SUMMARY REPORT
of the
NATIONAL BIODEFENSE SCIENCE BOARD
PUBLIC TELECONFERENCE
July 17, 2009

NBSB VOTING MEMBERS PRESENT
Ruth L. Berkelman, M.D.
Stephen V. Cantrill, M.D.
Roberta Carlin, M.S., J.D.
Albert J. Di Rienzo
Kenneth L. Dretchen, Ph.D.
John D. Grabenstein, R.Ph., Ph.D.
James J. James, Brigadier General (Retired), M.D., Dr.P.H., M.H.A.
Thomas MacVittie, Ph.D.
John S. Parker, Major General (Retired), M.D.
Andrew T. Pavia, M.D.
Eric A. Rose, M.D.
Patrick J. Scannon, M.D., Ph.D.

NBSB VOTING MEMBERS NOT PRESENT
Patricia Quinlisk, M.D., M.P.H., Chair

EX OFFICIO MEMBERS PRESENT (or designee)
Joseph Annelli, D.V.M., Animal and Plant Health Inspection Service, U.S. Department of Agriculture
Diane Berry, Ph.D., Chief Scientist, Director, Threat Characterization and Countermeasures, Office of Health Affairs, U.S. Department of Homeland Security
Richard Besser, M.D., Director, Coordinating Office for Terrorism Preparedness and Emergency Response, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services
Bruce Gellin, M.D., M.P.H., Director, National Vaccine Program Office, Office of the Secretary, Office of Public Health and Science, U.S. Department of Health and Human Services
Rosemary Hart, Special Counsel, Office of Legal Counsel, U.S. Department of Justice
Peter Jutro, Ph.D., Deputy Director, National Homeland Security Research Center, U.S. Environmental Protection Agency
Carter Mecher, M.D., Director for Medical Preparedness Policy, White House Homeland Security Council
Vincent Michaud, M.D., M.P.H., Director, Medicine of Extreme Environments, Office of the Chief Health and Medical Officer, National Aeronautics and Space Administration *(designated by Richard Williams, M.D.)*
Aubrey Miller, M.D., Office of Counterterrorism and Emerging Threats, Office of the Commissioner, Food and Drug Administration, U.S. Department of Health and Human Services *(designated by Boris Lushniak, M.D., M.P.H.)*

Diane Poster, Scientific Advisor, Chemical Science and Technology Laboratory, National Institute of Standards and Technology, U.S. Department of Commerce *(designated by Willie May, Ph.D.)*
John Skvorak, D.V.M., Ph.D., COL, Commander, U.S. Army Medical Research Institute for Infectious Diseases, U.S. Department of Defense

STAFF OF THE NATIONAL BIODEFENSE SCIENCE BOARD

Leigh Sawyer, D.V.M., M.P.H., CAPT, USPHS, Executive Director
Erin Fults, Scientific/Technical Writer
Don Malinowski, M.S. Program Analyst
Jomana Musmar, M.S. Policy Analyst
MacKenzie Robertson, Program Analyst
Brook Stone, M.F.S., LT, USPHS, Program Analyst

CALL TO ORDER CAPT Leigh Sawyer, D.V.M., M.P.H., Executive Director, National Biodefense Science Board (NBSB)

CAPT Sawyer called the public teleconference to order at 12:02 p.m. and called the roll. She noted that the teleconference was convened in order for the Board to hear the report of the Pandemic Influenza Working Group (PIWG), and to give the public an opportunity to hear the deliberations of the Board. CAPT Sawyer reviewed the Federal Advisory Committee Act rules. Due to the absence of the Chair, Patricia Quinlisk, CAPT Sawyer served as Chair and NBSB voting member John Grabenstein served as moderator.

OPENING REMARKS Nicole Lurie, M.D., M.S.P.H., Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services (HHS)

Dr. Lurie said that since arriving at HHS, the Department has put together a cross-agency task force dealing with the H1N1 situation. The task force meets daily for updates and has working groups related to surveillance, antivirals, and vaccines. USPHS Captain Clare Helminiak chairs the task force. Last week, HHS had a summit with the states to ask them to prepare for a potential mass vaccination program in the fall, if such a vaccination is deemed necessary.

Dr. Lurie further added that the Board's expertise will be necessary in helping to determine how a vaccine should be used once it's available, as well as deciding what the proper threshold is for implementing an immunization program. Her intent was to take the Board's recommendations to the H1N1 task force and to the Secretary of HHS, in order to decide whether there are additional issues that the Department needs to consider.

AGENDA OVERVIEW AND GOALS John Grabenstein, R.Ph., Ph.D., Voting Member, National Biodefense Science Board

Dr. Grabenstein noted that the PIWG was formed well before the H1N1 events of April 2009. He said that the purpose of today's call was to discuss the report developed by the Working Group, and to provide useful and timely advice to the Secretary and Department.

Dr. Grabenstein invited Dr. Robin Robinson from the Biological Advanced Research and Development Authority (BARDA) to update the Board on the events of the last month since the Bethesda meeting on June 18, 2009. Dr. Robinson said that all five manufacturers the Department contracted with have begun to produce the H1N1 vaccine at commercial-scale. Eighteen million doses have already been produced (assuming 15 mcg antigen per dose). The Department has contracted for a total of 193 million doses. Virus yields are toward the lower end of the expected range, roughly 1.4 doses per egg.

Commercial-scale production of the live attenuated vaccine experienced low yields with initial lots, but they are now using a second seed strain, yielding 2 logs higher. With that higher yield of virus titer than normally seen, the number of doses available would be limited by the ability to fill sprayers; with more bulk virus available than can be filled (at 10e7 pfu per dose) at present. Dr. Robinson stated that they are looking with other manufacturers at other sites within the U.S. to fill the sprayers, and are also looking at alternative ways of delivering the flu-mist-like product from the sprayer.

Regarding adjuvants, Dr. Robinson said that there have not been changes in the schedule or in the amount produced. The Department has contracted for enough adjuvant for 119 million doses of vaccine.

In order to have the monovalent unadjuvanted H1N1 vaccine available by September 15, the Department would have to make a decision by August 15, to direct the manufacturers to formulate the bulk antigen into usable product and fill containers. By August 15, roughly 60 to 80 million doses of bulk antigen (assuming 15 mcg/dose) should be available. The first clinical studies with the companies are starting next week. The Board will not know until September whether or not the 15 microgram dose is immunogenic.

Over 35 million treatment courses of antiviral medications are currently in State inventories (11 million of which were released by the Federal government to the States); however, little has been used to date. Dr. Robinson said that the Federal stockpile will be replenished to have a total of 44 million treatment courses. Going forward, about 20 percent of the Federal stockpile will be in dosage form suitable for children. The earliest intravenous form of Tamiflu and Relenza will be available in late fall. Dr. Robinson noted that the Department was considering whether more limited use of oseltamivir or zanamivir might be warranted to reduce the likelihood of resistance developing.

REVIEW AND DISCUSSION OF THE PANDEMIC INFLUENZA WORKING GROUP (PIWG) EXECUTIVE SUMMARY OF THE H1N1 STRATEGY AND DECISION MAKING FORUM Andy Pavia, M.D., NBSB Voting Member and Chair of the Pandemic Influenza Working Group

Dr. Pavia read through executive summary of the report, along with a few excerpts from the recommendations. The three key areas of discussion were H1N1 vaccine,

antivirals, and therapeutics.

Dr. Dretchen asked if the Centers for Disease Control and Prevention (CDC) might encourage administration of the vaccine in school settings. CAPT Fiore from the CDC said that there are no formal efforts for providing novel H1N1 in school settings, and that the CDC does encourage vaccinations in school settings. Dr. Grabenstein indicated that the PIWG report says that HHS should consider recommending school-based immunization delivery for children.

Dr. Robinson noted that if one assumes a 15 mcg dose at 0.5 ml, the vaccine could be available by September 15. The Food and Drug Administration (FDA) is still in the process of deliberating whether the vaccine would be licensed at the standard dose, 15 mcg with a strain change, based on previous years. Dr. Pavia pointed out that the FDA has not indicated that they would license the vaccine at the existing dose based on the strain change, and it was reconfirmed that this topic was within the purview of the Vaccines and Related Biological Products Advisory Committee (VRBPAC). Dr. Gellin asked if the Board should go forward with the vaccine, in the absence of data, and do what is done for seasonal vaccine. Given the uncertainties, Dr. Gellin further asked what would be the Board's assessment of how much vaccine should be bottled on August 15. It was reconfirmed by Dr. Robinson that on August 15, ~60 million bulk antigen would be available for use, and that approximately 30 days will be needed for fill-to-finish to have a complete product available for distribution.

Dr. Pavia stated a second concern regarding the potential risk and regulatory barriers facing possible antigen dosage changes. Dr. Grabenstein noted that the prescription information pamphlet that accompanies the vaccine vial actually declares the dose, not the label on the vial, and that can be changed to reflect the dosage. Dr. Pavia agreed that the prescription pamphlet could be developed fairly rapidly. Dr. Grabenstein proposed that the Board recommend to the Department that on, or about August 15, they begin to package several tens of millions of doses—with a precise number to be determined by the Department. Dr. Gellin reminded the Board about the importance of revisiting strategies in light of what happens after August 15.

Dr. Grabenstein recommended not settling on a finite number of doses during the call, because the population sizes of the various cohorts were not readily available. Dr. Eric Rose said that if the clinical data in September confirms that the 15 mcg dose is immunogenic, then the balance of the bulk antigen should be formulated into usable doses quickly thereafter.

Dr. Gellin noted that the Advisory Committee on Immunization Practices (ACIP) will be looking at the epidemiology and trying to best apply a vaccine for the largest benefit. Dr. Cantrill proposed scheduling NBSB teleconferences once a month for the next six months in order to stay on top of this dynamic situation. On the subject of antivirals, Dr. Pavia said that instead of the Board getting bogged down in antiviral strategy, other groups that include experts that have done resistance work, clinical trials, and modeling would be better lead contributors. Dr. Rose added that he did not think the question of

antivirals was an "in the weeds" tactical kind of question, but a strategic one.

RADM Schuchat said that the ACIP makes antiviral recommendations in conjunction with their annual influenza vaccine recommendations. CDC has also issued interim guidance on antiviral use regarding the H1N1 challenge. CAPT Fiore added that the ACIP proposed an antiviral recommendation last June with a focus on treatment. The ACIP also recommended that the CDC maintain a Website with updated information on treatment and use of prophylaxis for those who had risk factors for complications of influenza.

PUBLIC COMMENTS AND DISCUSSION

CAPT Sawyer introduced the public comment segment by sharing written comments sent to the NBSB Web site and Board. A formal letter written by RADM Gerald Quinnan and Dr. Robert Belshe, in response to the June 18-19 H1N1 Forum, was shared with the members and public. CAPT Sawyer also read an e-mail message received from Ellen Rice. Ms. Rice was concerned about the safety of adjuvant that may be added to H1N1 influenza vaccines; Ms. Rice hoped that people would be informed as to which vaccines will have adjuvants and which do not.

Further public comment was expressed live on the teleconference by Nicholas Kelley. His concern revolved around the availability of syringes in the Strategic National Stockpile (SNS) for distribution with vaccine doses in the fall. Dr. Robinson said that the Department has been in contact with the syringe manufacturers and that they have been making arrangements with the appropriations from Congress to procure adequate syringes and needles.

David Schonfeld from the public commented that he had not heard any information regarding clinical trials evaluating the immune response of children to the H1N1 vaccine. Dr. Robinson said that there would be pediatric studies for each of the vaccines. The studies will be conducted by the NIH and manufacturers.

Erin Mullen from the public asked if the NBSB is moving away from a previous recommendation that included priority for critical infrastructure and healthcare workers. Dr. Grabenstein indicated that the Board's current report is written to focus on vaccine supply and those at greatest risk of disease. Dr. Pavia said that recommendations on specific target groups are developed with the input of ACIP and CDC—so the Board is not developing recommendations for priority groups.

Jeff Bowman from the public asked if there had been any provisions for healthcare worker surveillance as part of monitoring vaccine effectiveness following confirmed exposures of H1N1. He also asked whether or not there were sufficient supplies of diagnostic kits available for providers to obtain confirmatory H1N1 testing, since State health departments limit access and private labs do not possess the confirmatory test. Dr. Pavia said that the Board recognizes the importance of having accurate diagnostics available for local epidemiological control. The National Vaccine Advisory Committee (NVAC) is dealing with issues related to safety monitoring recommendations.

Following public comments, Dr. Grabenstein asked the Board to focus on the procedural issue of adopting a document to convey to the Secretary and the Department. Dr. Grabenstein read the only change made to the document during the teleconference into the record. The change involved altering page 2 of the document—the first bullet comment on the H1N1 vaccine. The proposed change read as follows:

"Based on available data, the NBSB recommends that HHS set a goal of having several tens of millions of doses of unadjuvanted monovalent A/H1N1 vaccine available for clinical use not later than September 15th, 2009. To achieve this, HHS should pursue..."

Dr. Cantrill seconded the motion to amend. Prior to a vote, Dr. Rose asked if the remainder of the report could be adopted without amendment. There was no objection by the Board to Dr. Rose's suggestion.

Dr. Grabenstein noted that earlier the Board had tabled how to address antiviral use; whether to change from a strategic level as opposed to a clinical level, in terms of reserving certain classes of antivirals. Dr. Grabenstein pointed out that the Board has only scratched the surface with antivirals, and that the current issue is whether or not the NBSB should take on the matter of antivirals in the short term. After brief discussion, the Board offered HHS its assistance in addressing the questions of: the degree to which antivirals would be restricted to reduce the likelihood of resistance, or if they should be dispensed widely to reduce disease transmission.

Dr. Grabenstein restated the motion before the Board: to adopt the report of the Working Group with the amendment of the first bullet in the H1N1 vaccine section, and relay it to the Secretary and to the Department. Dr. Grabenstein said he felt it best to leave the antiviral matter as a verbal statement of intent, rather than quibble over wording.

NATIONAL BIODEFENSE SCIENCE BOARD VOTE

CAPT Sawyer called for a roll call vote on the motion. The motion passed unanimously, by all those present.

WRAP UP AND ADJOURN

On the question of having additional meetings, CAPT Sawyer noted that the intention of Dr. Lurie is to engage in more dialogue with the Board. CAPT Sawyer said that she will proceed with the Federal Register notice indicating that the Board will have regular meetings over the next couple of months. She thanked the experts for their participation in the meeting.

CAPT Sawyer adjourned the meeting at 2:05 p.m.

Enclosures – Public comments e-mails and formal letter.

From: pfinsgrafj@ijet.com [mailto:pfinsgrafj@ijet.com] **Sent:** Friday, July 17, 2009 2:50 PM **To:** OS NBSB **Subject:** RE: NBSB July 17, 2009 Public Teleconference - Telephone Number and Documents

I was disconnected from the call immediately before the time for public questions, and would ask that the following might be addressed:

1) Prompt consideration be given to discontinuing completely or partially the fill and finish process for seasonal influenza vaccine to accommodate all or most H1N1 Ag as it becomes available. The ratio of pandemic influenza viruses to seasonal influenza viruses at present is approximately 99 to 1 according to the CDC weekly report, and there is no evidence from the Southern hemisphere that seasonal influenza viruses make up a significant portion of influenza viruses after the pandemic H1N1 virus becomes established.

2) Strategic consideration be given to the use of resources - both manpower and medical supplies - for the administration of seasonal vaccine, which will likely provide very little benefit, as compared to a pandemic vaccine. Administration of seasonal vaccine is also confusing and could impact the number of people who would be willing to go back to the doctor for a second (or third) flu vaccine in a single season. There would be a time advantage and could be a significant public health advantage to suspending seasonal vaccine production and administration and devoting limited healthcare resources to vaccinating against pandemic influenza. The govt could also consider offsetting pharma losses for suspension of seasonal flu vaccine campaign.

Thank you, Joan Pfinsgraff, M.D. iJET Intelligent Risk Systems 410-573-3860 x415 (voice) 410-279-3441 (cell)

From: Bowman, Jeffrey **Sent:** Friday, July 17, 2009 2:44 PM **To:** OS NBSB
Subject: HCWs, HC Employers and 2009 H1N1 Countermeasures Strategy and Decision Making **Importance:** High

Dear Dr. Lurie and NBSB Members,

First… Thank you very much for your detailed work and scientific approach in the area of strategic response to H1N1 Pandemic Influenza.

During the July 17th teleconference, I was able to briefly present during public comment a smattering of HCW management issues related to illness surveillance, study of vaccine effectiveness, the importance of diagnostic testing in HCW exposure management, relation to Work Comp costs, relation to HCW absence, and concern for anti-viral over-utilization without confirmatory testing available to epidemiological investigations at the healthcare employer level. This is a complex subject matter with many more critical elements that seems to be missing from many of the national and state government planning efforts. In the realm of the healthcare industry management of human capital, there is great risk, cost, and threat to the extended infrastructure of public health in mounting an effective response to Pandemic Influenza which should be on the radar of policy and decision makers in government.

Related to this, there was a subsequent suggestion by a board member during the teleconference that the board should consider stockpile provisions for antivirals used in chemoprophylaxis. I feel this is an extremely important issue that has not been adequately addressed by any other federal authority – it is conspicuously absent from the CDC summits and teleconferences. Your Board may be the only group on record choosing to actually work this specific matter at this time.

I would like the opportunity to provide some ideas and express some concerns for the Board's consideration related to the significance of Health Care Enterprise and Health Care Workers (HCWs) in the context of the issues you are tackling. In addition, I would like to offer my availability to the board for further dialogue in this area. As a physician executive in human resources within the nation's largest non-profit health care system (Ascension Health), I have responsibility for development of employee health services, medical center occupational health services, work comp, disability, wellness, industrial hygiene, disaster/emergency response, productivity, investigations, and manager education/ accountability programs. We have recent, direct experience in managing several H1N1 cases resulting in HCW exposures. We are worried about government agency & community hospital coordination in many of our states. I do feel we have expertise to offer the Board in these areas which may help refine the completeness of your work.

Please feel free to contact me directly for further discussion.

My Best Regards,

-jlb-

Jeffrey L. Bowman, M.D., M.S. Medical Director – Human Resources, OAHP St. Vincent Hospitals and Health Services, Inc. 8402 Harcourt Road – Suite 501 Indianapolis, IN 46260 prvtoffc: 317-338-3463 hospmbl: 317-709-9353 jlbowman@stvincent.org

From: Ellen Rice [mailto:cefprice@comcast.net]
Sent: Friday, July 17, 2009 12:47 AM
To: OS NBSB
Subject: TELECONFERENCE

Dear NBSB/HHS Staff,

I am not able to phone in on July 17th, but I would like to put forward my deep concerns about an adjuvant being used in the flu vaccines being made to counteract the novel H1N1 flu virus.

I am a homemaker. I have two sons, both with allergies and a history of asthma. I am very, very worried about the novel H1N1 virus but I am even more worried about the potential use of the MF59 (squalene) vaccine adjuvant. I think MF59 could cause autoimmune diseases to develop in my sons.

I do understand that vaccine production is challenging and that the current production system is having problems getting enough antigen produced. Even so, I hope PEOPLE WILL BE INFORMED as to which vaccines have adjuvants and which do not. Please let us HAVE A CHOICE in the matter.

I would definitely have my sons get a flu vaccine this fall if I knew it had no adjuvants. If it comes with adjuvants. . . particularly if the adjuvant is MF59, then I would advise my sons to avoid the vaccine. I would also advise my community about my deep concerns.

These are challenging times. We are all hoping that the upcoming flu season is mild. It may not be. But please don't have us go from "the frying pan to the fire" by putting out a vaccine that harms us long term. Everything that I read about MF59 makes me think the numbers of reactions to it would far, far outnumber the reactions that occurred in the 1976 flu vaccination program.

Please protect us.

Ellen Rice
Olympia, WA

-----Original Message-----
From: PSC gquinnan USUHS.MIL
Sent: Friday, July 10, 2009 1:41 PM
To: OS NBSB; Pavia, Andrew
Cc: Carlin, Roberta; James, James; Di Rienzo, Albert; Cantrill, Stephen; Hamburg, Margaret A. (FDA); hamburg1, Margaret; Dretchen, Kenneth; Robert Belshe; Lurie, Nicole (HHS/OS); Quinlisk, Patricia; E Rose; Grabenstein, John; Fauci, Anthony (NIH/NIAID) [E]; MacVittie, Thomas; Berkelman, Ruth; Scannon, Patrick
Subject: Letter to Dr. Pavia

Dr. Pavia and NBSB Staff:

The attached letter is submitted by Bob Belshe and myself for your consideration and that of the NBSB at the meeting scheduled for July 17, 2009.

Best Regards,

Gerald V. Quinnan, Jr., M.D.
RADM (Ret), USPHS
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Phone: 301-295-3173
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Andrew T. Pavia, M.D.
Chief Division of Pediatric Infectious Diseases
University of Utah Medical Center
295 Chipeta Way, Williams Building
P.O. Box 581289
Salt Lake City, UT 84132

July 10, 2009

Dear Dr. Pavia:

It was a privilege to participate in the *H1N1 Countermeasures Strategy and Decision Making Forum* hosted by the Pandemic Influenza Working Group of the National Biodefense Science Board on June 18-19, 2009, and we extend our gratitude for being invited to participate.

We wish to take this opportunity to convey to you in writing some of the opinions we expressed at that meeting that we believe should be seriously considered in the course of development of the national strategy for evaluation and use of influenza vaccines incorporating the novel H1N1 antigen. Further, we suggest that the Board consider making recommendations on the following specific points:

1. Should vaccine containing novel H1N1 antigens be distributed and used before completion of extensive immunogenicity studies?

The concern underlying this question is that it is likely that the first wave of epidemic influenza will occur early in the season, perhaps even early in September, as indicated by the continued occurrence of outbreaks of influenza into this summer and past history of influenza pandemics. Ideally, immunogenicity studies would be completed before use of the novel vaccine antigens in licensed vaccines. However, the balancing issue in this case is that the time required to complete such studies is likely to result in unacceptable delay in availability of vaccine. It is conceivable that a one dose immunogenicity study could be conducted, and still allow the vaccines to be distributed in Mid august However, considering that it is already mid July and there are apparently no specific plans in place for such a study, it seems unlikely that immunogenicity data will be available on a timely basis to make a data driven decision by early August. If that is true, the only alternative to delayed release would be to release vaccines in the absence of new immunogenicity data.

In fact, there is extensive evidence that vaccines containing the novel H1N1 antigens should be highly immunogenic. There is extensive population-wide immunity to H1N1 antigens in the United States and worldwide as a result of the continued circulation of H1N1 viruses between 1918 and 1957 and again from 1977 to the present. This immunity is, of course, not fully apparent in the results of hemagglutination inhibition testing of sera from the general population, but will certainly be reflected in the responses induced when vaccine is administered. The evidence that supports this expectation includes the dramatic responses obtained in national clinical trials of influenza A/New Jersey/1976 and A/USSR/1977 in those same years. Some of this data was presented by Dr. Treanor at your meeting. It is notable that just as the A/New

Jersey strain was antigenically distinct from the strains that circulated before 1957, the current novel H1N1 strains are similarly distinct from recently circulating H1N1 strains. Consider additionally that H1N1 viruses have been actively circulating in all age groups for the past 30 years, conferring extensive priming to the general population, not just those alive before 1957. It is highly likely that individuals who have been repeatedly exposed to H1N1 viruses in the past will respond well to vaccines containing the novel H1N1 antigens.

Available data provides strong assurance that "standard" doses of current vaccines containing the novel H1N1 antigens will induce adequate antibody responses that confer protection to a degree similar to annual influenza vaccines. For inactivated influenza vaccines, the dose that has been used in recent years is 15 micrograms, which was an amount of antigen adequate for induction of antibodies against the A/New Jersey virus in a high proportion of vaccine recipients. Similarly, standard doses of live attenuated vaccine are very likely to suffice. It should not be necessary to await the completion of immunogenicity studies to begin formulation and distribution of vaccines. If clinical trials demonstrate subsequently that certain individuals will benefit from receipt of second doses of vaccine, recommendations can be appropriately modified.

2. Should the vaccine be targeted to all Americans, or mainly to those at highest risk of infections and complications of infections?

Based on the presentation given by Dr. Robinson, the amount of inactivated vaccine that is expected to be available in September is an amount sufficient to vaccinate a substantial proportion of the groups traditionally considered at high risk of complications from influenza and critical service providers. Additional doses will be available on a monthly basis thereafter that can be made available for other members of those groups.

The epidemiology of this virus to date suggests that most of the infections that occur will be in children. Targeting vaccine for use in children may significantly impact morbidity and mortality in that age group and reduce disease burden in the general population. Since there will not be sufficient inactivated vaccine in September to vaccinate a high proportion of children and others who should be targeted, emphasis on the use of live attenuated vaccine (single dose rather than two doses of inactivated vaccine) in children should be considered. It was stated at your meeting that availability of syringes for packaging of the live attenuated vaccine was a limiting factor with respect to the number and time of availability of doses to be released. It should be noted that the vaccine can be easily administered as drops, and there is ample evidence of safety and effectiveness when administered by this route. The manufacturer and FDA may be willing to consider amending procedures to permit formulation of the vaccine to be administered as drops, in order to increase the number of children who could benefit from receipt of this vaccine.

A vaccination program that attempts to deliver vaccine to all Americans will probably conflict with the delivery of vaccines to those groups who need it most; even more so if it is necessary to depend primarily on inactivated vaccine for immunization of children. One approach that has been proposed to address the issue that supply may not be sufficient to meet demand is to add adjuvant to vaccines and use them under Emergency Use Authorization. It is likely that the adjuvant planned will be dose sparing for some or all of the inactivated vaccines licensed in the United States. However, to the extent that the use of adjuvanted vaccines requires the

completion of immunogenicity studies before distribution of vaccines, their release will probably not be timely with respect to epidemicity in the early fall. It appears to us that the approach that is most likely to result in vaccines being available in the optimum time frame is the use of vaccines that can be released in an expedited fashion on the basis of amendments to existing licenses.

3. What approval or release mechanisms should be used to expedite availability of vaccines?

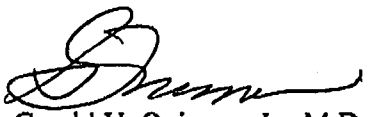
The availability of tens of millions of doses of inactivated and attenuated vaccines in August, September, October, and November hang in the balance, based on the approach adopted to address this problem. The options to be considered are approval of vaccines through license amendments, approval through new Biologics License Applications (BLAs), and release under Emergency Use Authorization (EUA). In our view, the introduction of a new H1N1 strain into vaccine production is a minor change in manufacturing which should easily lend itself to approval by amendments to existing licenses. A requirement for submission of new BLAs for documentation of the strain change is likely to introduce enormous uncertainty into the approval process and time line. Since approval of license amendments can occur rapidly, there should be no need for use of EUA for release of standard vaccines incorporating the novel H1N1 antigens. Invoking the EUA as soon as possible should facilitate release of products dependent upon process changes that would not be suitable for approval as license amendments. For example, the use of live attenuated vaccine administered by dropper may be more efficiently addressed using EUA. New licenses will undoubtedly be needed if adjuvanted vaccines are to be distributed as licensed products. Use of the EUA authority could enormously accelerate release of adjuvanted vaccines.

Based on these considerations and the concepts discussed above, we propose the following strategy for release of vaccines containing the novel H1N1 antigens. Standard vaccines should be released through the license amendment approval mechanism as early as possible, formulated in 15 μg doses for inactivated vaccines and in standard doses for attenuated vaccine. These vaccines should be distributed so as to reach the largest possible number of individuals in groups identified above. Clinical trials of immunogenicity of standard and adjuvanted vaccines should proceed as rapidly as possible, so that data may be taken into account as the season proceeds. If studies demonstrate that second immunizations are needed for certain groups, recommendations should be made to that effect. If the adjuvant is proven to be dose sparing, and the severity of the epidemic is seen to be so great that the use of adjuvanted vaccine in a massive immunization campaign is needed, the nation should be prepared to proceed expeditiously in that direction.

As stated above, we present only our personal opinions based on our experiences related to influenza vaccination. However, we do believe there is ample evidence to support them, and that consideration of these opinions should help inform policy making.

Thank you for your efforts to contribute to leadership on this important issue.

Best regards,



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CC:
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Margaret Hamburg, M.D., Commissioner of Food and Drugs
Anthony Fauci, M.D., Director National Institute of Allergy and Infectious Diseases, National Institutes of Health
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