

SUMMARY REPORT
of the
NATIONAL BIODEFENSE SCIENCE BOARD
PUBLIC MEETING
September 22, 2011

VOTING MEMBERS PRESENT

- *Patricia Quinlisk, M.D., M.P.H., *Chair*
- Georges C. Benjamin, M.D., FACP, FACEP(E), FNAPA, Hon FRSPH (by phone)
- Ruth L. Berkelman, M.D. (by phone)
- *Stephen V. Cantrill, M.D.
- Jane Delgado, Ph.D., M.S.
- *David J. Ecker, Ph.D.
- *Daniel B. Fagbuyi, M.D., FAAP
- *John D. Grabenstein, R.Ph., Ph.D.
- Kevin A. Jarrell, Ph.D. (by phone)
- *John S. Parker, Major General (Retired), M.D.
- *Patrick J. Scannon, M.D., Ph.D.

EX OFFICIO MEMBERS PRESENT

- *Andrew Flacks, HHS, ASPR Liaison to the Veterans Health Administration, Office of Public Health and Environmental Hazards, Veterans Health Administration, U.S. Department of Veterans Affairs (*designated by Victoria J. Davey, Ph.D., M.P.H.*)
- *Bruce Gellin, M.D., M.P.H., Director, National Vaccine Program Office, Office of the Assistant Secretary for Health, U.S. Department of Health and Human Services (HHS)
- Rosemary Hart, J.D., Special Counsel, Office of Legal Counsel, U.S. Department of Justice
- *Carole Hudgings, Ph.D. , Senior Advisor to the Deputy Director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), HHS (*designated by Hugh Auchincloss, M.D.*)
- Peter Jutro, Ph.D., Deputy Director, National Homeland Security Research Center, U.S. Environmental Protection Agency
- Randall L. Levings, D.V.M., Scientific Advisor, National Center for Animal Health, U.S. Department of Agriculture (by phone)
- *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.*)
- Tracy Dewese Parker, Ph.D., Office of Health Affairs, U.S. Department of Homeland Security (*designated by Sally Phillips, R.N. Ph.D.*)
- Bonnie Richter, Ph.D., Director of the Office of Illness and Injury Prevention Programs, Office of Health Safety and Security, U.S. Department of Energy (*designated by Patricia R. Worthington, Ph.D.*)

* Members of the NBSB Anthrax Vaccine Working Group

ANTHRAX VACCINE WORKING GROUP MEMBERS* - (EX-OFFICIO DESIGNEEES) – PRESENT

- *Richard Gorman, M.D., National Institute of Allergy and Infectious Diseases, NIH, HHS
- *Cynthia Kelly, M.S., Center for Biologics Evaluation and Research, Food and Drug Administration (FDA), HHS
- *Robert “Skip” Nelson, M.D., Ph.D., Office of Pediatric Therapeutics, Office of the Commissioner, FDA, HHS
- *Nicki Pesik, M.D., Office of Public Health Preparedness & Response, Centers for Disease Control and Prevention (CDC), HHS

STAFF OF THE NATIONAL BIODEFENSE SCIENCE BOARD

Leigh Sawyer, D.V.M., M.P.H., CAPT, U.S. Public Health Service; Executive Director
MacKenzie Robertson, Program Analyst
Jomana F. Musmar, M.S., Program Analyst, Contractor

CALL TO ORDER, ROLL CALL, AND CONFLICT OF INTEREST RULES CAPT Leigh Sawyer, D.V.M., M.P.H., Executive Director, National Biodefense Science Board (NBSB)

CAPT Sawyer welcomed the Board members and reviewed the guidelines for Federal advisory boards, as well as conflict of interest guidelines.

WELCOME AND INTRODUCTION

Patricia Quinlisk, M.D., M.P.H., NBSB Chair

Dr. Quinlisk welcomed the Board members, members of the NBSB Anthrax Vaccine Working Group (AV WG), and other participants and reviewed the agenda for the meeting.

OPENING REMARKS

Lisa G. Kaplowitz, M.D., M.S.H.A., Deputy Assistant Secretary for Policy and Planning, Office of the Assistant Secretary for Preparedness and Response (ASPR), HHS

Dr. Kaplowitz thanked the Board on behalf of the ASPR for their hard work, particularly their recent report on scientific investigation as an integral component of disaster planning and response. Regarding the current charge to the Board, Dr. Kaplowitz said that the Secretary of the Department of Homeland Security (DHS) determined in January 2004 that anthrax is a material threat to the United States. HHS has pursued a comprehensive strategy that includes investments in medical countermeasures (antibiotics and BioThrax, or anthrax vaccine adsorbed [AVA]) for the Strategic National Stockpile. However, there are policy challenges to using countermeasures, especially AVA, in the face of a widespread event. Dr. Kaplowitz stressed that no decision has been made on

* Members of the NBSB Anthrax Vaccine Working Group

whether to proceed with clinical trials of AVA in pediatric populations, but if an event occurs, the American people expect that the government and experts will have discussed the issue in advance. Dr. Kaplowitz said she looks forward to the deliberations of the NBSB and the public input from today's meeting.

Dr. Kaplowitz added that she is pleased with progress on the reauthorization of the Pandemic and All-Hazards Preparedness Act (PAHPA). HHS is partnering very closely with Congress and our partners within the federal government in terms of developing this reauthorization legislation. Finally, Dr. Kaplowitz welcomed Diane DiEullis, Ph.D., Deputy Director of the ASPR Office of Policy and Planning.

AV WG PRESENTATION AND DISCUSSION

Daniel Fagbuyi, M.D., FAAP, Chair, and John S. Parker, M.D., FACS, FCCP Major General (Retired), Co-Chair, Anthrax Vaccine Working Group, NBSB

Overview

Dr. Fagbuyi described the charge to the NBSB from the ASPR to evaluate the challenges of using AVA in pediatric populations for post-exposure prophylaxis (PEP). Following input from a wide range of stakeholders gathered at a public workshop in July 2011, the AV WG developed a draft executive summary for deliberation by the Board. This public meeting is an opportunity for NBSB voting and non-voting members, AV WG members, and the public, to comment on the draft executive summary of the report.

Drs. Fagbuyi and Parker walked through the executive summary, and a free flowing discussion ensued. The following summarizes suggestions for further improvement of the executive summary, which will be considered by the AV WG. In addition to legal, ethical, and logistical issues, Dr. Parker pointed out that the questions of if, when, and how to evaluate AVA in children are further complicated by the fact that current recommendations for PEP with AVA also include an immediate 60-day course of antibiotics. The concurrent use of vaccine and antibiotics may skew the findings of any evaluation of AVA given during an emergency event. Antibiotics effectively protect individuals against any spores that may have germinated within the body. However, other anthrax spores may remain in the body and germinate after the 60-day course; giving the vaccine soon after exposure would produce an immunological response that would prevent germination of these spores.

Dr. Parker explained that over 10 million doses of AVA have been given to adults, and the vaccine has a safety record that is acceptable to the Institute of Medicine (IOM) and the Advisory Committee on Immunization Practices (ACIP). In an emergency, AVA can be offered to adults ages 18–65 years under an emergency use authorization (EUA). However, because the safety and immunogenicity of AVA in children is not known, in an emergency, AVA could only be administered to children under age 18 years under an investigational new drug application application (IND) with the written permission of a parent or guardian. It is likely that 25 percent of any U.S. population exposed to an anthrax event will be children who would be offered both antibiotics and vaccine under IND. The question is whether to study AVA in children in the absence of exposure—that

is, pre-event—to assess safety, immunogenicity, dose ranges, reactions, and adverse effects or to study children only after an anthrax exposure occurs. The U.S. Government (USG) has plans in place to provide AVA under an IND to children following an anthrax attack.

Comments and Suggestions on the Executive Summary (by Section)

Background

- Studies of the AVA in adults have not yielded any remarkable findings regarding reactions, side effects, or response rates in different populations.
- It was acknowledged that compliance with a 60-day regimen of antibiotics may not be tolerated, and the side effects of a long antibiotic regimen are not trivial. In addition, because antibiotics alone may not provide full protection against anthrax spores, using antibiotics alone after exposure may result in recurrence of disease. It was noted that under the EUA for adults, AVA would be given in conjunction with a 60-day antibiotic regimen; the duration of antibiotics would not be shortened because of AVA use. There is no study comparing those who received vaccine with those who received antibiotics only. It was mentioned that the vaccine will not confer protection immediately, because the immune system requires time to mount a response.
- There is no way to test whether an individual has inhaled anthrax spores, so public health entities would offer treatment to the entire exposed population. Also clarify the mortality rates of anthrax exposure.
- Information about the adverse effects from the AVA package insert, the Centers for Disease Control and Prevention's (CDC's) vaccine information statement, and ACIP's 2009 *Morbidity and Mortality Weekly Report (MMWR)* recommendation should be referenced in the report.
- Clarify that both options for evaluating AVA in children (pre- and post-event) require parental permission before children are vaccinated.

Conduct of Clinical Trials

- It was noted by the group that the length of time required to start up a trial, conduct the trial, gather and analyze data, and validate the data is significant.
- The group acknowledged the difficulty of collecting data during an emergency response.
- The group suggested a graphic comparison of the types of research protocols (EUA, “non-research” IND) and the data-gathering methods that would be used, clarifying the government's intent for the research. The group suggested that a graphic comparison of the estimated time required for a subject to complete the study requirements under an EUA versus an IND protocol.

Post-Event Evaluation of AVA PEP

- The group understood that while there is no guarantee that AVA will not cause serious adverse events in children, the ACIP and American Academy of Pediatrics (AAP) believe that there is no reason to conclude that children are at higher risk of adverse events from the vaccine than adults.
- The group discussed the issue that public health entities would monitor all adverse events following vaccination either pre-event or post event, and some children would be asked to provide a blood sample, under a research IND. They recognized drawing blood poses little risk to the child. Only a small sub-group of children (perhaps a few hundred) would be enrolled in the research IND.
- The group said that the HHS should consider conducting an exercise that simulates a mass vaccination effort following an event. However, it was noted that this recommendation was outside the guidelines of the report.
- There were many instances where the group asked that terms be very well defined and that the definitions be easily understood.

Question 1: What are the risks and benefits of attempting to perform an AVA vaccine safety and immunogenicity IND research protocol in children pre-event versus after an event?

- The following issues raised by stakeholders were considered by the AV WG:
 - The true risk of AVA in children is not known.
 - There is no known benefit to vaccinating children in the absence of an event other than potential future benefit.
 - The occurrence of temporally related health problems following vaccination, whether causally related or not, may affect future uptake of the vaccine.
 - It may be difficult to get institutional review board (IRB) approval for a pre-event study.
- It was clearly pointed out that a pre-event study may be the only way to identify in advance potential serious adverse events that would be magnified in scope in a mass vaccination setting. However, also note that rare events may not be revealed in small studies.
- The group felt that information gathered from pre-event studies could be communicated to parents and may mitigate parents' hesitancy to accept the vaccine in a post-event setting.
- The group was well aware of the fact that parents are likely to have a different mindset about AVA following anthrax exposure than they would in the absence of an event.

Question 2: What are the challenges for administering this vaccine under an IND research protocol after an event and how do these challenges compare with ethical considerations for attempting to gather sufficient data to permit use under an EUA?

- It was pointed out that conducting a pre-event trial does not guarantee that sufficient data will be gathered to allow for vaccination of children under an EUA in a post-event setting. However, it was also pointed out the main purpose of the pre-event study was to better understand the safety and immunogenicity of the vaccine in children – the IND to EUA effort would be a secondary benefit and the study could be designed to allow sufficient data to be collected for evaluation of an EUA.

Question 4: How should the USG communicate these issues with parents, pediatricians, public health officials, and political officials before and in response to an anthrax attack?

- Informing the public should be an ongoing activity to ensure that individuals have sufficient information on which to base decisions, especially during stressful times.

Recommendation

- The group discussed the recommendation for a significant period of time. The group offered several suggestions to clarify the recommendation but to keep the language simple.
- During the discussion the group made it clear that a post-event adverse event evaluation will occur regardless of whether a pre-event study takes place.

General

- There was unanimous agreement that the document should be written in a style that the general public can read and understand.

PUBLIC COMMENTS

For a full transcript of the public comments provided at the meeting, please refer to the September 22, 2011 Public Meeting webpage on the NBSB website, available at: <http://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Pages/110922meeting.aspx>

Vera Hassner Sharav, President, The Alliance for Human Research Protection, provided written comments questioning the threat posed by anthrax, the efficacy of the vaccine, the safety of the vaccine, and the legal and ethical implications of studying the vaccine in healthy children who may receive no direct benefit. Please see her comments in the transcript.

Al Romanosky, M.D., Ph.D., of the Maryland Department of Health and Mental Hygiene, Baltimore, MD, emphasized the need to include information about mortality in the report, because it adds another layer of context to explain why studying AVA is important, in addition to information about identifying the immunogenicity and potential side effects in the pediatric population.

Claire Dwoskin of the National Vaccine Information Center said that in defense of children, the decision about evaluating AVA should be based on the strongest, most compelling logic and reason. Please see her comments in the transcript.

Meryl Nass, M.D., medical staff member at Mount Desert Island Hospital, said she has published articles (e.g., in *Infectious Disease Clinics of North America*) and testified before Congress about AVA. The efficacy of AVA in adults and children is uncertain, she said, and depends on several factors. Until you know what the attack looks like, there is no way to be sure about the efficacy of AVA—that is very clear in the literature, said Dr. Nass. Please see her comments in the transcript.

NEXT STEPS

It was agreed that Drs. Fagbuyi and Parker would revise the draft considering input from this meeting and circulate it for review by the AV WG. The full report and recommendations will be sent to the AV WG for comment and a final draft will be prepared and circulated to the full board and made available to the public in advance of a public teleconference, tentatively scheduled for the last week of October 2011. At that teleconference, the NBSB will vote on the final report and recommendations..

REAUTHORIZATION OF PAHPA

Zeno W. St. Cyr, II, M.P.H., Director of Legislative Coordination, ASPR, HHS

Mr. St. Cyr said there is wide, bipartisan support across both chambers of Congress to reauthorize PAHPA this year. Given the current political climate, however, Congress has no appetite for broad legislative changes that would provide sweeping new authorizations or new appropriations. Therefore, Mr. St. Cyr said, he envisions a reauthorization bill that tweaks the current legislation and fills in some of the gaps that remain since PAHPA was first enacted five years ago. Congress may consider some related legislation at the same time, such as reauthorization of Project BioShield (set to expire in 2013). Mr. St. Cyr said a number of stakeholder organizations have provided input to Congress for reauthorization of PAHPA. House Resolution (HR) 2405 is the bill introduced in the House to reauthorize PAHPA. It has cleared the Energy and Commerce Committee, and is now being scored by the Congressional Budget Office, and will proceed to the full House for vote once that process is complete.

The bill authorizes level funding annually through 2016 for the programs reauthorized in the legislation. It also reauthorizes funding for the Biodefense Medical Countermeasure Development Fund (which was authorized by PAHPA in 2006 but was never funded) and gives the Secretary and the ASPR more flexibility to use special reserve funds for advanced research and development. It clarifies the duties of the ASPR, strengthening the ASPR's role in coordinating emergency preparedness and response across the Federal government. It also provides the Secretary with authority to allow States, localities, etc., to temporarily re-assign Federal staff in those States or localities to assist with responses to public health emergencies. It requires HHS to annually report to congress on a Countermeasures Implementation Plan that would replace many of the annual reports currently required. It also requires HHS to better coordinate grant programs in consultation with DHS and other Federal partners, codifying efforts already underway

and being led by the ASPR. The bill seeks to provide more flexibility in the use of EUAs. Finally, HR2405 incorporates Project BioShield into the proposed legislation and would reauthorize it for five years, for a total of \$2.8 billion. Mr. St. Cyr noted that once the bill is passed, a remaining challenge will be securing appropriations at the authorized levels.

Staff from HHS interact frequently with Senate staff members, providing them with technical assistance on their efforts to draft the Senate's reauthorization legislation. Mr. St. Cyr hoped the Senate version of the bill would include authorization of the Strategic Investor Initiative, a private non-profit entity envisioned to be a source of venture capital for medical countermeasures development; that was a recommendation stemming from the Secretary's medical countermeasures review. He described the next steps in the legislative process and said that he believes there is enough agreement that PAHPA will be reauthorized this year, although appropriations will still be a challenge given the current fiscal environment.

DISCUSSION

Mr. St. Cyr clarified that under the House bill, an individual working in a Federally funded position at, for example, the State level (e.g., in an HIV/communicable diseases program) could be temporarily reassigned to help the State with a public health emergency effort if the State requested it. In response to a question about whether the NBSB is mentioned in PAHPA reauthorization legislation, he noted that the Board is not mentioned in the reauthorization bill, but the Secretary has the authority to maintain the Board as long as it is necessary and appropriate. So new legislation is not needed to sustain and extend the NBSB. Mr. St. Cyr added, in response to another question that the FDA seems to be happy with the new flexibilities provided by the proposed language regarding EUAs.

Dr. Fagbuyi hoped the legislation would give the ASPR more power to address issues in general and especially pediatric needs. Mr. St. Cyr responded that the ASPR, Dr. Nicole Lurie, is working to institutionalize efforts to address the needs of children and special populations in emergency preparedness and response planning. Children's needs have been a huge topic of conversation in the development of the PAHPA reauthorization bill, he added. Patrick J. Scannon, M.D., Ph.D., also hoped special populations would be included and that emergency planning would go beyond medical countermeasures to address, for example, the logistics of evacuating special populations.

Mr. St. Cyr, responding to a question, noted that the proposed House reauthorization bill allots money for improving capacity and situational awareness in public health, and that grants to schools of public health may be included in that funding.

CONCLUSION

CAPT Sawyer thanked all of the participants and Board members, especially the AV WG. She also gave special thanks to the NBSB staff for their hard work. Dr. Quinlisk thanked all the participants and adjourned the meeting at 2:00 p.m.