health or research reason to test? If the latter is true (research), the patient should not pay for it. If it changes what I do, what is the prevalence of disease and the sensitivity and specificity of the test? Rapid influenza tests are worse than a coin flip. Sometimes the information affects what I do - e.g., use of antivirals or need to test those hospitalized for ILI per my institution protocols. All the others are educated and sent home; I'm not going further with diagnostic tests.

We at Denver Health provided more than \$200 million in uncompensated care last year. Consider the overall costs to the health care system. Tests can be helpful in making decisions about antivirals, but is a rapid test helpful? Or do I really need a more accurate test?

Dr. Pavia: What's on CDC's wish list for surveillance and diagnosis?

CAPT Fiore: We always want more information. We participate in monitoring trends in virus resistance and characterizing viruses. We get information from established surveillance systems, but sometimes there are unusual infections and clusters, and we want to get diagnostic specimens and don't want the lack of availability or interest in testing to keep us from getting specimens. There are limits at the local level, at academic centers - especially during the peak when most of the cases are novel influenza. It's still useful for them to do a fair amount of diagnostic testing. I think they like having rapid diagnostics for planning around isolation and further testing.

Dr. Jernigan: For bacterial infections, you test and you get the type, the antimicrobial susceptibility, and that information is useful for management. You can send it up the chain, and that's useful. But influenza is the opposite. Detailed information is limited, and there's no commercial utility or market incentive to make the tests. If knowing the subtype affects management, then manufacturers may have some market incentive to make the tests. Short of that, we rely on public health and other subsidized surveillance to monitor what's happening.

Dr. Pavia: So should a strategic goal be to make antiviral resistance testing more available?

Dr. Jernigan: Yes. Now you need a test to distinguish, to look for the sequence of resistance markers, but you will miss some, and only functional assays detect new resistance.

Dr. Schonberger: With regard to a wish list, we could use more applicable population denominators or appropriate estimates of the proportion of persons vaccinated ideally by type of vaccine, calendar time period, and age group in the defined populations under surveillance for serious influenza disease as well as for serious influenza vaccine complications. For hospital-based surveillance centers, (e.g. HMOs) I could see the usefulness of such centers helping to estimate vaccine efficacy in their served populations - but to do this there needs to be a mechanism to determine whether positives, that is, cases of disease or adverse vaccine reactions, are part of the population for which denominators are available. We will need to try to arrange for reporting of each case patient's vaccine status (including type of vaccine and date received).

Although the military did not have access to such information back in 1976, perhaps the military system this fall could arrange to collect vaccination status information on individual cases of hospitalized patients with influenza disease, and/or adverse vaccine reactions, plus monitor the proportion of defined groups in the military that are vaccinated over time; such information could be of much potential benefit.

I have a question for FDA: When a company sells rapid diagnostic tests, and they call it FDA-approved, do they have to tell customers about the sensitivity and specificity of the tests, and include warnings about the potential for misinterpreting negative results given the low sensitivities of the tests?

Dr. Hojvat: The package insert with the kit has the data they gave us. That's data from a fixed point. CDC is looking at whether the virus has changed so much that the tests cleared years ago don't pick it up as well. We do say if the results are negative, you're advise is to culture; but I'm not sure whether they do or not.

Dr. Pavia: The hurdles are higher for a new entrant; PCR likely sets the bar higher.

COL Harms: Negative results are referred for further initial testing. Even with CLIA-waived tests, you follow the manufacturer's instructions. If the manufacturer says refer for further testing, you should do it.

Dr. Pavia: Despite the ACIP recommendation, the clinical community doesn't do that.

Dr. Cantrill: The data on the insert does not go to clinicians. Labs may try to get clinicians to do it, but clinicians are clueless.

Dr. Jernigan: We talked about IRR having a standard panel that would allow assessment of rapid tests once a season or sending [panels] to manufacturers to identify what's circulating.

We support eight or nine population-based surveillance efforts. One has lab-based testing and an active population of multimillions - we can look at vaccine status, age-specific hospitalization rates, etc., in them. There are also selected clinical sites where we can get influenza information. We're also starting weekly phone surveillance

(BRFSS) to get population data, and we have ILINet. The systems we had in place turned out to be pretty good, more robust than we anticipated.

Dr. Meltzer: The model that tried to estimate how many samples could be delivered to public health labs in the middle of an epidemic, also tried to estimate the capacity of labs to deal with the epidemic, (one was a influenza lab) and the lab capacity for response to bioterrorism events through the LRN network. The results showed labs had limited surge capacity, which is no surprise. Having more machines helps, but the biggest limitation is personnel and sometimes just the physical space. With limited capacity, you need to triage, plan up front, and stick to it. Analyzing 600 specimens per day is not enough to meet the need, and that's optimistic, because it pays no attention to the degradation of capacity during the pandemic; like school closings, workers going home, staff exhausted. You have to assume all the labs will be working at full capacity, and there will be no one to borrow from.

Here are some of the things we've learned: First, you should determine your total capacity and divide that by the number of tests per day per shift. Patient management is not a priority - that's separate. Public health testing and clinical management are separate. And you need to manage that strictly or the labs will be overwhelmed, and then they can't fulfill their essential public service.

Among the main goals for public health labs is to determine the burden of disease - the attack rate. CDC wants labs to report illness per day, each week, but that's not going to happen. The best solution would be well-designed sampling that gives an accurate reading, and expect that there will be large confidence intervals.

Hospitalization data are useless for planning, because the y-axis is missing data. With antiviral testing, we want to know, as the pandemic progresses, is the treatment working? That's essential information - virologic surveillance and antigenic transformation. Those are the four key issues. You can allow for flexibility, but those are the issues for both pandemic influenza and bioterrorism. It requires a change in culture, and I think people are starting to realize that with our first-wave outbreak.

In your communication to lab directors and to the people sending them samples, prioritization must be clear. Any expectations of markedly increasing capacity are not realistic. Then there's the international side; CDC will be overwhelmed if international sites need help.

Dr. Neuzil: I can think of at least one very good public health reason for individual clinical testing: to guide the use of antivirals or other scarce resources. Was anything learned about rapid tests from this outbreak? In regular seasonal influenza, I think the tests are better in children and when used earlier. Is it different for H1N1?

Dr. Jernigan: My data come from lots of adults. I think you may see better performance in kids, with higher viral loads, and when you test earlier. There are a number of variables that determine performance. It's hard to do any evaluation of comparability. The value of a positive result is clear - you can use that to support

decision-making about isolation or treatment. But a negative result - you can't do anything with that information. If you look at multiple viruses from different geographic samplings, you see that performance differs in the level of detection and sensitivity. Maybe we can identify bad performance, but we don't have enough information to say how to use rapid tests in the best way.

Dr. Neuzil: So for pediatric populations, we don't have the data we want.

Dr. Jernigan: Some data will be published soon.

CAPT Fiore: Rapid tests are usually performed a few days into the illness. We usually get tests about 5 days in. It's important to learn more.

William Sheridan, M.B. B.S.: With a sensitivity of 12%, the value of a negative result is negative - people might die. Should those tests be retired? The ED doctor's treatment is not guided by that. If the patient is sick, you treat him. Because influenza is evolving, and you add antigens to the vaccine yearly, shouldn't the diagnostic platform recognize those? Should development and approval mechanisms, to get diagnostic tests out, look more like the annual event?

Dr. Cantrill: That's why many clinicians don't have faith in rapid tests and evaluate the whole patient instead. If they're sick enough to come to the hospital and may have influenza, they may get antivirals regardless of the test results. Consider that case we heard about from Salt Lake City - there were issues beyond testing, there were many red flags.

Dr. Pavia: In that case, people ignored the clinical presentation because of a misunderstanding about a test that has poor performance.

Dr. Hojvat: For rapid tests, manufacturers are not required to follow-up on changes in the virus, but for nucleic acid tests we did add the requirement to monitor and adjust for seasonal influenza. We put the onus on manufacturers and FDA will follow-up.

Dr. Jernigan: The clinical use of the test plays a role. Sensitivity is affected by how the clinician uses the test.

Dr. Pavia: That might be used in addressing scarcity.

David Lakey, M.D.: We need to preserve the capacity to answer public health questions. In large States, we needed to identify pockets and move capacity around. We surged 10-fold, from 20 tests per day to now 400 per day. We added equipment, but not enough to meet demand. I got in one day what we usually get in one season - 1,000 samples. The challenge is case definition. Early on, you need a broad net, but in this situation, the case definition was so broad that too many met it. So we sent information to ED doctors, and once we defined the case more narrowly, that took some pressure off. It's important to identify whom to test. For example, where there were school closures, if they had one case, every school in the system sent us samples to test. Everyone who had traveled - their employers wanted them tested.

Surging is not just adding machines but also adding people, and not just in the lab, but in data entry, administration, etc. There's no way my public health lab can be the clinical diagnostic lab for the whole State. We have focused on answering public health questions, and we're pushing back on routine ILI, allowing some front-end screening before we get samples. We're helping others ramp up their capacity. When I saw how we would fall behind, we de-linked treatment and testing, because there was no way we could deal with the backlog.

CAPT Miller: Until recently, FDA had approved only two EUAs, but we've approved five more in the past 2 months. The Center for Biologics Evaluation and Research is presently involved in discussions concerning a possible EUA for a novel H1N1 vaccine. For devices, there were two approvals for in-vitro diagnostic tests and one for N-95 face masks. And there are two by the Center for Drug Evaluation and Research that are related to antiviral medications. There's nothing in our regulations, nothing formal, about a pre-EUA process, but we're trying to do as much groundwork as possible prior to an actual emergency.

Each of the FDA Centers differs somewhat in their approach, but the idea behind a "pre-EUA" is that it allows people to come to us with products before an emergency and provide information, so we could act more quickly if an emergency were declared. Again, there is no actual pre-EUA entity, it's just an FDA process to get pre-positioned for an actual emergency.

Mr. Gallagher: In Canada, and probably in other countries, the media and the politicians like numbers. We are asked for the latest numbers. It's difficult to curtail testing, even if the numbers have no meaning. That colors the public health effort.

Dr. Gellin: Is there guidance on antiviral treatment for people with diagnosed influenza - H1N1 and seasonal?

CAPT Fiore: Seasonal H1 may be back, and there's resistance to one antiviral. Last year, we had an alternative protocol that we suggested people use, and we'll probably suggest something similar. We're talking with ACIP. Combination therapy has problems, and there are not much data to support it. There may be some more guidance. The Southern Hemisphere might tell us something - e.g., if seasonal influenza fades, maybe the resistance problem goes away. It's a mess. There are limited drugs available, although maybe there are some in the pipeline available under EUA.

Dr. Gellin: There's no way to sort out the diagnosis part in the clinical setting?

Dr. Jernigan: We're not comfortable with the rapid test to guide management. PCR is better but not fast enough. Currently, States are limiting PCR testing to the severely ill.

Dr. Pavia: It may be better to know sooner what's circulating, but for clinicians, understanding what's in the community was paralyzing.

Dr. Grabenstein: The assays for H1N1 - are literally assays for H and N? Or just N? If the virus reassorted, who would find it?

Dr. Jernigan: The assay is for the H component; for N, if it's unsubtypeable using the H part, it gets further characterized. But without changes in hemagglutinin, it's unlikely to get tested fully. I think we would pick it up, but PCR is not intended as a neuraminidase surveillance system.

Dr. Huebener: Do we have a mechanism for knowing what our baseline is?

Dr. Jernigan: You always know what's submitted and the percent positive. Really, if there are biases in systems but they maintain, then trends can be monitored over time. Baseline is important. We have sampling methodologies to control for variability. You know who the submitters are and they stay the same, so there's some consistency. Our surveillance did well for ILI.

Dr. Elizabeth Higgs: In terms of diagnosis, the public health and clinical sides are in separate silos. The bridge is patient-oriented clinical research, which is missing. I was in Mexico after the peak, and 40% of ILI were novel H1N1 cases, so 60% weren't, and they were wasting antivirals by treating on presentation. Our diagnostics are limited both in sensitivity and specificity which impairs judicious and effective use of our strategic national stockpile (SNS). However, our influenza diagnostics can be improved.

In the Southeast Asia Infectious Disease Clinical Research Network, we built the capacity to diagnose and subtype influenza viruses within 24 hours. CDC and BARDA are evaluating a POC test influenza diagnostic and this effort should be accelerated. We should think beyond the public health response. Public health doesn't think about patient-oriented research. In Mexico, they had two runs of PCR testing daily at one hospital with the ability to run 600 tests daily. This capacity could be doubled. We could do that here. We need to upgrade the labs so that most major hospitals should have capacity using well accepted RT-PCR testing to diagnose novel H1N1 quickly.

With appropriate diagnosis and known antiviral susceptibility antiviral could be optimized both in terms of clinical use and stockpile management. With HIV a clinician would not pick a random antiviral. As more drugs are developed for influenza, we need to use them appropriately. I think CDC did the best they could with the influenza therapeutic recommendations last seasonal influenza season, but there were those who could not take inhaled Zanamivir essentially on solo M2 inhibitors for resistant seasonal H1N1, which has known 40% potential resistance development.

Dr. Pavia: Summarizing the challenges with diagnostics:

- Clearly, public health labs can't meet the clinical needs.
 - It's hard to manage the surge for public health demands, and we need to better understand the role of public health labs.
 - Also, there are barriers to creative solutions, such as the ability to rapidly link labs with increased capacity and move tests around. That should happen, and we could work on that.
- There's a need for better clinical testing to manage the situation with complex types of influenza, other viruses, and emerging resistance.
- So, there's a public health imperative to improve clinical testing and clinical capacity to make response more timely and effective.

There were some other important points that we'll capture and circulate.

ANTIVIRALS

Dr. Pavia pointed out that a number of issues must be considered with use of antivirals, the other important countermeasure: the amount available in the SNS, when to initiate use, the potential for drug resistance, and how to use them in patients with severe disease.

Influenza Antivirals for Pandemic H1N1: Medical Needs and Agents in Development—Frederick G. Hayden, M.D., University of Virginia

Dr. Hayden said WHO would be meeting next week to revisit their recommendations on H1N1. Current antivirals target two sites in the replication cycle: adamantines and neuraminidase. H1N1 is resistance-encoded, and there is only one approved class of drug to treat it. Other agents are in development, including host-directed agents.

Current antiviral agents are limited by various factors. For example, H3N2 resistance to amantadine also occurs with H1N1. Most human H1N1 is resistant to oseltamivir; in some H1N1 isolates, as well as H5N1, dual M2 and NAI resistance has been seen. Antivirals show limited efficacy against H5N1. The lack of approved parenteral agents raises questions, e.g., what is the oral bioavailability of oseltamivir in critically ill patients? Dr. Hayden said it may be better than we thought, but the numbers are small. With inhaled drugs, there are concerns about tolerability in seriously ill patients. There are also concerns about delivery of the drug to sites of replication in those with other respiratory disease. As a result of these limitations, very few treatment options exist for seriously ill patients.

Although the experiences from 1968 and 1977 are not directly applicable to the current H1N1 event, studies showed that antivirals could prevent about 60% of clinical disease, and were less protective against seroconversion. More recent studies of seasonal influenza showed that neuraminidase inhibitors (NAIs) were up to 90% effective for post-exposure prophylaxis in households; although protection against seroconversion was lower.

These data inform modeling and policy decisions on post-exposure prophylaxis to mitigate the impact of seasonal and pandemic influenza. As Dr. Ferguson noted, a lot of secondary transmission occurs early in households. Studies of post-exposure prophylaxis to prevent household transmission suggest that treatment given within 3 days of exposure may be effective in preventing the spread of disease.

A study of oseltamivir for post-exposure prophylaxis found it more effective in adults and adolescents than young children (ages 1–5 years). One fifth of young children who received oseltamivir as post-exposure prophylaxis still experienced influenza. Dr. Hayden concluded that socially targeted post-exposure prophylaxis with NAIs is effective and well tolerated in household for seasonal influenza, but secondary transmission occurs early, so quick intervention is needed. More data on young kids is needed; as effectiveness may be lower in that population. Also, inhaled zanamivir via the current device is not applicable for those under 5 years of age.

Older (1981) data comparing amantadine, rimantadine, and placebo for treatment of H1N1 virus in young adults showed that symptoms cleared within 48 hours after therapy. Dr. Hayden said the studies support the concept that antiviral intervention in naive populations helps when the virus is susceptible. With uncomplicated illness, the shedding pattern is truncated even without treatment. A 2003 study showed that oseltamivir reduced illness and complications (primarily bronchitis and pneumonia), and decreased hospitalization.

There are few data on whether treating hospitalized patients improves outcomes. In a nonrandomized study of adults, those who received oseltamivir had significantly lower 15-day mortality rates than those who received no therapy. The same study suggested that even delayed therapy for seasonal influenza in hospitalized patients is beneficial, said Dr. Hayden.

The best test to date involved H5N1 disease and was reported in 2008. It showed that without oseltamivir, only about one in 10 patients with H5N1 survived, but that number improved for both clades to 50% with oseltamivir. The findings are clinically important but incomplete. Another study showed a strong effect of time to transmission; many people come in for treatment at day 5 or 6, when viral pneumonia and acute respiratory distress syndrome may already be rapidly progressing.

Dr. Hayden said data from pediatric populations may be useful surrogates for novel virus. Children with influenza have a high upper respiratory tract viral load. The effect of treatment is not rapid.

Dr. Hayden summarized some data in press on reduction in viral RNA levels in relation to time of treatment initiation. The study involved hospitalized adult patients in Hong Kong who received: no treatment, oseltamivir within 1 day of symptoms, or oseltamivir within 2–3 days. Major co-morbidity and systemic corticosteroids slowed the decline of the viral load. Early antiviral treatment (within 1–3 days of symptoms) was associated with a decline in viral load; and the data correlated with earlier published data that antiviral treatment reduces the length of stay in hospitalized patients.

With H5N1, the success of oseltamivir treatment depends on the clade. A study of patients with fatal and nonfatal cases found that high viral load correlates with more severe disease. In this study, both groups of patients showed a relatively slow decline in viral load. Dr. Hayden said there is room for improvement in antiviral effects.

Most people recover without treatment. If antivirals are used for treatment, NAIs are the agent of choice because of resistance. The resistance of coexisting seasonal influenza should be taken into account. Oseltamivir is appropriate for pandemic H1N1, especially in cases of serious illness, pneumonia, or underlying conditions (e.g., pregnancy, asthma, obesity). In terms of safety, an argument can be made for using higher doses in more seriously ill patients. There are no clear data to support a clinical difference, but the question is under study in Southeast Asia for H5N1. It is reasonable to use inhaled zanamivir for mild to moderate disease, but it has not been studied in those with serious

illness or pneumonia. Dr. Hayden presented U.S. and global data on resistance of H1N1, H3N2, and influenza B to oseltamivir, zanamivir, and adamantanes, noting that oseltamivir resistance to H1N1 varied by country from zero to 100%.

Dr. Hayden described the differences in amino acid changes between H1N1 oseltamivir-resistant strains. He said it is unclear whether H1N1 can mutate to develop resistance to oseltamivir and transmit readily. Unpublished data suggest that if a resistant mutation is introduced, neuraminidase enzymes can still work pretty well, which is concerning, said Dr. Hayden.

In human H1N1, drugs interact in different ways with the site, yielding different susceptibility in resistance profiles. Some neuraminidase mutations are highly resistant to oseltamivir but susceptible to zanamivir. Dr. Hayden said peramivir is a concern because it may contribute to loss of clinical efficacy.

Dr. Hayden outlined what is still needed for antivirals from a medical perspective:

- More robust and rapid antiviral effects, which will likely translate to better clinical efficacy.
- Demonstrated safety and efficacy in high-risk populations, e.g., infants less than 1 year old, and people who are hospitalized or immunocompromised.
- A reliable form for administration to seriously ill patients, especially for those who can't take medicine orally.
- A method for managing antiviral resistance, which is a continued problem.
- Combination therapies.
- Simplified dosing for outpatients, e.g., a single dose or once-weekly prophylaxis.

A study of combination therapy in mice demonstrated the following important points:

- If the virus is M2-inhibitor-susceptible, then synergistic interactions occur in vitro and survival is increased in mice when amantadine treatment is combined with oseltamivir or ribavirin.
- If the virus is M2-inhibitor-resistant, there is no benefit to combining amantadine treatment with oseltamivir or ribavirin.
- Oseltamivir and ribavirin show primarily additive interactions in-vitro and in murine model.

One realistic option worth considering is oseltamivir plus ribavirin. A three-dimensional model shows an additive interaction and some areas of enhancement that might indicate synergy. A study of this combination in H5N1 showed evidence of differences in dose-response and an enhanced antiviral effect in lungs, and probably in other sites.

Another approach may be the use of immune modulators. There are some good data on pathogen-based selection. The combination of antiviral and celecoxib for H5N1 improved survival in mice compared with use of antiviral alone.

Dr. Hayden listed a number of anti-influenza agents that are being investigated. A March 2009 meeting of NIAID, BARDA, and others focused on new agents (the meeting summary is available), including host-directed approaches. There is potential for development of topical single-dose CS8958; it is in phase-2 trials, but no data have yet been reported. One new agent by Toyama, Favipiravir (T-705), targets polymerase. It has better in-vitro activity than ribavirin. Phase-2 trials of efficacy have been completed in Japan. The drug appears to have oral bioavailability, and Dr. Hayden called it interesting. The other drugs are all in phase-1 trials, and delivery issues are being addressed.

Of the new agents, several have antibodies that target group-1 hemagglutinins. There is potential inhibition by monoclonals that direct to specific areas. Model data show dose-related improvements in survival and efficacy.

Conducting clinical studies in hospitalized patients is very hard, Dr. Hayden noted. More effective diagnostic tools are needed. Hospitalized patients are a heterogeneous group; they have co-morbidities, co-infections, concomitant therapy, variable disease courses and pathogenesis, and many have exacerbation of underlying disease. Researchers face recruitment and trial design hurdles, e.g., getting informed consent from impaired patients, determining inclusion and exclusion criteria to get generalized data, and incorporating changing standards of care. According to the FDA draft document out for comment, investigators need to closely consider the endpoints of their studies. Also, there is a lack of experienced investigators and staff.

A study in hospitalized patients is trying to address the issue of endpoints. It is a randomized, controlled trial comparing oseltamivir and peramivir, which measures time to clinical stability and time to return to daily activity.

Dr. Hayden summarized the issues of concern for antiviral treatment:

- Medical need exists for parenteral agents for seriously ill patients, novel agents with new antiviral spectra, and new agents with less frequent dosing requirements.
- SNS diversification is warranted.
- Realistic development pathways are needed for new agents, especially combination therapy for hospitalized patients. Development would be enhanced by use of endpoints that are antiviral-oriented and a domestic hospital-based network for severe acute respiratory illness (SARI) studies.

Dr. Pavia commented that progress on new antiviral agents has been distressingly slow despite all the attention to pandemic influenza in the past 5 years.

GSK Zanamivir Strategy and Response to Novel H1N1— Judith Ng-Cashin, M.D.

Dr. Ng-Cashin said GSK recognizes the need for antivirals and is working to deploy its existing stockpile supplies, and rapidly maximize its production of its approved product, Relenza Rotadisk/Diskhaler. GSK is also investing in an alternative strategy to increase

global availability of inhaled zanamivir. The company is open to new approaches to clinical trial designs for IV zanamivir, which currently is not in active development.

Before the current outbreak, GSK's production capacity for the Rotadisk/Diskhaler was 1 million treatment courses per year. Since the outbreak, GSK reactivated production lines in North Carolina, France, and Australia. (Products from the Australian site are not approved for U.S. distribution.) Now, GSK can produce 49 million treatment courses this year, with a goal of 90 million per year. All of the inhaled products GSK can produce for this year has already been sold and accounted for. Therefore, production capacity is not adequate for global demand if a second wave of H1N1 arises, that is also oseltamivir-resistant.

To meet the potential increased demand for zanamivir, GSK is exploring an alternative presentation, the Rotacap/Rotahaler, for which production is more rapidly scalable. Rotacap/Rotahaler could be available for emergency use only, and production would not affect the production of the Rotadisk/Diskhaler. GSK is in negotiations with FDA and others about investing in the Rotacap/Rotahaler presentation.

With its current equipment, GSK could produce 20 million treatment courses of Rotacap/Rotahaler in 2009. With more investment in tools and starting materials, it could produce 50 million courses by mid-2010. The maximum capacity would be approximately 100 million courses per year using GSK facilities only. Unlike the Rotadisk/Diskhaler, other manufacturers could produce the Rotacap/Rotahaler. If both presentations were produced, GSK could potentially provide 60 million treatment courses this year, and a maximum of 190 million courses per year.

The IV form of zanamivir has been available since the early 1990s. Concern about pandemic influenza spurred interest from public health authorities in an injectable antiviral. IV-zanamivir provides high systemic exposure and addresses oseltamivir resistance. Initially, the product was proposed for pandemic preparedness only on the basis of animal data. Then, FDA asked GSK for studies on IV-zanamivir for severe seasonal influenza. Regulatory requirements evolved from providing a safety database with some evidence of efficacy from several small studies in 300–600 patients, to a superiority trial in more than 1200 patients. GSK's feasibility studies showed that the latter trial would take at least 10 years to conduct. GSK and FDA acknowledged that some compromise must be made.

The challenges Dr. Hayden mentioned about studying hospitalized patients with severe influenza are also challenges for studying IV-zanamivir. A placebo-controlled trial is not feasible, because treatment exists. A comparability trial is not appropriate, because oseltamivir and zanamivir have the same mechanism of action, and oral oseltamivir and IV-zanamivir show similar efficacy. Zanamivir might demonstrate superiority if the oral medication is not absorbed well, e.g., by severely ill patients, or if there is a high baseline rate of oseltamivir resistance (which may be evolving now). While influenza is not rare, enrolling hospitalized patients with confirmed influenza in a clinical trial is difficult. GSK estimates that it would be able to recruit about 150 patients worldwide per year.

Finally, it is difficult to develop a study of IV-zanamivir that balances the time urgency, operational feasibility, and the need for robust evidence of efficacy. Design of a phase-3 trial has been under discussion for 2 years. Ultimately, GSK held a closed meeting in September 2007 with FDA. GSK proposed a development and regulation package that included a large database to address efficacy and safety on the basis of: the approved inhaled product, data from completed preclinical and phase-1 trials of IV-zanamivir, and an innovative design for phase-3 trials using a precision-based approach. GSK and FDA could not come to agreement on the design of a phase-3 trial, so the development of IV-zanamivir was put on hold.

FDA's draft guidance for industry for the development of influenza drugs, presented in February 2009, reiterates many of the messages from the 2007 meeting between GSK and FDA. Dr. Ng-Cashin responded to the following important points identified in the draft guidance to consider in studying severely ill, hospitalized patients with influenza:

- Virologic endpoints are useful for data, but clinical endpoints are expected. However, acceptable clinical endpoints are not well defined.
- Inferiority studies are required.
- One suggested study design, randomized dose-response, has been considered by GSK, but the company has been reticent to give a sub-dose because it is concerned about acceptability.
- Another suggested study design is a superiority add-on study. However, with oseltamivir plus IV-zanamivir, GSK believes it would be difficult to demonstrate superiority, and such a study would require at least 1,200 patients.
- Finally, because outbreaks are unpredictable and enrollment is difficult, collaboration with networks is suggested.

Nebulized zanamivir has been administered to 126 subjects. Data from the nebulized form was used to determine safety and gather pharmacokinetic data for the oral inhaled formulation. GSK collected data from five clinical trials of nebulized zanamivir, and from another 79 patients who received it under a compassionate-use framework from 1999 to 2002.

At the onset of the current H1N1 outbreak, FDA contacted GSK about the appropriate regulatory mechanism to provide nebulized zanamivir for U.S. patients on a compassionate-use basis. GSK determined the most expedient approach is through an emergency IND, in which the individual-treating clinician acts as the principal investigator for a single patient. GSK has documentation based on limited data on how to treat. However, the supply of nebulized zanamivir is extremely limited. It was manufactured when GSK was actively developing the IV formulation. GSK feels it should be available worldwide for compassionate-use provided that appropriate regulatory mechanisms are in place. The remaining clinical trial material has been earmarked for compassionate-use. GSK has no intention to restart the manufacturing of zanamivir solution.

Following its meeting with FDA, and after reviewing the recent FDA draft guidance, specifically the guidance on clinical trial design in severe hospitalized patients, GSK sees no feasible path to registration; therefore IV-zanamivir remains on hold. GSK will consider a clinical development proposal from a third party for influenza antiviral drug development if it includes a clinical development plan that is reasonable, feasible, scientifically robust, and likely to lead to registration and approval. If the clinical development plan does not meet these criteria, GSK would not support a trial, execute the trial, or provide the drug. However, GSK would not prohibit a third party from sourcing the product from another licensed manufacturer.

**Peramivir: Pandemic Influenza Response, Advanced Clinical Development—
William Sheridan, M.B. B.S., BioCryst Pharmaceuticals**

Peramivir, an investigational drug, is a potent, specific influenza viral neuraminidase inhibitor (NAI) discovered at BioCryst using structure-based design, based on a high-resolution crystal structure of viral NA. Dr. Sheridan said BioCryst was encouraged to develop parenteral peramivir by the CDC, and brought the program forward in the U.S. under contract from BARDA in 2007. BioCryst is pursuing two indications for peramivir in the United States: acute, uncomplicated influenza and influenza requiring hospitalization. Parenteral peramivir is now completing phase-3 clinical trials conducted by BioCryst's partner Shionogi & Co. Ltd. in Japan and is ready to enter phase-3 trials in the United States for influenza indications.

Peramivir has been studied in vitro with a large variety of clinical isolates representing many different strains of influenza. These studies have characterized the unique laboratory susceptibility patterns to this novel NAI. Recently, Dr. Larisa Gubareva at the CDC has expanded her earlier research on susceptibility patterns of the 2009 pandemic influenza H1N1 strain. These expanded studies of 204 unique clinical isolates have demonstrated that this new virus is very sensitive to peramivir, with a median IC₅₀ of 0.09nM in the NAI chemiluminescence assay; the IC₅₀ for peramivir is significantly lower than that for either zanamivir or oseltamivir ($p < 0.001$). Peramivir improves survival in preclinical influenza models, including mouse and ferret models of highly pathogenic avian influenza H5N1. One day of peramivir treatment is active, and multiple days of treatment rescues most or all mice with H5N1. Similar results have been observed in ongoing murine experiments with seasonal influenza A (H1N1)/H274Y.

Extensive human pharmacology research has been completed for peramivir intramuscular injection and IV infusion, and our understanding of peramivir clinical pharmacology is now very thorough, including in special situations such as renal impairment and the elderly. Peramivir achieves very high plasma levels after parenteral administration, is not metabolized, and is cleared by renal filtration. It has a long half-life, especially compared with other NAIs. Because the drug is not metabolized, is widely distributed, and is excreted unchanged in urine, dosing regimens can be adapted easily for patients with renal impairment and for pediatric populations.

Clinical data has been generated for peramivir in several phase-2 and phase-3 studies, and the drug has been administered safely to more than 1,300 subjects in clinical studies. The

phase-3 studies in Japan have recently completed enrollment, but data from these studies is not yet available. The completed phase-2 study in Japan in 2008-2009 was a rigorously designed and executed randomized, double-blind, placebo-controlled trial comparing one short IV infusion of peramivir (two different doses were tested, 300mg and 600mg) with placebo in acute uncomplicated influenza. The primary endpoint was time to alleviation of symptoms (TTAS). The efficacy outcome was unequivocally positive, with all efficacy endpoints showing significant improvement over placebo. The time to alleviation of symptoms was 81.8 hours for placebo, and was shortened by about 22 hours with peramivir ($p=0.0046$). Time to resolution of fever was also significantly improved in the peramivir groups compared to placebo. Change in viral load, determined by nasal-pharyngeal swabs at baseline and at several protocol-specified post-treatment timepoints, is another important outcome, as it is a direct measure of antiviral activity. These evaluations showed that viral clearance was significantly accelerated in the 600mg peramivir group compared to placebo.

The safety experience for peramivir was very satisfactory in this study. Reported AEs were mild, and no serious AEs were reported in the 198 subjects administered peramivir in the study. The reported AEs were of similar frequency and severity grade in the placebo and treatment groups. These efficacy and safety results formed the basis of the peramivir phase 3 program in Japan.

BioCryst's phase-2 study of peramivir in patients with influenza requiring hospitalization was difficult to perform, and is the only study ever completed in this patient population. It required multiple sites and countries and enrollment extended over 2 Northern Hemisphere and 1 Southern Hemisphere season. An important issue for influenza clinical research is lack of awareness of influenza in the hospital setting. This problem seems partly due to lack of reliable diagnostic tests in emergency rooms – it is estimated that only 5% of patients hospitalized with influenza actually receive that diagnosis. Better access to confirmatory diagnostic tests would greatly improve the ability to recruit patients for such studies.

A placebo-controlled study was not practical for ethical reasons, so oral oseltamivir was used as a control, even though it is not approved for this indication. Two different doses of IV peramivir were evaluated, 200mg daily for 5 days and 400mg daily for 5 days. The primary endpoint was time to clinical stability, which was adapted from studies of community-acquired pneumonia.

A main goal of this study was to evaluate peramivir in a patient population with more serious disease or underlying risk factors for complications. The patient population enrolled consisted mostly of individuals admitted with chronic illness that worsened with influenza, and not patients with influenza-pneumonia. The study patients had good clinical outcomes, and BioCryst was pleased with the rapidity of clearance of the virus. Viral cultures were obtained from nasopharyngeal swabs at regular intervals. Overall, viral load was reduced rapidly with treatment. Detailed analyses of the viral culture data indicated that the baseline viral load was higher in subjects with less than 48 hrs of symptoms at enrollment, and in influenza B subjects. In the influenza B subjects, a

statistically significant dose-response was observed for peramivir 400mg vs peramivir 200mg. These results suggest that the plateau of the dose-response curve may not have been reached, and support evaluation of peramivir 600mg daily.

Looking at AEs, peramivir IV once daily for 5 days was generally safe and well-tolerated in adults hospitalized with acute influenza. On the basis of these findings, BioCryst is comfortable moving forward, and is discussing phase-3 trials with BARDA and FDA. The phase-3 proposals will be based on the draft FDA guidance published in February 2009. In addition, pediatric studies of peramivir are under development by the Division of Microbiology and Infectious Diseases in NIAID in collaboration with BioCryst.

Dr. Sheridan noted that hospital IRBs are slow to approve protocols. He asked whether a government agency could help prioritize clinical research in a pandemic setting. He stressed that the role of IRBs would not change, just their criteria for prioritization of review.

Dr. Sheridan described one case of compassionate use of peramivir under emergency IND regulations in Seattle. Data for the presentation was kindly provided by the investigator, Dr. Anna Wald, Seattle WA. This patient had had a bone marrow transplant and presented to the ED with respiratory and GI symptoms 2 days after the transplant. The patient was diagnosed with influenza A (subsequently confirmed to be due to the pandemic strain) developed bilateral viral pneumonia, and rapidly deteriorated despite treatment with oseltamivir, adamantane and ribavirin. Virus was detected by PCR in blood and stool as well as bronchoalveolar lavage specimens. Intubation, 100% inspired oxygen and positive end-expiratory pressure were required. Following a 10-day course of peramivir combined with oseltamivir, the patient's condition improved, allowing discharge from the intensive care unit and cessation of antivirals. Dr. Sheridan said that although the case provides anecdotal evidence, it illustrates the potential for successful use of peramivir for severe illness.

Emergency IND in individual cases is clearly an inadequate supply mechanism in the circumstance of a large demand. Existing quantities of peramivir finished drug product were manufactured for the clinical trial program, and will support the implementation of the phase 3 trials. Peramivir can be made available as a countermeasure for the current H1N1 pandemic, and BioCryst is fully cooperating with U.S. government agencies conducting the relevant evaluations. FDA has proceeded with a pre-Emergency Use Authorization (EUA) review of peramivir, and if an order is placed for the Strategic National Stockpile, BioCryst has the manufacturing supplies it needs to finish the product and make large quantities available. The manufacturing process is well developed.

Passive Antibody as a Therapeutic—John Beigel, M.D., MacroGenics, Inc.

Dr. Beigel described recent NIAID involvement with IV immunoglobulin (IVIG), noting that these activities were conducted when he was employed at NIAID. The threat of severe acute respiratory disease (SARS) without any antiviral treatment prompted looking for alternatives therapeutics. A study in Hong Kong demonstrated some efficacy using convalescent plasma to treat SARS. Although the study had many shortcomings, it

prompted NIAID to develop a SARS plasmapheresis study. Dr. Beigel said it took about 18 months to establish a SARS IVIG protocol, but the study eventually collected about 30 liters of convalescent plasma (much less than expected). By the time this was collected and manufactured into a IVIG product (lab scale), the end product lacked high-titer antibodies. The timeline from concept to product (GLP IVIG) was 4.5 years.

The threat of H5N1 also required a quick treatment, and there were concerns about resistance. Dr. Beigel said getting convalescent plasma from areas affected by H5N1 may be even harder than getting it from Hong Kong, so he and his colleagues developed a hyperimmunization plasmapheresis program for H5N1. The concept of plasma treatment for influenza was supported by a paper looking at eight studies during the 1918 influenza pandemic. The paper described the use of convalescent plasma for sick people and noted they had a lower mortality rate than others. Again, the study would not meet modern standards, but it offered some insight.

Early studies of hyperimmunized horse serum showed some protection in mice. Prompted by these studies and the H5N1 vaccine studies, Dr. Beigel designed a multiple-cohort study in which each cohort received higher doses than previously studied (90, 120, or 180 mcg), for four doses, in an effort to increase antibody titers. Both hemagglutination inhibition (HI) and microneutralization (MN) did not increase with higher doses of vaccine but did increase with subsequent vaccinations. However, serial vaccination did not increase the number of subjects who got to high-titer antibodies of HI (above 1:160).

The subjects chose their vaccine sites, with early data suggesting those receiving vaccine in the arm had higher HAI titers; so the study added a fourth cohort that received two doses of the vaccine in the deltoid or the buttock. Overall, the study had 126 subjects, 10 of which met the criteria for plasmapheresis. From those 10, investigators got about 30 liters of plasma. Nine units were manufactured into IVIG. Dr. Beigel said the titer of the output was higher than the input, but much lower than expected. Studies evaluating this are ongoing. The process for the IVIG effort took 2.5 years from concept to product. If preclinical and phase-1 trials were needed, the process would take even longer. Dr. Beigel broke down the timeline into the component parts and discussed each one's issues.

For example, manufacturing IVIG instead of using source plasma adds several months from the last unit of plasma collected (although in an urgent setting, it's possible the manufacturing process could be faster). Plasma is less expensive to manufacture. From a scientific standpoint, IVIG is preferred because antibody titers can be standardized and there are no confounding factors such as different drug volumes.

Plasma collection and development of IVIG are not as rapid as people think. Some steps could be optimized. The use of source plasma as the therapeutic could improve the timeline by 6–12 months, but you sacrifice some scientific benefits.

Dr. Beigel then compared polyclonal and monoclonal antibody-based treatment for emerging infectious diseases:

Polyclonal:

- Generated more rapidly
 - IVIG vs. plasma
- Less development expense
- Higher sustained manufacturing expense
- Heterogeneity/less potent
 - Advantage for resistance?
 - Most IgG not specific
- Large dose/volume
- May be easier to approve
 - Intrinsic targets unlikely

Monoclonal:

- Slower to develop
 - More technically difficult
- Higher development expense
- Lower sustained manufacturing expense
- Homogeneity/more potent
 - More consistent
 - Select neutralizing monoclonal antibody only
- Small dose/volume
- More difficult to approve
 - Treated as novel compounds

The timeline for developing monoclonal antibodies can reach 3–4 years. Dr. Beigel noted recent studies suggesting antibody isolation may be decreased from 6–12 months to 28 days, though this study was specifically looking at vaccines and not convalescent subjects. He said the time for monoclonal antibody engineering could be reduced from the current 6–12 months. Investigators are working to reduce the time to develop master cell lines from 12 months to 6 months. The time for manufacturing and release would stay the same. So while the timeline can be improved, it is still unlikely that monoclonal antibodies could be developed rapidly enough (with current technologies and approval processes) for emerging infectious diseases.

The NIH is developing a protocol for H1N1 to collect plasma from convalescent subjects and vaccines. The protocol is still in draft form and needs IRB and FDA approval. Discussions are underway with a manufacturer for IVIG. Depending on the course of the H1N1 epidemic, the protocol may use source plasma or IVIG.

Dr. Beigel concluded that passive antibody is an option for emerging infectious diseases, but it is labor-intensive. Plasma collection and IVIG development is not as rapid as assumed, but it's still faster than de novo drug development. In the best-case-scenario, plasma could be available in 3 months, and IVIG in 7–12 months. Monoclonal

antibodies are promising for emerging infectious diseases but would require some leaps in timeframes.

**TAMIFLU[®] (oseltamivir) Strategy for Unmet H1N1 Treatment Needs—
Regina Dutkowski, Ph.D., Hoffmann-La Roche**

Dr. Dutkowski said that before the 2007-2008 influenza season, resistance to oseltamivir was low, as evidenced by community surveillance. Naturally occurring resistance developed in 2007-2008 because of a mutation; resistance was not associated with use of oseltamivir in patients. Also, the resistant strain did not appear clinically worse than disease in patients with wild-type. The findings spurred Hoffmann-La Roche to study the incidence and clinical impact. Novel H1N1 is sensitive to zanamivir and oseltamivir.

The company's Influenza Resistance Information Study (IRIS) is seeking to improve early detection of resistance to all antivirals, and to better understand the clinical implications of resistance compared with susceptible viruses. It is an international, prospective study overseen by an international expert panel. Secondary objectives include examining the characteristics of circulating strains, determining regional changes in strains, evaluating signs and symptoms of patients with different subtypes, monitoring for resistance mutations at initial clinical presentation and after antiviral treatment, and comparing effects of antiviral treatment on clinical outcomes in patients with resistant or susceptible strains. The company hopes to enroll 1,200 patients over three seasons, and 400 have completed the study to date. The company plans to submit an end-of-season report at the end of 2009.

Hoffmann-La Roche is also studying alternative routes of administration of oseltamivir for critically ill patients (IV and nasogastric [NG] tube). The study will evaluate a single ascending dose in an open-label, randomized format. Three different IV doses are being compared to a 75-mg oral dose. IV oseltamivir has been well tolerated, with GI symptoms and headache being the most frequent AEs.

The company looked at the results of a study of NG oseltamivir in three patients with severe influenza (two had H5N1, one had H3N2). All three patients got double the usual dose. The authors concluded that oseltamivir was adequately absorbed in these patients. Dr. Dutkowski explained the decision to focus on NG administration for hospitalized patients:

- To mimic the oral pharmacokinetic profile, IV requires a 2-hour infusion and a more controlled setting for administration.
- Oseltamivir has high (80%) oral bioavailability.
- Oseltamivir has a well established oral safety profile.
- NG administration is usable in most sick hospitalized patients, including those on ventilators.
- NG administration is an opportunity to provide a more immediate alternative dosing regimen.
- There are no barriers to availability and long-term storage with an oral formulation.

Therefore, Hoffman-La Roche is supporting two ongoing investigator-led studies in Canada in hospitalized patients: one in uninfected patients who required intubation and mechanical ventilation, and one in patients infected with H1N1 who have severe respiratory syndrome. The company is discussing with FDA the possibility of IV TamiFlu for emergency use. It can produce a limited clinical supply by the third quarter of 2009. The first batch could be available by August, and 4,000 treatment courses could be produced by the end of 2009.

Hoffman-La Roche is also studying oseltamivir in immunocompromised patients and kids under age 1. Two studies have been initiated to assess the efficacy and safety of oseltamivir in transplant patients—one is focused on treatment, and the other focuses on prophylaxis. Both are double-blind, randomized, multicenter trials. The prophylaxis study is complete, and found that oseltamivir prophylaxis reduced the incidence of laboratory-confirmed infection (by viral culture or PCR) by 79.9%. The 12-week dosing regimen was well tolerated, and the AE profile was similar to placebo. No cases of resistance were identified.

The company is collaborating with NIH/NIAID on a study of infants less than 2 years. The study takes a cohort approach. Younger groups are enrolled if pharmacokinetic and safety profiles raise no concerns in older groups. As of April 2009, 40 patients were enrolled, mostly male and Caucasian. The youngest cohort—under 2 months—had four kids enrolled as of April. As of late April, 57 AEs had been reported; all but three were considered unrelated to treatment, and no seizures or neurological concerns were reported. The pharmacokinetic measures and other preliminary findings are promising. The study is ongoing. In the fall, the company is conducting a similar study in Europe.

Discussion

Dr. Pavia: There is frustration, clearly, around this topic. So let's explore that, recognizing that we're in a difficult position.

Debra Birnkrant: We have concerted efforts to communicate on antivirals for influenza. Regarding [FDA's] published draft guidance, we have received comments and will address those. In addition to frustration by pharmaceutical companies doing research, we have also heard how much we are communicating with them. Our goal is to develop perennial antivirals for the seriously ill, ensure adequate supplies of current products, and encourage development of new antivirals.

Dr. Pavia: There are considerations about study design and endpoints.

Elizabeth Higgs, M.D.: We are working internationally, and we are aware of the need for novel treatments for influenza. We were reminded last season when we saw the resistance. We are one point mutation from having no systemic treatment for pandemic influenza, so it's urgent to address. I've been in the middle of this, and I think we can work together, but we need some novel thinking. There are not a lot of treatment options because it's challenging, as we've discussed. Endpoints are good place to start: perhaps replication of the virus in a high-risk population, or maybe strain-specific endpoints. Maybe virologic clearance in high-risk populations is something to revisit.

Dr. Pavia: What models have we used in other diseases—with better endpoints?

Edward Cox, M.D., M.P.H.: We recognize how challenging it is to study drugs in severe disease and in hospitalized patients, but it's very important to understand the role of drugs and their effects in those situations. Informative trial design is important. We welcome other ideas, new ways to look at the issue.

In HIV, for example, we used surrogate endpoints, and that allowed us to identify early predictors of clinical outcome. There's been a lot of work in that area by [the Center for Drug Evaluation and Research]. But it's different for influenza. You can look at virologic markers, and that's useful, but the clinical endpoint is the effect on patient well-being, and that's right there in front of you, and you can measure it. So it's different from HIV.

There are real challenges in doing studies, but we all recognize the need. It may take more to get studies to happen. We do need new treatment models, especially different mechanisms that are not susceptible to resistance. Also combination therapy is an area to study more. It's important to plan for studies and try to answer questions.

Dr. Pavia: With H5N1, death is the common endpoint. The power to detect differences is [poor]. It's an overstatement to say the clinical endpoints are in front of us. Other than fever or duration of hypoxemia or intubation, it's too mixed, too subjective. Not enough patients have those hard endpoints to measure.

Dr. Gellin: We heard about the European Medicines Agency (EMA) approach. How is this working outside the United States?

Dr. Ng-Cashin: With IV-zanamivir, the European regulators were the same as FDA. In 2007, they wanted to wait to find out what FDA said.

Ms. Birnkrant: We have an open dialogue with other regulators, and we want to hear what they are doing.

Greg Martin, M.D.: In DoD, we've been approached to study combination therapy. Would that be helpful? Especially for patients with severe influenza who are hospitalized and we're not sure what they're resistant to.

Dr. Hayden: If you don't know what they're resistant to, it's sensible to use combination therapy, preferably dual therapy, which has been espoused by many. But the routine use of combination therapy is problematic. Most good quality data say that if the virus is amantadine-resistant, that doesn't add anything to the combination, so you're just increasing the risk with no potential benefit. There are different issues there, so I would not routinely embrace combination therapy. But there's an argument for using other agents with potential for value. I'd be cautious about using combination therapy routinely without more evidence from independent labs.

Dr. Cantrill: We need to adapt our planning to current reality. We need to be ready in 2-4 months. Beyond that, we're just preparing for the next pandemic. I hope NBSB's advice looks at the next steps. It requires some adjustment in where we stand between a cautious and a bold approach. If we proceed in our normal cautious way, we'll have a good vaccine next summer. NBSB focuses on products, but there is planning beyond products, e.g., major efforts on communications, plus effort to understand what's going on, surveillance, mitigation, and vaccination.

Dr. Pavia: Regarding the size of the stockpile, are we considering the right strategy? I hope that's being discussed. Dr. Robinson of BARDA echoed the urgency of the

situation, and we came to a boiling point yesterday. We're in a similar place for this. Some of the drugs can be used under EUA, and that pathway has to be considered. GSK did not discuss EUA.

Dr. Ng-Cashin: We have not considered that in the past. We were discussing with FDA what we currently have - 450 courses of IV-zanamivir for compassionate-use using an emergency IND. We might consider EUA. I can't decide that, but we have the active ingredients. We welcome more conversation with FDA.

Dr. Robinson: Strategically, there's still the problem of the timeline. What do we do with what we have in the SNS, and what should we buy for prophylaxis? We need a quick decision.

Dr. Cantrill: In Colorado, we can query pharmacies and suppliers about stocks. After 4–5 days of the April outbreak, we asked about oseltamivir, and they were wiped out. Hospitals don't stock it. So it's tough, even with what we have in the SNS. That supports the urgency of this issue.

Dr. Noble: We need ongoing, real-time recommendations for what works and what's available. Regarding access to oseltamivir and the SNS, we need communication, but it's important not to cry wolf, because that risks the reputation and credibility of the public health system.

Dr. Pavia: Summarizing the assumptions and goals for antivirals:

- Antivirals can ameliorate disease.
- There is evidence to support they work in patients with severe influenza. It is not level-1 evidence, but they work.
- Most illness will be concentrated in populations for which there are limited data, e.g., younger people, and people who are immunocompromised.
- There will be a rapid increase in need before we can ramp up anything that's not already manufactured.
- There is a real possibility that mutation will happen, and we might have a doubly resistant virus.
- We may have complicated recommendations because of coexisting viruses.

Our goal will be to ameliorate death and severe disability with what we have - either by treating the sickest or by using antivirals as prophylaxis to prevent the spread of disease. Those two approaches are mutually exclusive.

To deal with the sickest patients, we need good data on some vulnerable populations, but we also need options now for treating the sickest. Some alternatives can be used, like NG administration, but not new agents. We need to resolve the hurdles or find alternative pathways, e.g., use of new drugs during an emergency that develops data during use. We need some studies that collect data on very sick patients.

The final issue we didn't address is that clinical trials are difficult and slow. IRB review is terribly necessary for sick patients, but if you're doing multi-center trials, you can be dealing with 20 IRBs, 20 timelines, and 20 contracts. For EUA, single or central IRB or master contracts should be an option.

Dr. Hayden: Also, the development of a hospital network to do studies is important. It would give us an opportunity to learn about use of drugs in seriously ill patients. We'd be wasting an EUA if we're not getting good data or samples, and that would be a shame. I urge planning to develop networks. Again, this is just one event, and we anticipate others, so we need to deal with the issue more coherently.

Dr. Pavia: One more thing - despite the tensions among different perspectives, we have the same strategic goal of responding to a public health emergency. So we have more in common than we have differences.

Victoria Davey, R.N., M.P.H.: The Department of Veterans Affairs has a multi-trial system, and we're trying to create a master IRB.

Dr. Gellin: There are lots of estimates about days until things happen. What do you see as the next step for NBSB to advise on these issues?

Dr. Pavia: The problem with advisory groups is that we all have daytime jobs. Sometimes, what we're best at doing is bringing others together, catalyzing people who do work full-time on this. So, what NBSB can do is summarize the thoughts of a large number of people in documents that key people can review. We may look at issues with a different perspective. In light of our timelines, the key takeaways can be summarized in a short document that decision-makers can use. They will probably throw it back to their key staff with directives on what to address. The value of outside advisors is their lack of assumptions and willingness to ask hard question. But there's limited time to develop a work product.

Dr. Gellin: Dr. Quinlisk, what do you think the Board should add?

Dr. Quinlisk: Thank you all for coming, especially Dr. Pavia and NBSB staff. I'm amazed at all the thought that's gone into this. This has been very useful; some people are saying it's been the most productive meeting. So what do we do now? We need to take the lessons from the past 2 days and get our initial advice to people who make decisions. This is not the end of the process. There is a lot to discuss. We anticipate getting more information, so this is the beginning. We're already discussing another meeting; that's something NBSB can do to keep the momentum going. We welcome suggestions.

Dr. Cantrill: Our power is bringing together people who don't talk as often as they should, that we're not constrained, and that we're able to look broadly at the issues.

Dr. Grabenstein: What's your HHS timeline?

Dr. Gellin: Soon.

Dr. Pavia: With the time crunch, we need this to go up the chain quickly. We need someone high up (e.g., at the White House) to be involved soon. I'm glad there was a representative here from the White House. Thanks to Leigh Sawyer and the NBSB staff for putting this meeting together on short notice. Thanks to our panels, especially for being willing to expose themselves to criticism and tension. Thanks to the agency representatives who are willing to be honest and rethink things. We do have short timelines, and there is a lot to be done.

APPENDIX C

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

AGENDA

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

JULY 2009



H1N1 Countermeasures Strategy and Decision Making Forum

Hosted by the Pandemic Influenza Working Group

National Biodefense Science Board

Bethesda Marriott

5151 Pooks Hill Road

Bethesda, MD 20814

June 18-19, 2009

Day 1 - June 18, 2009

8:00-8:15 Welcome, Introductions
8:15-8:30 Goals

William C. Vanderwagen
Andrew Pavia

Decision Making - H1N1 Vaccine Strategy

8:30-9:00 H1N1 Vaccine Strategy
9:00-9:20 Novel Influenza A (H1N1) Update: Domestic and International Surveillance Update and Plans
9:20-9:50 Modeling-Impact of Interventions
9:50-10:00 Discussion

Robin Robinson
Anthony Fiore
Neil Ferguson

10:00-10:15 Break

10:15-10:35 NIH Clinical Trials Planned
10:35-11:20 Manufacturers Vaccine Development Plans
GlaxoSmithKline
Novartis Vaccines and Diagnostics
MedImmune, LLC
Sanofi Pasteur
CSL Limited

Linda Lambert
Bruce Innis
Rino Rappuoli
Raburn Mallory
James Matthews
Jillian Bennet

11:20-12:00 Panel Discussion on Clinical Trials:

Linda Lambert
Bob Belshe
Kathy Edwards
Wellington Sun
Kathy Neuzil

Questions to consider:

- Can we get it done?
- What are we missing?
- What do we absolutely have to have done?
- Options for streamlining

12:00-12:30 Pick up Box Lunch

12:30-1:00 Swine Flu Vaccine Version 2.0: Walter Dowdle
Decision Making Revisited

Vaccine Safety and Whether to Use Adjuvants

Moderator Lawrence Schonberger

1:00-1:15 Vaccine Safety Monitoring Daniel Salmon
1:15-1:35 Vaccine Safety: Basic Research Charles Hackett
1:35-2:00 Discussion

Adjuvanted Vaccine

2:00-2:20 Dose Sparing and Cross Protection John Treanor
2:20-2:30 Regulatory Implications Wellington Sun

2:30-3:15 Panel Neil Ferguson
Arnold Monto
Gary Noble
John Treanor
Wellington Sun
Robert Field
Brooke Courtney

Questions to consider:

- What are the implications of choosing or not choosing to use an adjuvant:
 - capacity
 - timing
 - international
 - ethical

3:15-3:30 Break

3:30-3:45 HHS Decision Plan - Work in progress
3:45-5:30 The Decision Process - Panel NVPO - Bruce Gellin/ASPR-Korch
ACIP - Kathy Neuzil/Anthony Fiore
NVAC - Gus Birkhead
VRBPAC - John Modlin
NBSB - Patty Quinlisk/Andrew Pavia
DHB - Greg Poland

Questions to consider:

- Where are the decision points?
- What science will be needed?
- Who will advise?
- Votes planned?

Discussion: Plan for timing of FACA meetings and votes needed; and additional steps needed

Day 2 - June 19, 2009**Diagnostics – Strategies for Use of Diagnostics in a Pandemic**

| | | |
|------------|--|--|
| 8:00-8:15 | Background | Andrew Pavia |
| 8:15-8:35 | Diagnostics and influenza pandemics: Lessons learned and future prospects | Dan Jernigan |
| 8:35-8:55 | FDA perspective: Diagnostics for pandemics and biodefense | Sally Hojvat |
| 8:55-9:15 | Influenza Diagnostic Algorithm and Identification Capability within DoD Clinical Laboratories. | Dan Harms |
| 9:15-10:15 | Panel Discussion | Steve Cantrill Anthony Fiore Dan Jernigan Sally Hojvat Dan Harms |

Questions to consider:

- What is the optimal role of diagnostic testing for public health surveillance during a pandemic? Is it appropriate to have different goals during different phases, or is it a compromise based on limited capacity?
- What are the benefits of comprehensive testing at large medical centers? Is testing of hospitalized patients an important part of surveillance? Are there other models of sentinel surveillance?
- What might be the benefits of an accurate point of care test? What degree of accuracy would be needed? Do these hypothesized benefits need to be tested?
- How can diagnostic testing be integrated into community mitigation efforts (for example for school closure, voluntary quarantine, post exposure prophylaxis)
- Public health laboratories have very limited capacity. Do they need to be supplemented by other sources? Should restoring public health capacity take precedence over using clinical capacity?

10:15-10:30 Break**Antivirals**

| | | |
|-------------|---|------------------|
| 10:30-11:10 | I. Antiviral drugs in the development II. What do we need from antiviral drugs | Fred Hayden |
| 11:10-11:30 | GSK Zanamivir Strategy and Response to Novel H1N1 | Judith Ng-Cashin |
| 11:30-11:50 | Advanced Clinical Development of Peramivir | William Sheridan |

| | | |
|-------------|--|--|
| 11:50-12:10 | Passive Antibody as a Therapeutic (<i>Work done at NIAID, NIH, HHS</i>) | John Beigel |
| 12:10-12:30 | Oseltamivir Strategy for Unmet H1N1 Treatment Needs | Regina Dutkowski |
| 12:30-1:00 | Panel Discussion | Ed Cox Debra Birnkrant Fred Hayden Judith Ng-Cashin William Sheridan John Beigel Elizabeth Higgs |

Questions to consider:

- What drugs might be available?
- Options for use during pandemic?
- Can we accelerate the science and clinical trials?
- Can we accelerate development of other agents?
- How do we ensure drugs for severe disease if novel H1N1 acquires Oseltamivir (and Peramivir) resistance?

1:00-1:15 Wrap up

1:15 Adjourn

1:30-2:30 *Optional Working Lunch Meeting – Consider Next Steps*

*For more information, please visit our Web site:
www.hhs.gov/aspr/ompsh/nbsb*

APPENDIX D

H1N1 COUNTERMEASURES STRATEGY AND DECISION- MAKING FORUM

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