

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION**

**Advisory Committee on
Immunization Practices (ACIP)**



**Summary Report
July 29, 2009
Atlanta, Georgia**

Table of Contents		Page
Acronyms		3-4
Agenda		5
Welcome and Introductions		6-8
Introduction and Goals of the Meeting		8-10
Novel Influenza A(H1N1) Epidemiology: United States		10-14
Novel Influenza A(H1N1): Global Update		14-16
Viral and Immunology Update		16-26
Vaccine Development and Formulations		26-29
FDA / VRBPAC Update		29-32
Overview of H1N1 Clinical Trials by NIAID / NIH		32-39
2009 H1N1 Vaccine and Critical Infrastructure Key Resources Priority Groups		39-42
Implementation Planning		42-44
Communications Strategy		44-50
Public Comment		50-52
ACIP Influenza Work Group Recommendations		52-74
Certification		74
Participant Roster		75-80

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACOG	American College of Obstetricians and Gynecologists
AHIP	America's Health Insurance Plans
BARDA	Biomedical Advanced Research and Development Authority / HHS
BLA	Biologics License Application
BMI	Body Mass Index
BRFSS	Behavioral Risk Factors Surveillance System
CAIS	Childhood / Adolescent Immunization Schedule
CAIV-T	Cold-Adapted Influenza Vaccine
CCHIS	Coordinated Center for Health Information and Service
CCID	Coordinating Center for Infectious Diseases
CDC	Centers for Disease Control and Prevention
CID	Committee on Infectious Diseases (CID) of the American Academy of Pediatrics (AAP)
CIKR	Critical Infrastructure Key Resources Priority Groups
CMS	Centers for Medicare and Medicaid Services
DBD	Division of Bacterial Diseases (of NCIRD)
DGMQ	Division of Global Migration and Quarantine
DHQP	Division of Healthcare Quality Promotion
DHS	Department of Homeland Security
DMID	Division of Microbiology and Infectious Diseases
DoD	Department of Defense
DSMBs	Data Safety Monitoring Boards
DVA	Department of Veterans Affairs
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GBS	Guillain Barré Syndrome
GID	Global Immunization Division
GMCs	Geometric Mean Concentrations
GMTs	Geometric Mean Titers
GSK	GlaxoSmithKline
HICPAC	Healthcare Infection Control Practices Advisory Committee
HPLC	High-Performance Liquid Chromatography Assay
HHS	Department of Health and Human Services
HMO	Health Maintenance Organization
HRSA	Health Resources and Services Administration
ID	Influenza Division (of NCIRD)
IDSA	Infectious Disease Society of America
IHS	Indian Health Services
ILI	Influenza-Like Illness
ILINet	Influenza-Like Illness Surveillance Network
IND	Investigational New Drug
IOM	Institute of Medicine
ISD	Immunization Services Division (of NCIRD)
ISO	Immunization Safety Office (of CDC/OD/Office of the Chief Science Officer)
MCO	Managed Care Organization
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
NACCHO	National Association of County and City Health Officials
NACI	Canadian National Advisory Committee on Immunizations

NBSB	National Biodefense Science Board
NCHM	National Center for Health Marketing
NCIRD	National Center for Immunization and Respiratory Diseases (of CDC/CCID)
NCPDCID	National Center for Preparedness, Detection, and Control of Infectious Diseases
NIAC	National Infrastructure Advisory Council
NIAID	National Institute of Allergy and Infectious Diseases
NIBSC	National Institute for Biological Standards and Control
NIH	National Institutes of Health
NIS	National Immunization Survey
NISAC	National Infrastructure and Analysis Center
NVAC	National Vaccine Advisory Committee
NVICP	National Vaccine Injury Compensation Program
NVPO	National Vaccine Program Office
NRVSS	National Respiratory Virus Surveillance System
OCSO	Office of the Chief Science Officer
OD	Office of the Director (of CDC)
OIP	Office of Infrastructure Protection
P&I	Pneumonia and Influenza
PEP	Post-Exposure Prophylaxis
PhRMA	Pharmaceutical Research Manufacturers of America
PREP Act	Public Readiness and Emergency Preparedness Act
SAGE	Strategic Advisory Group of Experts (WHO)
sBLA	Supplemental Biologics License Application
SHEA	Society for Healthcare Epidemiology of America
SMEs	Subject Matter Experts
UK	United Kingdom
US	United States
VAERS	Vaccine Adverse Event Reporting System
VFC	Vaccines for Children
VICP	Vaccine Injury Compensation Program
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSD	Vaccine Safety Datalink
VTEUs	Vaccine and Treatment Evaluation Units
WER	Weekly Epidemiologic Report
WG	Work Group
WHO	World Health Organization

MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention
1600 Clifton Road, NE, Tom Harkin Global Communications Center (Building 19), Atlanta, Georgia
July 29, 2009

	<u>AGENDA ITEM</u>	<u>PURPOSE</u>	<u>PRESIDER/PRESENTER(S)</u>
<u>Wednesday, July 29, 2009</u>			
8:00	Welcome & Introductions ▪ Administrative announcements		Dr. Dale Morse (Chair, ACIP) Dr. Larry Pickering (Executive Secretary, ACIP; CDC)
8:15	Introduction and goals of the meeting	Information	Dr. Kathy Neuzil (ACIP Influenza Work Group Chair)
8:30	Novel influenza A(H1N1) epidemiology in the United States	Information	Dr. Anthony Fiore (CDC/CCID/NCIRD/ID; ACIP Influenza Work Group Lead)
9:00	Novel influenza A(H1N1) epidemiology - global update	Information	Dr. Joshua Mott (CDC/CCID/NCIRD/ID)
9:15	Virology and immunology update	Information	Dr. Alexander Klimov (CDC/CCID/NCIRD/ID)
9:45	Vaccine development and formulations	Information	Dr. Robin Robinson (BARDA)
10:00	FDA/VRBPAC update	Information	Dr. Wellington Sun (FDA)
10:15	Overview of H1N1 clinical trials by NIAID/NIH	Information	Dr. Richard Gorman (NIH)
10:30	<i>coffee break</i>		
10:45	2009-H1N1 vaccine and critical infrastructure key resources priority groups	Information	Dr. Terry Adirim (Senior Advisor, Office of Health Affairs, DHS)
10:55	Implementation planning	Information	Dr. Pascale Wortley (CDC/CCID/NCIRD/ISD)
11:30	Communications strategy	Information	Dr. Kris Sheedy (CDC/CCHIS/NCHM), Associate Director for Communication Science)
11:50	Public comment		
12:00	<i>lunch</i>		
1:00	ACIP Influenza Work Group recommendations	Information Discussion Vote	Dr. Anthony Fiore (CDC/CCID/NCIRD/ID; ACIP Influenza Work Group Lead) Dr. Kathy Neuzil (ACIP Influenza Work Group Chair)
3:00	<u>Adjourn</u>		

Acronyms

BARDA	Biomedical Advanced Research and Development Authority/HHS	ISD	Immunization Services Division
CCHIS	Coordinating Center for Health Information and Service	NCHM	National Center for Health Marketing
CCID	Coordinating Center for Infectious Diseases	NCIRD	National Center for Immunization and Respiratory Diseases
DHS	Department of Homeland Security	NIAID	National Institute of Allergy and Infectious Diseases
FDA	Food and Drug Administration/ HHS	NIH	National Institutes of Health/HHS
HHS	U.S. Department of Health and Human Services	VRBPAC	Vaccines and Related Biological Products Advisory Committee
ID	Influenza Division		

Welcome / Introductions

Dr. Dale Morse, ACIP Chair

Dr. Kathleen Sebelius, Director, DHHS

Dr. Larry Pickering, ACIP Executive Secretary, CDC

Dr. Morse called the meeting to order, welcoming everyone to this special session of the ACIP. Dr. Pickering also offered his welcome to the July 2009 ACIP meeting on Novel Influenza A(H1N1). He indicated that before commencing the meeting, there was a special welcome and announcement from Kathleen Sebelius, Secretary of the Department of Health and Human Services (HHS).

Dr. Sebelius offered greetings to ACIP members, liaison organizations, *ex officio* members, liaison representatives, and others. She thanked everyone for being in Atlanta for the day for this very important meeting. Every year, the public health and health care communities join forces to protect America from seasonal influenza. This year the challenge has doubled. Like seasonal influenza, the novel H1N1 influenza virus is deadly. Like seasonal influenza, it will require a multi-faceted approach for prevention and control. In the three months since this new influenza virus was identified, it has spread worldwide and disrupted communities across the United States (US). The virus has disproportionately affected younger adults and children who have no prior immunity to it. While media attention has decreased over the summer, the threat from the virus has not. It is unknown how novel H1N1 influenza will present in the coming months. It is believed that impact will be a problem again once schools reopen in the fall. The President has outlined a national framework for response to the novel influenza A(H1N1) virus. That plan consists of four pillars of preparedness that will guide actions at all levels of government: surveillance, community mitigation, vaccination, and communication.

This committee plays a special and vital role in protecting the third pillar. Vaccination is the best way to prevent the spread of influenza. Scientists at the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the Food and Drug Administration (FDA) are currently working with vaccine manufacturers to prepare and test a safe and effective vaccine. While there are off-ramps built into the decision-making process if circumstances change, a voluntary vaccination program is anticipated to begin against the novel H1N1 influenza virus in the fall. ACIP recommendations will be critical in determining the scope of the program. As Dr. Sebelius has spoken to stakeholders, partners, and the public about the novel influenza A(H1N1) virus, she has emphasized that responsibility must be shared for responding to this public health threat. The members of ACIP have a unique role to play in the team effort in providing science-based recommendations that will determine how the novel H1N1 vaccine will be distributed. She and the entire federal government offered their gratitude for ACIP's advice. In closing, she thanked ACIP members for coming together for this very important ACIP meeting and for contributing their expertise to help make the best decisions about how to use the vaccine against the novel influenza H1N1 virus. Dr. Sebelius recognized that in the coming months, ACIP would continue to play a critical advisory role in the effort to keep the American people healthy.

Dr. Pickering recognized several people in the room who were to be in attendance throughout the duration of the ACIP meeting to assist with various meeting functions: Antonette Hill (Committee Management Specialist for ACIP), Natalie Greene, Tamara Miller, Tanya Lennon, and Suzette Law.

He also extended a welcome to those joining the meeting by cyberspace. For the first time, this ACIP meeting was broadcast via the internet so that the day's proceedings would be available to members of state health departments and immunization programs across the U.S., liaison representatives who were unable to attend in person, members of US and international agencies, and others interested in the deliberations.

Handouts of all presentations were distributed to the ACIP members and were made available for members of the public each day on the tables outside of the auditorium. Slides presented for this meeting are posted on the ACIP website, generally within one week of the end of the meeting, while the minutes of the meeting are posted within 90 days of the termination of the meeting.

Members of the press interested in conducting interviews with ACIP members were instructed to contact Mr. Tom Skinner for his assistance in arranging interviews, and the press table located in the auditorium was pointed out.

Recognizing the extent of the interest in this particular meeting, two additional rooms were reserved as overflow space for additional seating. These rooms were located across the hall from the auditorium where the meeting could be viewed in real-time via audio visual equipment.

To avoid interruptions during the meeting, those present were instructed to conduct all business not directly related to discussions of ACIP in the hallways to avoid disruptions to people in the audience. Attendees were also instructed to turn off all cell phones or place them in the vibrate mode to avoid disruption.

A quorum of 14 of the 15 ACIP members was present. Given that the meeting could not continue without a quorum, all appointed members were asked to return from breaks and lunch in a timely manner to participate in the meeting.

Topics presented at the ACIP meeting include open discussion with time reserved for public comment, which the committee considers to be very important. A time for the public comment period during this meeting was scheduled following the morning session and before any vote, so that public comment could be considered prior to a vote. Those who planned to make public comments were instructed to visit the registration table at the rear of the auditorium to have Antonette Hill record their name and provide information on the process. Those who registered to make public comments prior to the meeting were instructed to meet with Ms. Hill to verify that their names were listed and to receive any additional information.

With regard to disclosure, the goal in appointing members to the ACIP is to achieve the greatest level of expertise while minimizing the potential for actual or perceived conflicts of interest. To summarize conflict of interest provisions applicable to the ACIP, as noted in the ACIP policies and procedures manual, members of the ACIP agree to forego participation in certain activities related to vaccines during their tenure on the committee. For this particular meeting, given that votes to be taken involved priority groups rather than a specific product or a specific manufacturer's product, members of the ACIP who conduct clinical trials were permitted to vote.

Dr. Pickering extended special gratitude to the ACIP members, liaison representatives, and *ex officio* members for taking time from their busy schedules to consider this important subject. Particular gratitude was expressed to Drs. Morse and Beck who were recruited and agreed to attend this meeting despite their official tenure on the committee having ended.

The ACIP home page was shown on screen. The url is: www.cdc.gov/vaccines/recs/acip/
This website is updated at frequent intervals with current versions of the meeting agenda, minutes, presentations, and other information. Other useful resources also were shown, which included the following:

ACIP e-mail: acip@cdc.gov

MMWR: **Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009.**
www.cdc.gov/mmwr/pdf/rr/rr58e0724.pdf

Vaccine Safety: www.cdc.gov/vaccinesafety/

Next ACIP meeting: October 21-22, 2009

Registration Deadlines:

Non-US citizens 10/2/09

US-citizens 10/9/09

On line registration (required):

www.cdc.gov/vaccines/recs/acip/meetings.htm#register

No conflicts of interest were declared for this meeting.

Introduction and Goals of the Meeting

Kathy Neuzil, MD, MPH
Chair, Influenza Vaccine Work Group

Dr. Neuzil acknowledged that this was an extraordinary meeting of ACIP, and that it had taken extraordinary efforts on the part of many people inside and outside the agency to orchestrate it. She stressed that the highly inclusive membership of the Influenza Vaccine Work Group had been deliberate and thoughtful in its considerations, and comprehensive in its review of the issues. Representatives from many organizations have been included in the work group's calls, representing views of different segments of the population and of different groups. She then indicated that the goals of this specially convened ACIP meeting were to:

- Review current epidemiology and virology of influenza pandemic, vaccine supply and demand estimates, and implementation plans;
- Provide evidence-based recommendations on target groups for pandemic vaccination efforts based on currently available data, including top priority groups in event of local or national supply-demand mismatch;

- Provide recommendations that would allow the overall vaccination program, seasonal and pandemic, to be most successful (the work group has been referring to these as seasonal and pandemic vaccines for simplicity); and
- Recognize and acknowledge uncertainties, as well as the potential need to reconsider recommendations as more data become available.

With respect to the Influenza Vaccine Work Group process during June and July 2009, during the regularly scheduled ACIP meeting on June 24-25, a considerable amount of time was spent on the topic of novel H1N1. Since that time, there have been weekly teleconferences, on-going email and telephone discussions, and there was a long work group meeting on July 28, 2009.

To bring people up to date on some of the recommendations in the rest of the world and also some of the information that led the work group to this point, the World Health Organization (WHO) convened an extraordinary meeting of their Strategic Advisory Group of Experts (SAGE) on July 7, 2009 to provide guidance for the pandemic. The WHO has outlined their pandemic priorities to protect the integrity of the health care system and countries' critical infrastructure to reduce morbidity and mortality and reduce transmission of the pandemic virus within communities. The results of those deliberations have been published in the Weekly Epidemiologic Report (WER), which can be found at the following url: <http://www.who.int/wer/2009/wer8430/en/index.html>. The SAGE statement is as follows:

“All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.”

The US is making its own decisions and considerations, although it is important to know and have this information from other groups / countries.

There has already been considerable planning in the US in the event of a pandemic. The National Vaccine Advisory Committee (NVAC) and ACIP examined recommendations for prioritization of pandemic influenza vaccine prior to this pandemic. The primary goal of a pandemic response at that time was to decrease health impacts, including severe morbidity and death, and secondary pandemic response goals, including minimizing societal and economic impacts [HHS Pandemic Influenza Plan, 2005; <http://www.hhs.gov/pandemicflu/plan/appendixd.html>].

The US pre-pandemic planning guidance also considered a number of recommendations, included a number of groups, and included public engagements between 2005 and 2008. The priorities of a pandemic vaccine program recommended by the US Interagency Work Group outlined the following elements in 2007:

- Protecting those who are essential to the pandemic response and provide care for persons who are ill;
- Protecting those who maintain essential community services;
- Protecting children; and

- ❑ Protecting workers who are at greater risk of infection due to their job.

However, it is very important to note that this was pre-pandemic. Much of the planning focused on a severe pandemic scenario, with the potential for substantial disruption of critical infrastructure. It was fully acknowledged that the intent was to modify according to the pandemic epidemiology and vaccine supply expectations [HHS / DHS. Guidance on allocation and targeting pandemic influenza vaccine, 2007; <http://www.pandemicflu.gov/vaccine/allocationguidance.pdf>].

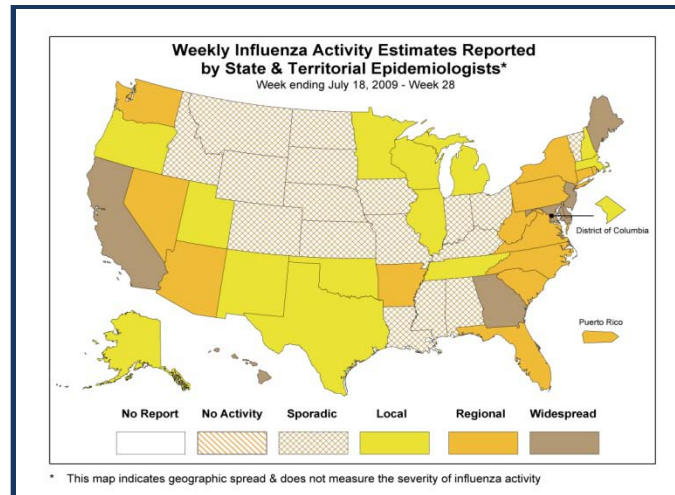
During this ACIP meeting, presentations were delivered on the following:

- ❑ U.S. Epidemiology Update (Dr. Anthony Fiore, CDC)
- ❑ World Epidemiology Update (Dr. Josh Mott, CDC)
- ❑ Virology and Immunology (Dr. Alexander Klimov, CDC)
- ❑ Vaccine Development (Dr. Robin Robinson, BARDA)
- ❑ FDA Update (Dr. Wellington Sun, FDA)
- ❑ Overview of Clinical Trials (Dr. Richard Gorman, NIH)
- ❑ Critical Infrastructure Issues (Dr. Terry Adirim, DHS)
- ❑ Implementation Planning (Dr. Pascale Wortley, CDC)
- ❑ Communications Strategy (Dr. Kris Sheedy, CDC)
- ❑ ACIP Influenza Workgroup Recommendations (Dr. Anthony Fiore, CDC and Dr. Kathy Neuzil, Workgroup Chair)

Novel Influenza A(H1N1) Epidemiology: United States

Anthony Fiore, MD, MPH
Influenza Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Fiore reminded everyone that during the June 2009 ACIP meeting, Dr. Lyn Finelli Surveillance Team Leader, provided a comprehensive epidemiologic update to that point on Novel Influenza A(H1N1). Moving forward, as of July 18, 2009, the assessment activity from state and territorial epidemiologists reflects that there continues to be activity, with widespread activity in some states:



Based on three seasons worth of data from the Influenza-Like Illness Surveillance Network (ILINet), to which over 2000 sentinel providers across the US report, during the 2007-2008 season there was an increase of activity in early May 2008 for provider visits for Influenza-Like Illness (ILI) that continued for several weeks that was well above baseline of what is typically observed during that timeframe.

The national data masks some important regional data that are important to consider. Region 1 (e.g., Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) showed a pattern somewhat similar to the national data, but with two peaks, the second of which was later than the national pattern. Region 2 (e.g., New Jersey, New York) was hit very hard by the outbreak in the spring and early summer, with a substantial peak of ILI that exceeded any of the rates that were observed in the previous two influenza winter seasons. Region 3 (e.g., Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, West Virginia) showed a pattern similar to the national data, with not as prominent a peak as seen in the national data during April and May.

Laboratory-confirmed novel influenza A(H1N1) case counts as of July 24, 2009 for the US included 43,771 laboratory-confirmed cases, with 5,011 hospitalizations and 302 deaths. Regarding case characteristics, 50% were male and 50% were female. The median age in all cases was 12 years, hospitalized cases 20 years, and deceased cases 37 years. Counts of confirmed cases were affected by guidance to focus testing on persons at risk for complications or who were hospitalized, which was intentional to permit state laboratories conducting the confirmatory testing to keep up with demand.

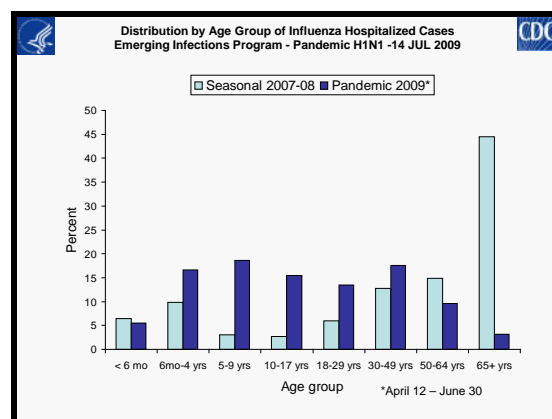
Weekly aggregate cases are currently reported. It is important to remember from the case counting data that as time has gone on and testing practices have changed, the data are somewhat skewed by that fact that sickest people are the ones most likely to be tested. More specifically with regard to laboratory-confirmed cases by age group, 4816 cases were 0 through 4 years of age (11%); 22,080 cases were 5 through 24 years of age (50%), 7434 were 25 through 49 years of age (17%), 2187 cases were 50-64 years of age (5%), 513 cases were 65 years of age or older (1%), and age was unknown for 6741 cases (15%). The theme of a striking age group difference from seasonal flu from novel H1N1 continues throughout the data. Due to rounding, percentages may not add up to exactly 100%. The rates per 100,000 population by age group of laboratory-confirmed cases tell a slightly different story, in that the

rates are highest in those 5 through 24 years of age (26.7), although they are also quite high in children less than 4 years of age (22.9), with lower rates as age groups increase.

Dr. Fiore presented data on the incidence of confirmed or probable influenza A(H1N1) by age group in the US earlier in the epidemic (e.g., March 15-May 16, 2009) in response to the ACIP's call in June for more refined case counting data of confirmed cases and for further examination of the younger age group (n=2672). For those less than 4 years old, rates are somewhat lower than rates in older school-aged children and decreasing rates with increasing age. With the rates being highest in school-aged children, because most children have relatively mild, a way to measure impact is by examining school dismissals related to novel influenza A(H1N1) mitigation measures. This was heavily influenced by policies in place at the time for school dismissal, remember that earlier in the outbreak, school dismissals were recommended in some instances for a single case in a school. Over time, that recommendation was eased off as more was understood about the lack of severity for most infections and the difficulty that closing schools poses for communities. From April 29 through May 27, 2009, at the peak of school dismissals in early May, nearly half a million school-aged children (n=468,282) were out of school with 726 schools closed.

In terms of hospitalizations by age group of laboratory-confirmed novel influenza A(H1N1), as of July 24, 2009 (n=5,011), moving from the highest to the lowest, the highest number was in the 5 to 24 year old age group (n=1718; 34%); 24 to 49 year olds (n=1184; 24%); 0 to 4 year olds (n=953; 19%); 50 to 64 year olds (n=658; 13%); unknown ages (n=273; 5%); and ≥ 65 years old (n=225; 4%). With regard to the hospitalization rate per 100,000 population by age group of laboratory-confirmed novel influenza A(H1N1) as of July 24, 2009 (n=4,738; does not include unknown age group of 273), children aged 0 to 4 had the highest rate at 4.5 / 100,000 followed by the school-aged and younger adult age group of 5 to 24 years at 2.1 / 100,000 [Rate / 100,000 by Single Year Age Groups: Denominator source: 2008 Census Estimates, U.S. Census Bureau at: <http://www.census.gov/popest/national/asrh/files/NC-EST2007ALLDATA-R-File24.csv>].

The Emerging Infections Program sites are the source of a large population-based dataset from May through July 2009 that shows that during this timeframe, there was essentially a winter season's worth of cumulative hospitalizations in 5 to 17 year olds and nearly a winter season's worth in the 18 to 49 year olds. The following illustrates the striking difference between seasonal and pandemic influenza as of July 14, 2009:



The 2007-2008 season was mild to moderate, probably the most active season over the last four winter seasons. The percentage of patients 65 and older among hospitalized patients was very high. The striking contrast to that is that during the pandemic, many more cases were observed in 6 months to 4 years old, 10 to 17 year olds, and the 30 to 49 year olds. It is not until the 50 to 60 year old age group until the percentage begins to approach what looks more like a seasonal percentage of cases.

In terms of underlying medical condition among persons hospitalized with laboratory confirmed influenza A(H1N1), detailed clinical information was collected on the first 268 hospitalized patients on which the investigators were able to obtain information in the April to May time period. The prevalence of underlying conditions amongst those cases was 20% in those 0 to 6 month of age, 40% in 6 month to 23 month, 50% in 2 to 4 year olds, 85% in 5 to 9 year olds, 62% in 10 to 17 year olds, 75% in 18 to 49 year olds, 87% in 50 to 64 year olds, 100% in 65 year olds and above [Jain et al, CDC unpublished data. Case series of patients with confirmed novel H1N1 infection who were hospitalized during April-May 2009].

Deaths by age group of laboratory-confirmed novel influenza A(H1N1) as of July 24, 2009 (n=302) included: 7 (2%) in 0 to 4 year olds, 48 (16%) in 5 to 24 year olds, 124 (41%) in 25 to 49 year olds, 71 (24%) in 50 to 64 year olds, 26 (9%) in \geq 65 year olds, and 26 (9%) of an unknown age. There has been a pediatric death reporting system in place since 2004. Over the last four influenza seasons, deaths due to laboratory-confirmed influenza in the 2005-2006, 2006-2007, and 2007-2008 seasons seasonal influenza deaths ranged from 46 to 88. Over the past influenza season, in the winter there were 67 deaths due to seasonal influenza, which was somewhat lower from previous years. However, there have been 23 pandemic-related pediatric deaths reported to date. The median age for deaths among children is 10 years compared to 7 years for the seasonal influenza in this past season.

To summarize the key epidemiologic findings, in terms of the distribution of cases, hospitalizations, and deaths, the highest incidence of laboratory-confirmed infections have been in school-aged children. The highest hospitalization rates have been among 0 to 4 year olds. The hospitalization rates for April through July 2009 have been similar to annual cumulative hospital rates for seasonal influenza among school-aged children and 18 to 49 year old adults. The fewest cases but highest case-fatality ratio has been in older adults. Distribution of cases by age group is markedly different compared to seasonal influenza. There has been a higher proportion of hospitalized cases in children and young adults, few cases in older adults, and no reports of outbreaks among residents in long-term care facilities. Long-term care facilities are typically one of the harbingers of a bad seasonal influenza. Of the hospitalized cases, 70% had an underlying medical condition that conferred higher risk for complications.

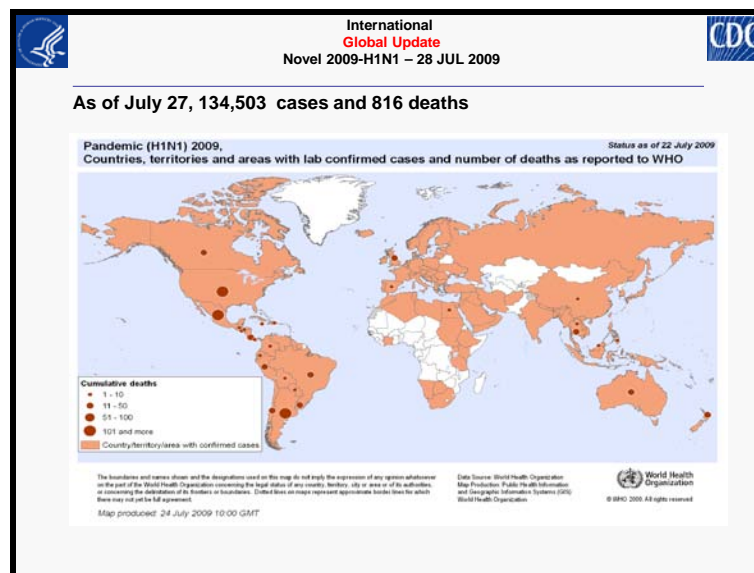
With respect to plans for surveillance studies, CDC will continue with the established surveillance systems. There is syndromic surveillance monitoring through established systems (e.g., ILINet, Biosense) for outpatient illness. There are also population-based surveillance platforms (e.g., Emerging Infections Program) that are monitoring hospitalizations. Pediatric deaths due to laboratory-confirmed influenza will continue to be monitored. Deaths due to pneumonia and influenza will be monitored in 122 cities through mortality surveillance using modeling of data from this system. Viral surveillance is monitored through WHO / National Respiratory Virus Surveillance System (NRVSS) labs throughout the country, through which specimens are collected from persons with ILI to test them for influenza and determine which sub-type they have. Additional surveillance studies are planned as well. There will be monthly telephone surveys for ILI attack rates by state run through the Behavioral Risk Factors

Surveillance System (BRFSS). While there will be monthly data, the investigators should be able to obtain rolling averages by week. This will give them a sense of what is occurring in the community and should capture the burden of ILI in communities in ways that medical visits / hospitalizations do not. CDC is also working with CSTE to improve methods for acquiring laboratory-confirmed deaths and hospitalizations.

Novel Influenza A(H1N1) Epidemiology: Globally

Josh Mott, PhD
Influenza Division
National Center for Immunizations and Respiratory Diseases
Centers for Disease Control and Prevention

Referring to the following map illustrating countries that have had confirmed novel A(H1N1) cases and deaths throughout the world, Dr. Mott pointed out that many countries across the latitudes of the world have had confirmed cases (n=134,503) and deaths (n=816) as of July 27, 2009. There has been a shift in testing practices from less severe to more severe cases almost uniformly throughout the world, and WHO continues to gather information on laboratory-confirmed cases from its regional offices.



Dr. Mott stressed that the number of cases was likely to be a gross under-estimation of what was actually occurring, given that many countries have shifted to clinical characterization and confirmation of less severe cases. Whether examining confirmed cases or syndromic surveillance, the locations that have experienced the most deaths also have reported the largest intensity of circulation to date.

In terms of CDC's international program, there are two primary objectives related to the pandemic response. The first is that there are many laboratory and technical resources throughout the world, as well as existing partnerships through agreements for established seasonal influenza surveillance and programs throughout the world, for which CDC can provide

assistance. CDC is working diligently to do this through the laboratory and epidemiologic resources. At the same time, CDC has a keen interest in what is occurring, particularly in the Southern Hemisphere where influenza is in its high season. In that regard, observing what is occurring with the novel influenza virus and the co-circulation of influenza virus can help to better understand changes in transmission, epidemiology, severity, changes in the virus itself, and the effectiveness of interventions. CDC working with existing partners throughout the world (e.g., Ministries of Health, WHO, and others) to: 1) enhance on-going communications and share information at greater frequencies than usual; 2) enhance surveillance and investigation, improving sentinel site surveillance and focusing on CDC platforms that have been doing this for many years; and 3) implement programs (e.g., through CDC platforms, sentinel sites, and international deployments) that can answer key research and investigation questions to answer epidemiologic and transmission questions where there are technical and infrastructural resources to do.

In terms of the current situation throughout the world as of July 27th, in Australia there were 17,061 cases, 2154 hospitalizations, and 50 Deaths. Of the hospitalizations, 27% (103 / 378) were in ICU. The overriding story is that in many locations, the novel H1N1 virus has moved to become a large majority of influenza viruses circulating in Australia and New Zealand. Victoria had the earliest wave of the outbreak and has moved through its first wave of the pandemic now, such that they have observed declines in ILI consultation rates over the last three to four weeks. In the State of Victoria, almost all of the viruses currently being detected are novel H1N1. That has not been quite the same story in other places. The pandemic is more at its peak or plateau in New South Wales and Western Australia. For example, in New South Wales, Sydney may be moving toward some declines in ILI consultations rates, but there are still increases in outlying and regional areas in New South Wales. There is an on-going rise in influenza activity in Western Australia. In all of these locations, H1N1 has moved toward some dominance. Many of the influenza viruses that are not novel H1N1 that have been sub-typed, many are H3N2, although there a lot of un-sub-typed viruses circulating.

In the rest of the world, the picture remains similar. In Chile and Argentina, there is a large dominance of novel H1N1 virus relative to seasonal viruses. This is somewhat less true in Brazil where much of the outbreak activity has been focused in the Southern part of the country. South Africa has been an exception to the rule so far where there is community spread of the novel H1N1 virus, but a large proportion of the viruses circulating are H3N2. In the Northern Hemisphere (e.g., US, Canada, England) almost exclusively novel H1N1 influenza virus is being found. In 2008, Western Australia went through an influenza B season and moved into a 2009 season that began as H3N2 with some H1N1, but now is predominated by novel H1N1. Australia's influenza season occurred somewhat earlier than their baselines have been for the last couple of years. South Africa went through a normally timed H3N2 season in 2009, but then began to observe community transmission of the novel virus. However, there has not yet been a second wave or peak to their influenza season as was observed in the US; however, there is a notable portion of novel virus.

There has also been activity outside of the most Southern countries, particularly in the tropical and developing regions. Thailand has had a surge in cases. They have moved from reporting 6000 cases and > 30 deaths on July 21st to 10,000 cases and 52 deaths on July 24th. There has been an increase in more severe illness being reported in Thailand, which is likely due to a real increase in illness as well as a change in their surveillance approach to focus on testing more severe cases. This is quite notable because the latitude reflects that there is sufficient transmission and notable burden of disease in the tropical region as well. CDC has a lot of platforms in these regions, so some of the more detailed and investigation questions to be

answered can be focused there—hopefully quickly from an epidemiological standpoint. The Northern Hemisphere cannot be overlooked. In European Union / EFTA Countries, there is still evidence of on-going transmission in Europe. Through Week 30, there remained a significant amount of activity.

In terms of the epidemiologic features of the novel virus in the Southern Hemisphere, little has been observed that differs from what has been observed in the US. There are high percentages of cases under than the age 20 (e.g., often over 50%). The distribution of severe illness clusters is usually in the 20 to 59 year age group. Pre-existing conditions (e.g., respiratory illness, asthma, pregnancy, metabolic disease) have all been reported in severe cases. It is difficult to assess risk factors and severity given differences in surveillance approaches in various countries. That said, the profile of these conditions in severe cases looks similar across the Southern Hemisphere. The pattern of the burden of cases with the greatest number of cases occurring at younger ages is also similar. The proportion of severe outcomes among cases appears to be greater in older ages. Time-to-treatment in several countries has been associated with severe outcomes, specifically time from onset to hospitalization. Indigenous and rural populations have been disproportionately affected, which is possibly a function of greater underlying health status and access to care.

In summary regarding the severity of cases in the Southern Hemisphere, there are many differences in the numbers of confirmed cases and the numbers of deaths by country. The numbers of cases is very much influenced by the testing practices that an individual country may choose to use. Most less-severe illness is not being confirmed in any country. There has typically been a concurrent rise in less-severe disease that accompanies increased reports of severe cases in any particular country. Shifts in testing practices to focus on more severe cases affects the case fatality rate, or the proportion of confirmed cases that have severe outcomes in any given country. This depends very upon the timing of the shift to focus on severe cases, which is not easily compared between countries. Adjusting for population size when assessing absolute numbers of deaths across various countries reduces observed disparities in severity. The epidemiology remains similar across countries, and the current viruses look similar to A/California/2009. Currently, there is no evidence to suggest something is “different” in any particular country.

Virology and Immunology Update

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Dr. Klimov provided a brief update of virology and immunology data on the pandemic H1N1 virus, which represented an update of what Dr. Nancy Cox presented at a previous ACIP meeting. Several major questions could be raised with respect to surveillance in terms of novel H1N1 and whether the virus is drifting genetically, whether it is drifting antigenically, whether the sensitivity of the virus against licensed drugs is changing, and whether there is evidence of reassortment between novel virus and seasonal viruses.

With respect to the genetic characterization, as illustrated by the phylogenetic tree for hemagglutinin (HA) genes of novel influenza virus, genetically the viruses appear to be homogeneous. Looking at a similar tree for seasonal influenza, there is much wider variability

within the HA gene. The novel phylogenetic tree is built up against the A/New Jersey/8/1976 H1N1, which shows the many differences there are between the previous 1976 virus and the recent pandemic virus of swine heritage. The phylogenetic tree for neuraminidase genes built against the A/New Jersey/8/1976 H1N1 again reflects wide genetic variability between the seasonal and pandemic viruses. The following table reflects the genetic distance between A/New Jersey/8/1976 and A/Texas/05/2009 compared with H3N2 viruses:

	HA Number of Nucleotides Different (%)	HA Number of Amino Acids Different (%)	NA Number of Nucleotides Different (%)	NA Number of Amino Acids Different (%)
A/New Jersey/8/1976 vs A/California/7/2009 (H1N1)	184 (11%)	44 (8%)	282 (20%)	82 (18%)
A/Victoria/3/1975 vs A/Brisbane/10/2007 (H3N2)	185 (11%)	57 (10%)	120 (9%)	47 (10%)

The number of nucleotide differences between 1976 and California 7 is 11%. At the level of amino acid differences, this is 8%. It is even higher at the neuraminidase level, with 20% at the nucleotide and 18% at the amino acid level. When these data are compared to H3N2 viruses, Brisbane/10/2007, the current vaccine strain for H3 component has many differences. It would be necessary to go back to A/Victoria/3/1975 H3N2 virus. Thus, the distance between A/New Jersey/8/1976 and recent viruses is approximately, at the nucleotide and amino acid level, between A/Victoria/3/1975 and A/California/7/2009.

The genetic and antigenic data are based on quite a number of viruses (n=861), which are either sequenced or antigenically characterized. Approximately 450 (n=449) viruses are characterized from North America, 81 from Central and South America, 106 from Asia and Oceania, and 225 from Europe. In total, 39 complete genomes have been sequenced for novel influenza H1N1 viruses.

The following table illustrates antigenic variability, or non-variability in this case, between novel H1N1 viruses:

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (CDC)													
STRAIN DESIGNATION	REFERENCE FERRET ANTISERA											Date collected	
	SW/IA/30N/J/8/76	WI/10	TX/14	IL/9	IA/09	CA/07	MX/4108	NY/18	TX/15	AS/59	Passage		
1 A/SWINE/IOWA/1930	320	160	5	10	5	5	5	5	5	5	XEXE3	UNKN	
2 A/NEWJERSEY/8/1976	160	640	10	20	10	10	5	5	5	5	SpFE7	UNKN	
3 A/WISCONSIN/01/1998	5	80	1280	1280	1280	640	640	640	640	5	C3/C3E2	1/23/98	
4 A/TEXAS/14/2008	80	160	320	2560	1280	1280	1280	1280	640	2560	M1/C2	10/15/08	
5 A/ILLINOIS/9/33304/2007	80	160	1280	2560	5120	2560	2560	1280	1280	5	C2	09/01/07	
6 A/IOWA/02/2009	40	160	1280	5120	5120	2560	2560	2560	2560	5	E2	02/13/09	
7 A/CALIFORNIA/07/2009	40	10	320	2560	1280	2560	1280	1280	1280	5	E3	04/09/09	
8 A/MEXICO/4108/2009	40	10	320	2560	1280	2560	640	640	640	5	C1/E2	04/03/09	
9 A/NEW YORK/18/2009	10	5	320	1280	640	1280	1280	640	640	5	E2	UNKN	
10 A/TEXAS/15/2009	20	10	640	5120	2560	2560	5120	2560	1280	5	C2	07/01/07	
11 A/BRISBANE/5/907	5	5	5	5	5	5	5	5	5	160	E2/E2	07/01/07	
TEST ANTIGENS													
Fatal cases													
12 A/UTAH/03/2009	20	5	160	2560	1280	1280	2560	1280	1280	5	C1	05/15/09	
13 A/WASHINGTON/14/2009	5	5	160	2560	1280	1280	1280	640	640	5	C2	05/07/09	
14 A/ARIZONA/07/2009	20	5	320	2560	1280	1280	2560	2560	2560	5	C1	05/07/09	
MDCK and EGG pairs													
15 A/NEW YORK/04/2009	5	5	320	2560	640	1280	2560	1280	640	1280	5	C1	UNKN
16 A/NEW YORK/04/2009	80	20	320	2560	1280	1280	2560	640	640	1280	5	E2	UNKN
17 A/NEW YORK/05/2009	40	20	320	2560	1280	1280	2560	1280	1280	5	C1	UNKN	
18 A/NEW YORK/05/2009	5	5	320	2560	1280	1280	2560	640	1280	1280	5	E2	UNKN
19 A/NEW YORK/35/2009	160	80	320	5120	2560	2560	5120	2560	2560	5120	5	C1	04/25/09
20 A/NEW YORK/35/2009	20	5	320	2560	1280	1280	2560	2560	2560	1280	5	E2	04/25/09
MDCK or EGG grown													
21 A/TEXAS/31/2009	10	5	320	2560	1280	1280	2560	2560	1280	1280	5	C1	05/12/09
22 A/MONTANA/01/2009	20	10	320	2560	1280	1280	1280	1280	1280	1280	5	C1	05/05/09
23 A/FLORIDA/09/2009	5	5	320	2560	1280	1280	2560	1280	1280	1280	5	C1	05/01/09
24 A/CALIFORNIA/19/2009	5	5	160	1280	640	640	1280	640	1280	1280	5	C1	04/30/09
25 A/NEW HAMPSHIRE/03/2009	20	10	320	1280	1280	1280	2560	1280	1280	1280	5	C1	04/28/09
26 A/GEORGIA/02/2009	5	5	320	2560	1280	640	1280	1280	1280	1280	5	C1	05/04/09
27 A/IDAHO/03/2009	5	5	320	2560	640	640	1280	1280	1280	1280	5	C1	05/05/09
28 A/MAINE/02/2009	80	10	640	2560	2560	2560	2560	2560	2560	5	C1	05/05/09	
29 A/NEVADA/04/2009	40	5	640	2560	1280	1280	2560	1280	1280	1280	5	E2	04/29/09
30 A/NEW YORK/45/2009	80	5	1280	2560	1280	1280	2560	2560	2560	5	E2	04/25/09	
31 A/MEXICO/4283/2009	160	40	1280	5120	2560	5120	5120	2560	5120	5120	5	C1/C1	04/15/09
32 A/MEXICO/4575/2009	320	80	1280	5120	5120	5120	5120	5120	5120	5	C1/C1	04/20/09	
33 A/GUATEMALA/450/2009	10	5	320	2560	1280	1280	2560	1280	640	1280	5	C1	05/01/09
34 A/COLOMBIA/330/2009	5	5	640	5120	2560	2560	2560	2560	2560	2560	5	C1	05/02/09
35 A/EL SALVADOR/351/2009	20	5	320	2560	1280	1280	2560	1280	1280	1280	5	C1	05/13/09
36 A/NONHABUR/02/09	40	10	640	5120	2560	2560	2560	1280	2560	5	C1/C1	05/04/09	
37 A/AUCKLAND/01/2009	5	5	640	2560	1280	1280	2560	1280	640	1280	5	C2/C1	04/25/09
38 A/AUCKLAND/03/2009	10	5	320	2560	640	1280	2560	640	1280	1280	5	C2/C1	04/25/09
39 A/ENGLAND/195/2009	20	10	640	5120	2560	5120	1280	1280	2560	5	X/C1	UNKN	
Reassortants													
40 A/CALIFORNIA/07/2009 X-1	5	5	640	5120	2560	2560	2560	1280	1280	2560	5	EX/E1	REASS
41 A/TEXAS/5/2009xPR8-IDCD	20	5	640	2560	1280	2560	2560	1280	1280	1280	5	VE2/E1	REASS

At the top of the table are a battery of reference viruses and a battery of reference ferret post-infection anti-sera. Not only are all swine viruses or like swine viruses from 1930 and A/New Jersey/8/1976, there is a copy of ferret anti-sera against viruses isolated from people infected with so-called classical reassortant viruses before the pandemic H1N1 appeared in the US. This table reflects that novel H1N1 viruses are quite different antigenically from A/New Jersey/8/1976. They are closer to recent classical swine reassortant cases before the appearance of novel influenza viruses, but not quite. Looking at CA/07 and MX/4108, NY/18, and TX/15, all of the viruses are pretty similar to each other antigenically. In this data, viruses isolated from fatal cases are not different antigenically from other viruses. They have viruses grown in MDCK cells and in eggs. Growing in eggs in many cases may cause the appearance of mutants, which would be antigenically different. In this case, no such difference is observed between MDCK-grown and egg-grown viruses. Foreign viruses from Mexico, Guatemala, Columbia, El Salvador, Thailand, New Zealand and England are similar to each other, similar to the US viruses, and similar to the reference CA/07 case. At the bottom of the table are two vaccine candidates, A/California/07/2009 X-1 high yield reassortant prepared using the classical technique, and the A/Texas/5/2009xPR8-IDCD prepared by using reverse genetics.

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (CDC)												
STRAIN DESIGNATION	REFERENCE FERRET ANTISERA											
	CA/04	CA/07	X-179A	MX/4108	NY/18	TH/102	TX/05	RG-15	ENG/195	AS/59	Passage	Date collected
1 A/CALIFORNIA/04/2009	320	1280	640	1280	640	320	1280	80	640	5	C2	04/01/09
2 A/CALIFORNIA/07/2009	1280	2560	1280	2560	2560	640	2560	320	1280	5	E3	04/09/09
3 A/CALIFORNIA/7/09 NYMC X-179A	5120	20480	2560	5120	5120	1280	5120	1280	2560	5	EX/E1	REASS
4 A/MEXICO/4108/2009	2560	5120	1280	1280	2560	640	2560	320	1280	5	C1/E2	04/03/09
5 A/NEW YORK/18/2009	1280	2560	1280	1280	1280	320	1280	160	640	5	E2	UNKN
6 A/NONTHANBURI/102/2009	2560	10240	2560	2560	2560	640	2560	320	2560	5	C1/C2	05/04/09
7 A/TEXAS/05/2009	640	2560	640	1280	1280	320	1280	160	640	5	X/C2	04/15/09
8 A/TEXAS/2009 PR8-IDCDC RG15	2560	5120	2560	1280	1280	640	2560	640	1280	5	VE/E1	REASS
9 A/ENGLAND/195/2009	2560	5120	2560	2560	2560	640	2560	5120	2560	5	X/C1	UNKN
10 A/BRISBANE/59/07	5	5	5	5	5	5	5	5	5	320	E2/E2	07/01/07
TEST ANTIGENS												
11 A/DELAWARE/03/2009	2560	5120	2560	2560	5120	640	2560	320	1280	5	E2	04/28/09
12 A/SOUTH CAROLINA/10/2009	1280	2560	2560	2560	2560	640	5120	160	1280	5	C1	04/15/09
13 A/ARKANSAS/04/2009	640	1280	640	1280	640	320	1280	160	640	5	C2	05/07/09
14 A/MICHIGAN/11/2009	1280	5120	1280	2560	2560	640	2560	320	2560	5	C2	05/04/09
15 A/CALIFORNIA/23/2009	1280	2560	640	1280	640	320	1280	160	1280	5	C2	05/26/09
16 A/MASSACHUSETTS/15/2009	640	2560	1280	1280	1280	320	2560	160	1280	5	C1	05/26/09
17 A/NEW YORK/6/1/2009	640	2560	640	1280	1280	320	2560	160	1280	5	C2	05/26/09
18 A/NEW YORK/7/1/2009	1280	5120	1280	1280	1280	640	2560	320	2560	5	C1	05/23/09
19 A/TEXAS/36/2009	1280	5120	1280	1280	1280	320	2560	160	1280	5	C1	04/29/09
20 A/MEXICO/INDRE4487(10)/2009	1280	5120	1280	2560	1280	640	5120	640	1280	5	E2/E1	UNKN
21 A/PARAGUAY/1/2009	1280	2560	1280	1280	1280	320	2560	160	1280	5	C1	06/04/09
22 A/CHILE/2408/2009	1280	5120	2560	2560	2560	640	2560	320	2560	5	C2/C1	06/08/09
23 A/CHILE/2085/2009	640	2560	640	1280	1280	320	1280	160	1280	5	C2/C1	06/05/09
24 A/JAMAICA/4422/2009	1280	2560	1280	1280	1280	320	2560	160	1280	5	C2	06/06/09
25 A/NARITA/1/2009	2560	5120	1280	2560	2560	640	2560	640	1280	5	E2/E1	UNKN
26 A/AUCKLAND/1/2009	1280	5120	1280	1280	1280	320	2560	320	1280	5	E2/E2	04/25/09
27 A/NEW ZEALAND/870/2009	640	2560	1280	1280	1280	640	1280	160	1280	5	C2	06/14/09
28 A/NEW ZEALAND/1680/2009	1280	2560	640	1280	1280	320	2560	320	1280	5	E2	06/19/09
FATAL CASES												
29 A/TEXAS/15/2009	2560	10240	2560	2560	2560	640	2560	320	2560	5	C2	04/15/09
30 A/UTAH/10/2009	1280	2560	1280	1280	1280	640	5120	320	2560	5	C2	06/05/09
31 A/UTAH/06/2009	1280	5120	1280	2560	1280	640	5120	320	2560	5	C1	06/12/09
REASSORTANTS-DIRECT TESTING												
32 A/TEXAS/05/2009-PR8-IDCDC RG18	5120	20480	5120	10240	10240	2560	10240	1280	10240	5	V/E3	REASS
33 A/TEXAS/05/2009-PR8-IDCDC RG20	2560	10240	2560	2560	2560	640	5120	640	2560	5	V/E3	REASS
34 A/NEW YORK/18/2009-PR8-IDCDC RG22	2560	5120	2560	2560	2560	1280	5120	320	2560	5	V/E3	REASS
35 A/CALIFORNIA/07/2009 186d MEDIMMUNE	5120	10240	5120	5120	2560	1280	5120	640	5120	5	EX	REASS
36 A/CALIFORNIA/07/2009 395N MEDIMMUNE	2560	5120	2560	2560	2560	1280	5120	320	2560	5	EX	REASS

The table above shows that the pattern remains stable. This includes viruses from fatal cases that do not differ. There are additional reassortants, including reassortants prepared by MedImmune, which is developing candidates for live influenza vaccine. These reassortants are similar antigenically to CA/07.

HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (NIMR)										
Passage	POST INFECTION FERRET ANTISERA									
	A/swIowa 15/30	A/NJ 8/76	A/Cal 4/09	A/Cal 7/09	X179A	TVR-153	A/Eng 195/09	A/Auck 3/09	A/Narita 1/09	A/Bris 59/07
REFERENCE VIRUSES										
A/Iowa/15/30	Ex	1280	<40	<40	<40	<40	<40	<40	<40	<40
A/New Jersey/8/76	Ex	320	640	320	640	320	160	320	640	640
A/California/4/2009	C1, MLE1	<40	160	2560	2560	2560	640	2560	2560	<40
A/California/7/2009	E1+1	<40	160	2560	2560	2560	640	2560	2560	<40
X-179A	Ex+1	<40	320	2560	2560	2560	640	2560	2560	5120
IVR153	Ex+1	<40	160	2560	2560	2560	640	2560	2560	<40
A/England/195/2009	MDCK3	<40	80	1280	1280	1280	320	1280	1280	2560
A/Auckland/3/2009	Ex+1	<40	320	2560	2560	2560	640	2560	2560	<40
A/Narita/1/2009	E2+1	<40	320	2560	2560	2560	640	2560	2560	5120
A/Brisbane/59/2007	E9	<40	<40	<40	<40	<40	<40	<40	<40	320
TEST VIRUSES										
A/Clermont-Ferrand/960/200MDCK2+1		<40	80	1280	1280	1280	320	1280	1280	2560
A/Perpignan/969/2009	MDCK2+1	<40	80	1280	1280	1280	640	1280	1280	2560
A/Toulouse/1026/2009	MDCK2+1	<40	160	2560	2560	2560	640	2560	2560	<40
A/Lyon/1041/2009	MDCK2+1	<40	160	2560	1280	2560	640	2560	2560	<40
A/Cyprus/S9/2009	MDCK3	<40	80	1280	1280	1280	640	1280	2560	<40
A/Cyprus/S14/2009	MDCK3	<40	160	2560	1280	1280	640	1280	2560	<40
A/Cyprus/S17/2009	MDCK2	<40	80	1280	1280	1280	320	1280	2560	<40
A/Cyprus/S25/2009	MDCK3	<40	160	2560	1280	2560	640	1280	2560	5120
A/Algeria/G594/2009	MDCK3	<40	160	2560	1280	2560	640	1280	2560	<40
A/Singapore/99/2009	MDCK 1+1	<40	160	2560	1280	2560	640	1280	2560	<40
A/Singapore/58/2009	MDCK 1+1	<40	160	1280	2560	2560	640	1280	2560	<40
A/Singapore/100/2009	MDCK 1+1	<40	160	2560	2560	2560	640	2560	2560	5120
A/Singapore/101/2009	MDCK 1+1	<40	160	2560	2560	2560	640	1280	2560	<40
A/Singapore/102/2009	MDCK 1+1	<40	160	2560	2560	2560	640	1280	2560	<40
A/Qatar/84/2009	MDCK4	<40	160	1280	2560	1280	640	1280	2560	<40
A/Mauritius/3/2009JS	MDCK3	<40	160	2560	2560	2560	640	1280	2560	<40

The above table reflects similar data, with the only difference being that there is somewhat high cross-reactivity between the 1976 virus and recent viruses. However, that could be explained by different ferret anti-sera. In addition, the 1976 virus had several varieties that could influence the results of testing.

		HI REACTIONS OF PANDEMIC INFLUENZA H1N1v VIRUSES (NIID)					
NIID-ID	Antigens	Passage History (E, Egg/C; MDCK)	Sample date	Ferret Antisera			
				Brisbane/59/2007 (H1N1) E No.2	California/07/2009 (H1N1) pdmE2+1 No.1	Nanta/1/2009 (H1N1) pdmE1 No.3	Nanta/1/2009 (H1N1) pdm C1 No.6
Reference Antigens							
1 07/09-130	A/Brisbane/59/2007	E4	2007/07/01	640	<10	<10	<10
2 08/09-713	A/California/07/2009	E2+2	2009/04/09	<10	1280	2560	1280
3 08/09-718	A/Nanta/1/2009	E2	2009/05/06	<10	1280	2560	1280
4 08/09-721	A/Nanta/1/2009	C2	2009/05/06	<10	1280	5120	2560
Test Antigens							
5 08/09-745	A/Osaka/2/2009	C1	2009/05/17	<10	1280	2560	1280
6 08/09-802	A/Sakai/2/2009	C1		<10	1280	5120	2560
7 08/09-821	A/Fukuoka-C/3/2009	C1		<10	1280	2560	1280
8 08/09-840	A/Fukushima/1/2009	C1		<10	2560	5120	2560
9 08/09-841	A/Wale/2/2009	C1		<10	1280	5120	2560
10 08/09-842	A/Wale/1/2009	C1		<10	1280	2560	1280
11 08/09-864	A/Myanmar/60/2009	C1		<10	1280	2560	1280
12 08/09-866	A/Shizuoka-0/97/2009	C1	2009/05/26	<10	1280	2560	1280
13 08/09-867	A/Hiroshima/200/2009	C4	2009/07/01	<10	1280	2560	1280
14 08/09-868	A/Hiroshima/207/2009	C1	2009/06/15	<10	1280	2560	1280
15 08/09-872	A/Niigata/690/2009	C2	2009/06/16	<10	640	2560	1280
16 08/09-873	A/Chiba-0/48/2009	C1	2009/06/02	<10	640	2560	1280
17 08/09-874	A/Chiba-0/51/2009	C1	2009/06/16	<10	1280	5120	1280
18 08/09-875	A/Yamaguchi/21/2009	C2	2009/06/03	<10	1280	2560	1280
19 08/09-876	A/Yamaguchi/23/2009	C1	2009/06/22	<10	2560	5120	2560
20 08/09-877	A/Osaka/180/2009*	C2		<10	1280	2560	1280

* Oseltamivir resistant virus

The table above, from Japan, shows that the same pattern of antigenic similarity is observed between the vast majority of recent pandemic viruses.

With regard to resistance of pandemic influenza H1N1 viruses to adamantanes (M2 blockers), of the 308 US and 78 foreign isolates tested, 100% were found to be resistant. In terms of resistance of pandemic influenza H1N1 viruses to neuraminidase inhibitors, of the 267 US isolates and 105 foreign isolates tested, none were resistance to zanamivir or oseltamivir. However, five oseltamivir-resistant cases were recently documented in the following: Denmark (n=1) after oseltamivir treatment, Japan (n=2) after oseltamivir treatment, Canada (n=1) after oseltamivir treatment, and Hong Kong (n=1) associated with a visitor from San Francisco to Hong Kong, who was hospitalized because she developed a high temperature at the airport. This case, as far as is known, has received no treatment with oseltamivir. Thus far, this case is the only one not associated with drug treatment.

Pertaining to immunity to 2009 H1N1 virus resulting from prior influenza infection or vaccination with seasonal influenza vaccine, less than 4% of individuals born on or after 1980 exhibited pre-existing, cross-reactive, neutralizing antibody titers of ≥ 40 to the pandemic virus; whereas, 34% of individuals born prior to 1950 had titers of ≥ 80 . Vaccination with recent seasonal trivalent influenza vaccines (TIV), resulted in a ≥ 4 -fold rises in cross-reactive antibody to the pandemic virus in only about 2% of children aged 6 months to 9 years, 12% to 22% of adults aged 18 to 64 years, and $\leq 5\%$ or less of adults aged > 60 years. Seasonal TIV with adjuvant induced similar cross-reactive antibody responses [NEJM submitted].

In conclusion, all 2009 pandemic H1N1 viruses are antigenically similar to A/California/7/2009, with minor genetic variability. There is no evidence of reassortment with seasonal or H5N1 viruses. The pandemic viruses are resistant to M2 blockers, but the vast majority are sensitive to the neuraminidase inhibitors oseltamivir and zanamivir. However, oseltamivir-resistance has been recently documented in 4 of 5 cases after treatment. Vaccination with contemporary seasonal influenza vaccines, with or without an adjuvant, induces little or no cross-reactive antibody to the 2009 pandemic H1N1 virus in any age group. Individuals < 30 years of age are serologically "naïve." A proportion of older adults appear to have pre-existing, cross-reactive

antibodies. While the virus is transmissible by respiratory droplets in ferrets, the level of transmissibility is lower than the level of transmissibility of seasonal influenza viruses. Further adaptation in mammals may be required to reach the high-transmissible phenotypes observed with seasonal H1N1 viruses.

Discussion

With respect to global cases, Dr. Morse noted that Dr. Mott had shown some differences in the proportion of cases that were due to novel H1N1 versus seasonal influenza strains in various locations of the world as well as within the same country at times. With that in mind, he wondered if differences were assessed that could help explain this (e.g., lack of reagents to test for H1N1, which could lead to a higher proportion of seasonal; or selective testing of un-typable A influenza that could lead to biases toward H1N1, et cetera).

Dr. Mott responded that ideally focus should be placed on the locations that attempt to maintain systematic sampling strategies, are conducting sub-typing, and have not had issues with laboratory surge capacity. A couple of the platforms CDC has around the world have been able to do this. In Australia, in Western and New South Wales in particular, the surge capacity issues did not have an impact in a way that has precluded people from being tested particularly early on. In other locations of the world, sometimes a large portion of sub-types may be novel H1N1 in places where only influenza A is being examined initially with a screening test. That was not included in any of the pie charts presented by Dr. Mott. The pie charts shown focused on those that have been typed as influenza A and novel H1N1. Those that were treated as non-H1N1 were seasonal. However, many of the seasonals may not yet have been sub-typed.

Dr. Sawyer noted that most of the data Dr. Fiore presented was from confirmed cases. He thought one of the struggles was going to be to try to anticipate the demand for vaccine in the community, which would in part be affected by how many people had already been (or at least thought they had been) infected. Thus, he wondered whether Dr. Fiore had any updates on estimates of the actual number of people affected in the community who were not tested / confirmed. The number 1 million has been floated around recently in the press.

Dr. Fiore replied that telephone surveys have been conducted to ask people if / when they had had an ILI in the past X number of weeks, depending upon the survey. ILI is defined by the surveys as being a febrile respiratory illness with cough and / or sore throat. The community surveys conducted in New York City, there was on the order of approximately 7% of people reporting that they had experienced an ILI in the previous several weeks. These surveys will be continued moving forward through the BRFSS, with a weekly rolling average of surveys that will be conducted each month. Therefore, those who have the syndrome that could be ILI will be identified. What will not be known from those surveys is the proportion who have novel H1N1 as compared to seasonal influenza.

Dr. Sawyer inquired as to whether there were any data outside of New York. New York was particularly heavily hit based on the confirmed case data. Thus, if they wanted to average across the country, it would be less than 7%.

Dr. Fiore responded that moving forward, the BRFSS would be a nationwide survey that would provide state-based information. The Emerging Infections Program also conducted a survey, which is just administered in Emerging Infection Program sites. However, this represents a good proportion of the US population in 10 states. They observed community illness levels in those surveillance areas that were roughly the same as New York City.

Dr. Marcy indicated that several months ago, ACIP was given the impression that use of oseltamivir by exerting pressure was not selecting out resistant organisms. The example given was that Norway, which does not use a lot of oseltamivir, had a considerable amount of resistance. Japan, which seems to hold the world's record for oseltamivir use, had very little resistance. The implication now appeared to be that there is, indeed, antiviral pressure selecting out these mutants. Given that, he requested further clarification.

Dr. Klimov responded that, returning to the development of 100% reassortant resistance of seasonal H1N1, and the example given in Norway in which reassortant antivirals were not highly used, Japan had 3% to 4% resistance at that time. That shows that using reassortant antivirals in some cases can lead to appearance of drug-resistant mutants. The question regards whether such a drug resistance mutant would be able to spread widely. What is observed currently is that novel H1N1 is not much different from what as observed before the Norway phenomenon. In some cases of treatment, the resistant virus can be isolated. The question now regards the extent to resistant virus is spreading. They cannot exclude that at some point this may occur. However, it is important to remember that oseltamivir has been used for many years to treat seasonal influenza and there was no spread of resistant viruses. It is believed that resistance of oseltamivir to seasonal H1N1 began when some additional advantage was associated with this mutation and the virus started to spread widely. Whether this can occur with the pandemic virus is unknown. The last normal season in the US and China was predominantly H1N1, while Europe predominantly had H3N2. Of H1N1 seasonal influenza, 95% in China during this season were sensitive to oseltamivir. Those viruses are from a different genetic and antigenic group of seasonal H1N1 viruses. Thus, this demonstrates that the spread of resistant viruses was associated with something else that was an advantage for the virus.

In regard to the hospitalization population rate per 100,000 population by age group, Dr. Meissner observed that the highest hospitalization rate was just under 5% in the 0 to 4 year old age range. For seasonal influenza, he thought that figure was 100 hospitalizations per 100,000 among health children up to 500 children per 100,000 with underlying medical conditions. Therefore, this figure was significantly lower than seasonal influenza. He wondered whether that could be interpreted as a measure of less severe disease.

Dr. Fiore replied that the rates were lower than had been observed in some past seasons for seasonal influenza. It is important to remember that the timeframe over which this was measured was fairly short and continued to be on-going. The seasonal influenza rates were from the end of the season, so those rates could be expected to increase somewhat. He did not know whether that reflected a measure of severity in that particular age group. He thought it remained to be seen. While they were happy that there had not been as many hospitalizations in that age group proportionally as there have been in some of the other age groups, that may reflect the early epidemiology of this pandemic thus far, which has been focused on school-aged children and young adults. It may be that the older age group has not had as many exposures as they might to seasonal influenza viruses at this point.

Dr. Neuzil thought the point about the period of time and what was being compared was important. While the relative rates may be lower, clearly the absolute rates were higher than any other age group. She also thought it was important to note that numbers were relatively small and that age groups were being collapsed, so they needed to be careful about the precision of some of these rates because they were less precise than some of the larger numbers available for seasonal influenza and the finer age categories.

Dr. Meissner stressed that it was a 20-fold difference, which was fairly significant even though he agreed that the numbers were small and it was an unusual time of year for influenza.

Dr. Schuchat indicated that the team had also assessed these types of rates in the affected areas, so this represented a national average of hospitalization rates per 100,000. If reviewing age-specific hospitalization rates in one of the areas highly affected, it was much closer to the seasonal rates in addition to the fact that it was a truncated, off season.

Dr. Chilton noted that Dr. Klimov's data indicated that about a third of older adults had protective levels of antibody against the novel virus, yet it seemed as though the protection for older people was greater than just a third of older adults. He wondered whether Dr. Klimov could account for the difference.

Dr. Klimov replied that they should have further discussion about cross-protective antibodies in that age category rather than about real protection, because to measure real protection they would have to have a real count of how many had pre-existing antibodies. It is known that there are some higher levels of cross-protective antibodies in the elderly. There is some thought that antibodies in the elderly could help to protect them. The age distribution of the disease suggests that this could be the case. It is difficult to know for certain, but the origin of those antibodies could be that some people were immunized with 1976 vaccine. Some of them could have antibodies induced by H1N1 viruses that circulated before 1957, which were related to the 1918 virus. The role of genes in immunity against the influence of viruses is also not known. Also, based on the serology for H5 viruses in the elderly, there is probably some non-specific cross-reactivity. The elderly age group appears to have antibodies that cross-react with novel H1N1 and sometimes with H5N1 viruses.

Dr. Englund asked Dr. Fiore to address future plans for including more age-specific data on upcoming or on-going surveillance in smaller age group increments.

Dr. Fiore replied that they would be able to use smaller age increments for hospitalization in the Emerging Infection Program sites.

With regard to the methods for case rates, Dr. Sumaya asked Dr. Fiore what the increased value was of having the case percentages represented from a proportion of different age groups versus the rates per 100,000 population per age group.

Dr. Fiore responded that one or the other could be used. People think of this in different ways, and incidence numbers are sometimes difficult to manipulate in one's head in terms of what they mean with regard to real impact. They are the same data examined in different ways.

Dr. Temte pointed out that there is a great deal of variation in the death rates. His home state, Wisconsin, has more cases than anybody, but they have a death rate that is basically what would be expected for seasonal influenza. Wisconsin has over 6000 documented laboratory-confirmed cases with 6 deaths. That is basically a 1 per 1000 death rate. They do have a very aggressive surveillance program and very good support from the state level, so many people have been tested. The more they expand the base of their pyramid, the relatively less important the peak of the pyramid is. He asked Dr. Fiore to address why there was such a disparity. In addition, he wondered whether the transmission studies were conducted in seasonally adjusted climates representing more of the cool dry season versus a warmer more humid season.

Dr. Fiore responded that what was likely being observed was the excellent system, with a lot of testing and identification of many cases. Other states may not have similar capacity and testing is being focused on the sickest people. In fact, testing in many areas is currently restricted to hospitalized cases or cases of a particular interest because they are at risk for severe complications. He thought that explained the differences by state.

Dr. Ehresmann noted that Dr. Fiore's data did not include a lot of pregnant women, although this was a group they would be addressing. In terms of the frequency of underlying risk conditions in the 65 and older age group at 100%, she wondered how broad "risk condition" was defined and whether it was possible to be older than 65 and not have other risk conditions.

Dr. Fiore replied that in the younger age groups, chronic risk conditions were one third. The way the data were broken down, being 65 did not automatically give them a chronic condition. Sometimes the data have been presented in a different way, such as "65 or a chronic condition" lumped together. That is just chronic medical conditions, and they are defined as they are for seasonal influenza as a pre-existing heart problem, lung problem, diabetes, cancer, immunosuppression, neuromuscular disease, neurological disease, and so forth. He was not certain how many pregnant women were represented the confirmed cases at this point, other than that it was several dozen.

Dr. Schuchat thought that about 6% of the cases were pregnant as compared to about 1% of the general population, so it was a pretty elevated relative risk. Approximately 6% to 8% of the deaths have been in pregnant women, which was consistent with the higher risk of complications for seasonal influenza and pregnancy. While those numbers may not be exact, this was what she was able to immediately recall.

Dr. Fiore agreed to check this information and further respond to the committee.

Dr. Neuzil added that they had to shorten the presentations to fit everything in. Clearly, pregnancy was discussed during the last ACIP meeting as well as in the work group. The work group felt that the data supported that pregnant women are a high risk group for this pandemic.

Dr. Judson acknowledged that early on when they were dealing with so few cases, logically they had to group in different age categories than normally utilized. However, with tens of thousands of cases currently, as the committee deliberated on targeting by age, they must confront that a lot of the data to this point had been presented in groups that did not allow them to have the defining capability they would prefer. There was 0 to 4, with the next category being 20 years and covering pre-school through adults. The next grouping covered 25 years, which immunologically and epidemiologically was a more coherent group, and then there was the over 65 age group, which had always been an extremely variable group from moderate risk at 65 to incredibly high risk in the 70s, 80s, and 90s. This type of grouping had not been done previously. The data on hospitalized cases through the Emerging Infections Program used less than 6, 6 months to 4 years, 5 years to 9 years, 10 years to 17 years, and so forth. He wondered whether they planned to try to rationalize this so that the committee could utilize age groupings with which they were familiar and which had been used consistently throughout many years.

Dr. Fiore responded that the age groupings the committee was used to seeing was gathered through the population-based surveillance sites or in special studies and not through the surveillance systems that were feeding them the data for the large age groups at this point. Those systems are in place and are active, such as the Emerging Infections Program. He

thought they would be able to break down the age groups somewhat more finely for ILINet. Important to keep in mind was that the aggregate case reporting would probably soon stop. As the pandemic swept across the nation, there would be a return to the systems utilized in the past, partly due to the concern that only the sickest people were being testing and they were getting an increasingly odd picture of what the pandemic looked like based upon confirmed laboratory cases across the country. They could anticipate seeing finer age groupings in hospitalization data, the community surveys, and the ILINet data.

In thinking about designing a vaccination program, Dr. Birkhead (NVAC) thought it would be beneficial to split out school-aged from college-aged groups. He wondered whether they had any data from the Emerging Infections Program that would give them a sense of whether the risk dropped off after school-age, high school age, or whether it continued to be high in the young adult group. That would seem to be pertinent in terms of who to target for vaccination.

Dr. Fiore responded that there were two places at which the data could be broken down more finely. One was by going back to the early line list-based case reporting that ended in mid-May to the end of May. The rate among 12 to 18 year olds was 2.56 per 100,000; among 19 to 24 year olds 1.26; and among 25 to 49 year olds 0.44. So, it decreased with age. That was breaking out the young adult group of 19 to 24 year olds. The other place these data could be acquire was through the Emerging Infections Program, which had recently broken down the data into somewhat finer age groups.

Dr. Bresee replied that these data were broken down that morning. They found that the rate of hospitalization for 5 to 18 year olds was .54 per 10,000 and in 19 to 23 year olds was .43 per 10,000—about a 20% decrease in the slightly older age group. This was from the period of time when novel H1N1 was circulating during the spring and early summer.

Dr. Fiore clarified that that was for hospitalization, while the date he just gave was for confirmed cases.

Dr. Poland (ACP) requested an update on the issue of health care workers and H1N1 infection in both ways (e.g., them acquiring the virus and potentially transmitting it in the context of the hospitalized patients). He also wondered whether health care workers who had acquired the virus had been in the setting of aerosolization procedures.

Dr. Fiore responded that infections have been observed in health care workers. There was a recent *MMWR* addressing this issue. A number of health care workers were thought to have acquired their illness in the community, though others were thought to have acquired their illness within the hospital. Certainly, health care workers without person protective equipment would be at risk for acquiring influenza from patients just as they were during seasonal influenza. The magnitude of that risk remained uncertain at this point. In terms of nosocomial transmission (e.g., health care workers transmitting novel influenza to patients) there were a couple of instances of patients acquiring influenza while hospitalized with an incubation period suggesting they acquired it in the hospital. With respect to aerosolization procedures, the health care workers who acquired the virus were in the setting of routine patient care. He did not know whether there were cases of health care workers engaging in a high risk procedure such as an intubation without other sorts of exposure who acquired the virus.

Dr. Mott added that this was an important issue that had added a challenge to health care workers and the response in many international settings. There have been several situations in which illness had limited the ability for hospitals to respond to surges, particularly illness in ICU

care workers because they are difficult to replace quickly. At the same time, many health care workers have stayed home due to fear. There have been high absenteeism rates in international settings among health care workers, which has presented a challenge. The transmission studies are still being worked out in terms of transmission within the health care setting, but it has been observed among nurses, doctors, and those in ICU care settings.

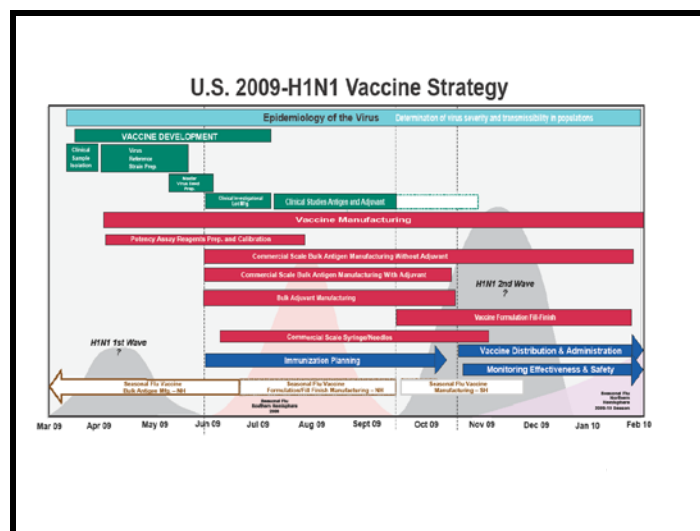
Dr. Schaffner (NFID) noted that there had been recent news reports indicating that there had been a surge of H1N1 novel infections in the United Kingdom (UK). He wondered if Dr. Mott had any insight about this, and whether it was perhaps a surveillance artifact. In the Southern Hemisphere, there had been reports that a substantial proportion of patients admitted to the hospital had presented with illness that was initially afebrile.

With regard to the UK, Dr. Mott responded that there was on-going disease activity and that there had been recent reports of increases in less and more severe illnesses and deaths there as well. Clearly, transmission was on-going. The UK's routine surveillance system shows a rise in ILIs that appears as though they are progressing into a season well in advance of their normal season. The question remained with regard to what would occur for the rest of summer period as they moved into the fall. Surveillance artifacts played a role into the media aspect as well. With a move away from reporting only confirmed cases to reporting many people with ILI syndromically, many additional cases become reported. In terms of clinical presentation in the Southern Hemisphere, there had definitely been afebrile presentations in various countries. The surveillance and testing practices made it difficult to compare the relative portion of those in different places, but it was certainly a feature.

Vaccine Development and Formulations

Robin Robinson, Ph.D.
HHS / ASPR / BARDA Director

Dr. Robinson reported that the vaccine strategy, as depicted by the following table, had moved into the three elements of vaccine development, manufacturing, and distribution:



With respect to vaccine development, the first sets of clinical trials are underway, two of which are being conducted outside of the US with some of the vaccines that could possibly be used in the US in the fall. These are being tested with and without adjuvant at different dosages, assessing immunogenicity with one and two doses. These are running parallel with longer term clinical trials for which data will be available later. Data will be available from the immunogenicity trials approximately two months after their start time. NIH and three of the other manufacturers were to soon begin clinical trials.

In terms of the manufacturing element, vaccines are in "the can," adjuvant has been made, and they are moving forward with ancillary supplies of the manufacturing of those. Manufacturers, FDA, and the National Institute for Biological Standards and Control (NIBSC) in the UK have been working on potency assay reagents. There may be a slight delay in the potency assay reagents in the US, but the NIBSC will be providing those, so it should be seamless as far as the manufacturers having supplies to go forward from August through at least October.

With regard to an immunization program, this certainly seemed to have started with the Flu Summit that the Secretary announced for state and local health officials who should seriously be considering this. Further discussions were also underway within CDC in terms of the distribution of the vaccine and how that would work.

In terms of the H1N1 vaccine timelines and issues, clinical lots needed for the clinical trials have been formulated using surrogate HPLC assays as opposed to standard assays. The comparability of those will be assessed as soon as the potency assay reagents are received by the manufacturer so it will be known whether the 15 mcg in the clinical dose is really 15 mcg or 17 mcg. The clinical studies have begun, so data should be available in latter September to early October with respect to inform vaccine formulation and the safety profile. Licensure of seasonal monovalent antigen-alone vaccine formulation was recommended by VRBPAC on July 23, 2009 as a strain change to the existing BLA as a supplement. That would allow manufacturers to begin formulating the vaccine required to move forward. H1N1 vaccine formulated with adjuvant may be considered under an Emergency Use Authorization (EUA) as opposed to being a licensed product. Discussions are moving forward as to what the conditions would be in which adjuvants would be utilized. A decision to or not to use adjuvants had not been made at this point. However, it is important to be prepared in the event of a worst case scenario. H1N1 vaccine availability by September 2009 was recommended by National Biodefense Science Board (NBSB) on July 17, 2009. One of the production availability schedules will consider that as a possible scenario.

A number of issues are involved with inactivated, subunit vaccine production. It has been reported in the media that there have been low production yields, which should not be surprising as this is observed in seasonal influenza. This occurred with the H5N1 vaccines as they were being produced over the last five years. However, increases in production yields have been observed for current production. The virus must be passed through eggs a number of times to be able to get a virus seed that grows well in eggs and has a larger number of hemagglutinins on the individual varion. Another issue is the seasonal vaccine campaign completion. Most of the manufacturers are completing on time, will finish in August, and will have the vaccine distributed. However, one manufacturer is experiencing difficulty and may not finish until September. BARDA is working with them to determine what impact that would have not only on H1N1 vaccine production, but also on seasonal influenza vaccine. The goal has always been not to interfere with seasonal influenza vaccine manufacturing campaigns. An additional issue pertains to the availability of potency assay reagents, which is expected to be seamless, but there have been and could be other problems. Syringe fill finish manufacturing capacity is a

very relevant point as they move forward with respect to how much vaccine will be available in pre-filled single dose syringes. BARDA is working with the manufacturers to make what manufacturers have available, and also to contract manufacturing sites in the US, which can also help to fill as many single dose syringes as possible moving forward.

Certainly, determination of the targeted population for H1N1 vaccination by ACIP during this meeting would affect the amount, timing, and type of H1N1 vaccines. There are multi-dose vials, single-dose pre-filled syringes, and sprayers for the FluMist® like product. Four manufacturers are producing the inactivated sub-unit vaccines (e.g., CSL, Novartis, sanofi pasteur, and GSK), while MedImmune is producing a product similar to FluMist®. If adjuvants were to be used, not only would the products mentioned as a licensed vaccine be utilized, but also the adjuvants would be used in a pre-formulated adjuvant presentation. From Novartis this would be with one vial of antigen and adjuvant combined and from GSK, there would be separate vials of adjuvant and antigen that would have to be mixed. There are studies underway at the NIH known as “Mix and Match” studies that would support use of sanofi pasteur’s and CLS’s antigens with the GSK AS03 adjuvant. Those data are likely to be available no sooner than October for at least the first dose.

With respect to H1N1 vaccine procurements to date for the civilian population, of which the active duty Department of Defense (DoD) population would receive a small portion, the following have been acquired:

	Acquisition #1	Acquisition #2	Totals
H1N1 Vaccine Product (M)			
Bulk Vaccine Antigen, Inactivated (15 ug HA/dose)	107.1	74.7	181.8
Bulk Vaccine Virus, Live, Attenuated (10⁷ pfu/dose)	6.8	6	12.8
Subtotal	113.9	80.7	194.6
Bulk Adjuvants, Oil-in-Water Emulsions (M)	45.4	74.9	120.3

Of the 181.8 doses of bulk vaccine antigen procured, approximately 20 million doses are ready to be formulated. Of the 12.8 million doses of live attenuated virus vaccine have been procured, which has already been made into bulk product. It may be possible for the amount of live attenuated vaccine to be much more than originally anticipated if an alternative form of presentation is available (e.g., dropper form). The FDA and HHS are pursuing a way to have more of the product available under a licensed pathway. In total, approximately 195 million doses have been procured to date. The Department plans to purchase more antigen moving into August. To date, 120.3 million doses of bulk adjuvants have been procured of the two different oil-in-water emulsions from GSK and Novartis. There will be further deliberations with regard to if and how much more adjuvant will be purchased depending upon the conditions moving forward.

With regard to projections of what would be available, in September about 40 million doses of the licensed product would be available (not at the forward deployable site, but actually lot released from the manufacturer to go to the distributor to then be forward deployed), followed by 80 million doses each month. As there are better production yields moving forward, that number is anticipated to change from 120 to 160 million doses. If life attenuated vaccine becomes available in another presentation form, that number would go much higher. The number is not expected to decrease. If vaccine began in October, data from the clinical studies will inform usage as opposed to the September rollout. Then 120 million doses would be available in October, followed by 80 million doses each month thereafter. If adjuvants were

used, this would depend upon the antigen sparing effect observed with the adjuvants. If it is 2-fold, the number of doses would be doubled.

There is also the issue regarding whether the vaccine can be distributed as quickly as the vaccine is produced. This issue is currently being addressed at the Department level, with CDC having the lead on distribution. There are currently five manufacturers: sanofi Pasteur, Novartis, GSK, MedImmune, and CSL. There is a central distribution system, McKesson, that CDC uses for the distribution of the VFC program. Manufacturers supply this wholesale distributor with the product, and the wholesale distributor sends the product to the various sites. In this case, the five manufacturers would be sending their product to McKesson. The details of the contracts are being explored. From the wholesale distributor, following repackaging, the central allotment system that is in place would be utilized based on the orders that state and local sites (e.g., health departments, PODs, other public sites, private providers) submit to CDC. The difference in this case is that public and private providers will be involved in the distribution scheme. An exercise is anticipated in August to work through logistical planning issues.

FDA / VRBPAC Update

Wellington Sun, MD Director, Division of Vaccines and Related Products Applications Office of Vaccine Research and Review, CBER / FDA

Dr. Sun reminded everyone that Dr. Baylor presented an update during the June 2009 ACIP meeting, since which there had been progress. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) convened a meeting on pandemic (H1N1) 2009 influenza vaccine on July 23, 2009 during several questions were addressed. There was discussion at length regarding the licensure pathway through a strain change supplement to the seasonal BLA; one versus two doses at the initiation of a vaccination program; immunization of special populations; use of adjuvants; post-marketing safety evaluation; and assessment of vaccine effectiveness.

There are several regulatory pathways for use of pandemic (H1N1) 2009 influenza vaccine, including a new BLA, a supplement to the seasonal license, Emergency Use Authorization (EUA), or a treatment IND (although this is really not relevant to the H1N1 vaccine).

The currently licensed US influenza vaccines include the following:

Vaccine	Manufacturer	Type	Age Group
Seasonal			
Afluria®	CSL	Inactivated	≥ 18 years old
Fluarix®	GSK	Inactivated	≥ 18 years old
FluLaval®	GSK	Inactivated	≥ 18 years old
Fluvirin®	Novartis	Inactivated	≥ 4 years old
Fluzone®	sanofi pasteur	Inactivated	≥ 6 months old
FluMist®	MedImmune	LAIV	2 to 49 years old
Pandemic			
H5N1	sanofi pasteur	Inactivated	18 to 64 years old

The strain change supplement is the approach taken with seasonal influenza vaccine. Operationally that means that the manufacturers submit a dossier, which includes only a supplement under existing license that includes passage histories of seeds, HAI analysis, carton, label, and prescribing information. No new clinical data are required. A supplement under existing license for an LAIV requires information pertaining to passage histories of seeds, HAI analysis, carton, label, prescribing information, and limited clinical safety data. The rationale is that a strain change implies that there is sufficient information on the strain changes from the seeds, and that there are data from extensive previous clinical experiences with the seasonal vaccine. This means that the H1N1 pandemic vaccine will have the same age range indications, dosage, and formulations as the seasonal vaccine.

This is applicable only to the non-adjuvanted vaccines with currently licensed manufacturing processes. This pathway is believed to be the most direct pathway to a vaccine as early as possible. The strain change supplement without new clinical data at the time of licensure relies on non-clinical, CMC information; clinical data in the BLA for seasonal influenza vaccine; and age range. The dose and dosing regimen for the pandemic (H1N1) 2009 vaccine will be the same as for each licensed seasonal vaccine. The vaccine will be formulated at 15 mcg / dose of HA for inactivated, $10^{6.5-7.5}$ FFU / dose for LAIV. Again, this is applicable to non-adjuvanted vaccines only, when manufactured by the licensed egg-based manufacturing process. The rationale for these decisions is that in the event of urgent public health need, this pathway provides the most direct regulatory pathway to licensure. Historical data suggest that vaccines containing 15 µg / dose of H1N1 antigens or $10^{6.5-7.5}$ FFU / dose of LAIV would be immunogenic. Complete data from proposed clinical trials of inactivated monovalent H1N1 vaccine and post-dose 2 data of LAIV will be submitted post-licensure. Modifications can be made if indicated by data from post-licensure clinical trials.

This draws on a historical precedent with regard to licensure of monovalent pandemic (H1N1) 2009 vaccine based on historical precedent (e.g., 1986 Strain A/Taiwan/1/86), influenza A/Taiwan/1/86 H1N1 virus represented a new antigenic variant of influenza A (H1N1) which caused outbreaks in Asia in March through May 1986, affecting mostly younger age groups. Manufacturers were requested to produce a split-virion monovalent influenza A/Taiwan/1/86 H1N1 virus vaccine. This was licensed by CBER as a strain change to seasonal TIV with no new clinical data. At that time ACIP made recommendations on the use of H1N1 A/Taiwan/1/86 monovalent vaccine based on similar data to what was presented earlier in the day on ferrets and human sera, which were as follows [MMWR Aug 15, 1986/35(32);517-21]:

“Individuals < 35 years old in recommended groups should receive both the standard trivalent vaccine and the monovalent A/Taiwan/1/86(H1N1) vaccine.”

“High-risk person > 35 years old, or any person who wishes immunization, may receive the supplemental vaccine (optional).”

Regarding the clinical trial basic design concepts, early on the FDA realized that clinical trial data needed to be developed for the H1N1 vaccine, and actively engaged the manufacturers. There was consensus amongst the manufacturers that this should be a monovalent vaccine. The trials are designed to inform dose, dosing regimen, and safety. A common design was communicated to all of the licensed manufacturers. These will be randomized, double-blind, controlled, dose ranging studies assessing 2 doses (0,21d) with a post-dose 1 immunogenicity assessment. The age stratification to be used is 6 months to 35 months, ≥ 3 to 9 years of age, ≥ 18 to 64 years of age, and ≥ 65 years of age. Adult and pediatric studies will be conducted concurrently in the interest of having data as soon as possible. For those manufacturers with

adjuvants, it was recommended that these be evaluated for dose sparing properties. The clinical trials were targeted to begin as early as possible, with the recommendation that they be conducted under US IND. The following clinical trial basic design table summarizes what was communicated to the manufacturers, bearing in mind that each manufacturer will essentially adapt this to their products:

Age range	7.5 µg HA	15 µg HA	30 µg HA	3.8 /7.5/15 µg HA + adjuvant
	N	N	N	N
6m-3y	100	100	-	100/antigen dose
≥3-9yo	100	100	-	100/antigen dose
≥18-64yo	100	100	100	100/antigen dose
≥65yo	-	100	100	100/antigen dose

These trials are designed to answer the critical questions: 1) Are current seasonal dosages sufficiently immunogenic?; 2) Are one or two doses required?; and 3) Are adjuvants dose-sparing?

The clinical trial endpoints are largely in accordance with current pandemic influenza guidance with immunogenicity 21 days post each vaccination, assessing the proportion of seronegatives with HAI \geq 1:40 and the proportion of seropositives with \geq 4-fold rise in HAI (seroconversion rate). Others endpoints include GMT, immunogenicity at earlier time points (e.g., 14 days after vaccination), and microneutralization titers. Safety endpoints include solicited local and systemic events within 7 days of vaccination; unsolicited adverse events; serious adverse events (SAEs) documented monthly; new onset medical conditions documented monthly; baseline and post-vaccination safety labs, especially with the use of adjuvants; and 6- to 12-month follow-up periods after the last dose of vaccine [Guidance for Industry, Clinical data needed to support the licensure of pandemic influenza vaccines, May 2007].

The Emergency Use Authorization (EUA) is a regulatory pathway for use of products before they are licensed, which is sanctioned by Section 564 of the Federal Food, Drug, and Cosmetic Act. Several conditions must be met: 1) there has to be a declaration of a national emergency by the HHS Secretary, which was done on April 25, 2009; and 2) the FDA Commissioner, in consultation with the Directors of NIH and CDC, must determine that there is a serious or life-threatening condition or disease. There must be scientific evidence that the product may be effective; that the known and potential benefit outweighs risks; and that there is no adequate, approved, available alternative. Some EUA scenarios would be the use of a currently unapproved product, such as vaccines with adjuvants; or the unapproved use of approved products, such as approved vaccines for unapproved age groups.

During the VRBPAC meeting, manufacturers delivered presentations, from which Dr. Sun extracted the following estimated timelines:

- Start commercial production: June – July
- Start of clinical trials: July 22 – August
- Post dose 1- Ab data: Available mid September
- Post dose 2- Ab data: Available late September
- Commercial lots: Available 4-6 weeks after the US government fill / finish decision

In summary, 2009 H1N1 is a declared pandemic and national emergency. The severity of the on-going disease in the US thus far is comparable to seasonal influenza; however, rates are higher among pediatric / adolescent populations, with the course and severity of pandemic in the fall uncertain. Licensure of a supplemental monovalent pandemic (H1N1) 2009 vaccine as a strain change is consistent with experience with seasonal vaccines and past regulatory actions. A strain change BLA supplement formulated at 15 µg/dose of HA or 10⁷ FFU/dose will allow for the earliest availability of licensed vaccines. The clinical trial design is for developing early immunogenicity data to inform any dose and schedule modifications. Adjuvanted vaccines are options to be evaluated. The VRBPAC struggled with what the age group breakpoint should be for 2 doses of H1N1 vaccine. They recommended that a plan be developed for immunization of 0 through 6 months olds. Regulatory pathways are available for usage of all vaccine options, if required. Post-marketing surveillance will be conducted of safety and assessment of vaccine efficacy / effectiveness.

Overview of H1N1 Clinical Trials by NIAID / NIH

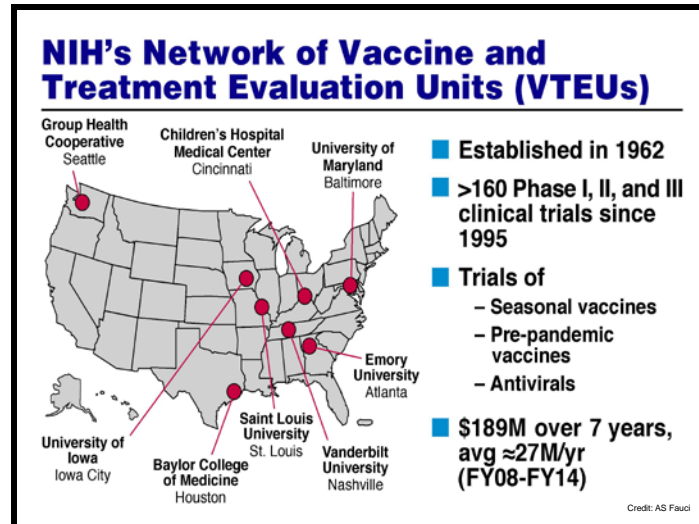
Richard L. Gorman, MD
Division of Microbiology and Infectious Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Dr. Gorman indicated that in April and May, areas identified for possible NIAID trial support included licensure or EUA; studies in special populations (e.g., young infants, pregnant women, immunocompromised individuals); help in informing policy and identifying gap areas, which has become the primary focus (e.g., acceleration of the availability of 1 versus 2 dose data in different populations; administration with seasonal influenza vaccine; different dosing intervals; use of different adjuvanted products; possible mixing stockpiled vaccines and adjuvant).

For the initial H1N1 vaccine trials, NIAID has elected to utilize five separate protocols. These data are not intended to support licensure, but are being conducted under an IND that is currently in effect. The plan is for these trials to be complementary to the company-sponsored clinical trials. The five NIAID align with the following plan for assessing the data:

- 1 versus 2 doses of unadjuvanted CSL vaccine in healthy adults
- 1 versus 2 doses of unadjuvanted sanofi pasteur vaccine in healthy adults
- 1 versus 2 doses of unadjuvanted sanofi pasteur vaccine in healthy children
- co- versus sequential-administration of TIV and H1N1 vaccine in adults
- co- versus sequential-administration of TIV and H1N1 vaccine in children

The following depicts a national treasure, NIH's network of Vaccine and Treatment Evaluation Units (VTEUs) that have been in place since 1962:



Since 1995, the VTEUs have conducted over 160 Phase I, II, and III clinical trials. They have been instrumental in the development and licensure of seasonal vaccines, pre-pandemic vaccines, and the study of antivirals. The level of activity for these 8 centers over the previous 12 weeks has been mirrored by many other government agencies and individuals.

Regarding the details of the three trials NIAID will soon institute, the 1 versus 2 doses of H1N1 vaccine in healthy populations includes 3 protocols. The goal of these trials is the rapid availability of immunogenicity data. There will be 2 doses, 15 μ g or 30 μ g, given 21 days apart. For the sanofi pasteur and CSL vaccine in the adult trials, there will be 400 subjects enrolled in each protocol, of whom 100 will be between 18 to 64 years of age and 100 will be 65 years of age and older per dose group (n=800 total adult or elderly subjects). The sanofi pasteur pediatric trial will include 600 children who are divided into groups of 6 months to < 36 months, 3 years to 9 years, and 10 years to 17 years, with 100 per dose group in each age stratum. The endpoints for all of these studies will be safety and immunogenicity. SAEs and AEs will be collected until 6 months post-dose 2. The investigators will assess 4-fold rises in HAI and the proportion with titers \geq 1:40 at day 21 and 42 for all subjects. There will be early immunogenicity data points post each dose, with additional blood draws at 8 to 10 days following these doses. This will be a subset of vaccinated subjects in which all of the adult subjects will have those data drawn and a subset of the pediatric subjects will be taken. The reason for a subset of the pediatric subjects is to minimize the number of blood draws for those populations. The lead principal investigators for these studies are Pat Winokur at the University of Iowa and Karen Kotloff at the University of Maryland.

For the co- and sequential-administration studies, there will be 2 protocols assessing the safety and immunogenicity of co- and sequential-administration of inactivated H1N1 vaccine and TIV. The investigators will assess H1N1 vaccine before, after, and at the same time as TIV. There will be 2 doses of 15 μ g sanofi pasteur H1N1 vaccine administered 21 days apart, and 1 dose of TIV. There will be 400 adults ages 18 to 64 years of age, and 400 adults ages 65 years and older. There will be 600 primed children who are either above the age of 9 or who have received the ACIP definition of being primed by receiving 2 doses of seasonal vaccine in the previous year. There will be 50 children per group in the following groups: 6 months to < 36 months, 3 years to 9 years, and 10 years to 18 years. The protocol for unprimed children is in the finalizing stages. The endpoints for these studies will be safety and immunogenicity. SAEs

and AEs will be collected 6 months post dose 2, and there will be 4-fold rises in proportion with titer \geq 1:40 by HAI. The lead principal investigator for these studies will be Sharon Frey from St. Louis.

The last major clinical research activity that will be implemented in this first round of studies will be a mixing and matching of vaccine and adjuvant. The safety and immunogenicity will be assessed of mixing stockpiled vaccine antigens and adjuvants from different manufacturers. The vaccines presently under consideration are CSL's and sanofi pasteur's H1N1 vaccine. The adjuvant will be GSK's AS03. These will be mixed at the bedside prior to administration. The protocol is divided into five groups: 3.75 μ g with AS03; and 7.5 μ g and 15 μ g with and without AS03. There will be 2 doses given 21 days apart. At this point, the IND for sanofi pasteur / AS03 was submitted July 23, 2009 and has been finalized, with the CSL / AS03 IND to follow. The lead principal investigators will be Lisa Jackson of Seattle Group Health; and Kathryn Edwards at Vanderbilt.

Other studies that are in the late stages of development, but have not yet been submitted to IND packages, include: 1) additional H1N1 vaccine studies in pregnant women; and 2) a study that does not involve H1N1 but hopefully will inform the use of H1N1 vaccines, which is a safety and immunogenicity study of TIV in pregnant women. This trial was initiated on June 11, 2009 in VTEUs and subcontract sites in 2nd and 3rd trimester women. These women will be given a single dose of 2008-2009 TIV (Fluzone®, Fluarix®). Responses will be assessed 28 days post-vaccination. As of July 27, 2009, 52 women have been enrolled. The principal investigator is Shitel Patel of Baylor. In the Fall 2009, a follow-on study is planned using the 2009-2010 TIVs as they become licensed. There are 4 licensed US manufacturers of inactivated vaccine. In late April to early May, following the Secretary's announcement, the Division of Microbiology and Infectious Diseases (DMID) reviewed the pandemic influenza vaccination plan to determine data gaps. As a result, they realized that there was scant data for the use of TIV in pregnant women.

Discussion

Dr. Neuzil noted that the work group had also struggled with one versus two doses. She was pleased to see Dr. Sun's timelines suggesting that there might be some data post-dose one in September, which would be very informative as vaccination campaigns rolled out. She inquired as to whether there were also timelines on the NIH trials to better understand whether this information would be available to inform decisions.

Dr. Sun responded that at this point, the only thing standing between NIH and the initiation of these trials is product availability. The manufacturers and BARDA are working diligently to get these to NIH as rapidly as possible. The project timelines at this point are to begin the first or second week of August, with timelines that look very similar to the manufacturers' timelines to make data available to ACIP.

Dr. Meissner requested that Dr. Sun comment on why the trials planned to measure HAI antibody rather than microneutralization titers, given that neutralization titers better reflect functional antibody.

Dr. Sun replied that all of their licensed products have been on the basis of HAI titers, and they have a certain amount of experience of these. The FDA is not really changing anything from the way licensing is done with seasonal influenza in terms of endpoints.

Given that there is limited experience with the adjuvants MF59 and AS03, Dr. Meissner inquired as to whether there was a need for a placebo arm in any of these trials.

Dr. Gorman responded that the trials as presently designed do not have placebo arms. They argued the use of these, but felt that historical data with influenza vaccines at different dosages available to NIH made those not as useful as they might have been.

Dr. Sun added that some of the trials conducted by the manufacturers do have placebo groups, and for others the control will be the unadjuvanted vaccine.

Dr. Marcy inquired as to whether thimerosal would be included in the multi-dose vial, noting that public acceptance would be an issue, especially among the very young who are at high risk.

Dr. Robinson replied that currently multi-dose vials will contain thimerosal based on guidance that was given to the manufacturers by FDA.

Dr. Marcy asked whether there were good data that 30 mcg would be sufficiently immunogenic in the elderly as opposed to 60 mcg where there seems to be fairly good data that seroconversion and rise in GMTs is significantly better than 15.

Dr. Sun responded that this was another active DMID discussion. There was concern about the immunogenicity at different dose levels. They were hoping to do mild dose ranging with 15 and 30. If there was no response to 15 and there was a better response to 30, they might be able to predict that. That was balanced against the understanding of the potential shortage of antigen supply for the season. If they tested 60 and it turned out to be the only effective dose, it would create another set of scenarios that they did not exactly know how to deal with.

Despite the phenomenal work done to date, Dr. Ehresmann wondered whether it was realistic to continue to promote the idea that vaccination could begin in October. Her concern was that many of the messages that had gone out to the states in planning and the public through the media suggested that a pandemic vaccine would be available in October. Given the information provided during this meeting, the October data may not be realistic. With that in mind, she inquired as to whether there were plans in place to get alternative messages out to the public.

Dr. Robinson responded that this was debated heavily at the NDSB meeting in June and earlier in July. September and October were presented as possible dates, based on which they saw early what the numbers would look like. They were looking for guidance from ACIP and others to have one message going forward. They were hoping this discussion would occur during this meeting.

Dr. Schuchat acknowledged that these were extremely important issues, because any start date would be challenging for the public health community, providers, and the public. The most important message she had was that CDC is committed to frequent, timely information sharing and communication. There are communications plans in place, which were to be presented later in this meeting. Clearly, it is confusing for the public to have a seasonal influenza vaccination effort as well as a likely H1N1 vaccination effort. The states are working hard to be ready by October. They must understand the tradeoffs between when they hope to start pandemic vaccination, trying to start earlier if conditions warrant doing so, and trying to address the uncertainties about production and information. While everything was not clear at this point, CDC wanted everyone to prepare as if the vaccine would be ready mid-October, with some

contingency planning for a smaller scale earlier start if conditions and decision making warranted this.

Dr. Sawyer pointed out that a pragmatic issue that needed to be addressed was taking the correct vaccine out of the refrigerator. He wondered whether BARDA and the FDA had any influence on the manufacturers in terms of packaging the vaccines such that people could easily differentiate between seasonal and pandemic vaccine.

Dr. Sun responded that, as shown in his presentation, the submission of the supplement includes carton label and prescribing information. They are in the process of negotiating with all manufacturers to address such issues.

Dr. Baker pointed out that seasonal influenza vaccine was already available, so vaccination administration for seasonal influenza should begin as soon as possible. She inquired of Dr. Gorman what the ethical consideration was behind administering last year's seasonal influenza vaccine to pregnant women, given that there was no benefit to those women or their children from last year's vaccine. It is known that while uptake in pregnant women has been low in previous seasons, cumulatively millions of pregnant women have been immunized. She wondered whether the concern was safety.

Dr. Sun responded that the considerations were ethical and practical. The 2008-2009 seasonal influenza vaccine was the only vaccine available to be tested. The ethics were that it is a recommendation by a government body that seasonal influenza be given to pregnant women. There are limited data for that recommendation. Thus, they were attempting to increase the amount of knowledge about safety and immunogenicity in that particular population. This protocol has been through seven IRBs with no comments on the ethics of the study.

Dr. Baker asked whether blood was being drawn from the babies. The minor risk would be from blood draw, which is uncomfortable and inconvenient. She also wondered whether sufficient women would be included in the protocol such that safety could be determined.

Dr. Sun responded that he did not know whether blood was to be drawn from the babies. With regard to the issue of safety, the targeted enrollment is 200 women.

Dr. Lett did not believe they would be ready to make a decision to begin vaccination in October if data were not going to be available until the end of September. She also wondered whether there were still plans to have pre-filled syringes and thimerosal-free H1N1 vaccine available in the pediatric formulation.

Dr. Robinson responded that for both seasonal and H1N1 vaccine there would be pre-filled single-dose syringes and multi-dose vials.

Dr. Lett inquired about the interval of three weeks, and the exploration of potentially shorter intervals. She wondered whether they would know this by the end of September in terms of the 2-dose schedule.

Dr. Sun responded that this information would not be available by the end of September.

Given that it was still possible that only half of the doses projected (e.g., 60 million versus 120 million doses) might be available for October if the vaccine was not sufficiently immunogenic at 15 mcg, Dr. Lett requested further comments.

Dr. Robinson replied that if the clinical studies show that 15 mcg is not immunogenic and 30 mcg is, that would cut the supply of the antigen-alone formulation in half basically. If this occurs, all options will have to be considered, including the adjuvant option if there are data to support the adjuvant having an antigen-sparing effect and being immunogenic.

Dr. Neuzil indicated that during the afternoon, scenarios would be put forth based on the supply projections for October, as well as other possible scenarios should either the supply be less or the antigen be doubled, in terms of how that would change the priority groups.

Dr. Judson thought it was critical that ACIP and others be given a better idea of when the final results would be available for use in making recommendations. Dr. Sun showed 9 groups of 100, which was good for its statistical simplicity. However, in terms of the widely differing outcomes that may result in each of those groups, and having group size or sample size be driven somewhat by the statistical power the investigators were attempting to achieve to evaluate those differences, the categories (e.g., lower dose antigen, over 65 group, serious adverse events) would not likely fit neatly into the sample groups of 100.

Dr. Sun responded that Dr. Judson's comments echoed those made by their colleagues at the FDA. In the design of these studies, the investigators chose to be splitters rather than lumpers, knowing that lumping is somewhat easier statistically than splitting. The goal that NIAID was tasked with was to help inform policy makers and not be driven by licensure. The data will be collected in groups of 100, but assessments will be made of safety and immunogenicity data in close to real-time such that these data can be disseminated as deemed appropriate by the leadership at NIAID. They will not be waiting until there are 100 in each group either for safety signals or for immunogenicity signals before those data are disseminated.

It was noted that on-going studies will be conducted by NIH and the manufacturers on the immunogenicity tract with licensure type studies in parallel, so there will be data simultaneously or somewhat later that would have the necessary statistical power.

Dr. Kevin Ault indicated that he was an investigator at Emory with the pregnancy and influenza trials. Although ACIP was informed of one of the trials, there will be a series of subsequent trials that involve analysis of transfer of antibodies to the baby.

David Johnson, from the industry perspective, reiterated a comment made earlier regarding the release of vaccine and when vaccination programs may begin, pointing out that it was important to remember that from industry the license, requirements for packaging and labeling, CBER requirements for lot release, et cetera must be in place. Once in place, it would be approximately a 4- to 6-week period before vaccine would actually be available for shipping.

Dr. Beck noted that Dr. Robinson indicated that there was an anticipated second wave of H1N1, which seemed to differ from the suggestion that there was a decline in the number of new cases.

Dr. Robinson replied that the slide to which Dr. Beck referred was created in May as a prototypic pandemic slide, which did not reflect what was currently occurring.

Dr. Keyseiling (SHEA) expressed concern about the pandemic schedule of a 21-day interval between doses versus a seasonal schedule of a 28-day interval. In the pediatric age group, there could be a problem unless there is a more permissive recommendation for seasonal

vaccination, assuming that eventually both vaccines would be administered concurrently. He thought it would be problematic to have a 3-dose interval for one product and a 4-dose interval for the other.

Dr. Sun responded that when the design was developed for the H1N1 clinical trial, they had in mind the compressed timeframe. Hence, they communicated to the manufacturers that these trials should be conducted with 21-day interval. The current label for seasonal influenza vaccine the interval is 28 days. He thought they would have to be fairly flexible in information on that point.

Dr. Tan (AMA) wondered whether there was any visibility on when the decision to fill / finish the bulk would be made and what was guiding that decision. Obviously, that represents the 4- to 6-week gap that would result in supply earlier or later.

Dr. Robinson responded that those discussions were currently underway within the department and with the manufacturers to acquire harder numbers for when the start dates would be for fill / finish. One problem regards when the manufacturers will be out of their fill / finish manufacturing sites to have a change over and be able to do the formulation and fill / finish for H1N1. Certainly, the factors involved regard whether the FDA will accept the recommendation of VRBPAC for a standard antigen dosage of 15 mcg or 10^7 . There are other factors moving forward that will depend on ACIP's deliberations as well.

Dr. Kinsinger (DVA) wondered whether the 4 manufacturers' inactivated formulations would be interchangeable in the event that two doses were recommended.

Dr. Sun replied that because they were using the route of a strain change supplement, it was anticipated that the dosage guidance would most likely reflect what is currently recommended for the seasonal vaccine. However, this issue remained in internal discussion at CBER. Whether the different manufacturers' products would be interchangeable was somewhat analogous to what was occurring in reality in that, from one year to the next, one may not receive the same manufacturer's vaccine. He thought as long as the dosages were the same, they would want to consider these to be interchangeable in terms of first or second dose.

Dr. Hackey (DoD) reminded everyone that during the last ACIP meeting, they were informed that it would be difficult for the existing public health infrastructure to conduct a mass immunization program and deal with their other duties as assigned. With that in mind, even if there was adequate vaccine, if an adjuvant would reduce the number the doses from 2 to 1, he wondered whether consideration had been given to pursuing an adjuvanted formulation to reduce the burden on the public health infrastructure. Also during the last ACIP meeting, they were informed that the FDA would be working with international partners, particularly those in the EU in terms of sharing clinical trial data. He wondered whether the EU data would be available before the US data, and whether that could potentially be used for an earlier decision.

Dr. Robinson answered that what Dr. Hackey pointed out was only one of many factors for adjuvant usage. This consideration will be part of the calculus that goes forward.

Dr. Schuchat added that while during the last ACIP meeting there were discussions regarding challenges with the public health infrastructure, since that time emergency funding was appropriated for states, with second rounds of emergency funding forthcoming. There is an intensive planning effort to assure as great a success as possible. She noted that later in the day, there would be an update on the implementation planning process. The issue with

adjuvants was less a question of one dose or two versus no immune response being achieved with the regular formulations and whether large responses could be achieved with adjuvants. Regarding the sharing of information from the international trials, it was her understanding that they would have access to these data.

Dr. Sun pointed out that there was currently no licensed adjuvant in influenza vaccines in the US. Hence, use of an adjuvanted vaccine under an alternate regulatory pathway of EUA is really a very complex decisions in terms of assessing risk / benefits. In terms of sharing information, WHO has requested that all who are developing vaccines and running clinical trials share the data. The mechanism for the FDA still has to be worked out, because these trials are conducted by manufacturers and the information is considered proprietary.

Regarding the post-marketing surveillance clause mentioned by Dr. Sun, Robert Malone (Focus Diagnostics) inquired as to whether they were anticipating post-marketing surveillance with HAI endpoints and lab-confirmed ILI endpoints just in the case of EUA or for the licensed with supplement vaccines. In addition, he wondered if they would be assessing the full range of special populations in cohorts or a subset.

Dr. Sun responded that the post-licensure safety and effectiveness studies are the subject of large groups who are currently collaborating in discussion with the CDC, FDA, and other regulatory agencies. That is a work in progress. The question regarding diagnostics is very important with respect to how H1N1 2009 pandemic will be distinguished from seasonal H1N1. That is part of the challenge, and the investigators will be assessing the effectiveness component of the post-licensure monitoring.

Dr. Strikas (NVPO) pointed out that there are published data showing that 7.5 mcg of an activated seasonal vaccine are immunogenic in adults less than 60 years of age. If the trials that industry is conducting find that 7.5 mcg of unadjuvanted H1N1 vaccine is immunogenic similar to 15 mcg, he wondered whether that would constitute a strain change that FDA could undertake to license 7.5 mcg for certain populations of adults.

Dr. Sun responded that the strain change is really to license based on the current dosage and schedule. If there are clinical data subsequent to that, further modification and recommendations would be necessary.

2009 H1N1 Vaccine and Critical Infrastructure Key Resources Priority Groups

**Terry Adirim, MD, MPH, Senior Advisor
Office of Health Affairs
Department of Homeland Security**

Dr. Adirim indicated that the Critical Infrastructure Key Resources Priority Groups (CIKR) is not only a representative of the Department of Homeland Security (DHS), but also is a member of the federal interagency work group that drafted the Guidance on Allocating and Targeting Pandemic Vaccine that was released in July 2008 [[http://www.pandemicflu.gov/vaccine/ allocationguidance.pdf](http://www.pandemicflu.gov/vaccine/allocationguidance.pdf)]. For this presentation, Dr. Adirim focused specifically on CIKRs.

The allocating and targeting guidance had several overarching goals, one of which was the protection of society by protecting critical infrastructure groups. A primary objective was to protect workers who are at especially high occupational risk and / or who are performing a pandemic function. These groups are at the top of the prioritization strategy. Dr. Adirim stressed that the primary objective of vaccination in CIKR sectors is not to reduce absenteeism per se. Rather, vaccination is targeted to protect workers with critical skills, experiences, or licensure status whose absence would create bottlenecks or collapse of critical functions in a severe pandemic. It is noted in the guidance that other pandemic response strategies (e.g., engineering controls in workplaces; changing work practices to reduce close contact with others; use of personal protective equipment such as facemasks, good hand washing, et cetera), and worker education are likely to have greater impact in decreasing absenteeism.

A couple of studies were conducted in support of the federal interagency work that may be useful to the ACIP. In 2007, DHS and HHS tasked the National Infrastructure Advisory Council (NIAC) with providing recommendations on prioritization and distribution of pandemic countermeasures to essential workers in the nation's CIKR sectors. The final report and recommendations were released in January 2007, and was very informative to that work that was done. The key issue areas that they addressed included the following:

- Identifying and defining "critical services" that must be maintained during a pandemic
- Defining criteria and principles for critical services prioritization
- Defining critical services priorities
- Identifying critical employee group(s) within each priority critical service who are critical to the functioning of that sector
- Building a structure for communication and dissemination of resources
- Identifying principles for effective implementation by DHS and HHS

This work was done with the owners and operators of the various sectors; that is, this information was generated from those who work within those sectors.

Dr. Adirim indicated that she was going to focus on two of the sectors because she believed that these would come into play in the ACIP's recommendations. The first regarded the health care sector. According to the Bureau of Labor Statistics, the healthcare sector has 13.5 million employees. Of the healthcare facilities, 76% are offices of physicians, dentists, and other health practitioners. Hospitals and medical centers constitute 2% of all establishments, but employ 40% of workers. Critical healthcare services identified as important in a pandemic include healthcare delivery, medical providers, home healthcare, residential care, retail and outpatient care sites, support supply chain (e.g., community emergency management, et cetera), and death care services. It was noted that the various groups within the healthcare sector had different lists based on whether they had a function, which put them around sick people. This work group determined that the healthcare sector includes 6,999,725 critical workers or 51.8% of the sector.

The second group is the emergency services sector, which includes traditional first responders, or those people who are critical as a first line defense against terrorist attacks and natural disasters. This group is typically thought of as being composed of law enforcement, firefighters, and emergency medical services (e.g., EMTs and paramedics) as critical first line defenders against terrorist attacks or natural disasters. The work group determined that this sector's workforce comprises approximately 90% to 95% of responders and also includes fire, EMS, law enforcement, emergency management, local jail / corrections, and communications officers

(e.g., people who staff 911 call centers). With this particular sector, there are different risk factors based on their exposure to people who are sick. It was determined that in this sector, there are approximately 2,257,419 critical employees.

Another study that supported the interagency work group was completed by the National Infrastructure and Analysis Center (NISAC) Office of Infrastructure Protection (OIP), with OHA. This was a mathematical modeling study, which examined the potential impact of a severe pandemic on the US population, CIKRs, and the economy. Their assumptions for the mathematical model were similar to other mathematical models that were done, which included a 2% case fatality rate, 30% attack rate, with an assumed 40% absentee rate at the peak of the waves. Consistent with other studies, these study results showed that early interventions strategies would be beneficial (e.g., school dismissal, vaccines, antivirals) in terms of delaying and mitigating a pandemic; that healthcare system would be highly stressed and alternative care strategies would be needed; that even in a severe pandemic, most CIKR systems (other than public health and healthcare) would continue to function if mitigation strategies were utilized; and that health care costs could be \$80 billion, and gross domestic product losses could be \$100 billion in the first year. This modeling is currently being updated based on H1N1 epidemiology.

Dr. Adirim shared the following prioritization tiers to impress upon everyone that in the face of a less severe pandemic scenario, ACIP's recommendations were consistent with the interagency work group's intent:

Vaccine Prioritization Tiers and Target Groups	Category	Target group	Estimated number*	Severe	Moderate	Less severe
		Homeland and national security	Deployed and mission critical pers.	700,000	Red	Red
		Essential support & sustainment pers.	650,000	Red	Red	Red
		Border protection personnel	100,000	Red	Red	Red
		National Guard personnel	500,000	Red	Red	Red
		Other domestic national security	50,000	Red	Red	Red
		Other active duty & essential suppl.	1,500,000	Yellow	Yellow	Yellow
	Healthcare and community services	Public health personnel	200,000	Red	Red	Red
		Emergency health care providers	3,200,000	Red	Red	Red
		Quarantine and home health providers	2,500,000	Red	Red	Red
		Health care providers in LTCFs	1,600,000	Red	Red	Red
		Community support & emergency mgmt.	600,000	Yellow	Yellow	Yellow
		Pharmacists	100,000	Yellow	Yellow	Yellow
		Mortuary services personnel	50,000	Yellow	Yellow	Yellow
		Other important health care personnel	300,000	Yellow	Yellow	Yellow
	Critical infrastructure	Emergency services sector pers. (EMS, law enforce. & fire services)	2,000,000	Red	Red	Red
		Units of pandemic vaccine & antiviral	50,000	Red	Red	Red
		Communications/IT, Electricity, Nuclear, Oil & Gas, and Water sector personnel	1,500,000	Yellow	Yellow	Yellow
		Personnel testing & evaluation pers.	400,000	Yellow	Yellow	Yellow
		Critical operational & regulatory government personnel	400,000	Yellow	Yellow	Yellow
		Banking & Finance, Chemical, Food & Agriculture, Pharmaceutical, Postal & Shipping, and Transportation sector personnel	3,000,000	Yellow	Yellow	Yellow
		Other critical government personnel	400,000	Yellow	Yellow	Yellow
	General population	Pregnant women	3,100,000	Red	Red	Red
		Infants & toddlers 0-20 mo old	10,300,000	Red	Red	Red
		Household contacts of infants < 6 mo	4,300,000	Red	Red	Red
		Children 3-18 yrs with high risk cond.	6,500,000	Red	Red	Red
		Children 3-18 yrs without high risk	58,500,000	Yellow	Yellow	Yellow
		Persons 19-64 with high risk cond.	36,000,000	Yellow	Yellow	Yellow
		Persons >65 yrs old	38,000,000	Yellow	Yellow	Yellow
		Healthy adults 19-64 yrs old	123,600,000	Green	Green	Green

The categories include Severe, Moderate, and Less Severe. Moving toward a less severe scenario, critical infrastructures tend to fall out. Health care is all across the top tier because the guidance talked about frontline health care providers or practitioners who have direct patient care responsibilities. The critical infrastructure group appears across all severities, including less severe, in the emergency services sector.

In summary, prioritization of CIKR occupational groups are envisioned as necessary in a severe pandemic where sickness / absenteeism are at a level (both total and duration) that the fundamental operations / continuation of key activities are threatened. H1N1 is not projected to have that level of impact. Health care workers and emergency services workers are placed in Tier I because of the necessity of needing the maximum number workers available to meet the increased demand for services. They are at greater risk than the general population for exposure / infection by the nature of their job. Social distancing is not generally a practical,

consistently implementable strategy for them. They are exposed to sick people and infections in a way that is neither discretionary nor avoidable. With explanation that prioritization is based upon the epidemiology, most CIKR organizations / businesses will understand and accept prioritization decisions. DHS will work to explain and get the message out to CIKRs.

Implementation Planning

Pascale Wortley, MD, MPH Immunization Services Division Centers for Disease Control and Prevention

Dr. Wortley reported on implementation planning, indicating that they were working toward a mid-October launch date. The program will involve allocating vaccine across the country to states on a pro rata basis. Distribution will be organized and coordinated by the federal government. At the state level, public health will direct where vaccine is distributed. In most states, that will include a combination of public health and many types of private sector sites, similar to where seasonal influenza vaccine goes.

Funds have been made available for accelerated planning and early implementation in the amount of \$195 million, with \$262 million provision that is in flux. Initial awards are scheduled to be distributed July 31, 2009. That will account for up to 50% of the total amount that states can request at that time. Detailed budget for both amounts combined will be due August 31, 2009 and the remainder of funds will be awarded by the end of September. Future funds are anticipated for implementation.

In terms of distribution of vaccine, CDC has been exploring two options: 1) centralized distribution similar to what is done for the VFC program, although it would be an augmented program; and 2) direct shipping from manufacturers to state-designated ship-to sites. In both options vaccine will go to state-designated locations, but the number of locations and frequency of shipments would vary according to the option. The centralized distribution option would offer more flexibility in terms of number of places vaccine could be directly shipped. Plans are also underway for shipping of ancillary supplies. Syringes, needles, sharps containers, and alcohol swabs are going to be provided. A great deal of work is going into meshing the shipment of those supplies with the vaccine.

With respect to financing, Dr. Wortley reminded everyone when last they met, CDC had formed a steering committee with public health partners. That group has a financing subcommittee that has been extremely busy. Some of the general challenges anticipated include variability of insurance coverage; under-insurance; and variability of reimbursement rates for administration, particularly with respect to Medicaid. H1N1-specific challenges include the anticipated broader use of non-traditional vaccination settings, as well as unplanned strains on already stressed state budgets. One of the first tasks of the subcommittee was to develop recommendations to put before NVAC, which were recently voted on. The following recommendations were approved:

- First dollar coverage for H1N1 vaccine
- Reimbursement rate of providers by public / private insurance plans to equal the Medicare reimbursement on a voluntary basis for private insurance
- Federalization of Medicaid payment at the Medicare rate, given the large fluctuation among states

- Development of formalized relationships allowing community vaccinators to bill insurance plans
- A policy to allow community vaccinators to bill Medicaid via roster billing
- Funding to states for implementation of mass vaccination

Another area on which the subcommittee is actively working is development of a policy for vaccination administration fee for uninsured patients. The issue regards whether to do something similar to or different from the VFC program, in that VFC program providers are asked to vaccinate uninsured persons who are unable to pay the administration fee.

The following statement was provided by America's Health Insurance Plans (AHIP) on behalf of its members when the subcommittee asked them about insurance reimbursement for administration:

"Every year health plans contribute to the seasonal flu vaccination campaign in several ways:

- a) Health plans communicate directly with plan sponsors and members on the current ACIP recommendations and encourage immunization; they also provide information on where to get vaccinations, and who to contact with any questions.
- b) Just as health plans have provided extensive coverage for the administration of seasonal flu vaccines in the past, public health planners can make the assumption that health plans will provide reimbursement for the administration of a novel (A) H1N1 vaccine to their members by private sector providers in both traditional settings e.g., doctor's office, ambulatory clinics, health care facilities, and in non-traditional settings, where contracts with insurers have been established."

Given the emphasis on engaging the private sector, there is a lot of work underway related identifying and engaging providers such as provider organizations at the national level, the retail sector, community immunizers, pharmacists, and volunteer organizations). These connections are beginning in states. One activity in which a number of states have engaged is that, as they are reaching out to their provider community, they are in the process of creating pre-registration mechanisms so that providers who are interested in vaccinating can let their interest be known. This effort was led by one state that developed this idea, and a number of other states have been very enthusiastic about the idea.

Other developments include simplification of doses administered reporting requirements, in that there is no longer a requirement to report priority group, just by age group. For logistical reasons that is an important change in terms of data collection. The inclusion of a vaccination card with vaccine shipments is also being explored. This would be a wallet side tri-fold or bi-fold card that would contain important information that vaccinees would receive. That would be shipped out with vaccine. A logistics working group is in the process of being created that will include people from CDC and BARDA, and which will carefully assess the very complicated pathway in place for getting vaccine to the end user. Another document being created is an H1N1 Vaccine Provider Agreement. This is analogous to an agreement that providers sign with the VFC program, with the important difference that it is much simpler. The intent is to not create barriers, but providers are receiving free vaccines and some type of agreement must be signed. There are some policies issues tied to that document, including the issue of uninsured patients. As soon as that document is cleared, the subcommittee will share it with ACIP. They have let the states know that this is being developed so that efforts are not duplicated.

Other materials are in planning. A number of people are preparing difference guidance documents on various topics, as well as materials for state and local planners. Topics that guidance documents and materials will address include vaccine ordering and allocation; target / priority groups; school-located vaccination, including addressing issues related to FERPA; provider office guidance; safety monitoring; large scale clinic planning; tribal populations; and Q & A on multiple topics.

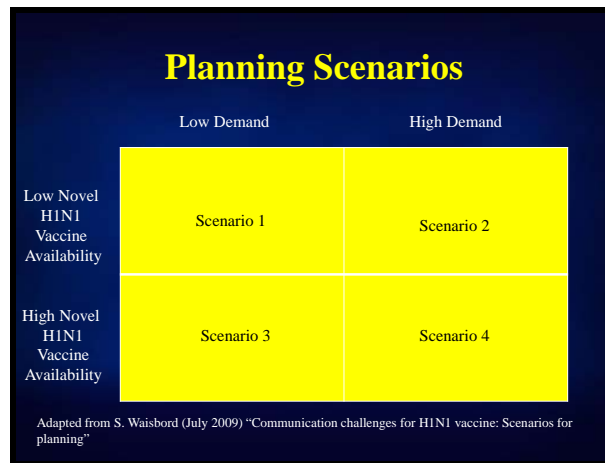
Key remaining uncertainties include timing of vaccine availability, amounts of vaccine that will be available, distribution method, and priority groups / target populations. The results of this ACIP meeting were anticipated to resolve key unknown issues and accelerate planning. The subcommittee will continue to move forward in partnership with states and others to guide and facilitate their planning.

Communications Strategy

Kristine Sheedy, PhD
Associate Director for Communication Science
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention

Dr. Sheedy reported that following the tremendous information demands placed on the CDC Communication Team in the spring, they began to think about how to plan and prepare moving forward, particularly in the face of so much uncertainty and so many unknowns that have made the prospect of planning fairly daunting. One certainty is seasonal influenza, with which CDC has a lot of experience in communicating. Thus, the team began with the use of promotion of seasonal flu vaccine as a starting point, which can be expanded and adapted. Using the limited time available, the team decided to plan for a limited number of key scenarios and is prepared to adapt the approach, messages, and materials. In addition, work is underway to improve internal processes and surge capacity, identify and train spokespeople, continue transparent and frequent communication on the situation and the steps that are being taken, and conduct audience research and message testing.

In terms of the scenario-based planning approach, clearly there are too many possible scenarios to plan for all of them. As the team began to think through this and listed all of the potential variables that could impact the communication approach and things that they would need to respond to, the result was a very a large and complicated matrix. Therefore, they decided that scenarios should be developed based on key variables that will have the most impact on communication approaches, which are vaccine availability and public demand. Consideration was given to those two key issues and challenges within each to develop just a few scenarios. Once the scenarios were developed, careful consideration was given to the general approach that would be needed, key challenges and issues that might arise, and the development and testing of overarching messages and messages related to challenging issues within various scenarios (e.g., vaccine prioritization, safety concerns), channels, and audiences. There is a separate but highly coordinated effort underway to engage in in-depth thinking about the types of vaccine safety messages that will be needed and the various situations that may be faced on that front. Using demand and availability, the four major scenarios are as follows:



A number of planning assumptions were made as the team began to think about these four major scenarios. It was assumed that seasonal influenza vaccine would likely be available prior to novel H1N1 influenza vaccine, that there would be ample seasonal influenza vaccine and limited but increasing supplies of novel H1N1 vaccine, and that eventually there would be ample supplies of seasonal and novel H1N1 vaccines available. It was assumed that they would begin within Scenario 1 or 2 and would hopefully move to Scenario 3 or 4, with the understanding that there may be movement back and forth. As difficult as it is to predict what is going to occur on the supply side, it is even more challenging and complicated to try to predict what may occur on the public demand side. The major assumptions with regard to public demand are that it may vary with populations, and that it may change suddenly and significantly. Included in the considerations about demand are those factors that are known, through experience and research, to impact demand for influenza vaccine, such as:

- Perceptions / indications regarding when influenza viruses are expected to begin circulating
- Actual circulation of influenza viruses
- Severity and visibility of initial cases
- The population groups most affected and / or most severely affected
- Beliefs regarding personal susceptibility to severe disease: Are people like me becoming very ill?
- Ease of access to vaccination
- Provider recommendation
- Past experience with vaccine and influenza
- Vaccine risk perception / assessment
- Vaccine benefit perception / assessments: Do the vaccines work? Are antivirals a safer or more effective option?

Dr. Sheedy briefly described each of the four scenarios and discussed the broad approach that would be needed for each. She stressed that throughout the season, the basic message would be encouragement for people to get vaccinated and to do so as soon vaccine is available, while explaining to everyone that immunity will not wear off even if vaccinations are received as early as August.

In Scenario 1, there is a match between low demand and low vaccine availability, which was basically the current situation. In a Scenario 1 setting, it is important to continue to communicate why there are concerns about this new virus, what steps are being taken to make

novel H1N1 vaccine available, and who is recommended to receive it when it is available. The use of seasonal influenza vaccine should be encouraged.

Scenario 2 is one in which there is high demand and low vaccine availability. In this setting, risk communication principles and approaches dominate. There should be communication about the reasons for lack of vaccine and the rationale for a tiered approach if applicable. They should not be afraid to express personal disappointment that there is not enough vaccine to meet demand, because that is what everyone desires. Other protective steps should be emphasized, being cautious not to over-promise on any interventions.

In Scenario 3, there is low demand and high vaccine availability. In this setting, the social marketing approach would dominate. Tailored and motivating messages should be delivered to those recommended for vaccination. Awareness should be increased regarding disease risks, vaccine benefits, and safety.

Scenario 4 is one in which there is high demand and high vaccine availability. In this scenario, communication efforts would likely best be used to help with distribution and delivery challenges. Vaccine safety concerns should be responded to quickly, even coincidental events that occur after vaccination or very rare adverse events that can only be identified when large populations are receiving vaccine.

Within each of these scenarios, several unique issues might arise in terms of influenza vaccine communication. In practice it will be difficult to differentiate between seasonal and novel H1N1 illness, but people are going to want to know what they have. Messages should prepare people for this and focus on general guidance that is applicable to all flu. Messages comparing novel H1N1 influenza with seasonal influenza should not inadvertently foster or support public perceptions that seasonal influenza is a mild disease. Many people who are considered to be at high risk do not self-identify as being at high risk. This poses a major communication challenge. Vaccination recommendations that involve children and pregnant women can be expected to generate heightened concern about vaccine safety. In certain scenarios and under certain circumstances, consumer demand for choice may be mistaken for consumer demand for vaccine. Those two things are very different, and it may be that in some cases, people just want to know that if they want the vaccine, it is available to them. Variation in vaccines and immunization recommendations and approaches, as well as variation in vaccination practices between locations and providers will raise questions and concerns. This will be more salient for some scenarios than others, but equity is always an important issue that will have to be addressed.

In terms of channels and products, flexibility is key. Emphasis will be on channels and products that are best suited for dynamic communication environments, such as: news media (including outreach to ethnic media), web and new media, distribution of key points to partners, some print materials, only very generic PSAs that would be appropriate for any scenario, and partnerships. Moreover, widespread support will remain essential. Health care providers, the public health community, and state and local political leaders supporting public health recommendations and guidelines will be very important. State and local communication efforts are absolutely paramount, because all of these messages and efforts must be tailored and localized. CDC speaks regularly to the National Information Coalition, which will continue to be important. Transparency in processes and approaches is also highly important. Actions will be as or more important than statements (e.g., getting vaccinated versus encouraging vaccination). Effective communication can help alleviate, but cannot solve, problems related to bad, inadequate, or absent policies, recommendations, systems, or products. The combination of sound, science-

based public health policies and recommendations with effective communication has the potential to save lives, prevent serious illness and disability, and reinforce social norms around the importance of vaccines.

Discussion

Dr. Neuzil noted that one concern of the work group is that “novel H1N1 vaccine” is a very difficult term to say in that it does not easily roll off of the tongue. Having discussed this at length, the work group recommends the use of a very simple term such as “pandemic vaccine” to avoid confusion in the fall.

Dr. Sheedy concurred that the term “novel H1N1” was technical and potentially confusing, and that more simplified terminology would be preferable.

Dr. Sawyer wondered whether specific messages had been designed for physician providers regarding the topic of it not being too early to immunize. Promotion of early seasonal vaccine has been part of the strategy; however, if novel H1N1 vaccine is available in September or October, some people may believe that is too early. Several years ago the message to physicians was that it could be too early, although this was to mitigate shortages. Based on what he had observed thus far, there had not been sufficient messages to physicians to provide the background for the new stance that it was not too early. He encouraged the inclusion of references in all communication efforts to support that stance.

Dr. Sheedy replied that there are plans in place, and their scientific staff have informed her that it is okay to tell people that it is not too early to vaccinate in August or September. There is a satellite course for providers that includes this message among others. Bill Atkinson is the lead on provider education and messaging issues. He and Dr. Sheedy have discussed this extensively, including the various ways that message can be disseminated. CDC is fortunate to have wonderful distribution and reach in terms of being able to reach numerous providers. There are courses, conference calls, and updates, and articles will be prepared that can be placed in publications that reach providers.

Dr. Sawyer noted that in June, ACIP heard about the two models for distribution. He wondered how close CDC was to a decision, given the importance for local planners of training providers on how to order from a central distributor.

Dr. Wortley responded that the decision was imminent, and was expected to be made that week.

Dr. Schuchat said the expectation was that providers would work with their state and local health departments regardless of which distribution method went forward. While the timing was imminent, as noted earlier, one state has already pre-registered their providers to be able to order through the state to the federal assets. While there would soon be greater clarity, some states are already planning and efforts are being made to share best practices in that regard. CDC is also looking forward to the provider organizations helping with this in terms of doing the push (e.g., through professional organization, to members, back to state and local agencies) once there is clarity.

Dr. Chilton pointed out that CDC does an excellent job of communicating, at least with professionals, in the spring each year. Although the agency could have been accused of “flip-flopping,” it was able to effectively change the message and get it widely disseminated.

However, in thinking about the communication strategy, he did not think they should allow for a low demand scenario. There was not time to wait to find out whether there was going to be a bad pandemic during the fall. Instead, he thought they needed to create a high demand situation and that they should not be passive. With regard to the concern about having a high demand / low supply scenario, focus groups have been helpful in showing that there is some degree of lack of self-interest; that is, being willing to give the vaccine to people who really need it the most. The focus group suggested that health care workers, emergency responders, and young children be given the vaccine. Presumably it was not the young children who voted that way. So, they are willing to let other people have the vaccine if there is a situation of high demand and low supply. Thus, he thought they needed to sell it and somehow communicate the fact that there could be a severe epidemic in the fall with severe results, without frightening the population too much.

Dr. Sheedy clarified that she did not mean to imply that the current scenario was not one in which they were not taking steps to encourage vaccination. The ACIP vote during this meeting and the ability to discuss recommendations would provide them with a wonderful opportunity to begin speaking directly to those people who they hope will get the vaccine, to explain why it is being recommended for them, and to lay the foundation for encouraging people to get both pandemic and seasonal influenza vaccines. She reminded everyone that they would do what they could to encourage people to seek vaccination, discuss its importance, and increase demand. However, some factors that impact demand are actually beyond the control of communication. That includes what people bring to it in terms of their past experiences, their existing perceptions about the vaccine, disease severity, prevalence, et cetera.

Dr. Sumaya requested specifics regarding plans to reach out through communications to harder to reach communities (e.g., rural, minorities, under-served), and he asked whether there had been or would be input from these communities in the development of the communication strategies.

Dr. Sheedy responded that they have not had the level of input that she thought they should; however, historically they have had good luck working with the media that reach those communities and with local partners to help reach them. A number of partnerships are in place with organizations who reach these groups. There are plans for translation of key documents and materials. However, she acknowledged that they had not been able to reach out to acquire direct input from those groups.

Dr. Marcy inquired as to whether there would be a separate vaccine information statement for the H1N1 vaccine.

Dr. Sheedy replied that there would be.

Dr. Lett inquired about the Public Readiness and Emergency Preparedness Act (PREP Act), about which they are receiving questions. People are asking about the intersection with the normal Vaccine Injury Table. The PREP Act is helpful for explaining liability coverage for people involved in vaccination and planning. It appears that if someone has an injury, they can be compensated. However, she wondered if people could also be compensated through the usual Vaccine Injury Table.

Geoff Evans (National Vaccine Injury Compensation Program) indicated that a one-page handout was available on the information table that addressed the PREP Act, which provides liability protection for covered countermeasures and will also set up a compensation program.

In terms of how this would play out with respect to the Vaccine Injury Compensation Program (VICP), which covers seasonal trivalent influenza vaccine in which the Vaccine Injury Table functions, versus the H1N1 vaccine that will have a table created as part of the PREP Act, is not clear at this point. He emphasized that it is important that there be as much separation between the two campaigns as possible for vaccine safety monitoring purposes, as well as the determinations that will be important in these two programs—more specifically the H1N1 program—in terms of being able to distinguish, as much as possible, the adverse events related to one versus the other.

Dr. Baker pointed out that immunization for pregnant women had been recommended for more than a decade, yet uptake remains at a high of 15%. A pregnant woman is unlikely to do anything that is not recommended by her obstetrical care provider. Clearly, there is a problem. With that in mind, she wondered whether consideration had been given to ways to convince obstetrical care providers to at least recommend the vaccine so that women could acquire seasonal and H1N1 vaccine offsite. Pregnant women are an important high risk group.

Dr. Sheedy replied that her team spent a full day recently locked in a room brainstorming about some of these tougher issues, this being one of them. They agree completely that while they can try to reach pregnant women directly, it is the providers who are key. These women see their providers frequently, so the team did discuss how they could better work with American College of Obstetricians and Gynecologists (ACOG) and other groups to reach their members and engage them more. Consideration was also given to the types of materials and tools the team could provide to make it easier and more convenient for physicians to raise the issue with their pregnant patients.

Dr. Schuchat pointed out that in contrast to seasonal influenza, the H1N1 situation had offered the unfortunate opportunity of being able to highlight some of the horrible outcomes pregnant women are suffering. A paper was recently published about pregnancy complications from H1N1 that highlights the complexities and challenges of influenza in pregnant women. The hope is that the clinician community that serves these women will pay attention and the CDC can work with them to develop good messages and tools for women.

Dr. Meissner presented an opposing view to the current discussion, based partly on a commentary by Dr. Tony Fauci in the *New England Journal of Medicine* that began with the recognition of the 1918 pandemic that resulted in over 20 million deaths worldwide. This commentary pointed out that there were two additional pandemics in the last century with ancestors of the 1918 strain; however, each pandemic was less severe than the preceding one and the pandemic occurring now is really a fourth generation ancestor of the 1918 strain. Increasingly less severe disease is being observed as each pandemic occurs. While this is likely in part due to improvements in public health and medical care, it is also likely that there are genetic changes in the virus. The virus may be trading virulence or pathogenicity for transmissibility. In fact, that appears to be what is occurring in the US and throughout the world based on what they heard earlier in the morning. This raised the question in Dr. Meissner's mind about the potential hazards of administering a swine flu vaccine to tens of millions of people when there are very limited data about the safety of this vaccine. As pointed out, Guillain-Barré Syndrome (GBS) is less likely to occur in the young age group that would be the primary target of this vaccine; however, many other issues may arise. Conversely, if the vaccine is vigorously endorsed for many people and it turns out to be a relatively mild illness, which appears to be the case, he thought ACIP would lose credibility in terms its recommendations. There did not appear to be an evolutionary advantage to this virus to acquire greater pathogenicity. It seemed more likely to be less severe. A virus does not want to

kill its host, have an adult stay home from work, or have a child out of school—it would rather be passed from one host to another. With that in mind, they could make an argument that this may be a mild season. However, it may very well go the other way.

Dr. Schuchat responded that it is very important to raise and discuss issues, because this meeting represented a day of important and serious deliberations. It is always said that no vaccine and no medical product is without risks. It is important for ACIP as a committee to consider benefits and risks in any equation. With season influenza and H1N1, each individual who has been infected has a somewhat different story. Even with what is believed to have occurred with 1918 influenza, 98% of people survived. The impressions, even with good epidemiology, are challenging. There are many factors (e.g., individual, school, community, et cetera experiences). ACIP's purview is to consider the spectrum of illness that this virus is known to cause to think through the data presented, consider what populations appeared to be affected most severely, what interventions should be implemented, et cetera. For vaccines to work ideally, they must be used before exposure. Not knowing the exact circumstances that can be expected in the fall and winter if vaccines are not utilized or are used in a highly limited manner is a major challenge.

Dr. Sheedy said she thought it was okay for them to share these dilemmas with the public. They public may have interesting thoughts and ideas to share about this. Public engagement sessions are planned in a number of cities throughout the US in August to deliberate some of the issues.

Regarding terminology, Dr. Judson thought the use of the term “pandemic” was acceptable if that meant what most people thought, “It is everywhere and it affects many people.” That is basically the WHO definition. To the extent that the term means that it is more severe, they would be tying it to a name that is probably not justified by the science. In terms of what is known and has been observed thus far, by 2010 H1N1 will likely be one of several seasonal virus strains with no more measurable severity or impact than some of the other strains experienced in the last 50 to 90 years. The challenge is dealing with two different vaccines for four different viruses, which probably do not differ in terms of how they would affect the individual or the individual with underlying risk factors.

Dr. Temte pointed that as ACIP moved toward universal recommendation of influenza vaccination, this season posed a good opportunity to make in-roads with communication. There would be a clear benefit during this season to be aggressive with pregnant women and other such groups. Thus, he thought they should use this opportunity in terms of the broader picture for expanding recommendations for seasonal influenza. At the same time, he believed they had to be very careful not to oversell this virus. As Dr. Meissner mentioned, nothing is known about the safety of the H1N1 vaccine. Dr. Temte also worried greatly that if they promoted the vaccine heavily and then something negative occurred, credibility would indeed be lost. They must also be careful about labeling the vaccine, in that if they label it as a pandemic vaccine, this could cause problems for future pandemics should anything negative occur this season. For example, the swine flu vaccine provokes negativity.

Public Comment Session**Lyn Redwood
The Coalition for SafeMinds
(Sensible Action For Ending Mercury-Induced Neurological Disorders)**

Hi. Thank you for the opportunity to speak here today. I represent the Coalition for SafeMinds. I'm very concerned about the fact that thimerosal will be utilized in the preparation of the swine flu vaccine. As you know, back in 1999, we were told that thimerosal was being removed or eliminated from vaccines. What we've witnessed over the last several years is the increasing use of thimerosal in flu vaccines that are now administered to pregnant women. We do know that the thimerosal from vaccines is able to cross the blood-brain barrier and accumulate in the brains of infant primates. I would assume that the same thing happens in infants. That's something that we're completely ignoring. That, in addition to the fact the EPA already estimates 1 out of every 6 pregnant women has levels of mercury in their body that can cause neurological damage to their unborn children. So, I would highly recommend that you please consider making a recommendation for thimerosal-free flu vaccines for pregnant women.

I also wanted to remind the committee about another study that was published in *Lancet* in 2006 where they looked at 50,000 women over five flu seasons and they compared those who received flu vaccine to those who did not. They found that absolutely no difference in the incidence of flu or flu-related illnesses in those two groups. Also, when they looked at the children, following them up, there was also no difference in their incidence of flu as well. So, I think we need to be very careful about assuming that this flu vaccine is going to be safe and effective in pregnant women.

To get this vaccine to market by the fall, none of the safety studies will be completed yet. We know that pregnant women and young children will be among the first to receive this experimental vaccine and are also the ones that are most vulnerable to vaccine side effects. Given these concerns, I would like to ask the Advisory Committee for Immunization Practices to respond to some of these questions:

- Should a squalene-based adjuvant be used and what studies have demonstrated that it is safe to combine thimerosal with squalene?
- Both CSL and sanofi pasteur have indicated that they can make pandemic mercury-free vaccine. Will ACIP state a preference for mercury-free vaccines for pregnant women, young children, and vulnerable populations such as premature infants and immunocompromised children? I want to remind you that this was actually recommended by the Institute of Medicine in 2001 in their report on thimerosal-containing vaccines and neurological development.
- How much mercury will be in multi-dose vials and what dose of mercury will be given to premature infants, pregnant women, and adults? We know from a study done here at Grady Hospital by Greg Stajich that premature infants developed elevated levels of mercury after exposure to just 12.5 mcg of hepatitis B vaccine. One infant in that study developed a mercury blood level of 23 mcg. CDC identifies a toxic blood level of mercury as 10 mcg. So, I think we need to look at that issue very closely.

- ❑ Given that the National Vaccine Advisory Committee identified a gap in demonstrating the safety of simultaneously administering multiple vaccines during a given office visit, will ACIP recommend administration of H1N1 vaccine separately as a precaution to be able to permit identifying, tracking, and analyzing; and, if necessary, removing the vaccine from the market as was the case in 1976?
- ❑ All flu vaccines to date are considered a Category C drug, which means they have never been evaluated for carcinogenic or mutagenic potential. We also have absolutely no animal reproductive studies, and we have no idea if this vaccine could cause fetal harm. We do know that if a pregnant woman develops flu during pregnancy, there's an increase risk of schizophrenia in her offspring. We don't know if administering a flu vaccine could cause that same time of response by stimulating the immune system, causing a pulse of cytokines and opening the blood-brain barrier. That type of question is only going to be answered if we follow the infants. From what I heard today, the only thing that we are really looking at in the infants is their immune response. So, we need to do much better than that. We need to look at whether or not the children who have received this vaccine later on in life have any adverse neurological sequelae.

In closing, I urge you to please consider these concerns as you move forward today with making recommendations regarding influenza immunization. Thank you very much.

Kelly Moore
Tennessee Immunization Program

Since Tennessee's pre-registration process has been alluded to a couple of times I'll give an update. Our programmers are actually this week finishing the programming on that on-line registration system for the private sector. We have had a lot of enthusiasm as we have presented the concept around the state, so we are really encouraged that that will allow us to understand who is interested and how many doses they may be interested in. One of the challenges that we face that we are looking for help on is the large retail pharmacy chains that are interested in partnering with us. We are trying to find better strategies to engage them at a corporate level instead of having to work with individual outlets, and trying to manage shipping to their distributors hopefully so that they can take distribution over from that point. Logistically, in echoing what Pascale was talking about, we are finding a lot of interest and success in the private sector. There are still some logistics challenges we're looking for good answers for. Thanks.

ACIP Influenza Work Group Recommendations

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Dr. Fiore indicated that he was charged to present the results of the many work group discussions that occurred through teleconferences, emails, et cetera regarding the considerations for prioritization guidance.

The novel influenza A(H1N1) pandemic poses unique challenges to making vaccine recommendations. There is persistent transmission in the US since the introduction of the virus and there is potential for an early second surge. Vaccine clinical trials and large-scale production must proceed simultaneously. Recommendations for use must be made before licensure to provide basis for implementation planning. There remains uncertainty about the arrival date of the vaccine, the amount of vaccine that will be available early, the pace that the supply will increase over time, the ability to implement recommendations, and the number of doses needed.

A summary of key epidemiologic findings in terms of the distribution of cases, hospitalizations, and deaths is as follows:

- The highest incidence of lab-confirmed infections is in school-aged children
- The highest hospitalization rates are among 0 through 4 year olds
- Hospitalization rates for April through July 2009 approach cumulative rates for seasonal influenza among school-aged children and 19 through 49 year old adults
- The fewest cases but highest case-fatality ratio is in older adults
- The distribution of cases by age group is markedly different compared to seasonal influenza
- There is a higher proportion of hospitalized cases in children and young adults
- There are few cases in older adults
- No outbreaks have occurred among the elderly in long-term care facilities
- Of the hospitalized cases, 70% have had an underlying medical condition that confers higher risk for complications
- Pregnancy is a higher risk condition, with 6% of the hospitalized cases in the early case series being pregnant women; and the upcoming *Lancet* article shows that the incidence of hospitalization in pregnant women was approximately four times that of the general population

Obesity among persons with novel influenza A(H1N1) has also arisen as a potential issue. According to non-published data from CDC, obesity has been conjectured as a possible additional risk factor. Found thus far in the data is that the prevalence of obesity, defined as having a body mass index (BMI) of ≥ 30 , among the general adult population is 34%. The prevalence of morbid obesity (BMI ≥ 40) is 6%. The prevalence of obesity among persons who died with lab-confirmed influenza A(H1N1) is 68 / 179 (38%), with 13 / 179 (7%) being morbidly obese. Among 68 obese persons who died, 39 (57%) had a previously known medical condition that confers higher risk for influenza complications. Among the 13 morbidly obese who died, 9 (70%) had a previously known medical condition that confers higher risk for influenza complications. The conclusion from this is that the prevalence of obesity among the general population must be kept in mind, and many of these obese and morbidly obese patients had other predisposing underlying medical conditions—an indication for seasonal influenza, for example. The work group's conclusion is that current evidence was not sufficient to establish obesity as a new independent risk factor.

In summary of the key findings from virologic and immunologic studies, no significant antigenic changes have been observed among novel influenza A(H1N1) viruses since April 2009. The hemagglutinin of novel influenza A(H1N1) viruses is somewhat similar to H1 subtype viruses that circulated during 1920s-1940s, which suggests the possibility that this has been the cause of some of the cross-reactive antibody to nH1 that has been detected among some of the older adult participants in vaccine studies. This cross-reactive antibody is not observed among children and young adults. Cross-reactive antibody to nH1 was detected among the following participants in vaccine studies: 6% to 9% of those aged 18 through 64 years; 33% of those

aged >60 years; and 0% of children. The results from clinical studies are being awaited to determine whether older adults with some pre-existing immunity might need only a single dose.

Two scenarios were reported earlier in the day regarding two potential vaccine scenarios, one with a vaccine available as early as September and the other with availability in mid-October of as many as 120 million doses.

The work group began their deliberations with a series of planning assumptions to understand the baseline as they embarked on their discussions, including the following:

- The severity of illness and groups at higher risk for infection or complications will be similar to what has already been observed; on-going studies will determine whether this is accurate
- Antigen content, reactogenicity, and immunogenicity of adjuvanted vaccine cannot be assessed before trial data are available; given this, the adjuvanted discussion was basically taken off of the table during the work group's deliberations
- The safety profile and antigen content of unadjuvanted novel H1N1 vaccines will be similar to that of seasonal influenza vaccines
- Adequate supplies of licensed unadjuvanted vaccine can be produced for all by approximately February 2010
- Enough vaccines for all will not be available before the next pandemic wave in the fall
- Pandemic vaccine and seasonal vaccine availability will likely overlap and both will be recommended for many populations groups
- Two doses will be needed for protection; on-going studies may further inform this, but the working assumption is that two dose will be needed
- Initial demand for vaccination will be approximately the same as for seasonal vaccine, but could increase quickly if community transmission increases
- Vaccine distribution will be timely
- Implementation will pose many challenges; however, this was not the focus of the work group's discussions

Definitions used during the work group's discussions included the following:

- Supply:** Number of vaccine doses available for distribution
- Availability:** Ability of a person recommended for vaccination to be immunized in a local venue
- Targeting:** Recommendation that immunization programs encourage and promote vaccination for certain population groups
- Prioritization:** Recommendation to provide vaccine to certain population groups before others

The first question the work group tackled was: Are new recommendations needed? The latest iteration of the pandemic vaccine prioritization guidance was developed for pre-pandemic planning in 2007. The stated intent of this guidance was that the guidance was to be modified according to pandemic epidemiology and vaccine supply expectations. Much of the planning focused on severe pandemic with the potential for substantial disruption of critical infrastructure. The work group's conclusion was that current evidence from epidemiologic and immunologic studies, and updated information on vaccine supply and availability timelines, indicate the need to revise the recommendations made during pre-pandemic planning.

The second question the work group addressed was: Which groups should be targeted with initial vaccine allocations? Consideration included severity of illness and risk for complications during nH1N1 outbreak, frequency of illness during nH1N1 outbreak, contribution of particular groups to overall burden of severe illness, protection of healthcare system functions, reduction of societal impact, and the potential for indirect protection of more vulnerable contacts. Five groups were identified as being important to target initially. Dr. Fiore stressed that while the work group included numbers with these five groups, the numbers were for planning purposes only and were not intended to be demographic assessments of how many subjects are actually in each group.

The first group is pregnant women (n=approximately 4 million). Pregnant women are at higher risk for complications for seasonal influenza and have been at higher risk in past pandemics. Deaths have been reported among pregnant women during 2009 pandemic, and there has been a higher rate of hospitalization among pregnant women compared to other groups. There is also a potential for protection of infants who cannot be vaccinated. First of all a pregnant woman is about to become a close contact of someone who cannot be vaccinated. There is also the possibility, as has been shown in some studies of seasonal influenza, that passively transferred maternal antibodies might protect newborns.

The second group considered important as an initial target group is household contacts and caregivers for children younger than 6 months of age (n = approximately 5 million). This is probably the number that is most difficult to determine, given that it includes people in the household with the newborn as well as daycare providers who care for children less than six months of age. The rationale behind this group is that young infants < 6 months old cannot be vaccinated with the currently licensed vaccines, young infants are at higher risk for influenza-related complications, and a cocooning effect might be achieved that would provide indirect protection.

The third group considered important to target is healthcare personnel and emergency medical services (n = approximately 14 million). "Emergency medical services" were defined as persons in an occupation (e.g., emergency medical technicians, firemen) who routinely provide emergency medical care in communities as part of normal job duties. The rationale for selection of the population is that they are a potential source of infection for vulnerable patients, increased absenteeism could reduce healthcare system capacity, and influenza A(H1N1) infections among healthcare workers have been reported (community- and workplace-acquired).

Children and adolescents from 6 months through 18 years of age (n = approximately 78 million) represent the fourth target group selected. The rationale behind selection of this group is that they have the highest incidence of illness. Explosive outbreaks in schools was a prominent feature of the Spring 2009 epidemiology. Children < 5 years old are at highest risk for hospitalization, they are a source of infection for the community and in schools, and their illness keeps parents home from work.

Adults aged 19 through 64 with certain medical conditions make up the fifth target group selected (n = approximately 34 million). Of the adults hospitalized with nH1N1 infections, about 70% had a medical condition that confers higher risk for influenza-related complications. Medical conditions that confer a higher risk for influenza-related complications include chronic pulmonary, cardiovascular, renal, hepatic, cognitive, neurologic / neuromuscular, hematological or metabolic disorders, and immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus).

The work group conclusion was that these five target population groups should be the initial focus of immunization efforts, recapped as follows:

- Pregnant women (4M)
- Household contacts and caregivers for children younger than 6 months of age (5M)
- Health-care and emergency medical services personnel (14M)
- Children and adolescents from 6 months through 18 years of age (78M)
- Persons aged 19 through 64 years who have medical conditions associated with a higher risk of influenza complications (34M)

Thus, the total initial target group is projected to be approximately 134 million people. While this seems like a very large group compared to the vaccine supply, it is important to remember that seasonal influenza vaccine coverage in these groups is only about 20% to 50%. Although better uptake is hoped for in these groups, the work group felt that it was important not to try to match initial supply precisely with 100% coverage estimates for these groups, given that this is unlikely to be achieved. These initial target groups represent approximately 44% of the total population.

The work group engaged in considerable discussion about young adults, which the work group refers to as Option B. Option B is to expand the age group of children 6 months through 18 years of age to 6 months through 24 years of age (n= approximately 102 million). Again, the rationale behind this is that these groups have the highest incidence of illness, explosive outbreaks in schools were a prominent feature of the Spring 2009 epidemiology, children < 5 years old are at highest risk for hospitalization, are a source of infection for community and in schools, and illness keeps parents home. It is difficult with the national data available to determine whether there is a large difference between a 19-year old and a 15-year old. The work group conclusion was that Option B would slightly alter the five target population groups that should be initial focus of immunization efforts to the following:

- Pregnant women (4M)
- Household contacts and caregivers for children younger than 6 months of age (5M)
- Health-care and emergency medical services personnel (14M)
- Persons 6 months through 24 years of age (102M)
- Persons aged 25 through 64 years who have medical conditions associated with a higher risk of influenza complications (34M)

Now the total initial target group would be approximately 159 million or slightly more than 50% of the US population. Again, seasonal influenza vaccine coverage in these groups is only 20% to 50%.

Another question addressed by the work group was: Is guidance on prioritization within initial target population needed? If supply estimates are accurate, the need for prioritization is lessened. The projected 120 million doses anticipated in October exceeds number of doses of influenza vaccine ever given in a single influenza season. A major limitation on the vaccination program with this supply would be making vaccine accessible quickly to all. However, the supply estimate assumes that all manufacturing, licensure, and distribution steps will proceed smoothly. Therefore, the work group conclusion was that guidance is needed on how programs and vaccination venues should prioritize vaccination if availability is very limited because availability and demand at the local level will vary even if projected supply estimates are achieved, and projected initial supply estimates might not be achieved.

The work group considered two strategies. Strategy 1 was to vaccinate as many as possible in the initial target groups. This strategy assumes that some but not all providers / programs will have a limited initial supply and demand might vary considerably in the early weeks. This strategy would also provide vaccination for smaller high risk / occupational groups within the primary target groups for prioritization when the supply is very limited. Strategy 2 would focus vaccination efforts on smaller high priority groups, and assumes that availability will be limited and demand will be high in the early weeks. The strategy would also expand programs to include the larger target groups as availability increases.

During these discussions, the work group reflected on the 2004 experience, during which there was a vaccine shortage due to a manufacturer being unable to deliver vaccine. The result was that prioritization guidance was developed to address the groups thought to be at higher risk first due to the limited supply of vaccine. There was a substantial drop in the 2004-2005 shortage season in all targeted groups, even though some of the groups were intentionally prioritized to the front of the line to be vaccinated, including health care workers. There was a fair amount of delay in coverage, even in reaching the baseline coverage that had been achieved in 2003. The lesson was that prioritization can lead to unexpected consequences. During the 2004 season, coverage declined even in groups prioritized, and excess vaccine remained at the end of the season [Source: CDC, NHIS. <http://www.cdc.gov/flu/professionals/vaccination/pdf/vaccinetrend.pdf>; Preliminary data from 2007-08 influenza season].

Key work group considerations when vaccine demand exceeds supply were that vaccination providers and immunization programs will need to balance the need to administer vaccine to as many persons as possible as quickly as possible with need to prioritize vaccination for smaller subgroups. In addition, availability might vary greatly even at the local level. Flexibility is needed to adapt to changes in availability and demand.

With regard to what strategy should be used to provide access to as many target groups as possible, the work group conclusion was to recommend Strategy 1:

- Recommend vaccination of as many as possible in initial target groups
Assume some but not all providers / programs will have a limited initial supply and demand might vary considerably
- Prioritize to smaller high risk / occupational risk groups when demand exceeds supply
- Provide flexibility to programs and providers to vaccinate as many as possible quickly, but prioritize when supplies are limited

In terms of who should be prioritized if vaccine demand exceeds availability, the work group concluded that while vaccine demands exceed availability, protection of persons who are at higher risk for influenza-related complications due to novel influenza A(H1N1), or who are at high risk for occupational exposure and furthering transmission in healthcare settings would constitute the highest priority. Within the larger initial target group, the smaller prioritization group would include the following:

- Pregnant women (4M)
- Household contacts of infants < 6 months old (5M)
- HCP / EMS with direct contact with patients or infectious materials (9M)
- Children aged 6 months through 4 years (18M)
- Children with chronic medical conditions (6M)

The total of the highest priority groups is approximately 42 million. The number of doses needed for high 2-dose coverage of these groups falls within the lower estimates of initial supply projections. As a reminder, seasonal influenza vaccine coverage in these groups is only 20% to 50%. With regard to who should be vaccinated as availability increases, the work group conclusion was that when vaccine availability is sufficient at the local level to routinely vaccinate initial target populations, vaccination against novel influenza A(H1N1) is also recommended for healthy adults aged 19 through 64 years old. In terms of when persons 65 or older should be vaccinated, currently available information indicates that adults aged 65 years and older are at lower risk for infection than younger persons for novel influenza A(H1N1). The work group conclusion was that vaccination should be offered to persons aged 65 or older once vaccination programs are capable of meeting demand for vaccination from younger age groups. However, the recommendation to offer vaccine to persons aged 65 or older might need to be reassessed as new epidemiologic, immunologic, or clinical trials data warrants, and should be assessed in context of global need for novel H1N1 vaccines.

Based on the work group's considerations and deliberations, the following recommendations were developed:

Work Group Recommendation (1): The initial efforts should focus on vaccination of as many as possible in initial target groups, including:

- Pregnant women
- Household and caregiver contacts of children younger than 6 months of age
- Health-care and emergency medical services personnel
- Children from 6 months through 18 years of age
- Persons aged 19 through 64 years who have medical conditions associated with a higher risk conditions

Work Group Recommendation (2): When vaccine demand exceeds availability, subgroups within target groups that should be prioritized where feasible are:

- Pregnant women
- Household and caregiver contacts of children younger than 6 months of age
- Health-care and emergency medical services personnel with direct contact with patients or infectious materials
- Children 6 months through 4 years old
- Children with chronic medical conditions

Work Group Recommendations (3): When vaccine availability is sufficient at the local level to routinely vaccinate initial target populations, vaccination against novel influenza A(H1N1) is recommended for healthy adults aged 19 through 64 years old. Vaccination of persons aged 65 or older should be offered once vaccination programs are capable of meeting demand for vaccination from younger age groups. Vaccination with seasonal vaccine should begin as soon as seasonal vaccine available for persons aged 65 or older.

Work Group Recommendation (4): Given that H1N1 vaccine supply and availability are projected to increase quickly over time, and more information on the need for 2 doses will be available, vaccine should not be kept in reserve for later administration of the second dose. Seasonal influenza vaccination should begin as soon as it is available for all groups currently recommended for seasonal vaccine [Prevention and control of seasonal influenza with vaccines:

Recommendations of the ACIP, 2009. July 24, 2009; <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm>. Seasonal and pandemic inactivated vaccines may be administered on same visit. Clinical trials are on-going that will further determine whether there are any problems with administering the vaccines simultaneously, but it is not believed that there will be any issues.

Option B work group recommendations merely changed the wording in a such a way that instead of 6 months through 18 years of age, the recommendation is from 6 months through 24 years of ages. Thus, the recommendations would be as follows should Option B be selected:

Work Group Recommendation (1): Initial efforts should focus on vaccination of as many as possible in initial target groups, including the following:

- Pregnant women
- Household and caregiver contacts of children younger than 6 months of age
- Health-care and emergency medical services personnel
- Persons from 6 months through 24 years of age
- Persons aged 19 through 64 years who have medical conditions associated with a higher risk conditions

Work Group Recommendation (2): When vaccine demand exceeds availability, subgroups within target groups that should be prioritized where feasible are:

- Pregnant women
- Household and caregiver contacts of children younger than 6 months of age
- Health-care and emergency medical services personnel with direct contact with patients or infectious material
- Children 6 months through 4 years old
- Children with chronic medical conditions

Work Group Recommendation (3): When vaccine availability is sufficient at the local level to routinely vaccinate initial target populations, vaccination against novel influenza A(H1N1) is recommended for healthy adults aged 25 through 64 years old. Vaccination of persons aged 65 or older should be offered once vaccination programs are capable of meeting the demand for vaccination from younger age groups. Vaccination with seasonal vaccine should begin as soon as seasonal vaccine available for persons aged 65 or older.

Work Group Recommendation (4): Given that nH1N1 vaccine supply and availability is projected to increase quickly over time, and more information on the need for 2 doses will be available, vaccine should not be kept in reserve for later administration of the second dose. Seasonal influenza vaccination should begin as soon as it is available for all groups currently recommended for seasonal vaccine [Prevention and control of seasonal influenza with vaccines: Recommendations of the ACIP, 2009. July 24, 2009; <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm>]. Seasonal and pandemic vaccines may be administered on same visit.

The work group decided that they would like to have further information about the 19 through 24 year old age group. Dr. Fiore reminded everyone that the data from the aggregate reporting lumped a large group of 5 years to 24 years of age, which was a source of consternation for many people. When further broken down, confirmed and probably cases from March 15-May 16, 2009 are as follows: 2.60 for 5 to 11 year olds; 2.56 for 12 to 18 year olds; and 1.26 for 19

to 24 year olds. There is a fairly steep drop-off in incidence in the early line list data with the 12 to 18 year age group compared to the 19 to 24 year old age group [C Reed et al. CDC, unpublished data].

Discussion

Dr. Sumaya inquired as to whether the work group's vote on Strategy 1 was unanimous, or if there was any dissent.

Dr. Neuzil responded that the rationale was that there may be 120 million doses in October. The work group felt that the larger target group of 135 million met all of the criteria for initial vaccination (e.g., severity of illness, burden of illness, et cetera) and wanted to cover all of the them. Based on anticipated uptake, the work group made the assumption that coverage would be less than the 135 million in the larger initial target group, and that there would be plenty of vaccine to cover the anticipated number of vaccinees under Strategy 1. Strategy 2 was to begin with 41 million individuals; however, reflecting on the 2004 season, the work group was concerned that selecting this strategy would miss the opportunity to reach the broader group. The work group also recognized that there will be local supply / demand mismatches, so they needed to provide some guidance in that situation. Therefore, it was basically either start with the priority group of 41 million or start with 135 million. The work group preferred to start with 135 million. They did not take a formal vote, but there was some consensus on the strategy selection.

Dr. Fiora agreed.

Dr. Sumaya inquired as to whether any consideration was given to proceeding slower as they watched the pandemic evolve and more data became available.

Dr. Neuzil replied that the assumption was that if the pandemic progressed as it had been, there would be outbreaks early in the fall. That also drove the strategy decision.

Dr. Sawyer requested more insight into the work group thinking about the 19 to 24 year old group. Given the projections just laid out for vaccine supply and uptake, he assumed that uptake would be far less than 80%, especially with 19 to 24 year olds. Therefore, he was interested in understanding why the work group did not follow the same equation about vaccine availability and demand and immediately move to Option B, which goes up to 24 year olds. In addition, Dr. Sawyer inquired as to whether it was correct that including the 19 to 24 year old age group added 24 million to the initial group.

Dr. Fiore responded that there is limited information to suggest that this group is at much greater risk for infection than older adults. It seemed like an arbitrary cutoff that was likely dictated by surveillance reporting. It is a larger group to consider vaccinating, and there is a fairly large step-off of incidence of confirmed infections in 18 to 24 year olds. Adding the 19 to 24 year old age group does add 24 million to the initial group. With the groups overlapping to some extent, it is probably somewhat less than that. For example, there are some pregnant women in there who are already recommended.

Dr. Turner (ACHA) indicated that he was speaking to ACIP as the President of ACHA, its board, and its Vaccine Preventable Disease Committee, which would strongly support Option B. He reminded everyone that college students left campuses in mid-May. Had H1N1 struck last November, he believed there would have been much higher rates of disease among students.

The campus where he is currently working has a small student population but has already had about 50 students with the virus. It appears that the congregate living, learning, and social conditions are the primary risk factors in transmission of this disease. This is why it is being seen in school children, camps, military academies, et cetera. The most compelling reason for making sure that the college population is vaccinated is that they are vectors for the disease in communities. It has been observed for 25 years that in Charlottesville, Virginia outbreaks of infectious diseases always begin with college students and move peripherally to the rest of the community. The college students interact with the community. They volunteer in daycares, hospitals, nursing homes, et cetera. They student teach, tend bar, are waiters and waitresses, et cetera. Thus, it seemed to make good public health sense to vaccinate the college population since epidemiologically it seemed that they were at higher risk for getting disease and being hospitalized. Approximately 32% of college students are vaccinated for seasonal influenza each year according to ACHA's data, which is fairly good uptake. He believed they would see fairly good uptake with H1N1 vaccine as well. Therefore, he reiterated strong support for Option B.

Dr. Ehresmann pointed out that although it was noted that there was a drop in the 19 to 24 year old age group, they were still at 1.26 per 100,000 population, which was still higher than the 1 year old age group.

Dr. Fiore answered that they must recognize that this was from several sources of data and that the data were picked up at different times. The incidence data he showed was collected in the early stages of the outbreak when there was line list reporting. The aggregate reporting data from the system that took over in about May captures a different age group and captured the fact that incidence increased over time because there were more infections. Thus, the data were not comparable because they were two different snapshots.

Dr. Neuzil added that the other important point was that as the age groups increased, the overwhelming majority of people who are hospitalized or die have underlying high risk conditions. Thus, many of the people in the high risk category are being captured; whereas, only 40% to 50% of 0 to 4 year olds have high risk conditions. That is not so much a distinction between 18 to 19 to 24. The truth is, the work group had a lot of trouble with this because the numbers get very small when data are divided. There really was no consensus. There were differing opinions on whether to stop at 19, which would be consistent with the seasonal recommendations and would also be simple, or to go up to 24 based on fairly limited data.

Noting that Work Group Recommendation (2) included children with chronic medical conditions, Dr. Duchin (NACCHO) suggested that all children 6 months to 18 years of age be added back to Work Group Recommendation (3) that advises on who to immunize when the supply is adequate; that is, add back all children who do not have chronic medical conditions.

Dr. Fiore responded that Recommendation (2) was only for the situation early on when demand may exceed availability. It was not meant to be a follow-up to the prioritization slide. If all goes well, Recommendation (2) will not be activated.

From a practical point of view, Dr. Marcy thought it was far easier to start with a smaller focused priority group and then expand as availability increases. From the providers' point of view, to begin with a large group and then tell people they are not longer eligible would be very difficult. He, therefore, he would vote for the smaller group that expanded rather than a larger group that would have to be shrunk under certain circumstances.

Dr. Baker thought that using smaller groups and expanding was totally confusing. If at the beginning they achieved 35% uptake in the five targeted groups and the 19 to 24 years olds were added, that would still represent less than 50 million people. If that was doubled because of a need for 2 doses, that would still only be 100 million. Making so complex that the eligible groups change frequently is going to be problematic. There will be mismatches locally no matter what. The opportunity to vaccinate people has always been lost when this type of prioritization is utilized. Therefore, she strongly pled for the idea of Option 1 with the addition of the 19 to 24 year old group based on their incidence. While that group may not shed as much virus as young children, they certainly move throughout society at a much higher rate than young children.

Dr. Judson agreed with Dr. Baker. By most current assumptions, it appears that there will be a good match between vaccine supply and demand. What they do not want to do is lose time and have to start over in December or January with an expanded program. He thought they should get out as much vaccine to as wide a group as possible immediately.

Patsy Stinchfield (NAPNAP) also agreed with Dr. Baker. Typically what occurs with messages is that the first message seems to stick the longest. Therefore, she thought it would be much harder to narrow and then go broad than to start broad. It takes providers and parents a long time to get second messages. The media wears out and moves on to other topics. Well into the pandemic people were still saying they never traveled to Mexico.

Dr. Morse noted that the broader group also included the school-aged population, which has its own logistical issues with respect to reaching large numbers of children in a limited amount of time. New York has a number of counties with over a million people and 60 or so school districts. Even if they immunized one school district a day, it would take up to 6 months to get 2 doses in. Therefore, logistically they should not miss opportunities to reach groups.

Dr. Birkhead (NVAC) thought it would be better to word the recommendation different than to say "if there is a mismatch locally," which raises the issue of incompetence. He thought the idea of flexibility should be built in. For the under 5 year old age group, it would be relatively easy to get vaccine out through the VFC providers. School-aged children would probably take more planning and vaccination in that group would likely take place over a longer period of time. He suggested saying, "At the local level, there is flexibility in terms of which groups should be vaccinated in which order because there are different strategies." That would get away from the implication that the supply was not being managed adequately.

Dr. Schaffner (NFID) pointed out that tight prioritization would result in vaccine being unused.

Dr. Sawyer expressed concern that if they did not initially include the 19 to 24 year old group, the opportunity would be lost to ever capture them.

As a member of the Influenza Work Group, Dr. Englund was pleased that they focusing all of the attention on the 5 years of age to 24 year old group. However, she was not hearing much about the other groups and she thought they needed to determine whether there was agreement about the other groups. She personally very much agreed that all of the other groups were very important and should be included.

Dr. Baker clarified that Option 1 includes the five initial groups and adds 19 to 24 year olds. She thought most of the people who said they agreed also agreed with pregnant women, children through 18, young adults, et cetera.

Dr. Baker thought the recommendation included persons 19 through 24 with or without underlying conditions.

Dr. Neuzil responded that they were not included in the first group. What Dr. Englund was speaking of were the other groups: pregnant women, household and caregiver contacts of children younger than 6 months of age, health-care and emergency medical services personnel, and persons aged 19 through 64 years who have medical conditions associated with a higher risk conditions. They did not believe they heard any disagreement about these groups, and what was up for discussion was whether it should be 6 month through 24 years versus 6 months through 18 years, with a change in the next bullet from 19 through 64 years to 25 through 64 years. The point of the discussion is 18 or 24.

Dr. Baker clarified that her initial comment was that the group should go through 24 years of age.

Dr. Judson noted that the 18 to 24 year olds had about half the attack rate as the 12 through 18 year olds. After 18 it fell.

Dr. Bresee indicated that the data that compares rates up to 18 and 18 to 24 are pretty sparse. The work group's consensus was that the data were sparse enough that the assumption might be made that the rates of disease, the rates of outcomes in the group approaching 18 and those slightly older than 18 were probably relatively equivalent. The EIP data shown earlier reflected about a 20% lower rate of hospitalization among 18 to 24 year olds compared to those 5 to 17 years of age. There might be a step-off of risk of severe disease in the slightly older group, but it is probably relatively slight.

Dr. Baker realized the data were limited. She stressed that her interest in including 19 to 24 year olds was not because of their risk for hospitalization—it was because they are transmitters.

Dr. Birkhead (NVAC) noted that while they were focusing on 19 to 24 years of age, the focus of the discussion initially was college students, which is a different and smaller group for whom there are already specific recommendations for meningococcal vaccine, which is probably a relatively easy group to vaccinate, and which is a group that already has fairly high uptake for seasonal influenza vaccine. The recommendation could be focused on a high risk setting for disease transmission in which vaccine could be relatively easy administered; that is, focus on college students rather than 19 to 24 year olds.

Dr. Temte thought purely from a clinical standpoint, the discussion he had heard trying to smudge the borders around priority groups really rang true. Instead, an easily identifiable target was needed. After dealing with this in the past with other prioritizations, he thought that this would fall apart when actually dealing with patients. What ultimately happens is that people do not get vaccinated. He thought the real problem was not going to be having enough vaccine, but would instead be getting enough deployed.

It seemed to Dr. Chilton that a first step might be moving to accept the recommendations up to age 18, and then after that they could make a supplemental motion to include the 19 to 24 year olds if desired.

Dr. Morse inquired as to whether the intent was to vote on each recommendation separately, or all four together.

Dr. Neuzil said that the work group did not envision breaking the recommendations out separately; however, she liked the idea because she would not want a member to vote “no” because they did not want to include 19 to 24 when they agreed with every other group. If this was done in two stages and the 19 to 24 year old group was approved, obviously the language would wrap it all in.

Dr. Judson expressed concern that if they went to 19 to 24 without pre-existing conditions, they would lose any focus on priority targeting. It is important to remember that 75% or more of people who are 19 to 24 are in the regular work force and are not college students volunteering in daycare centers.

Dr. Ehresmann inquired as to whether the assumptions that were laid out would be acknowledged in the recommendations.

Dr. Schuchat suggested that the committee consider the unadjuvanted licensed vaccine. The charge for ACIP was two-fold: target populations and whether there should be prioritization. Other decisions such as off-ramps, early fill, et cetera were under the purview of other groups. She thought it would be perfectly fine to state that ACIP might not recommend the same groups for an adjuvanted vaccine.

Dr. Neuzil reminded everyone that within the work group discussions and for the discussions with the full ACIP, adjuvanted vaccines were taken off the table because antigen content, reactogenicity, and immunogenicity could not be assumed for that. If clinical trial data become available, this may be reassessed in the future. However, this discussion and vote should focus on what is presumed will be licensed and unadjuvanted.

Dr. Morse clarified that the charge to the ACIP was not to make recommendations about whether to vaccinate, but was rather to make science-based recommendations pertaining to prioritization of who should be vaccinated, based on current assumptions, in the event that a vaccination program moved forward. He stressed that the primary purpose was to assist state and local partners in their planning efforts.

Louisa Chapman (Medical Epidemiologist, CDC) inquired as to whether it was intentional for the ≥ 65 group to be left out of this recommendation. While this group may be at lower risk of infection, they remain at higher risk for death if infected.

Dr. Morse responded that the ≥ 65 group would be addressed in a later recommendation.

Motion: Recommendation (1)

Dr. Chilton motioned to accept Recommendation (1) as written and to decide separately upon the 19 to 24 year old group. Dr. Sawyer seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 0 abstentions.

If the concept was that these recommendations were based on evidence, Dr. Beck inquired as to what the evidence was in support of 18 to 24 year old age group.

Dr. Morse replied that different datasets addressed this to some extent, but not completely. That was partially due to the differences in how the various surveillance systems categorized the age groups. For example, there are some data from New York, but the subset is very small. Thus, as usual, there is some incomplete, evolving, dated information. They must work with what they have.

Dr. Neuzil added that this was a very difficult issue. Ideally, age should be a continuous variable to determine where a real change is made. For example, is a 64-year old that different from a 65-year old? This is partially an artifact of the way the data are provided. There are not enough numbers to assess age as a continuous variable year by year to determine the perfect cut point. In fact, between the ages of 19 and 24 the data are simply very limited.

Dr. Beck replied that while he recognized this, it was the practical issue that they were being called to vote on something. Thus, he wanted to know what available, reliable information they could act on. Based on what he was hearing, it appeared that there was not sufficient information upon which to make a decision.

Dr. Neuzil responded that the information they had was the small amount of information presented by Dr. Fiore that showed that 19 to 24 year old age group had a high incidence of disease, but a lower severity (e.g., hospitalization rate). In addition, other issues were raised that the work group considered, such as transmission.

It seemed to Dr. Baker that the most robust number they heard was that as of July 24, 2009 there were 43,771 cases, half of which were in 5- to 24-year olds. That did not say anything about severity, but there were some deaths in that group—virtually all in people with underlying medical conditions. However, there is a major disease burden. While they did not have the best possible data, 19 to 24 year olds are virtually impossible to capture. College is one venue where they might be accessed, but there may be other locations as well. This age group penetrates society in service / entry level jobs, so there is likely to be a great deal of transmission from this group. She also thought that uptake in all of the other groups would be less than they hoped.

Dr. Judson suggested that based on the data, they might as well go to 34 or 44 years of age. If they were calling this “targeting” or “prioritizing” they could probably only go so far and still have it pass any reasonable test of targeting or prioritizing. He was fine with making a universal recommendation first come, first served until all of the vaccine is gone.

Dr. Schuchat pointed out that another aspect which had not been mentioned was that as they considered the 19- to 24-year old age group, they were basically saying to consider them as a group rather than focus on those 19- to 24-year olds with an underlying risk factor. In general, people who have risk factors do not think that they have underlying risk factors (e.g., asthma, diabetes, other chronic conditions). This is particularly true of younger people, who do not believe they have risk of anything. There are issues with college attendees versus other groups that may have congregate settings in that age group who may not have the advantages of college students. Therefore, as they thought about age, setting, or risk factors, self-identification should be taken into consideration.

Dr. Neuzil responded that this was why the work group in general actually did not consider subsets of 19- to 24-year old. They liked the age because it was easy to identify.

Dr. Baker pointed out that this consisted of only 24 million people.

As with other issues that ACIP has face, Dr. Morse pointed out that they had been asked to weigh the evidence and to make science-based recommendation in an area where the information was incomplete or still evolving. The data on burden of disease, which is an essential criterion decision, is still emerging in this group but suggests that on an individual basis it is comparable to seasonal influenza in terms of severity. However, on a population basis, it is more than that. It affects younger age groups and is spreading in a susceptible population with little immunity. As such, it has the potential for causing a large number of deaths merely through higher attack rates. Therefore, they must take into consideration the fact that on a population basis there is a potential for this spreading more widely in these age groups and potentially resulting in more deaths than would be expected on a seasonal basis due to there being so many more susceptible.

Patsy Stinchfield (NAPNAP) noted that 19- to 24-year old travel frequently via air to and from home / college and abroad. Therefore, she thought the mobility of this group should be considered in terms of potential transmission. There is at least one paper out about the role that airline travel has.

Motion: Addition of 19 to 24 Year Olds to Recommendation (1)

Dr. Sawyer motioned to add all 19- through 24-year olds to Recommendation (1). Dr. Baker seconded the motion. The motion carried with 13 affirmative votes, 1 negative vote, and 0 abstentions.

Dr. Englund suggested that children with chronic medical conditions be specified as children less than 18 in the setting of limited supply.

Dr. Neuzil responded that it was meant to be children younger than 19 years of age. This is a different issue. These are the people with the highest risk for severe disease.

Dr. Sawyer requested clarification about when this recommendation is meant to come into play (e.g., on the local level when supply and demand at mismatched, or nationally if the early returns are that supply is inadequate).

Dr. Neuzil responded that there were several scenarios, and the group received many pleas from many organizations to help them with this by not making the recommendation so broad. There could be shortages at various levels. There could be a national supply shortage if the estimates projected were not met. They heard from local health departments and hospitals that if a hospital did not have a sufficient supply, but had a captured population, they needed to now how to prioritize. Thus, the work group offered some direction that in such a situation vaccine would first be given to those with direct contact.

Dr. Morse suggested moving to Recommendations (3) and (4) in the event that a vote could be packaged together.

Dr. Beck expressed confusion as it remained unclear whether this was intended to be a local or national recommendation. They said before that delivery would be wrapped up with those would have to do this at the local level; however, ACIP could not dictate to them. Therefore, it was not clear to him how this would work.

Dr. Neuzil replied that it was intended to be flexible because more information will be forthcoming. If in September the national estimates were much lower, ACIP would not have to reconvene. They could simply state that it was time to prioritize because the contingencies would have already been thought through and voted upon.

Dr. Morse inquired as to whether there was an application in the individual providers office if faced with a limited supply.

Dr. Neuzil responded that the work group did address this issue. Certainly, there will be local supply / demand mismatches. Perhaps they could better word this, but the intent was to acknowledge that supply was not the only issue. Demand within a practice, a hospital, a community will be very different.

Given that this season would be a nightmare in terms of messaging due to seasonal and pandemic vaccines, Dr. Baker wondered whether all of these decisions must be made immediately.

Dr. Schuchat thought the set of recommendations under consideration addressed Option A, which was that there would not be a sub-prioritization within these groups unless circumstances required this. She thought they accepted this in taking the first vote. She did not think there was any value in delaying.

Speaking as a local / state health department representative, Dr. Ehresmann thought it was beneficial to have this type of information available. Regionally, across the country, and within states there can be differences with the supply of the vaccine. Having something in place that providers and public health know is available is very important in terms of reducing panic. Nevertheless, she appreciated the importance of the message that this was "just in case" contingency planning for providers only if needed.

Patsy Stinchfield (NAPNAP) pointed out that the principle addressed in terms of how the work group could be most helpful was to provide guidance and be flexible. They were not prescribing specifically who had to implement the policy adopted by ACIP; therefore, she thought providers would find this to be helpful.

Dr. Fiore explained that Recommendation (2) was a follow-on from Recommendation (1) in the event that there was a need to prioritize within the larger target group. Recommendation (3) would address the next group in line when vaccination is sufficient at the local level to vaccinate routinely the initial target population. This would now be 25- through 64-year old. The next group following that would be those over age 65, emphasizing the use of seasonal vaccination in that group while novel H1N1 vaccination is being used in younger age groups.

Dr. Neuzil pointed out how difficult this was. The work group had to presume how much vaccine there would be and who would be vaccinated. Dr. Robinson provided the work group with estimates to enable them to do that. Based on the 120 million doses that are anticipated in October 2009, the work group felt comfortable with the first group everybody voted on. They did not feel comfortable going this far. That is, they decided against first come, first served. Recommendation (3) would come much later, perhaps in about November, unless more supply was received than anticipated. The work group based their recommendations on Scenario 1.

Dr. Sawyer inquired as to whether the recommendations were intended to be sequential: first 19 to 64 year olds followed by 65 and above. If sequential, he wanted further information about why the line was drawn here.

Dr. Fiore replied that there are more data for these age groups, and this matches fairly well with aggregate reporting data. There is a fairly steep drop off of incidence in confirmed cases per 100,000 in that age group: 25 to 49 is 0.44; 50 to 64 is 0.20; and over 65 is 0.06.

Dr. Marcy noted that when he originally said he thought there should be targeted groups versus universal availability because it would be easier to expand, he was concerned about availability. At the beginning there will be plenty of availability. However, it was not clear to him at what point they would decide that there would not be enough availability and that cohorts should be limited. His concern was that availability is a "moving target."

Dr. Morse clarified that the initial amount available would not be sufficient to reach all of the groups. He agreed that it would change over time.

Dr. Marcy asked whether, when vaccine was very available at first, a physician might decide he or she had ample product to give it to those ages 19 to 64.

Dr. Neuzil responded that this was where they were making a distinction. The recommendation was for the first 150 million people. In fact, with the guidance they were given earlier in the day, they could essential vote on Recommendations (2) or (3) in October. The work group was focusing on half of the population, approximately 150 million people who should be targeted based on epidemiology, severity, lack of antibody, et cetera.

Dr. Marcy thought that brought them back to Dr. Baker's point, which was the one big message at the beginning.

Dr. Neuzil responded that she would say the one big message was Recommendation (1) upon which they had already voted.

Dr. Baker pointed out that the first bullet of Recommendation (3) needed to read "25 through 64 years of age."

Dr. Ehresmann inquired as to whether Recommendation (3) was a decision that would be made at the local level, or if it was to be made national as an expansion. She wondered how much autonomy the state and local levels would be given in terms of moving to the next step.

Dr. Fiore responded that the work group feeling was that this type of decision would not be made at the national level unless it became clear that there was some uniformity of availability and demand. Some areas are likely to exhaust the number of people interested in being vaccinated in the initial target groups earlier than others and may move on. While it could lead to confusion if there were major differences across the country, he did not think a move had to be made to the next group on a particular date.

Given that supplies would be tallied nationally, it was not clear to Dr. Morse whether the decision would be left entirely to state and local groups or whether there would be some national weigh in.

Dr. Schuchat replied that the intent at this point was the pro rata allocation of doses around the country to state or program areas. There is likely to be variable demand in different communities potentially related to disease occurrences and geographic variability. She anticipated local decision making about extending vaccine to other groups once they had exhausted demand within the initial groups, for those who still had vaccine. There could be a point in the season during which demand in some states is exhausted, while considerable demand continues in other states. There could be some shift of the allocation by state to a process that better matches demand wherever it is.

Dr. Schaffner (NFID) stressed that this was what he was talking about earlier, that if there was no longer demand in a certain area for vaccine, providers would wonder how long they had to keep unused vaccine waiting for people in the priority group to present. This happens every time there is prioritization. The only sin is vaccine left in the refrigerator.

Dr. Judson agreed.

Reflecting on the lessons learned from 2004, Dr. Lett preferred that the language make a statement that offering vaccine to other groups could occur fairly soon.

Dr. Beck thought the work group did a great job giving them an idea of how prioritization would work out over time. However, he wondered whether they were trying to do too much during this meeting with too little information that they did not necessarily have to do at this point. He was more concerned about having a single message going out to the public that could be easily understood and manageable. Then as they learned more over the next several months, they could adjust as necessary at that time. He feared that they were putting themselves in a box trying to do the impossible. While he thought this was good preparation, he suggested that they stay with the vote they had made on Recommendation (1) and end it there at this point.

Dr. Sawyer agreed, pointing out that they were called to this meeting to prioritize—not to map out the entire strategy. He was also concerned that it would be confusing if they tried to include the whole population. Even with the rosier projections, there would not be enough vaccine for the other groups before the October ACIP meeting. Therefore, he liked the suggestion that they take up the remainder of the recommendations in October.

Dr. Englund agreed that Recommendation (3) could wait; however, she believed that Recommendation (4) needed to be voted on during this meeting.

Dr. Morse inquired as to whether tabling Recommendation (3) would affect production.

Dr. Robinson replied that it would not have any impact. While BARDA will review the numbers ACIP recommended, they would continue as if they were going to immunize hundreds of millions of people until they found that the demand did not meet that.

Dr. Neuzil pointed out that the work group's thinking was also that they did not want vaccine left in the refrigerator. The first group through 24 years exceeds the October supply and represents somewhere above half the population. The work group presumed lower than 100% coverage. This is a generous first recommendation.

Dr. Baker motioned to accept the Recommendation (4) as written. Dr. Judson seconded the motion. No vote was entertained at this time as discussion continued.

Dr. Schuchat indicated that planning scenarios had been issued to states so that they could determine how they would reach possible populations. States are looking to ACIP for clarity or more specificity in their planning. She thought one issue that was emerging was the difference between the general adult population with an underlying condition and the general adult population that does not likely have such a condition. For planning purposes, she suggested differentiating using providers' offices for those with underlying conditions from occupational settings, pharmacies, retail settings, et cetera. It was not clear whether public health representatives would be comfortable putting off a decision until October, given that it may limit the ability to enroll providers, pharmacies, other private sector partners, et cetera.

Dr. Morse indicated that it would affect New York's planning as they would be left in limbo in terms of whether to go forward or gear up for the population in the mid age groups, and also in terms of the prioritization if there was a fall-back, if for some reason there were only 20 million doses that would be exhausted in the first two months.

Dr. Lett also did not believe planning could wait until October. She thought it would be much easier to tell people that they could basically take all-comers after prioritizing certain groups in the beginning. If they keep asking providers to hold clinics over and over, there will be clinic fatigue, particularly following early seasonal clinics.

Dr. Ehresmann agreed that in terms of planning purposes states were in a vacuum of information. She thought the more information they could give states, the better. Therefore, if the group felt it was possible to vote on all four recommendations during this meeting, that would be the best option from a planning perspective.

Dr. Campos-Outcalt (AAFP) thought they would have to say something about the other two groups (e.g., healthy 24 to 64 and those over 65). If they say nothing, there would be an unknown about whether to vaccinate these groups. He also thought they needed to prioritize in a certain way. Those 65 and above were the last priority, but in a normal year they would be at the top of the priority list and are used to presenting early for their shots. They will present early for their seasonal flu shots and will want to know why they cannot also receive the H1N1 vaccine as well. Some thought should be given to that; however, they should not receive the H1N1 vaccine right away because they will use up all of the vaccine. The issue must be addressed in some way.

Dr. Temte indicated that AAP and AAFP convene their annual scientific meetings in early to mid October before the next ACIP meeting. Therefore, he thought it was important to reach resolution. In terms of what had been decided so far, age is simple to identify clinically and through data systems, immunization registries, electronic medical records, billing data base, or vital records. Thus, it should be fairly easy for systems to quickly enumerate what their need could be. The rest is fairly easy to identify through ICD-9 and CPT coding.

For Recommendation (3), Dr. Englund recommended amending the terminology to read, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, to routinely vaccinate . . ." to have consistency at the local level. She also recommended voting on Recommendations (2), (3), and (4).

This was not acceptable to Dr. Baker.

This was also not acceptable to Dr. Judson, who thought that each recommendation should be voted upon separately.

Dr. Baker indicated that she would be willing to amend her motion for Recommendation (4) to include Recommendation (2).

Dr. Morse suggested that since Recommendation (4) seemed to be universal, it made sense to vote on it separately.

Motion: Recommendation (4)

Dr. Baker motioned to accept Recommendation (4) as written. Dr. Judson seconded the motion. The motion passed unanimously with 14 affirmative votes, 0 negative votes, and 0 abstentions.

Motion: Recommendation (2)

Dr. Ehresmann motioned to accept Recommendation (2) with an amendment to revise the last bullet to read, "Children less than 19 years of age with chronic medical conditions." Dr. Baker seconded the motion. The motion passed unanimously with 14 affirmative votes, 0 negative votes, and 0 abstentions.

Dr. Ehresmann motioned to accept Recommendation (3) with an amendment to the first bullet to read, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, to routinely vaccinate initial target populations, vaccination against novel influenza A(H1N1) is recommended for healthy adults aged 25 through 64 years old" and to correct the typographical error in the second bullet to read, "Vaccination of persons aged 65 or older . . ."

Dr. Schuchat thought it would be helpful if the committee was going to vote to separate Recommendation (2) into two votes, given that the phrasing of the second bullet included some conditionality.

Dr. Neuzil thought it was important for people to understand the intent of the work group. While the language may not be precise, based on the supply data the intent was to have a large first group. This was sequential. Only if needed (e.g., very early pandemic wave, very limited supply, highly increased severity, et cetera) would the first group be taken down to the 40 million. The work group was looking at this incrementally. In the very first work group call, it was agreed that if there were no supply issues and no roll out of supplies, they would be recommending vaccinating everyone. However, that was not the work group's charge and that was not what they were told to do. That would also not be particularly helpful at the local and state levels.

Dr. Ehresmann indicated that she was flexible about breaking up the recommendation, but because these were important issues and the hour was getting late, she wanted to ensure that they covered everything.

Dr. Schuchat pointed out that much of the discussion had been about supply and risk of disease. Because there is not information about these particular vaccines, safety was taken off the table. However, people were discussing programmatic issues. When this vaccine goes into large numbers of people, things will happen to those people, some of which will be random and some of which will be vaccine-associated. Bad things happen more frequently to people 65 and older that may or may not be vaccine-related. Therefore, as they thought about a program that differed from seasonal influenza and tried to institute as good a safety monitoring and communication system as possible, it would be worth considering the challenges of interpreting signals in the elderly. This has been a challenge in the past.

With that, Dr. Ehresmann suggested dividing the motion.

Dr. Sawyer did not believe they could separate the two groups. Making a recommendation on 25 to 64 and remaining silent on 65 and above made no sense. He preferred that they remain silent on this entire recommendation until they received further information, with the recognition that they would have time to do so in October.

Dr. Ehresmann clarified that her intent was to march through these systematically so that they could have a discussion on all of them during this meeting, but break it up in case there were problems with the linkage.

Dr. Judson agreed that this recommendation should be for healthy adults older than 25 and that they not use an arbitrary cut off that was not supported by any data seen so far—that they be offered vaccine if they want it. He suggested that this vaccine and this virus are next year's seasonal flu. Hopefully they would not be having this discussion next summer.

Dr. Neuzil clarified that the work group discussed this recommendation with many liaison representatives, and felt that it was worth splitting out based on the epidemiology and antibody data reviewed. Both groups may ultimately fall into the category, but the work group did believe that there was evidence to support dividing these.

Dr. Judson noted that the cut off was not 65. It was born after 1950.

Motion: Recommendation (3a)

Dr. Ehresmann motioned to accept the first component of Recommendation (3a) with an amendment to read, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, to routinely vaccinate initial target populations, vaccination against novel influenza A(H1N1) is recommended for healthy adults aged 25 through 64 years old." Dr. Lett seconded the motion. The motion passed with 8 affirmative votes, 6 negative votes, and 0 abstentions.

Dr. Lett suggested that Recommendation 3b be worded in the same way as 3a with the phrase "in consultation with state and local health departments."

Dr. Schaffner (NFID) could not imagine how this could be operationalized from the point of view of public health or clinicians—the distinction in a sequence of events. Life is too chaotic for that.

Dr. Seward wondered whether it would be easier to implement if all of the recommendations were simply put into a list in sequential order.

Dr. Lett said she fluctuated between the need for prioritization and not wanting vaccine to go wasted. What Dr. Seward was suggesting offered people a framework within which to think about the issues in the beginning while they wait to better understand supply and demand.

Dr. Pickering said the issue was that when vaccine is available it should be utilized. The question regarded whether (3b) was sequential or simultaneous to (3a).

Dr. Neuzil stressed that they had a first group of 160 million potential vaccinees. Now they were deciding whether there should be a second group of everybody else, or there should be two more incremental groups.

Dr. Ehresmann clarified that they already voted for the 25 to 64 year old age group, and now they were simply wrapping it up to say that the final group would be 65 and older.

Dr. Englund motioned to accept Recommendation (3b) revised as follows, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, and initial target populations and healthy adults less than 65 years of age have been routinely vaccinated, vaccination against novel influenza A(H1N1) is recommended for persons age 65 and older," with the rest of this recommendation to remain the same. Dr. Ehresmann seconded the motion.

Dr. Neuzil thought she was hearing people say that at the same time it was rolled out in 25 to 64 year olds, it could be rolled out in 65 or older. The original intent of the work group, based on the planning assumptions, was for this recommendation to be sequential. The planning assumption was that there would be a pandemic wave before there was ample vaccine. That was the task that the work group was asked to address.

Dr. Lett thought that from a practical point of view, they would not want to turn people away. For example, grandparents or parents may want to be vaccinated along with a child in a public venue. She was concerned that too much emphasis was being placed on sequential vaccination.

Dr. Ehresmann pointed out that it was important to consider that because these decisions could be made at the local level, it may be the case that a local venue may decide to implement (3a) and (3b) closely or simultaneously. This would not preclude simultaneous administration to these two groups, but it would leave it sequential should there be issues requiring a particular order.

To consider a compromise between the need to prioritize and the desire not to turn people away, Dr. Duchin (NACCHO) inquired as to whether the group would consider amending the first bullet to read, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, vaccine is recommended for healthy adults aged 25 and older." This way there would be only two major stratifications and people could use their own judgment about how they apply the recommendation.

With regard to the recommendation for those 65 and older, Dr. Fiore pointed out that the way it was phrased was deliberately softer for that group. The idea was that it should be recommended for the 25 to 64 year old group, but the idea was to offer it to 65 and older but to

focus on seasonal vaccine for the short-term. The data are unclear in terms of whether that age group will need the pandemic vaccine or will benefit from it.

Dr. Symaya thought they were losing track of the main purpose of the emphasis of the target groups by bringing in other groups at this time under (3a) or (3b). He thought that this would simply add more confusion.

Dr. Englund stressed that the reason for having the 65 or older age group was based on the epidemiology, with a significantly lower attack rate incidence of confirmed influenza of 0.06 per 100,000. This was based on data.

Drs. Englund and Ehresmann withdrew their motion to accept Recommendation (3b) revised as follows, "When vaccine availability is sufficient at the local level, in consultation with state and local health departments, and initial target populations and healthy adults less than 65 years of age have been routinely vaccinated, vaccination against novel influenza A(H1N1) is recommended for persons age 65 and older," with the rest of this recommendation to remain the same.

Motion: Recommendation (3b)

Dr. Englund motioned to accept Recommendation (3b) revised as follows, "Vaccination should be offered to persons aged 65 or older once vaccination programs are capable of meeting demand for vaccination from younger age groups. The recommendation to offer vaccine to persons aged 65 or older might need to be reassessed as new epidemiologic, immunologic, or clinical trials data warrants and in the context of global need for novel H1N1 vaccines. Vaccination with seasonal vaccine should be encouraged and should begin as soon as seasonal vaccine available for persons aged 65 or older." Dr. Ehresmann seconded the motion. The motion passed with 11 affirmative votes, 0 negative votes, and 0 abstentions.

Certification

I hereby certify that to the best of my knowledge, the foregoing Minutes of the July 29, 2009 ACIP Meeting are accurate and complete:

Date

Dale Morse, M.D., M.S. Chair,
Advisory Committee on
Immunization Practices (ACIP)

List of Attendees

Non- US Citizens

Bablani	Pankaj	India
Butt	Tausif	United Kingdom
Chu	Susan	United Kingdom
Dekonor	Emmanuella	United Kingdom
Djalo	Mamadu	Guinea-Bissau
Edelman	Laurel	Canada
Florez	Jorge	Colombia
Galacho Campoy	Juan Miguel	Spain
GENTILE	ANGELA	Argentina
Ismail	Shainoor	Canada
Kamiya	Hajime	Japan
Lagos	Rosanna	Chile
Landry	Monique	Canada
Law	Barbara	Canada
Mike Unyime	Anthony	Nigeria
Muñoz	Alma	Chile
Naus	Monika	Canada
Omer	Saad	Pakistan
Raina	Ajit pal Singh	India
Romano-Mazzotti	Luis	Mexico
Schuind	Anne	Belgium
Sever	Perica	Canada
Shindman	Judith	Canada
Tan	Litjen	Singapore
York	Laura	Canada

US Citizens

Abramson	Allison	United States
Adirim	Terry	United States
Ambrose	Christopher	United States
Arnold	Kate	United States
Arthur	Phyllis	United States
Ault	Kevin	United States
Baggs	James	United States
BAILOWITZ	ANNE	United States
Baker	Carol J.	United States
Bandell	Allyn	United States
Bardenheier	Barbara	United States
Baylor	Melisse	United States
Beck	Robert L	United States
Begley	Anne Marie	United States
Birkhead	Guthrie	United States
Blankas-Hernaes	Nida	United States
Bocchini, Jr.	Joseph	United States
bonita	betty	United States

Bova	Bernice	United States
Brace	Sherry	United States
Bradfield	Debi	United States
bradley	sharon	United States
Bravo-bonilla	jose	United States
Brent	Patricia	United States
Brewer	Katherine	United States
Buchanan	Anna	United States
Buchanan	Martha	United States
Buehler	James	United States
Burkholder	Brenton	United States
Bush	Kim	United States
Cadaret	Ken	United States
Cameron-Sayre	Paula	United States
Campos-Outcalt	Doug	United States
Cannon	Patricia	United States
Capriotti	Linda	United States
Carey	Kathy	United States
Cary	Donna	United States
Casasanto	Peter	United States
Chaney	Mike	United States
Cheek	James	United States
Chilton	Lance	United States
CHISHOLM	DENISE	United States
Chuan	Yuan	United States
Clover	Richard	United States
Cochrane	Donna	United States
Coelingh	Kathleen	United States
Coit	Rennie	United States
Colwell	Chris	United States
Cooney	Lenore	United States
Copeland	Julie	United States
Cuomo-Whitney	Susan	United States
Daborowski	Nancy	United States
Dalrymple	Donald "Dack"	United States
dayton	lilyan	United States
DeGrasse	Enjoli	United States
DeGregorio	Margaret	United States
Dennis	Betty	United States
DeNoon	Daniel	United States
Dinovitz	Richard	United States
Drews	Judy	United States
Dubin	Gary	United States
Duchin	Jeffrey	United States
Dunn	Kaye	United States
DuVall	Sarah	United States
Dzubin	Shannon	United States
Ehresmann	Kristen	United States
Englund	Janet	United States
Etkind	Paul	United States

Evans	Geoffrey	United States
Evans	Jim	United States
Farley	Jim	United States
Felice	Pamela	United States
Ferraro	Ralph	United States
Filipski	Brian	United States
Fischer	Neal	United States
Fix	Amy	United States
Friedland	Leonard	United States
Frost	Phillip	United States
Fuller	AManda	United States
Gargano	Lisa	United States
Garrett	W. Matthew	United States
Geddes	Cathy	United States
gensheimer	kathleen	United States
Gorman	Richard	United States
Greenberg	David	United States
Grimm	Sandy	United States
Gurunathan	Sanjay	United States
haber	penina	United States
Hachey	Wayne	United States
Hadley	Jennifer	United States
Hage	Raymond	United States
Halsey	Neal	United States
Hammer	Sandra Jo	United States
Hannan	Claire	United States
Harshman	Robert	United States
Hay	Kelly	United States
Haywood	Regina	United States
Heaton	Penny	United States
Herrera	Guillermo	United States
Hitt	Emma	United States
Hosbach	Philip	United States
Howe	Barbara	United States
Hsiao	Jane	United States
Hughes	Michael	United States
Innis	Bruce	United States
Jackson	Kimberley	United States
James	Andrea	United States
Jolly	Tilman	United States
Jones	Marolyn	United States
Juan	Sempertegui	United States
Judson	Franklyn	United States
Kalish	Scott	United States
Kanesa-thasan	Niranjan	United States
kasparian	loucine	United States
Keyserling	Harry	United States
Khan	Farid	United States
Khoury	Peter	United States
Kingsley	Mary Lee	United States

Kinsinger	Linda	United States
Knorr	Alberta	United States
Kroger	Andrew	United States
Kudis	Amanda	United States
Laird	Susan	United States
Lancaster	Karen	United States
Lance	Judy	United States
Lavelle	Tara	United States
Lee	Houghton	United States
Lett	Susan	United States
Lewin	Clement	United States
Lorick	Suchita	United States
Lovell	Ethan	United States
Malinoski	Frank	United States
Malone	Robert	United States
Marcy	S Michael	United States
Marill	Michele	United States
Marlowe	Steven	United States
Mason	Dean	United States
Matthews	James	United States
Mazur	Marie	United States
McDevitt	Sue Ann	United States
McFarland	Jeffrey	United States
McKenna	Maryn	United States
Medley-Lane	B. Sue	United States
meeker	charlie	United States
Meissner	Cody	United States
Michaels	Jacqueline	United States
Miller	Marie	United States
Miller	Mike	United States
Moore	Kelly	United States
Morita	Julie	United States
Morse	Dale	United States
Muhammad	Riyadh	United States
Mulligan	Mark	United States
murphy	linda	United States
Neale	Todd	United States
Netoskie	Mark	United States
Neuzil	Kathy	United States
Nuzzo	Jennifer	United States
Owen	Bill	United States
Paradiso	Peter	United States
Peeler	Kelly	United States
Peterson	Diane	United States
Pietroski	Nancy	United States
pillsbury patton	carol	United States
Poland	Gregory	United States
Provost	Denise	United States
Puch	Alan	United States
Rathore	Mobeen	United States

Ray	Jill	United States
Redwood	Lyn	United States
Reeves-Hoche	MK	United States
rennels	margaret	United States
Rhodes	Brenda E.	United States
Richards	Steve	United States
Roehm	John	United States
Rousculp	Matthew	United States
Rowe-West	Beth	United States
Rozen-Adler	Nuphar	United States
Sawyer	Mark	United States
Schaffner	William	United States
Schell	James	United States
Schoenstadt	Lorraine	United States
Schuchat	Anne	United States
Scott	Laura	United States
Seib	Katy	United States
Shelton	Jerry	United States
Sherman	Alli	United States
Shiff	Jeffrey	United States
SIEVERT	ALAN	United States
Steber	Christian	United States
Stobbe	Michael	United States
Stoddard	Jeffrey	United States
Strikas	Raymond	United States
Stuerke	Stacy	United States
Sumaya	Ciro	United States
Sun	Wellington	United States
Sylvester	Gregg	United States
Talley	Sandra	United States
Tammi	Stacy	United States
Tasker	Sybil	United States
Temte	Jonathan	United States
Thomas	Lonnie	United States
Thomsen	Pamela	United States
Townsend	Tiffany	United States
Trigg	Monica	United States
Trizzino	John	United States
Tsai	Theodore	United States
Turner	James	United States
Turski	Theresa	United States
Uzzalino	Sandra	United States
Van De Velde	Steve	United States
Vaughn	David	United States
Vaupel	Christine	United States
Vigliarolo	Peter	United States
Wallace	Fred	United States
Warner	Amy	United States
Watson	Diane	United States
Wexler	Deborah	United States

Whitney	Ellen	United States
Wichser	Colleen	United States
Williamson	Donald	United States
Yamauchi	Terry	United States
Young	Collette	United States
Yu	Hongjie	United States
Yuan	Chuan	United States
Zimmerman	Richard	United States