

**CHALLENGES IN THE USE OF
ANTHRAX VACCINE ADSORBED (AVA)
IN THE PEDIATRIC POPULATION
AS A COMPONENT OF
POST-EXPOSURE PROPHYLAXIS (PEP)**

**A REPORT
OF THE NATIONAL BIODEFENSE SCIENCE BOARD**

October 2011

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EXECUTIVE SUMMARY

In the event that *Bacillus anthracis* (*B. anthracis*) spores are released in the United States, the current plan of the U.S. Department of Health and Human Services (HHS) is to ensure that anthrax vaccine adsorbed (AVA) is made available to adults and children.¹ In this emergency scenario, AVA would be offered in conjunction with antibiotics to prevent the development of infection and illness following exposure to anthrax spores, a form of therapy termed “post-exposure prophylaxis” (PEP).² Antibiotics would offer prompt (but temporary) protection, and vaccination would offer delayed (but extended) protection against infection. However, a complex array of scientific, medical, ethical, legal, regulatory, and administrative issues complicates the use of AVA for PEP in children. This report, prepared by the National Biodefense Science Board (NBSB), discusses these issues and presents several options for resolving them and a recommendation.

The NBSB is a federal advisory committee authorized in December 2006 by the Pandemic and All-Hazards Preparedness Act (PAHPA). The NBSB provides expert advice and guidance to the Secretary of HHS, on scientific, technical, and other matters of special interest to HHS regarding current and future chemical, biological, radiological, and nuclear agents, whether naturally occurring, or accidentally or deliberately released. The NBSB also provides advice on issues related to public health emergency preparedness and response.³ (The roster of the NBSB is provided in Appendix 1.)

The U.S. Government (USG) has stockpiled finite amounts of AVA as a key component of PEP following an anthrax attack. Since the 2001 anthrax attacks, federal and local

¹ For the purposes of this report, “adults” are individuals 18 to 65 years of age. The terms “children” and “pediatric population” are equivalent as used here, and refer to individuals younger than 18 years of age.

² Post-exposure prophylaxis (PEP) is short-term prophylactic treatment administered to reduce the likelihood of an infection after the potential exposure to a pathogen. This World Health Organization definition is available at www.who.int/hiv/topics/prophylaxis/en/.

³ U.S. Public Law 109-417. Title 42 USC sections 219a and 247d-7f; 120 Stat. 2831 (2006). For NBSB Charter, available at www.phe.gov/Preparedness/legal/boards/nbsb/Documents/amendcharter-nbsb-2010.pdf

officials have conducted exercises to evaluate the USG response following a hypothetical terrorist attack using *B. anthracis* spores. Recently, the Dark Zephyr Senior Officials Exercise again highlighted the continuing policy and response challenges the Nation faces in addressing the potential need for AVA PEP for special populations, particularly children younger than the age of 18, who comprise nearly 25 percent of the U.S. population.⁴

This report focuses on children because they comprise a large percentage of the population; there are no clinical data on the use of AVA in children, whether for pre-exposure vaccination or for PEP; and the HHS Food and Drug Administration (FDA) has not licensed AVA for use in children. Further, in her remarks at a public workshop hosted by the NBSB Anthrax Vaccine (AV) Working Group (WG) on July 7, 2011, HHS Assistant Secretary for Preparedness and Response (ASPR) Dr. Nicole Lurie stated the following:

“If there were a widespread anthrax release right now, we would confront a situation where anthrax vaccine has never been tested or used in children. We're not even sure what the dose is for children. We would be in a situation of having to use emergency procedures and an IND to administer vaccine to individuals younger than 18. We also would need to act very quickly in the face of a public health emergency.”

Although the safety and immunogenicity of AVA in adults has been evaluated extensively, there are no data about the safety or immunogenicity of AVA (for pre- or post-exposure prophylaxis) in children. Thus, HHS is addressing a key question, i.e., whether to conduct a research study of AVA in children now, before a public health emergency occurs? The answer to the question is not straightforward because of ethical, legal, and societal concerns and constraints. Another issue that has come up frequently in media discussions is the perceived lack of a threat, or lack of perception of a threat, with

⁴ (1) The Dark Zephyr Exercise scenario was based on an intentional, large-scale outdoor release of *B. anthracis* spores in a major metropolitan area to examine response plans, key decisions, and policy issues associated with this type of event. The exercise scenario required senior officials from all levels of government to consider widespread application of post-exposure medical countermeasures over an entire Metropolitan Statistical Area and possibly beyond. In the context of the Dark Zephyr Exercise, the health effects of the hypothetical attack overwhelmed hospital resources over a large area, and produced many cases of disease and many deaths, including children. The desire by civic officials to avoid evacuation of many square miles of contaminated and potentially contaminated populated area, and concern about re-aerosolization of spores contributed to interest in preventing infection after the point when antibiotics would be discontinued. Within the geographic area addressed by the exercise, there was a need to provide post-exposure prophylaxis, including AVA, to an aggregate population of approximately 7.6 million people. Census data indicate that 22.6 percent, or approximately 1.7 million, of these people would be younger than 18 years of age. (2) U.S. Bureau of the Census. USA Quick Facts from the U.S. Census Bureau. Available at quickfacts.census.gov/qfd/states/00000.html.

anthrax. A fundamental issue is that no one wants to subject children to any risks that are not balanced by a potential therapeutic benefit. Any vaccination carries certain risks, however small, when compared to the risk of contracting anthrax as a result of a bioterrorism event. If a segment of the U.S. population is exposed to *B. anthracis* spores, HHS is prepared to implement the current Advisory Committee for Immunization Practices (ACIP) recommendations for use of AVA PEP.⁵ (See Appendix 2 for background information on ACIP.) AVA is the only anthrax vaccine licensed in the United States; it is licensed for use in adults 18 to 65 years of age for pre-exposure vaccination.⁶ The vaccine is not licensed for use as PEP for any age group,⁷ although studies are being conducted in adults to support this indication.

However, if the Secretary of HHS declares a public health emergency following a release of *B. anthracis* spores, the FDA can issue an emergency use authorization (EUA) that allows adults to receive AVA as prophylaxis on a voluntary basis. At present, the only way children could receive AVA for any reason is under a FDA- and IRB-approved investigational new drug application (IND), which would allow the administration of AVA to individuals younger than 18 years of age. Multiple state and local public health authorities have told federal officials that there will be an array of logistical, operational, communication, and other challenges in administering AVA under two differing regulatory mechanisms for different populations (i.e., an EUA for adults and an IND for children).

In addition to these regulatory differences governing the administration of AVA, the vaccine would be offered to the pediatric population without knowing whether it is safe and capable of inducing antibodies against *B. anthracis* bacteria (that is, immunogenic). However, obtaining safety and immunogenicity data in children in advance of a possible urgent need is constrained by legitimate scientific challenges, ethical concerns, and regulatory constraints on subjecting children to any risks the vaccine might pose with no clear direct personal benefit to vaccinated children at the time of the study or in the future.

⁵ Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

⁶ In the United States, FDA is the only authority that can approve or license a drug, vaccine, or medical device. An FDA-approved product is licensed for one or more particular uses. For example, the FDA has licensed AVA only for use as a pre-exposure vaccine for adults age 18 to 65. The FDA has not licensed AVA for any use in children, nor has the FDA approved AVA for use as PEP in adults. The discussion in this paper focuses on uses of AVA that have not been approved by FDA.

⁷ (1) Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, www.biothrax.com. (2) Food & Drug Administration. Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order. Fed. Reg. 2005;70:75180-98.

As explained below, two types of INDs are described in this report, a non-research IND and a research IND. The current HHS plan, should an anthrax emergency occur, is to make antibiotics and AVA PEP available to children under a non-research IND, after parents or legal guardians provide written consent.⁸ The two research INDs described below differ primarily in their timing. A pre-event research IND would be conducted before *B. anthracis* spores are released, whereas a post-event research IND would occur after spores are released.

Given these complexities, the NBSB was asked to consider whether HHS should act now to increase national preparedness by conducting clinical trials with AVA in children prior to a public health emergency. In a letter to the Chair of the NBSB on April 27, 2011 (see Appendix 3), Dr. Lurie asked the Board to address the following questions, and ultimately provide a recommendation on the best course of action to prepare for the potential use of AVA in children younger than 18 years of age:

- (1) What are the risks and benefits of attempting to perform an AVA vaccine safety and immunogenicity IND research protocol study in children pre-event versus after an event?
- (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?
- (3) What pre-planning should the U.S. government have in place to optimally perform an investigational protocol post-attack?
- (4) How should the U.S. government communicate these issues with parents, pediatricians, public health officials and political officials before and in response to an anthrax attack?

To respond to the ASPR's request, the NBSB formed the AV WG working group (see Appendix 4 for the AV WG membership roster), which held meetings and workshops to solicit input from academic scientists, physicians and other healthcare providers, representatives from professional pediatric organizations, and federal professionals (from stakeholder agencies) to hear their views and discuss the issues. As a result, the AV WG developed background information on the "Characteristics of *B. anthracis* and Anthrax," "Use of and Responses to AVA," and "ACIP Recommendations for the Use of AVA and Antimicrobials in a Public Health Emergency Following Exposure to *B. anthracis*

⁸ The CDC IRB has already determined that the post-event IND for administration of AVA is not "research" under HHS 45 CFR 46 regulations. This IND application has been filed with the FDA.

Spores;” responses to the four questions posed by Dr. Lurie; two options for HHS consideration; and the recommendation below.

The AV WG and the NBSB deliberated at length how best to protect children during a public health emergency that involves the release of *B. anthracis*, given the absence of data about the safety or immunogenicity of AVA PEP in individuals younger than 18 years of age. Before conducting clinical research among children, it is necessary to address the ethical and legal concern that children are unable to give informed consent on their own behalf. When it becomes necessary to conduct clinical research in children to evaluate the safety and efficacy of medical products or devices, USG statutes and regulations dictate how the research must be conducted.

The NBSB recommendation shown below reflects the need to obtain crucial safety and immunogenicity data about the use of AVA in individuals younger than 18 years of age in advance of a public health emergency.

NBSB RECOMMENDATION

The NBSB recommends Option 1 (see Section VII), in light of the current HHS plan to follow the ACIP recommendations for the use of AVA for PEP following exposure to *B. anthracis* spores:

This issue should be referred to an appropriate review board to formally address the ethical considerations. This board should include ethicists and public representation. If the ethical considerations are adequately addressed, HHS should develop a plan for and conduct a pre-event study of AVA in children, to include a research IND. HHS should submit the study protocol to one or more institutional review boards, and comply with the 21 CFR 50.54 / 45 CFR 46.407 federal review process.

This recommendation should be revisited if new anthrax vaccines or other therapeutic countermeasures become available.⁹

⁹ The HHS Biomedical Advanced Research and Development Authority (BARDA) announced September 15, 2011, new contracts to support, “the advanced development of a novel next-generation anthrax vaccine and a new type of anthrax antitoxin” (excerpted from the press release available at www.hhs.gov/news September 15, 2011). The objectives of the new contracts are to develop a vaccine that “could be administered as a spray in the nose and given by non-medical personnel, making administration easier and potentially increasing the number of people [per hour] who could be vaccinated against this potentially fatal infection. Similarly, the new anthrax antitoxin medication could be administered by conventional injection, making the medication much easier and faster to administer than current anthrax antitoxins, which must be administered intravenously. This would greatly facilitate antitoxin administration in an emergency.” Even

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I. INTRODUCTION

In April 2011, Assistant Secretary for Preparedness and Response (ASPR) Dr. Nicole Lurie noted that the U.S. Government (USG) requested that the National Biodefense Science Board (NBSB)¹⁰ consider issues related to the use of anthrax vaccine adsorbed (AVA) in children. The impetus for the request was to strengthen public health measures against a biological weapons attack using *Bacillus anthracis* (*B. anthracis*), the bacterium that causes anthrax, by ensuring that special populations are considered in U.S. preparedness and response activities. (Special populations include children, the elderly, pregnant women, and individuals who are immunocompromised.) In her request, Dr. Lurie focused on the current absence of information about the use of AVA as a medical countermeasure to protect special populations, particularly children.

In response to Dr. Lurie's request, the NBSB formed the Anthrax Vaccine Working Group (AV WG), and sought information from stakeholders, including federal and non-federal subject-matter experts. HHS decided to focus on the pediatric population (defined in this report as individuals younger than 18 years of age) because they comprise a large percentage of the population; there are no clinical data on the use of AVA in children, whether for pre-exposure vaccination or post-exposure prophylaxis (PEP); and the HHS Food and Drug Administration (FDA) has not licensed AVA for use in children.

This NBSB report, "Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP)," describes the challenges of administering AVA to children before versus after an attack with *B. anthracis* spores. The report also includes background information, responses to four questions posed by Dr. Lurie in her April 2011 letter to the NBSB, two options for HHS consideration, and a recommendation.

so, these hypothetical new products would eventually face the same issues confronted with AVA in this report: when and how to test them among children.

¹⁰ U.S. Public Law 109-417. Title 42 USC sections 219a and 247d-7f; 120 Stat. 2831 (2006). For NBSB Charter, available at www.phe.gov/Preparedness/legal/boards/nbsb/Documents/amendcharter-nbsb-2010.pdf

Stakeholder Engagement

To obtain information and advice from subject-matter experts and other stakeholders, the AV WG held two workshops. The first stakeholder-engagement workshop, “Vaccine to Protect Children from Anthrax,” held on July 7, 2011, opened with a description of a plausible intentional, large-scale, outdoor release of *B. anthracis* in a major metropolitan area (see the agenda attached as Appendix 5). The AV WG hosted a question-and-answer session to learn the opinions of those in attendance, and engage them in a discussion of the issues (see Appendix 6 for list of workshop attendees).

During the July 7, 2011, AV WG workshop, Dr. Lurie clarified her request:

- I’m not asking the NBSB at all to evaluate the threat of anthrax.
- I’m not asking NBSB to design a trial or to design a protocol.
- I’m not asking NBSB to be an institutional review board (IRB).
- What I am asking the NBSB to do is to make recommendations about the need for trials and the need for data pre-event, versus at the time of an event. If in either situation the NBSB recommends that we conduct clinical studies, please identify particular issues HHS needs to consider.

The following day, the AV WG convened an invitation-only workshop, “Medical Countermeasures for Children – Anthrax Vaccine” (see Appendix 7 for the agenda and Appendix 8 for the list of attendees). Based on the discussions, the working group developed a draft Executive Summary to include background information and responses to the four questions posed above and their recommendation.

The AV WG presented a draft Executive Summary at the September 22, 2011, public meeting of the NBSB.¹¹ Participating members of the public offered comments on the draft Executive Summary as did NBSB members. The AV WG revised the document to take into account these discussions.

II. BACKGROUND INFORMATION

The AV WG considered a range of scientific, regulatory, legal, ethical, and policy issues in its deliberations about the use of AVA in children. Background information from these deliberations is summarized below under three headings: “Characteristics of *B. anthracis* and Anthrax,” “Use of and Responses to AVA,” and “ACIP Recommendations for the Use of AVA and Antibiotics in a Public Health Emergency.”

¹¹ For further information on the National Biodefense Science Board (NBSB), see www.phe.gov/preparedness/legal/boards/nbsb/pages/default.aspx.

Characteristics of *B. anthracis* and Anthrax

- Anthrax is a disease caused by infection with *B. anthracis*, a gram-positive, nonmotile, spore-forming bacterium. Anthrax spores can withstand harsh conditions, then germinate to form colonies of bacteria when conditions are favorable. Anthrax is primarily a disease of wild and domestic animals. Humans typically contract the disease through contact with infected animals or spore-contaminated animal products, such as hair or hides. Depending on the site(s) of infection, anthrax can occur in a cutaneous, gastrointestinal, or inhalation form.
- The virulence of *B. anthracis* derives from its capsule and toxin. The capsule enables the bacterium to evade the host immune response. The toxin is composed of three proteins: protective antigen (PA), edema factor (EF), and lethal factor (LF). To produce active toxin, PA must bind to receptors on cells of infected host animals, thus forming channels that allow EF and LF to enter cells and kill them.¹²
- Anthrax in humans had become extremely uncommon in any form in the United States, until the autumn of 2001 when spores of *B. anthracis* distributed in letters through the U.S. mail caused an outbreak of cutaneous and inhalation cases. Eleven of the 22 cases in 2001 were diagnosed as inhalation anthrax, 5 of which were fatal (45%); 11 cases were cutaneous anthrax.¹³
 - Approximately 95 percent of naturally occurring human cases of anthrax are cutaneous, according to CDC¹⁴ and IOM,¹⁵ and the mortality rate for untreated cutaneous anthrax is 20 percent. If treated with antibiotics, cutaneous anthrax is rarely fatal.
 - The CDC¹⁶ and IOM¹⁷ data indicate that mortality rates for inhalation

¹² Jang J, Cho M, Chun JH, Cho MH, Park J, Oh HB, Yoo CK, and Rhie I G. The Poly- γ -D-Glutamic Acid Capsule of *Bacillus Anthracis* Enhances Lethal Toxin Activity. *Infect. and Immunity* 2011; 79 (9): 3846–3854.

¹³ Jernigan DB, Raghunathan PL, Bell BP, et al. Investigation of Bioterrorism-related Anthrax, United States, 2001: Epidemiologic Findings. *Emerg Infect Dis* 2002;8:1019-28.

¹⁴ Centers for Disease Control and Prevention. Questions and Answers about Anthrax. Available at: www.bt.cdc.gov/agent/anthrax/faq/.

¹⁵ Stroud C, Viswanathan K, Powell T, Bass RR, editors. *Prepositioning Antibiotics for Anthrax*. Washington, DC: National Academies Press, September 2011. The IOM report is available at www.iom.edu/Reports/2011/Prepositioning-Antibiotics-for-Anthrax.aspx.

¹⁶ Centers for Disease Control and Prevention. Questions and Answers about Anthrax. Available at: www.bt.cdc.gov/agent/anthrax/faq/.

¹⁷ Stroud C, Viswanathan K, Powell T, Bass RR, editors. *Prepositioning Antibiotics for Anthrax*. Washington, DC: National Academies Press, September 2011. The IOM report is available at www.iom.edu/Reports/2011/Prepositioning-Antibiotics-for-Anthrax.aspx.

anthrax could be higher—approximately 75 percent, even with all possible supportive care including appropriate antibiotics. These statistics are based on limited and incomplete information. The IOM report further states that, “If terrorists released *B. anthracis* over a large city, hundreds of thousands of people could be at risk of the deadly disease anthrax—caused by the *B. anthracis* spores—unless they had rapid access to antibiotic medical countermeasures (MCM). The spores can be inhaled, be ingested, or come into contact with the skin. Inhalation anthrax is considered the most severe bioterrorism threat because the spores can travel significant distances through the air...”

- Anthrax is rarely transmissible from human-to-human.¹⁸
- There is no test to determine which individuals have inhaled *B. anthracis* spores. The HHS plan is to offer PEP (antibiotics and AVA) to all adults and children likely to have been exposed.
- The risk of exposure or infection through re-aerosolization of spores is unknown. Theoretically, any *B. anthracis* spores remaining in the environment after their initial release could become airborne, thus posing a continued risk of inhalation disease for an unknown period of time.
- Inhalation anthrax occurs after *B. anthracis* spores are inhaled into the lung. There is insufficient evidence available from the two English- and three foreign-language case reports of pediatric anthrax to classify the typical presentation of inhalation anthrax or treatment responses in children, or to compare children to adults with inhalation disease. In particular, clinicians have very little information about inhalation anthrax in infants or toddlers.
- Based on available evidence about inhalation anthrax in adults and children, the following observations are possible:
 - Among adults, inhalation anthrax presents with a prodromal phase (often described as “flu-like”). The most common symptoms or findings at admission are abnormal lung findings, fever or chills, tachycardia, fatigue or malaise, cough, dyspnea, and nausea or vomiting. These symptoms are typically accompanied by non-headache neurological symptoms such as

¹⁸ Cutaneous anthrax has rarely been transmitted from one person to another. Discharges from skin lesions may contain *B. anthracis* bacteria. Spreading of other types of anthrax has never been reported. Available at: www.bt.cdc.gov/agent/anthrax/pdf/cutaneous_anthrax_qa.pdf.

dizziness, visual changes, and syncope, which are not typical of routine influenza infection.

- The three children with inhalation anthrax for whom signs and symptom data were published manifested dyspnea and abnormal lung exams; however, none had either non-headache neurological symptoms or nausea or vomiting. Therefore, it might not be possible to develop accurate screening procedures to diagnose inhalation anthrax in children based on symptoms in adults.
- Adult patients typically have abnormal chest x-rays characterized by pleural effusions or widened mediastinum. Both pediatric patients with inhalation anthrax who had chest x-rays displayed similar abnormalities.

Use of and Responses to AVA

- If the Secretary of HHS declares a public health emergency, the FDA Commissioner is authorized to issue an EUA under certain circumstances.¹⁹ Under an EUA, medical countermeasures to diagnose, treat, or prevent serious or life-threatening diseases for which no adequate, approved, and available product exists can be disseminated quickly for the protection and safety of the U.S. population. However, adequate data must indicate the product is safe in the population(s) for which it is being authorized for use. For example: AVA is considered safe and effective in the adult population in a 5-dose pre-exposure regimen; based on this, AVA can be used in adults under an EUA for an unapproved use e.g., such as PEP, with FDA approval.²⁰
- All the AVA available for use during a public health emergency is stored in the Strategic National Stockpile (SNS), which is maintained by CDC.
- AVA has been licensed for human use in the United States since 1970, and is the only licensed human anthrax vaccine in the United States. It is a cell-free filtrate containing *B. anthracis* PA as the principal immunogen. For general-use prophylaxis (i.e., pre-exposure vaccination), immunization consists of a series of five intramuscular injections of 0.5 milliliters each. Doses are administered at

¹⁹ 21 USC 360bbb-3. For more information, see www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm.

²⁰ ACIP recommendations for PEP for previously unvaccinated persons include a description of how AVA can be made available for an unlicensed indication. “Because AVA is not licensed for PEP, administration of AVA as a component of PEP is available under an IND application (IND #10061, held by CDC) and may be made available under an EUA.” The PEP regimen included in the IND protocol includes children aged 0-17 years.

time 0 and 1, 6, 12 and 18 months. Booster injections of 0.5 milliliter at one-year intervals are recommended to maintain immunity.²¹ The CDC is studying alternative dosing regimens in adults.

- AVA is licensed for pre-exposure immunization to prevent disease caused by *B. anthracis*, in persons 18 to 65 years of age at high risk of exposure. In the United States, AVA is used commonly to protect military personnel, and at-risk laboratory personnel. The vaccine is not FDA-licensed for PEP in any age group.²²
- Data about the safety of clinical use of AVA in adults have been published in multiple clinical trials and epidemiologic studies, and laboratory investigations (see Appendix 9). Published reports include dozens of follow-up studies of millions of vaccinated military personnel.²³ The total military experience with AVA since 1998 involves more than 2.5 million vaccinated personnel who, collectively, received more than 10 million doses of licensed vaccine. In its 2002 report on the safety and efficacy of the anthrax vaccine, an Institute of Medicine panel stated, “After examining data from numerous case reports and especially epidemiologic studies, the committee also concluded that AVA is reasonably safe.”²⁴ The principal adverse events that can be objectively attributed to AVA include injection-site reactions (e.g., tenderness, redness, itching, lump, bruise), muscle aches, temporary limitation of arm movement, headaches, fatigue, allergic or hypersensitivity reactions (e.g., anaphylaxis).²⁵ (See Appendix 10 for a copy

²¹ (1) Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, www.biothrax.com. (2) Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

²² (1) Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, www.biothrax.com. (2) Food & Drug Administration. Biological Products; Bacterial Vaccines and Toxoids; Implementation of Efficacy Review; Anthrax Vaccine Adsorbed; Final Order. Fed. Reg. 2005;70:75180-98. (3) Military use: www.anthrax.mil.

²³ This information is based on multiple dozens of studies and reports, summarized in the following references: (1) Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. The Anthrax Vaccine: Is it Safe? Does it Work? Washington, DC: National Academy Press, April 2002. The IOM report is available at www.nap.edu/catalog/10310.html. (2) Friedlander AM, Grabenstein JD, Brachman PS. Anthrax. In: Plotkin SA, Orenstein WA, Offit PA, ed. Vaccines, 6th ed. Philadelphia: Elsevier, 2011: in press. (3) Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. The ACIP report is available at www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

²⁴ Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. The Anthrax Vaccine: Is it Safe? Does it Work? Washington, DC: National Academy Press, April 2002. The IOM report is available at www.nap.edu/catalog/10310.html.

²⁵ (1) CDC Vaccine Information Statement for Anthrax Vaccine, March 10, 2010, at www.cdc.gov/vaccines/pubs/vis/downloads/vis-anthrax.pdf. (2) Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. The ACIP report is available at www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

of the current BioThrax prescribing information.²⁶⁾ AVA is described in various scientific studies as efficacious in adults, a conclusion supported by sentinel occupational studies (of textile workers), and the results of multiple non-human primate (NHP) studies.²⁷

- No clinical, safety, or dosing data are available for any use of AVA in children, and the product is not licensed for administration to children. The preferred route of injection (i.e., subcutaneous or intramuscular) for children has not been established.²⁸ In adults, subcutaneous administration elicits more frequent injection-site reactions, compared to the intramuscular route.²⁹ However, the subcutaneous administration of AVA in adults induces higher antibody concentrations more rapidly than does intramuscular administration.³⁰ During a public health emergency declared by the Secretary of HHS, AVA could be administered to children under an IND in conjunction with antibiotic treatment, which is considered standard of care and a significant component of PEP if a child is exposed to *B. anthracis*.

²⁶ Biothrax is the commercial name for the FDA-licensed anthrax vaccine adsorbed.

²⁷ (1) Joellenbeck LM, Zwanziger L, Durch JS, Strom BL, editors. The Anthrax Vaccine: Is it Safe? Does it Work? Washington, DC: National Academy Press, April 2002. The IOM report is available at www.nap.edu/catalog/10310.html. (2) Friedlander AM, Grabenstein JD, Brachman PS. Anthrax. In: Plotkin SA, Orenstein WA, Offit PA, ed. Vaccines, 6th ed. Philadelphia: Elsevier, 2011: in press. (3) Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. The ACIP report is available at www.cdc.gov/mmwr/PDF/rr/rr5906.pdf. (4) Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, www.biobthrax.com. Food & Drug Administration. Biological products; Bacterial vaccines and toxoids; Implementation of efficacy review; Anthrax vaccine adsorbed; Final order. Fed Reg 2005;70:75180-98. Military use: www.anthrax.mil.

²⁸ Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

²⁹ Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

³⁰ Marano N, Plikaytis BD, Martin SW, Rose C, Semenova VA, Martin SK, Freeman AE, Li H, Mulligan MJ, Parker SD, Babcock J, Keitel W, El Sahly H, Poland GA, Jacobson RM, Keyserling HL, Soroka SD, Fox SP, Stamper JL, McNeil MM, Perkins BA, Messonnier N, Quinn CP; Anthrax Vaccine Research Program Working Group. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: A randomized trial. JAMA 2008;300:1532-43, erratum 2252.

ACIP Recommendations for the Use of AVA and Antimicrobials in a Public Health Emergency Following Exposure to *B. anthracis* Spores³¹

- **ACIP recommendations for PEP after inhalation exposure for the general adult population:** To prevent inhalation anthrax, ACIP recommends "...a post-exposure regimen of 60 days of appropriate antimicrobial prophylaxis combined with 3 SC [subcutaneous] doses of AVA (administered at 0, 2, and 4 weeks post-exposure as the most effective protection against inhalation anthrax for previously unvaccinated persons..." [adults 18 to 65 years of age]. "[A]ntimicrobial therapy should be initiated as soon as possible. Ideally, the first dose of vaccine should be administered within 10 days. Because AVA is not licensed for postexposure use, the vaccine will likely be made available either through an IND or an EUA during a public health emergency. In general, the peak serologic response to anthrax vaccine occurs 10–14 days after the third dose. To ensure continued protection, persons for whom vaccination has been delayed should extend antimicrobial use to 14 days after the third dose, even though this practice might result in use of antimicrobials for >60 days. Antimicrobials should not be used for <60 days in previously unvaccinated persons who have been exposed to aerosolized *B. anthracis* spores."
- **ACIP recommendations for PEP after inhalation exposure for children:** "The use of AVA in children is not contraindicated in a post-event setting that poses a high risk for exposure to aerosolized *B. anthracis* spores. During such an event, public health authorities will determine whether, under the existing non-research IND, to offer vaccine to children aged 0-17 years. Under this IND, 3 doses of vaccine would be administered in conjunction with 60 days of appropriate antimicrobial therapy."³²
- ACIP recommends the administration of three doses of AVA as the vaccine component of PEP for adults and children because it has been shown in non-human primates (NHPs) that late germination of *B. anthracis* spores can occur after an antibiotic regimen is completed.³³ Vaccination with AVA protected

³¹ Currently, there is no diagnostic test to determine whether an individual has actually inhaled *B. anthracis* spores.

³² The HHS plan is that all children be offered AVA PEP. The IND referred to in the ACIP quotation has now been approved.

³³ (1) Friedlander AM, et al. Postexposure prophylaxis against experimental inhalation anthrax. *Journal of Infectious Diseases* 1993;167:1239-42. (2) Glassman HN. Discussion of industrial inhalation anthrax. *Bacteriological Reviews* 1966;30:657-659 (commenting on pages 646-657). (3) Gochenour WS Jr., et al. On the recognition and therapy of simian woolsorter's disease. *Journal of Hygiene (Cambridge)* 1963;61:317-325. (4) Henderson DW, et al. Observations on the prophylaxis of experimental pulmonary anthrax in the monkey. *Journal of Hygiene* 1956;54:28-36.

NHPs against bacteria that emerged due to late germination of *B. anthracis* spores,³⁴ but this effect has not been studied in humans for ethical reasons.³⁵

- ACIP recommends several antimicrobial agents as potential components of PEP:³⁶ “Oral ciprofloxacin, oral doxycycline, and parenteral (IM) penicillin G procaine have been shown to be effective for PEP use in a NHP model, and are FDA approved for a 60-day course for inhalation anthrax (post-exposure) in all age groups.... Although antimicrobials such as ciprofloxacin or doxycycline are typically not administered to children, the severity [and consequences] of anthrax is [are] sufficient that treatment with these antimicrobials is warranted and recommended for children who have been exposed to aerosolized *B. anthracis* spores.”
- Antimicrobial agents can have undesirable side effects and such effects were a commonly cited reason for discontinuation of antimicrobial PEP among 73 (78%) of the 93 persons in the Washington, D.C., postal center during the bioterrorism events of 2001.³⁷ Persons who do not complete the recommended 60-day course of antibiotics could develop clinical disease if *B. anthracis* spores germinate after they stop taking antibiotics.
- ACIP comments on the needs for research include the following: “Research priorities for future studies on the currently licensed anthrax vaccine should include immunogenicity; additional evaluations of the dosing schedule (including the maximum time between boosters); additional long-term human safety studies; the number of vaccine doses required for PEP; the optimal duration of antimicrobial use in post-exposure settings; antimicrobial susceptibility and treatment studies; optimal alternative antimicrobial agents for children, older adults (aged >65 years), and pregnant women; and the safety of anthrax vaccine in clinical toxicology studies among pregnant animals. Future research should include the groups for whom AVA is currently licensed, as well as children, older

³⁴ (1) Friedlander AM, Grabenstein JD, Brachman PS. Anthrax. In: Plotkin SA, Orenstein WA, Offit PA, ed. Vaccines, 6th ed. Philadelphia: Elsevier, 2011: in press. (2) Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. The ACIP report is available at www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

³⁵ (1) Friedlander AM, Grabenstein JD, Brachman PS. Anthrax. In: Plotkin SA, Orenstein WA, Offit PA, ed. Vaccines, 6th ed. Philadelphia: Elsevier, 2011: in press. (2) Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. The ACIP report is available at www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

³⁶ Advisory Committee on Immunization Practices. Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

³⁷ Jefferds MD, Laserson K, Fry AM, et al. Adherence to antimicrobial inhalational anthrax prophylaxis among postal workers, Washington, D.C., 2001. Emerg. Infect. Dis. 2002;8:1138-44.

adults, and pregnant women. These research questions also should be addressed as new potential anthrax vaccines are identified and considered for use in humans.... Information regarding the efficacy and safety of AVA in children and older adults also is needed, as is additional information regarding the safety and efficacy of AVA when used during pregnancy. Future research should include trials to obtain this information and to develop dosage recommendations for children.”

III. CRITICAL ISSUES AND QUESTIONS CONSIDERED BY THE AV WG

During its deliberations, the AV WG considered a range of key issues and questions as a preliminary step to responding to the four questions posed by Dr. Lurie in her April 2011 letter to the NBSB. The following section summarizes AV WG discussions about specific topics.

HHS proposed plan for PEP following exposure to *B. anthracis* spores

As indicated above, the current HHS plan, in the event of the release of anthrax spores, is to ensure that AVA and antibiotics are made available to all children and adults following their actual or potential exposure to anthrax spores. Vaccination with AVA under these emergency conditions would be entirely voluntary, and—for individuals younger than the age of 18—would require permission from a parent or legal guardian under the current non-research IND mechanism intended for providing AVA PEP to children. The differences between using an EUA or non-research IND for distribution of AVA PEP during an event are described in Table A (next page).

Table A. Differences Between the Administration of AVA PEP Under an EUA or a Non-Research IND Following the Release of *B. anthracis* Spores.

| Processes for Administering AVA PEP under an EUA or Non-Research IND | Post-event EUA for Adults | Post-event Non-Research IND for Children |
|---|----------------------------------|---|
| Information provided to parents and other adults; questions answered | Yes | Yes |
| Documentation of informed permission collected from parents and other adults (agreeing to vaccine administration) | No | Yes |
| Acceptance of AVA PEP | Voluntary | Voluntary |
| Gathering data for research purposes | No | No |
| Safety assessment | Yes, but limited* | Yes, but limited* |

* The Vaccine Adverse Event Reporting System (VAERS) is designed to collect information about adverse events (AE) and likely would be employed to collect AE data on all adults and children who receive AVA PEP. This mechanism for collecting data is not considered to be research. (*Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.³⁸)

Although the AV WG did not focus on the issue of how best to administer antibiotics to young children, nor was it a charge to the NBSB, the Board supports ongoing efforts to develop palatable, effective formulations of approved antibiotics for children younger than age nine that can be stored in the SNS and made readily available in an adequate quantity. A 2003 report of the National Advisory Committee on Children and Terrorism recommended that a liquid form of antimicrobials be made readily available in sufficient quantity for children younger than nine years of age, because of difficulty swallowing or chewing drug tablets or capsules. HHS is trying to develop a means of rapidly reconstituting or preparing antibiotic countermeasures in a liquid form (e.g., palatable solutions or suspensions) that children could swallow repeatedly over a multi-month therapeutic regimen. The Board notes that the utility of antibiotics as a countermeasure against *B. anthracis* presumes that the bacterial strain used in possible, future attack is antibiotic-sensitive. Dissemination of an antibiotic-resistant strain of anthrax would vastly complicate the public-health response.

³⁸ The definition of "adverse event" is available at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32.

What is the best way to gain some assurance and information about the safety and immunogenicity of AVA in children?

HHS is considering two approaches to gain some assurance and information about the safety and immunogenicity of AVA in children (see Table B). Both approaches include conducting studies in children under a research IND. The major difference would be the timing of when research studies are conducted, before or after an event in which *B. anthracis* spores are released.

The first approach is to conduct a research study in children ***before*** another anthrax emergency occurs. For children to participate in this pre-event research IND, parents would need to provide written consent for their child to receive the vaccine, and provide blood specimens and report symptoms after vaccination. The second approach, to be conducted ***after*** *B. anthracis* spores are released, would involve asking a subset of parents³⁹ whose children already had received AVA PEP under the non-research IND if they would agree for their child to provide blood specimens and report symptoms following vaccination. Therefore, the second approach would entail conducting a limited research study of AVA in children during the course of a public health emergency.

Key differences in these two approaches are summarized in Table B (next page).

³⁹ The number of parents asked and how they would be selected is not known at this time.

Table B. Differences Between Conducting a Research IND Before Versus After the Release of *B. anthracis* Spores

| Processes for Conducting Research INDs | Before <i>B. anthracis</i> Spores are Released (Pre-event research IND) | After <i>B. anthracis</i> Spores are Released (Post-event research IND) |
|---|--|--|
| Time available for parents to consider information about risks and benefits | More time | Less time |
| Voluntary acceptance of AVA vaccination as part of a research IND | Yes | Not Applicable - Children already would have received AVA PEP |
| Safety Assessment | Yes | Yes |
| Immunogenicity assessment (blood sampling to measure antibody response) | Yes | Yes |
| Opportunity for assessing various dosing regimens or routes of administration | Yes* | No** |

* Pre-event, dose-response studies in children may only be possible if similar dose-response studies in adults allow data on immunogenicity to be obtained, thus making it possible to compare immunogenicity using different dosing regimens or routes of administration in adults versus children.

**Testing of alternative dosing regimens would not be possible, as the same dose as that used in adults would be administered (absent data from a pre-event study that would support an alternate dose or dosing regimen).

In summary, as part of preparedness planning for an event involving *B. anthracis*, the post-event response, as currently envisioned, would include administering AVA PEP under an EUA for adults 18 to 65 years of age, and a non-research IND for children younger than 18 years of age. The primary purpose of a research IND (conducted either before or during a response to an anthrax emergency) is to gather systematic data on the safety and immunogenicity of AVA PEP in children. Conducting a pre-event study in children might make it possible to know about the safety and immunogenicity of AVA should an anthrax emergency occur and the vaccine is made available to many children. Secondly, the data may support an EUA (rather than a non-research IND) for administering AVA PEP for children in the future.

Conduct of Clinical Trials

Typically, during the development and testing of clinical products, clinical trials are designed as age-adjusted, dose-response studies to evaluate the safety and efficacy (or immunogenicity) of a medical product (e.g., a vaccine), using rigorous methods that generate data to guide a determination of the optimal dosing regimen for each age group or special population.

The length of time required to start up a trial, conduct the trial, gather and analyze data, and validate the data is extensive and may take years.

Standard procedures and approaches for evaluating new medical products include a protocol review and approval by institutional review boards (IRBs), and review by an independent data safety and monitoring board. Testing a vaccine in this conventional manner provides the optimal situation for gathering evidence-based information about a new medical product or new uses for a previously approved product. A primary responsibility of a data safety and monitoring board is to evaluate on a regular basis serious adverse events or unusual or unsuspected reactions after administering the new product. Gathering these data is critical to assuring the safety of volunteers who participate in the trial. Well-designed clinical trials minimize risk in every way possible for individuals who participate in the study.

The FDA, CDC, and National Institute for Allergy and Infectious Diseases (NIAID), a component of the National Institutes for Health (NIH), in consultation with external clinical pediatric clinical trial experts have considered several approaches to learn about the safety and immunogenicity of AVA in children prior to and/or during a public health emergency involving the release of *B. anthracis* spores. The proposed pre-event research IND for testing AVA in the pediatric population would be designed to evaluate AVA PEP in sequential studies beginning with an older pediatric group first (e.g., teenagers) and, based on the outcome, to test the vaccine in progressively younger age groups. The data safety and monitoring board would be asked to review data from an older group before proceeding to enroll the next younger age group.

What are the ethical and regulatory issues to consider before conducting studies of AVA in children?

Moving forward with clinical trials intended to generate data on the safety and immunogenicity of administering AVA to children requires adherence to regulatory and ethical principles designed to protect children who are involved in clinical research.

The foundational concepts of human subject protection are reflected in the U.S. Code of Federal Regulations (CFR):⁴⁰

- Appropriate balance of risk and potential benefit (21 CFR 56.111 (a)(1-2);

⁴⁰ (1) “Criteria for IRB Approval for Research” (21 CFR 56.111) is available at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=56.111. (2) “Additional Safeguards for Children in Clinical Investigations” (21 CFR 50 Subpart D) is available at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.4.

- Equitable selection of subjects (21 CFR 56.111 (a)(3));
- Voluntary informed consent, appropriately documented (21 CFR 56.111(a)(4-5); and
- Additional safeguards for children (21 CFR 50 Subpart D)

Enrolling children in any type of research requires additional protections beyond those afforded to adults who participate in research of their own volition.⁴¹ Research involving children is governed by numerous laws, regulations, and processes that are designed to protect children because they are considered a vulnerable population, partly due to the inability of children to provide legal consent to participate in a research project.⁴²

Equitable selection of children as research subjects. Subjects should only be enrolled in a clinical investigation that is necessary to answer an important scientific question about the health and welfare of children. The objective must be a “public health benefit” for children (for example: licensure of a product or the development of an EUA). Children should not be enrolled unless it is essential and when there is no other option. Adults capable of informed consent should be enrolled prior to adolescents and younger children, to obtain data that provides a foundation to justify exposing children to known (and unknown) risks of the experimental intervention (21 CFR 56.111 (a)(3) and see the Belmont Report.⁴³

General justification of research risk. The foundation on which this principle is based requires that the research question be well-defined and the plan for conduct be reasonably expected to give useful results. A basic criterion for IRB approval of research is that the risks to the subjects are reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result (21 CFR 56.111(a)(2)). This criterion is modified by the additional protections for children enrolled in FDA-regulated clinical investigations, in that there is a limit to the level of risk that the pursuit of knowledge can justify.

Additional protections for children (21 CFR 50 subpart D). Research involving children must be restricted to either “minimal risk” (21 CFR 50.51) or a

⁴¹ (1) 21 CFR 50, subpart D. (2) 45 CFR 46, subpart D.

⁴² National Bioethics Advisory Commission (NBAC), Ethical and Policy Issues in Research Involving Human Participants. Vol. II, Bethesda, MD. August 2001. Available at: citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.67.7929&rep=rep1&type=pdf#page=209.

⁴³ The Belmont Report, Ethical Principles and Guidelines for the protection of human subjects of research. (April 1979). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. Available at: ohsr.od.nih.gov/guidelines/belmont.html.

“minor increase over minimal” (21 CFR 50.53) risk, absent a potential for direct benefit to the participating child, or must present risks that are justified by anticipated direct benefits to the child; the balance of which (i.e., risk and potential benefit) is at least as favorable as any alternatives (21 CFR 50.52). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research⁴⁴ defined minimal risk as those risks normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children. Although the term “healthy children” was dropped from the published definition, most ethicists and U.S. Federal panels (e.g., Secretary’s Advisory Committee on Human Research Protections [SACHRP]) and the Institute of Medicine [IOM]) agree with this limitation.⁴⁵ Generally, the administration of experimental drugs or biological products is neither normal nor routine, and therefore not minimal risk, and thus such an intervention could not be approved by an IRB under 21 CFR 50.51.

CFR requirement that children be “at risk” for anthrax

A preventive intervention offers a prospect of direct benefit if (and only if) the person receiving that intervention is “at risk” from the disease. Thus, a shared requirement of 21 CFR 50.53 (which requires that children enrolled in a clinical trial have a “disorder or condition”), and 50.52 (which requires a prospect of direct benefit to children participating in a trial) is that children must be “at risk” for developing anthrax disease. Whether or not children are “at risk” for anthrax disease (and thus may benefit from vaccine administration) is the major question distinguishing an “event” (the release of *B. anthracis* spores) from a “pre-event” setting. Absent being “at risk” for anthrax disease, the administration of AVA is not approvable under either 21 CFR 50.52 or 21 CFR 50.53. In addition, the absence of data about the safety and immunogenicity of AVA in children does not support the conclusion that AVA administration presents no more than a minor increase over minimal risk (21 CFR 50.53).

⁴⁴ Report and Recommendations - Research Involving Children, National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1977, is available at videocast.nih.gov/pdf/ohrp_research_involving_children.pdf.

⁴⁵ (1) Secretary's Advisory Committee on Human Research Protections (SACHRP), Office for Human Research Protections (OHRP), available at www.hhs.gov/ohrp/index.html. (2) Field MJ, Berman RE, editors. Ethical Conduct of Clinical Research Involving Children, Washington, DC: National Academies Press, 2004. The IOM report is available at www.iom.edu/Reports/2004/Ethical-Conduct-of-Clinical-Research-Involving-Children.aspx.

Applying U.S. rules and regulations during a public health emergency

During a public health emergency involving the release of *B. anthracis* spores, health officials would define a pediatric population in which the risk of administering AVA is justified by the anticipated direct benefit to the children, and the relationship between the anticipated benefit and the risk is at least as favorable to the children as that presented by available alternative approaches i.e., not receiving the vaccine and receiving antibiotics alone, or no PEP treatment at all (21 CFR 50.52). The post-event non-research IND for administering AVA to children has been reviewed and approved by FDA, and the CDC IRB. The CDC IRB can make their review and determination available for State, Territorial, Tribal, and Local public health authorities' review and IRB approval, as needed. The post-event research IND could be approved under 21 CFR 50.53, because it does not involve administering AVA to children (who already would have received the vaccine under the post-event non-research IND). (For further explanation of IRB approval processes and options, see Appendix 11.)

Applying U.S. rules and regulations in a “pre-event” setting⁴⁶

As indicated above, administering AVA to children would present more than a minor increase over minimal risk, and thus cannot be approved under 21 CFR 50.51 or 50.53. If a release of *B. anthracis* spores occurs, AVA administration could be approved under 21 CFR 50.52 for children potentially exposed to spores.

Currently, U.S. children are not at immediate risk from anthrax and would not benefit directly from pre-event AVA administration, thus a pre-event research IND could not be approved under 21 CFR 50.52. However, protocols that are not approvable by a local IRB under 21 CFR 50.51, 21 CFR 50.52, or 21 CFR 50.53 can be referred to the FDA Pediatric Advisory Committee (PAC) for review under 21 CFR 50.54.⁴⁷ The PAC would evaluate the scientific and ethical acceptability of such a protocol, and advise and make recommendations to the Commissioner of the FDA and the HHS Secretary on whether the research could proceed under 21 CFR 50.54 and 45 CFR 46.407.

⁴⁶ FDA guidance on applying U.S. rules and regulations to conduct a pre-event research IND is available at www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf. Information about the HHS Office of Human Research Protections (OHRP) guidance is available at www.hhs.gov/ohrp/policy/populations/guidance_407process.html. These guidances and processes for implementing them are harmonized and implemented cooperatively if the research is regulated by FDA and funded or conducted by HHS (which is the case for the pre-event research IND).

⁴⁷ The FDA PAC has been chartered to advise FDA and the HHS Secretary regarding the ethics, design, and analysis of clinical trials related to pediatric therapeutics and pediatric ethical issues including research involving children as subjects as specified in 21 CFR 50.54 and 45 CFR 46.407, available at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/ucm116525.htm.

Required Findings Under 21 CFR 50.54 and 45 CFR 46.407

The FDA PAC can determine that a clinical investigation in question satisfies the conditions of 21 CFR 50.51 (45 CFR 46.404), 21 CFR 50.52 (45 CFR 46.405), or 21 CFR 50.53 (45 CFR 46.406) as applicable, or that all of the following conditions are met:

- The clinical investigation (research) presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
- The clinical investigation (research) will be conducted in accordance with sound ethical principles; and
- Adequate provisions are made for obtaining the permission of the parents or guardians of their children and soliciting the assent of older children as set forth in 21 CFR 50.55 and 45 CFR 46.408.

The FDA PAC must determine that all three of these conditions are satisfied in order to recommend that a clinical investigation can proceed under 21 CFR 50.54 and 45 CFR 46.407.

Public trust: HHS plans and recommendations in the event of an anthrax emergency

Plans mandated, executed, or recommended by the USG must adhere to U.S. laws, rules, regulations, and established decision-making processes. To gain public trust in HHS plans and recommendations developed to strengthen public health measures against a biological attack using *B. anthracis* spores, it is critical that discussions about preparedness planning be conducted in as public a manner as possible, and be open to all relevant questions. Discussions that involve the public should include the risk-benefit deliberations that are central to the IRB process.

Under optimal circumstances, it can be difficult for any individual to decide whether to participate in clinical research. Asking parents to decide whether to allow their child(ren) to participate in research can be even more difficult. The process of gaining informed parental permission assumes that a parent or legal guardian has been given and has understood sufficient information about the potential risks and benefits to their child(ren) of participating in a clinical trial. (For further discussion about the informed permission process, see Appendix 12.)

As indicated above, an accepted balance of potential risks and benefits for pediatric research stipulates that if there is no direct benefit to the child, the risks must be extremely low (i.e., approvable under 21 CFR 50.53). Therefore, a key question considered by the AV WG is at what point can children be considered “at risk” for anthrax disease in the absence of an anthrax event. Could children be considered at risk

of exposure to *B. anthracis* spores by virtue of living in a city where an anthrax attack has occurred? If so, would the perception of risk need to be supported by data and some probability of a future event?

The case could be made that children are at risk of anthrax exposure now because the United States experienced an anthrax attack in 2001. Also, a proposal to conduct a pre-event research, safety and immunogenicity study of AVA in children might persuade an IRB that the benefits of a pre-event pediatric vaccine trial outweigh the risks. However, such an assessment would be better conducted in a transparent, public forum than in a closed IRB process, as required in 21 CFR 50.54 /45 CFR 46.407. An issue HHS could emphasize to parents and legal guardians is that no pediatric safety or immunogenicity data will be available for AVA before an attack, unless HHS conducts a pre-event trial of AVA safety and immunogenicity in children.

IV. INFRASTRUCTURE CONSIDERATIONS PRIOR TO AN ANTHRAX EMERGENCY

The infrastructure required for distributing AVA and antibiotics as PEP after a large-scale release of *B. anthracis* spores is necessarily complex. It would involve first-responders and federal, state, and local health officials; reliable and consistent communication among all entities; and an efficient system for distributing medical countermeasures (antibiotics and AVA). A large-scale response to an anthrax attack would be effective only if all personnel involved are appropriately trained, and provided with any equipment necessary to protect themselves.

Infrastructure issues for HHS consideration:

- Is the supply of antibiotics and AVA sufficient to meet potential demand during an anthrax attack?
- How can mass vaccination of adults and children deemed to be exposed to *B. anthracis* spores be accomplished efficiently and effectively? Mass vaccination would be more complicated and time-consuming than dispensing antibiotics, regardless of whether the vaccinations in children are performed with or without a research IND. Parents and the general public will have questions that need immediate, perhaps time-consuming, responses.

V. COMMUNICATION AND MESSAGING

An essential component of preparedness and response planning is the development of an effective system of communication, and clear, consistent, comprehensive messages that can be understood by everyone involved, including the public. The risks and consequences of an anthrax attack are sufficiently high to make communication and messaging a priority of the USG.

Participants at the July 7, 2011, AV WG stakeholder-engagement workshop voiced opinions that public perception of the risk of anthrax exposure is low, which allows the fear of vaccination to predominate for some. Many participants viewed the probability of an anthrax attack as low. However, most recognized the dangerous consequences that could result from exposure to *B. anthracis* spores, should an attack occur. These and related issues make it necessary for the USG, in partnership with state and local health officials and other stakeholders to develop information in advance of an anthrax emergency on the health risks associated with an anthrax attack, and plans to prepare for and responding to such an emergency.

Also at the July 2011 AV WG workshop, state and local public health officials said that a lack of emergency communication materials prepared in advance could make it difficult to administer AVA PEP to adults or children, should *B. anthracis* spores be released. The FDA and CDC are working to prepare, review, and approve information about the health risks of becoming infected with *B. anthracis*, and HHS should continue its efforts to prevent and mitigate those risks in advance of an anthrax attack.

A related issue that could compromise an effective response to an anthrax attack is the lack of resources and staff at state and local health departments to develop and disseminate information about the risks of anthrax exposure and vaccination rapidly to a large target audience. The administration of antibiotics and AVA PEP following the release of *B. anthracis* spores would occur over a period of months, thus making it possible for health officials to provide information at various time intervals.

The 2009-10 H1N1 pandemic demonstrated the importance of consistent messaging coordinated across all levels of government, and of multidirectional communication among public health officials. Information about the evolving pandemic was difficult to communicate clearly, which underscores the need for clear and consistent messaging, should an anthrax emergency occur. HHS may want to review lessons learned from the H1N1 pandemic and decide how best to apply them to the effort to develop communications about the administration of AVA to children advance of an anthrax emergency.

VI. NBSB RESPONSES TO THE FOUR QUESTIONS FROM THE ASPR

If a segment of the U.S. population is exposed to *B. anthracis* spores, HHS is prepared to follow the current ACIP recommendations for administering AVA PEP to all exposed or possibly exposed individuals, including adults who want the vaccine and children whose parents or legal guardians give permission. In this emergency situation, AVA PEP could be administered to millions of children at a dose and interval that has never been studied in this age group. The recommendation of the NBSB is that the best way to prepare for the use of AVA PEP in children during a public health emergency is to study the vaccine under a pre-event research IND designed to obtain data that could be used subsequently to guide the administration of AVA PEP by age group, if widespread use in children becomes necessary during an emergency.

In general, the primary objective of clinical trials in a pre-event setting is to conduct systematic, well-controlled studies that produce definitive information about the safety and efficacy of a medical product or device. The primary objective(s) of conducting a pre-event trial of AVA in children would be to determine a safe and immunogenic regimen of vaccination for children younger than 18 years of age.

1. What are the risks and benefits of attempting to perform an AVA vaccine safety and immunogenicity IND research in children pre-event versus after [as part of the response during] an event?

A. Pre-Event Evaluation of AVA PEP

A1. The *risk of administering AVA to children, in a sequential evaluation from oldest to youngest, under a research IND pre-event (when there is no imminent threat from exposure to *B. anthracis*).*

- (1) The risks of AVA in children are not known. However, the risks associated with vaccinating adults are well documented and described in the BioThrax prescribing information (see Appendix 10), the publications cited in Appendix 9, and the 2010 ACIP recommendations.⁴⁸
- (2) There is no known benefit to vaccinating children in the absence of an imminent threat from exposure to *B. anthracis* other than potential future benefit.
- (3) The occurrence of short-term adverse effects following vaccination, whether causally related or not, may affect future acceptance of the vaccine after an event has occurred.

⁴⁸Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

- (4) A local IRB likely would be precluded from approving a pre-event research IND to test AVA safety and immunogenicity in children. Rather, the protocol must be reviewed through a federal panel process established under 21 CFR 50.54 and 45 CFR 46.407.

A2. The *benefits* of administering AVA to children under a research IND *pre-event* (when there is no imminent threat from exposure to *B. anthracis*).

- (1) Children who have been immunized may be protected from anthrax infection and disease. However, the duration of protection is unknown.
- (2) In the event of a public health emergency, the U.S. pediatric population could then receive AVA PEP according to a regimen that has been demonstrated to be safe and immunogenic. The preferred route of administration could be established based on scientific evidence.
- (3) In the absence of an emergency involving exposure to *B. anthracis*, parents would have ample time to consider whether their children should participate as volunteers in a pre-event study of AVA PEP.
- (4) Conducting pre-event trials of AVA PEP, starting with older children first, is more likely to yield useful data than conducting these studies during a public health emergency. Pre-event studies would be conducted in a controlled setting to reduce the likelihood of errors that could result due to the haste or confusion that can be anticipated during an emergency.
- (5) Conducting pre-event trials of AVA PEP would allow the opportunity to perform dose-ranging studies, a standard approach to studying a product used for the first time in a new age group. Dose-ranging studies may produce information allowing for dose-sparing regimens.
- (6) The preferred route of administration (intramuscular [IM] or subcutaneous) of AVA PEP to children could be resolved.
- (7) A pre-event study may identify in advance potential common adverse events that may be magnified in scope in a mass-vaccination setting. However, rare adverse events are unlikely to become evident in small studies. Based on data gleaned from studies of administering AVA to adults, finding serious adverse events in children in a pre-event study is unlikely.
- (8) Information gathered from pre-event studies could be communicated to parents and may mitigate the hesitancy of some parents to accept AVA PEP for their children in a post-event setting.

- (9) The process of public discussion under 21 CFR 50.54 of the proposed pre-event research IND may enhance public trust in USG planning.

B. Post-Event Evaluation of AVA PEP in the Absence of Pre-Event Evaluation

B1. The risks of administering AVA PEP to children under a non-research IND⁴⁹ post-event (during the course of a public-health emergency response when there is an actual or imminent threat from exposure to *B. anthracis*).

- (1) If a segment of the U.S. population is exposed to *B. anthracis*, the risk to children of infection and death could be enormous. A general risk of vaccinating the pediatric population is incurred from not testing AVA PEP prior to such a public health emergency, by foregoing information that later could be found important to the design of the public-health response during an emergency.
- (2) In the absence of safety and immunogenicity data, AVA PEP would be administered to children, with parental permission under a non-research IND, following ACIP recommendations.⁵⁰
- (3) In the event of a public health emergency involving the release of anthrax spores, the response will include federal, state, and local government agencies; first-responders; healthcare providers; decision-makers involved in large-scale responses; adults, parents, and legal guardians; as well as many other segments of society. A response effort involving such diverse entities is likely to be complicated and rushed, and the implementation of a post-event research IND (i.e., collecting blood specimens and symptoms from children who already have received AVA PEP) would need to be merged into an already complex and difficult series of decisions and actions.
- (4) In addition to administering AVA, current ACIP recommendations include the use of antibiotics for 60 days as a component of PEP. The use of antibiotics may complicate the interpretation of data collected for determination of safety of the vaccine, as antibiotics may be a confounding variable. Specifically, it might not

⁴⁹ AVA will be administered under a non-research IND in the absence of data that would allow for the issuance of a pediatric EUA for administering AVA. A post-event research IND would not include the administration of AVA, but rather the evaluation of the child's response. Thus, any potential health risks of administering AVA to children are relevant only to the non-research IND, and not to the post-event research IND.

⁵⁰ Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

be possible to distinguish side effects or adverse effects of an antibiotic from those of AVA PEP.

B2. The *benefits* of administering AVA PEP to children under a non-research IND post-event (in the absence of a pre-event evaluation, and when there is an actual or imminent threat from exposure to *B. anthracis*).

If an anthrax emergency occurs, children would be offered AVA in conjunction with antibiotics as a part of the ACIP recommendations for anthrax PEP under a non-research IND. Parents and legal guardians who give permission to enroll their children in this non-research IND also can consider enrolling their children in a post-event research IND.

- (1) Some potential benefit to children enrolled in a post-event research IND⁵¹ may accrue from participating and receiving close monitoring for adverse events.
- (2) Any children who participate in a post-event study of AVA PEP might then know as a group whether the vaccine was immunogenic, and therefore have some expectation of being protected against *B. anthracis*. However, the duration of protection is unknown.
- (3) Rare events would more likely be identified in a post-event situation because of the large number of children who probably would be given the vaccine.
- (4) Parents are more likely to agree to their children being vaccinated when they perceive the risk of disease to be high.

Preparation for a national and potentially global threat from the use of *B. anthracis* spores by terrorists is a major priority for U.S. national security. The current absence of safety and immunogenicity data for using AVA PEP in children is a major challenge HHS will face during such an event. The Public Readiness and Emergency Preparedness (PREP) Act allows for medical compensation to recipients of countermeasures, should serious adverse events occur in children who receive AVA.⁵² (See Appendix 13 for details).

⁵¹ The research IND absent administration of AVA, can be approved under 21 CFR 50.53 without any prospect of direct benefit given the extremely low risk of the blood draws and symptom reporting.

⁵² (1) Anthrax countermeasures are currently covered by a PREP Act declaration. Available at: edocket.access.gpo.gov/2008/E8-23547.htm. (2) HRSA's Countermeasures Injury Compensation Program (CICP) provides compensation to individuals for certain injuries incurred from administration of countermeasures covered by PREP Act declarations at www.hrsa.gov/gethealthcare/conditions/countermeasurescomp. (3) General information about the PREP Act is available at publichealthemergency.hhs.gov/Preparedness/legal/prepact/Pages/prepqa.aspx.

2. What are the challenges for administering this vaccine under an [non-research] Investigational New Drug (IND) after an event and how do these challenges compare with ethical considerations for attempting to gather sufficient data to permit use under an Emergency Use Authorization (EUA)?

The challenges of conducting a definitive study post-event or during an event are summarized in the responses to question 1. The challenges of implementing the ACIP recommendations (through the non-research IND) paired with implementing a research IND might be reduced by preparing public health officials and the public about the plan in advance of an emergency. Table C (next page) provides a simplified comparison of the post-event non-research IND and the post-event research IND. After an emergency has occurred, however, parents and legal guardians who opt to provide AVA PEP to their children will require detailed information that clearly describes the risks and benefits of the non-research IND and the research IND. A small number (approximately a hundred) of these parents will be asked whether their child(ren) can participate in the post-event research study, and provided answers to their questions on site. It also may be necessary to provide multiple avenues of communication, that parents may use to obtain answers to any questions they might have.

Table C. Comparison of Processes for Conducting the Post-event Non-research IND to the Post-event Research IND

| Processes for Conducting Post-event INDs of AVA PEP in Children | Post-event Non-Research IND | Post-event Research IND |
|---|--|---|
| Information provided to parents and questions answered | Yes | Yes |
| Acceptance of AVA PEP | Voluntary | Voluntary |
| Documentation of informed permission collected from parents and guardians -Agreeing to vaccine administration -Agreeing to blood sampling and symptom data collection | Yes No | No* Yes |
| Research-oriented data gathering | No | Yes |
| Immunogenicity assessment: Blood sampling to measure antibody response | No | Yes |
| Safety assessment | Assessment via spontaneous reports from healthcare providers and others (e.g. VAERS) | Active solicitation of adverse events via reports and other means |
| Opportunity for assessing various dosing regimens or routes of administration | No | No |

*Only parents of children who have already received AVA under the non-research IND would be approached to enroll their child(ren) in the post-event research IND. The team for the research IND would approach a small subset of parents whose children received AVA PEP under the non-research IND.

Other challenges include, but are not limited to, logistical concerns, communications, and operational issues for administering a vaccine under a non-research IND protocol during an emergency event. How would public health officials communicate to parents and legal guardians what they are doing and why, in a short period of time and during a crisis? How would public health officials explain to parents that, by enrolling their child(ren) in a research study, the information gained about the safety and immunogenicity of AVA PEP could provide critical information for guidance on the future use of the vaccine?

The data collected under a pre-event research IND protocol would be most valuable for determining its safety and immunogenicity in children, but also could be considered by FDA as support for issuing an EUA to allow the administration of AVA PEP to children during a public health emergency. If the FDA were to allow the administration of AVA PEP to children under an EUA, rather than a non-research IND protocol, it would mean that all populations (pediatric and adult) could receive the vaccine under the same regulatory mechanism, which could expedite countermeasure delivery in a crisis.

3. What pre-planning should the U.S. government have in place to optimally perform an *investigational protocol post-attack*?

In the event that anthrax spores are released in the United States, the current HHS plan is to ensure that AVA PEP, in combination with antibiotics, is made available to all at-risk children and adults. As indicated above, it would be necessary to administer AVA PEP under a non-research IND protocol to individuals younger than 18 years of age. Individuals 18 years and older would receive the vaccine under an EUA. Table D entitled "Estimated Time Required to Administer AVA Under an EUA versus an IND," appears in Appendix 14. The table compares selected activities in offering injectable medical countermeasures (MCM) under an EUA versus a non-research IND, and indicates the time required to administer the vaccine is approximately the same.

HHS may want to develop information for public release to explain the following:

During a public health emergency that involves the release of *B. anthracis*, a critical challenge will be to convey to the American public the current reasoning behind the HHS plan for administering AVA PEP to children. Before AVA can be administered to children, parents will need to be informed that this vaccine has not been tested for its safety or immunogenicity in children (if true at that point), and understand the risks and benefits the vaccine could provide. The message needs to include information about the risks of becoming infected with *B. anthracis*, and the risk of disease and of death. Parents will need to know that there is no way to accurately determine who has and who has not been exposed to *B. anthracis*. This puts parents in the position of needing to decide whether AVA PEP should be administered to children without knowing the definitive risk of infection their children might face.

Any printed, visual, or audio media intended for public communication will need to be reviewed, as is customary, by appropriate USG departments and agencies, emergency responders, state and local health officials, and the public using are established clearance systems in place for publically released documents. Messaging in multiple languages and formats will be needed. These messages should be field-tested for comprehensiveness and clarity, before the emergency occurs.

HHS needs to have in place a pre-approved, post-event non-research IND and research IND:

The primary goal of the post-event research IND is to generate data about the safety and immunogenicity of AVA in children. A secondary goal is to generate data that could be used to support the use of AVA PEP under an EUA. The data gathered in this post-event, research IND might also be used to adjust the dosage regimen or other aspects of

treatment of using AVA PEP at a later time following the same event. This research IND is under development by CDC.

Both protocols, for the non-research IND and the research IND, need to be approved by the FDA and appropriate IRB(s). The non-research IND for administering AVA PEP to all children whose parents provide permission would be part of the emergency response. The research IND would be in conjunction with the emergency response, and would be offered to a subset of the pediatric population receiving vaccine under the non-research IND. Both protocols should be disseminated to all appropriate federal and state public health authorities before an anthrax emergency occurs to allow integration into national, state, and local preparedness planning. Those parents who agree for their children to provide blood specimens and symptom information during a post-event scenario would have signed up for both the non-research IND to gain access to the vaccine, and the research IND to agree to the blood sampling and symptom recording.

Although the use of antibiotics is not part of the initial AVA PEP research IND for children or the EUA (for adults), it is important to develop a plan for monitoring antibiotic and vaccine administration and follow-up for adverse events. The HHS plan for administering antibiotics also should be clearly understood and processes defined by all public health authorities.

| |
|--|
| <p>4. How should the U.S. government communicate these issues with parents, pediatricians, public health officials and political officials before and in response to an anthrax attack?</p> |
|--|

Informing the public should be an ongoing activity to ensure that individuals have sufficient information on which to base decisions, especially during stressful times. The mission of HHS is to protect the public health, including that of children, who represent nearly 25 percent of the U.S. population. HHS plans for mitigating an anthrax attack need to be shared with local and state health officials, other public health authorities, parents, the general public, and all healthcare institutions and providers.

Over the years, CDC has been a critical USG resource for developing communications about the risks and benefits associated with health issues, and for engaging the public and health professionals. The White House Office of Public Engagement is also an important emergency response communicator with the public and relevant stakeholders. At the state level, various Departments of Public Health routinely disseminate information about urgent health issues. HHS should leverage these assets to create information materials that can be utilized by states, the public, and all forms of the media. HHS regulations and policies reflect the position that children are unique and that discussions, interventions, or

recommendations that involve children must engage parents and pediatricians as well as other subject-matter experts.

VII. OPTIONS CONSIDERED BY THE NBSB

OPTION 1 - Conduct a pre-event research IND: HHS should develop and implement a pre-event, research IND to test the safety and immunogenicity of AVA in the pediatric population. The protocol would be designed to evaluate AVA PEP in sequential studies beginning with the oldest pediatric group first and, based on the outcome, to test the vaccine in younger age groups. (A data safety and monitoring board would be asked to review the data before proceeding to enroll the next younger age group.) The full protocol should outline the data points that need to be collected and why, i.e., to include clear goals, the number of participants needed to ensure the data are statistically reliable, information for parents about AVA PEP and the design of the study, parental permission documents, and recruiting documents. These materials would be submitted to one or more IRBs, and must undergo the public review as required in 21 CFR 50.54 /45 CFR 46.407.⁵³

The results of this pre-event, research IND should yield important information about the safety and immunogenicity of age-appropriate doses of AVA PEP in children, and also eventually could be considered by the FDA as support for making AVA PEP available to children under an EUA, rather than a non-research IND. If the FDA were to allow the administration of AVA PEP to children under an EUA, it would mean that all populations (pediatric and adult) could receive the vaccine under the same regulatory mechanism, which could expedite countermeasure delivery in a crisis.

OPTION 2 - Do not conduct a pre-event study. Instead, conduct a post-event research IND: In the event of a public health emergency involving the release of *B. anthracis* bacteria or spores, the HHS plan is to follow current ACIP recommendations to administer AVA PEP and antibiotics to children, with parental permission, under a post-event, non-research IND. In addition to this post-event, non-research IND, HHS also could offer a small number of children, with parental permission, the opportunity to participate in a research IND to gather some safety and immunogenicity data about AVA PEP (by means of blood sampling and symptom records). Data from this post-event study would likely not be of the same quality as data gleaned from a pre-event study, but may be sufficient to meet the FDA criteria to move from an IND to an EUA by gathering

⁵³ FDA guidance on this process is available at www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf, and OHRP guidance is available at www.hhs.gov/ohrp/policy/populations/guidance_407process.html. These guidance and processes for implementing them are harmonized and implemented cooperatively if the research is regulated by FDA and funded or conducted by HHS (which is the case for the pre-event research IND).

data about the safety and immunogenicity of AVA PEP, adverse events, and possibly, to adjust the dosage. This research IND also is under development.

VIII. NBSB RECOMMENDATION

The NBSB recommends Option 1, in light of the current HHS plan to follow the ACIP recommendations for the use of AVA for PEP following exposure to *B. anthracis* spores:

The issue should be referred to an appropriate review board to formally address the ethical considerations. This board should include ethicists and public representation. If the ethical considerations are adequately addressed, HHS should develop a plan for and conduct a pre-event study of AVA in children, to include a research IND. HHS should submit the study protocol to one or more IRBs, and comply with the 21 CFR 50.54 / 45 CFR 46.407 federal review process.

This recommendation should be revisited if new anthrax vaccines or other therapeutic countermeasures become available.⁵⁴

IX. RATIONALE

The AV WG and the NBSB deliberated at length how best to protect children during a public health emergency that involves the release of *B. anthracis*, given the absence of data about the safety or immunogenicity of AVA PEP in individuals younger than 18 years of age. The Board's recommendation is intended to balance the complex array of scientific, medical, ethical, legal, regulatory, and administrative issues that complicate the use of AVA PEP in the pediatric population.

Before conducting clinical research among children, it is necessary to address the ethical concern that children are unable to give informed consent on their own behalf. When it becomes necessary to conduct clinical research in children to evaluate the safety and efficacy of medical products or devices, USG statutes and regulations dictate how the

⁵⁴ The HHS Biomedical Advanced Research and Development Authority (BARDA) announced September 15, 2011, new contracts to support, "the advanced development of a novel next-generation anthrax vaccine and a new type of anthrax antitoxin" (excerpted from the press release www.hhs.gov/news September 15, 2011). The objectives of the new contracts are to develop a vaccine that "could be administered as a spray in the nose and given by non-medical personnel, making administration easier and potentially increasing the number of people [per hour] who could be vaccinated against this potentially fatal infection. Similarly, the new anthrax antitoxin medication could be administered by conventional injection, making the medication much easier and faster to administer than current anthrax antitoxins, which must be administered intravenously. This would greatly facilitate antitoxin administration in an emergency." Even so, these hypothetical new products would eventually face the same issues confronted with AVA in this report: when and how to test them among children.

research must be conducted. The recommendation by the ACIP, that AVA may be used in children during or following an anthrax emergency, highlights the need to obtain crucial safety and immunogenicity data about the use of this vaccine in individuals younger than 18 years of age. Indeed, the ACIP call for research into pediatric dosing presages this Board's recommendation. The pre-event clinical trial would be designed to reduce risks to study participants, while producing information intended to guide the appropriate use of AVA in a post-event scenario.

If a pre-event study of AVA PEP were performed, and sufficient safety and immunogenicity data were collected sufficient to support an EUA, a post-event evaluation of AVA PEP (as described above under a research IND) may not be necessary. However, administering a vaccine for the first time to large numbers of children younger than 18 years of age poses an unknown risk in the midst of the public-health response to a wide-scale anthrax attack. The Board accepts the USG threat analysis and recognizes that the dissemination of *B. anthracis* spores is a threat to the U.S. population, including its large proportion of children. It is therefore important to obtain safety and immunogenicity data before an anthrax event occurs.

The AV WG and the NBSB debated how best to obtain scientifically valid safety and immunogenicity data about AVA PEP for children. In its deliberations, the Board:

- (1) Considered the processes and value of a pre-event study of AVA in children;
- (2) Took into account concerns about the use of children as subjects of research;
- (3) Weighed the possibility of not being able to complete a pre-event study; and
- (4) Concluded that it would be in the best interests of children, their parents, and the USG to attempt to gather the safety and immunogenicity data about AVA PEP in children prior to an anthrax event, rather than to wait for a future crisis to attempt to gather that information.

X. APPENDICES

Appendix 1. Roster of the National Biodefense Science Board

Voting Members

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Appendix 2. Advisory Committee on Immunization Practices (ACIP)

The ACIP was established in 1964 by the U.S. Surgeon General. The Committee provides advice and guidance to the HHS Secretary, Assistant Secretary for Health, and the Director of the CDC regarding: (1) the control of diseases for which a vaccine is licensed in the United States; (2) the most appropriate use of vaccines; and (3) population groups and/or circumstances in which a vaccine is recommended.

The ACIP has 15 voting members, including a chairperson, all of whom are non-government employees. There is one consumer representative, and all members are screened for any conflicts of interest. There are eight non-voting ex-officio members who represent other government agencies involved in immunization activities. (There are 30 non-voting liaison organizations comprising representatives of professional societies and organizations responsible for vaccine development and immunization programs). The ACIP uses working groups to review scientific data and give special reports regarding specific vaccine issues.

The ACIP uses the following information to make its recommendations: disease epidemiology; vaccine immune response, efficacy, effectiveness and safety; feasibility of program implementation; economic aspects of immunization; and public comments solicited at each ACIP meeting.

The ACIP has issued recommendations on anthrax vaccination (including PEP) for adults, AVA use in children, and PEP for children, and has issued a statement concerning the need for more research on AVA. These recommendations and related information have been published in MMWR, 2010.⁵⁵

⁵⁵ Advisory Committee on Immunization Practices. Use of Anthrax Vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR 2010;59(RR-6):1-30. Available at: www.cdc.gov/mmwr/PDF/rr/rr5906.pdf.

Appendix 3. Letter from HHS Assistant Secretary for Preparedness and Response Dr. Nicole Lurie to NBSB Chair: Charge to the Board



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Assistant Secretary for
Preparedness & Response
Washington, D.C. 20201

APR 27 2011

Patricia Quinlisk, M.D., M.P.H.
Chair, National Biodefense Science Board
State Epidemiologist and Medical Director
Iowa Department of Public Health
321 East 12th Street
Lucas State Office Building
Des Moines, IA 50319-0075

Dear Dr. Quinlisk and Members of the National Biodefense Science Board (NBSB):

The U.S. Government (USG) has stockpiled Anthrax Vaccine Adsorbed (AVA) to provide post-exposure prophylaxis (PEP) for at-risk populations following an anthrax attack. National-level exercises regarding government response following an anthrax attack conducted over the years, and most recently the Dark Zephyr Senior Officials exercise, have highlighted the continuing policy and response challenges we face in addressing the potential for vaccine prophylaxis of special populations, such as children. We have no safety, immunogenicity, or efficacy data in pediatric populations that would permit the U.S. Food and Drug Administration to evaluate the product for use under an Emergency Use Authorization (EUA). This signifies that any policy decision to use AVA as a public health measure after an attack would require some form of investigational protocol in pediatric populations while adults would receive the vaccine under less stringent EUA status. This scenario presents an array of logistical, clinical, and communication challenges. While on the surface it would appear that a simple solution is to gather the safety and immunogenicity data in pediatric populations in advance of urgent need, there are legitimate countervailing concerns regarding subjecting children to risk with no clear benefit at the time of the study.

The NBSB has the expertise, experience, and demonstrated ability to deliberate on difficult issues such as these. Therefore, I would like the Board to consider particular issues around the use of AVA, primarily in pediatric populations, but also considering other special populations who would not otherwise be covered under an EUA, or under current product approved uses. I would like the Board to address the following questions and ultimately to provide a recommendation on best course of action to prepare for a potential use of AVA vaccine in a pediatric population:

1. What are the risks and benefits of attempting to perform an AVA vaccine safety and immunogenicity IND research protocol study in children pre-event vs. after an event?
2. What are the challenges for administering this vaccine under an Investigational New Drug (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 Emergency Use Authorization.

3. What pre-planning should the U.S. government have in place to optimally perform an investigational protocol post-attack
4. How should the U.S. Government communicate these issues with parents, pediatricians, public health officials and political officials before and in response to an anthrax attack?

In performing your deliberations, I encourage the Board to obtain Stakeholder views on these issues using whatever means is deemed most appropriate. I look forward to learning of your recommendations at the next NBSB public meeting on September 22 – 23, 2011. Thank you for your diligence in ensuring the public health preparedness of our nation.

Sincerely,

Nicole Lurie, MD, MSPH
Assistant Secretary for Preparedness and Response

Appendix 4. Roster of the NBSB Anthrax Vaccine Working Group

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Appendix 5. Agenda, “Vaccine to Protect Children from Anthrax,” Public Engagement Workshop, July 7, 2011, Washington, DC



**Vaccine to Protect Children from Anthrax
Public Engagement Workshop
Hosted by the Anthrax Vaccine Working Group
National Biodefense Science Board**

Agenda

July 7, 2011

In-Person Attendance:

Washington Plaza Hotel
10 Thomas Circle Northwest
Washington, DC

Teleconference Number:

Listen ONLY

Toll-Free Dial-In Number: 866-395-4129
International Dial-In Number: 706 -758-9284
Conference Passcode: ASPR

9:00 am – 9:10 am

Welcome

*Nicole Lurie, M.D., M.S.P.H.
Assistant Secretary for Preparedness and Response
Rear Admiral, U.S. Public Health Service
U.S. Department of Health and Human Services*

9:10 am – 9:15 am

Introductions

*Leigh Sawyer, D.V.M., M.P.H.
Executive Director, National Biodefense Science Board
CAPT, U.S. Public Health Service
U.S. Department of Health and Human Services*

Overview of Agenda and Goals of Workshop

*Daniel Fagbuyi, M.D., FAAP
Voting Member, National Biodefense Science Board
Chair, Anthrax Vaccine Working Group*

*John S. Parker, M.D., Major General (Retired)
Voting Member, National Biodefense Science Board
Co-Chair, Anthrax Vaccine Working Group*

- 9:15 am – 9:30 am Anthrax Scenario**
William (Mike) Moore, M.E.P.
Office of Preparedness and Emergency Operations
Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services
- 9:30 am – 9:40 am Discussion 10 minutes**
- 9:40 am – 9:55 am May 2011 White Powder Incident in DC Public Schools**
Beverly Pritchett, FACHE, Colonel (Retired)
Senior Deputy Director
Health Emergency Preparedness and Response Administration
DC Department of Health
- 9:55 am – 10:05 am Discussion 10 minutes**
- 10:05 am – 10:20 am Anthrax Vaccine Adsorbed (AVA) BioThrax**
Cynthia L. Kelley, M.S.
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
- 10:20 am – 10:30 am Discussion 10 minutes**
- 10:30 am – 10:45 am BREAK**
- 10:45 am – 11:00 am Current US Government Posture on Anthrax Therapies**
Nancy Messonnier, M.D.
CAPT, U.S. Public Health Service
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services
- 11:00 am – 11:10 am Anthrax Vaccine Adsorbed: An Overview of Safety Studies**
Theodore J. Cieslak, M.D., FAAP, FIDSA
Colonel, MC, FS
Chief Consultant to the Surgeon General
U.S. Department of Defense
- 11:10 am - 11:20 am Discussion 10 minutes**
- 11:20 am – 11:40 am Public Comment**
- 11:40 am – 12:40 pm LUNCH (1 hour)**
- 12:40pm – 4:05 pm Multiple Facilitated Discussions**
- 4:05 pm – 4:20 pm Public Comment**
- 4:20 pm – 4:30 pm Appreciate and Adjourn**

Appendix 6. List of Attendees “Vaccine to Protect Children from Anthrax,” Public Engagement Workshop, July 7, 2011, Washington, DC Hosted by the Anthrax Vaccine Working Group*

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**Appendix 7. Agenda, “Medical Countermeasures for Children: Anthrax Vaccine,”
Invitation-Only Workshop, July 8, 2011, Washington, DC**



**Medical Countermeasures for Children - Anthrax Vaccine
Invitation Only Workshop
Hosted by the Anthrax Vaccine Working Group
National Biodefense Science Board**

Agenda

July 8, 2011

In-Person Attendance:

Washington Plaza Hotel

10 Thomas Circle Northwest

Washington, DC

9:00 am – 9:05 am **Welcome and Introductions**
Leigh Sawyer, D.V.M., M.P.H.
Executive Director, National Biodefense Science Board
CAPT, U.S. Public Health Service
U.S. Department of Health and Human Services

9:05 am – 9:25 am **Overview of Workshop Agenda and Goals**
Recap of July 7 Workshop and Recurrent Themes/Questions
Daniel Fagbuyi, M.D., FAAP
Voting Member, National Biodefense Science Board
Chair, Anthrax Vaccine Working Group

John S. Parker, M.D., Major General (Retired)
Voting Member, National Biodefense Science Board
Co-Chair, Anthrax Vaccine Working Group

| |
|---|
| 9:25 am – 2:15 pm PRESENTATIONS AND DISCUSSIONS |
|---|

15 min presentation followed by up-to 15 min discussion each

9:25 am – 9:55 am **Dark Zephyr Exercise**
William (Mike) Moore, M.E.P.
Office of Preparedness and Emergency Operations
Office of the Assistant Secretary for Preparedness and Response
U.S. Department of Health and Human Services

- 9:55 am – 10:25 am** **Current U.S. Government Posture on Anthrax Therapies**
Nancy Messonnier, M.D.
CAPT, U.S. Public Health Service
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
U.S. Department of Health and Human Services
- 10:25 am – 10:35 am** **Anthrax Vaccine Adsorbed: An Overview of Safety Studies**
Theodore J. Cieslak, M.D., FAAP, FIDSA
Colonel, MC, FS
Health Policy and Services
Chief Consultant to the Surgeon General
U.S. Department of Defense
- BREAK (10 minutes)**
- 10:45 am – 11:15 am** **Emergency Use of AVA (BioThrax)**
Cynthia L. Kelley, M.S.
Center for Biologics Evaluation and Research
Food and Drug Administration
U.S. Department of Health and Human Services
- 11: 15 am - 11:45 am** **Considerations of Pediatric Vulnerabilities**
Steven Krug, M.D., FAAP
Children’s Memorial Hospital
Chairperson, Disaster Preparedness Advisory Council
American Academy of Pediatrics
- 11:45 am – 12:45 pm** **LUNCH (1 hour)**
- 12:45 pm – 1:15 pm** **Ethical Framework and Regulatory Issues**
Robert “Skip” Nelson, M.D., Ph.D.
Office of Pediatric Therapeutics
Office of the Commissioner
Food and Drug Administration
U.S. Department of Health and Human Services
- 1:15 pm – 1:45 pm** **Safety/Efficacy of AVA in Children**
Possible Post-Event Protocols
Nicki Pesik, M.D.
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- Nancy Messonnier, M.D.*
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1:45 pm – 2:15 pm **Safety/Efficacy of AVA in Children**
Possible Pre-Event Protocols
Preparing for an EUA
Richard L. Gorman, M.D.
National Institute of Allergy and Infectious Diseases
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BREAK (15 minutes)

| |
|---|
| 2:30 pm – 4:30 pm FOCUSED DISCUSSIONS |
|---|

Questions for the July 8 Workshop

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| |
|--|
| 4:30 pm – 5:00 pm NEXT STEPS/WRAP-UP |
|--|

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Appendix 8. List of Attendees “Medical Countermeasures for Children – Anthrax Vaccine,” Invitation-Only Workshop, July 8, 2011, Washington, DC. Hosted by the Anthrax Vaccine Working Group*

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Appendix 9. Safety Studies of AVA in Adults

An extensive set of human safety studies involving anthrax vaccination of adults has been published. These studies involved cohort studies of acute symptoms (references 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11), hospitalizations (12, 13, 14, 15), disability evaluations (16, 17), periodic physical-examination and clinical-laboratory parameters (18), and reproductive outcomes (19, 20, 21, 22), as well as primary and secondary review of spontaneous reports to the Vaccine Adverse Event Reporting System (VAERS) (23, 24, 25). Several of the cohort studies span multiple years after immunization (multiple decades, in some cases) (8, 9, 12, 13, 14, 15, 16, 18, 20, 26, 27, 28, 29). Multiple studies employed active surveillance, defined as data collected at fixed time points without relying on a recipient to take special effort to report a symptom or condition (1, 4, 8, 9, 10, 29, 30). Other studies featured systematic surveillance, that is, data collected automatically and electronically, without any reporting action required by a clinician or a vaccine recipient (6, 11, 12, 13, 14, 15, 16, 18, 20, 21).

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BIOTHRAX safely and effectively. See full prescribing information for BIOTHRAX.

**BIOTHRAX (Anthrax Vaccine Adsorbed)
Suspension for Intramuscular Injection Initial
U.S. Approval: 1970**

-----**RECENT MAJOR CHANGES**-----

- Indications and Usage (1) December 2008
- Dosage and Administration (2.1, 2.2) December 2008

-----**INDICATIONS AND USAGE**-----

BioThrax is a vaccine indicated for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in persons between 18 and 65 years of age at high risk of exposure. Since the risk of anthrax infection in the general population is low, routine immunization is not recommended. The safety and efficacy of BioThrax in a post-exposure setting have not been established.

-----**DOSAGE AND ADMINISTRATION**-----

- Immunization consists of a series of five 0.5 mL intramuscular doses. Administer 1 dose at 0 and 4 weeks and 6, 12, and 18 months.
- Individuals are not considered protected until they have completed the full vaccination series.
- Subsequent booster injections of 0.5 mL of BioThrax at one-year intervals are recommended for those who remain at risk. (2.2)

-----**DOSAGE FORMS AND STRENGTHS**-----

- Suspension for injection in 5.0 mL multidose vials containing 10 doses each. (3,11)

-----**CONTRAINDICATIONS**-----

- Severe allergic reaction (e.g. anaphylaxis) after a previous dose of BioThrax. (4)

-----**WARNINGS AND PRECAUTIONS**-----

- Administer with caution to patients with a possible history of latex sensitivity because the vial stopper contains dry natural rubber and may cause allergic reactions. (5.1)
- Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus. (8.1)

-----**ADVERSE REACTIONS**----- The

most common ($\geq 10\%$) local (injection-site) adverse reactions observed in clinical studies were tenderness, pain, erythema and arm motion limitation. The most common ($\geq 5\%$) systemic adverse reactions were muscle aches, fatigue and headache. (6)

Serious allergic reactions, including anaphylactic shock, have been observed during post-marketing surveillance in individuals receiving BioThrax.

To report SUSPECTED ADVERSE REACTIONS, contact Emergent BioSolutions at 1-877-246-8472 or VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

-----**DRUG INTERACTIONS**-----

- Immunosuppressive therapies may diminish the immune response to BioThrax. (7.2)

-----**USE IN SPECIFIC POPULATIONS**-----

- Safety and effectiveness of BioThrax have not been established in pregnant women or nursing mothers, or in pediatric or geriatric populations. (5, 8.1, 8.3, 8.4, 8.5)

See Section 17 For PATIENT COUNSELING INFORMATION.

Revised: December 2008

FULL PRESCRIBING INFORMATION CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

⁵⁵ Emergent BioSolutions, Lansing, MI, www.biobrax.com. Only the first page of 16 of the package insert has been provided here. For full package insert information, see: www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/UCM074923.pdf

Appendix 11. Mechanisms that Could Be Used to Obtain IRB Approval for Administering AVA to Children

Based on U.S. regulations, policies, and guidance documents, there are three options for assuring prompt IRB review of an IND, should an anthrax attack occur. The first two options apply to any IND; the third option applies to the non-research IND for administering AVA to children.

- (1) **Local IRBs could refer to the recommendation of a “facilitated” or “central” IRB.** For this option to be available, the organization responsible for the IND in question would designate the formation of a facilitated or central IRB, which would review the IND and issue a recommendation. A local institution (hospital, clinic, etc.) could then refer to the recommendation of the facilitated or central IRB, and accept that recommendation in full, or choose to modify it to accommodate local needs. There would be no need for the institution's own IRB to review the IND separately. In this model, one or more local IRBs are able to perform an expedited review of the IND by relying on the full review of the central IRB. For HHS-funded or HHS-conducted research, each institution hosting a local IRB must have an assurance (i.e., federal government-wide assurance [FWA]) that designates a central IRB. Institutions engaged in “event-related” research (e.g., an anthrax emergency) could rely on a designated IRB (possibly the HHS NIH Public Health Emergency Research Review Board [PHERRB]⁵⁷) through this assurance mechanism. These assurances can and should be arranged ahead of time, or quickly established at the time of the event.

- (2) **The USG could designate emergency response teams to conduct a post-event research IND.** Another option is for the USG to deploy designated emergency response team(s) in such a way that local institutions are not engaged in research. Utilizing this option means the approval of local IRBs may not be necessary. Guidance on how to implement this option is available at www.hhs.gov/ohrp/policy/engage08.html, with the relevant passage cited below.

Office for Human Research Protections (OHRP) guidance states that:

“Institutions (including private practices) not selected as a research site whose employees or agents provide clinical trial-related medical services that are dictated by the protocol and would typically be performed as part of routine

⁵⁷ For further information on the PHERRB, see page 33, Appendix 5 of the report from the National Biodefense Science Board. Call to Action: Include Scientific Investigations as an Integral Component of Disaster Planning and Response. Washington, DC: U.S. Department of Health and Human Services, April 2011. Available at: www.phe.gov/Preparedness/legal/boards/nbsb/Documents/nbsbrec14.pdf.

clinical monitoring and/or follow-up of subjects enrolled at a study site by clinical trial investigators (e.g., medical history, physical examination, assessment of adverse events, blood test, chest X-ray, or CT scan) provided that all of the following conditions also are met: a) the institution's employees or agents do not administer the study interventions being tested or evaluated under the protocol; b) the clinical trial-related medical services are typically provided by the institution for clinical purposes; c) the institution's employees or agents do not enroll subjects or obtain the informed consent of any subject for participation in the research; and d) when appropriate, investigators from an institution engaged in the research retain responsibility for: overseeing protocol-related activities; and ensuring appropriate arrangements are made for reporting protocol-related data to investigators at an engaged institution, including the reporting of safety monitoring data and adverse events as required under the IRB-approved protocol.”

In other words, if the AVA vaccine is administered, for example, by representatives from CDC or other public health personnel, and not by clinicians employed by the hospital or clinic at which the AVA is being administered, the approval of the IRB at that local site may not be necessary. Local IRB approval is required of institutions if their employees (or agents) are engaged in the research. The provision of supportive clinical services, including screening of individuals seeking the vaccine, may not qualify as being engaged in the research. It may also be possible for the personnel administering the vaccine to be considered public health employees during an event, rather than employees of the local institution.

- (3) **FDA regulations allow the immediate administration of AVA PEP to children under the non-research IND, while local IRBs consider the research IND.** A third option for obtaining IRB approval pertains to the post-event non-research IND, which does not qualify as research under HHS regulations (45 CFR 46.102(d)), because it would not involve any systematic data collection. By utilizing this option, the approval of a single, central IRB under FDA regulations may be sufficient to initiate administering AVA PEP to children while obtaining local IRB approval to conduct the research IND, as follows:

HHS regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge” (45 CFR 46.102(d)). FDA regulations define a clinical investigation as “any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an

experiment is any use of a drug except for the use of a marketed drug in the course of medical practice” (21 CFR 312.3b). Thus, administration of AVA under an IND where the only data to be collected is through public health surveillance mechanisms (i.e., under the non-research IND) may qualify as a “clinical investigation” under FDA regulations (and thus require the approval of one IRB), but may not qualify as research under HHS regulations (and thus not require the approval of local or institutional IRBs). (The term “non-research IND” is used in this report because the CDC IRB has made the determination to use the term to describe the administration of AVA PEP to children following the release of *B. anthracis* spores.)

OHRP has noted that there is a precedent for utilizing option three (should an anthrax emergency occur), because a similar decision was made during the SARS outbreak, when the use of an in vitro diagnostic device under an investigational device exemption (IDE)⁵⁸ was determined by OHRP to not be research under HHS regulations. Thus, the large- scale administration of AVA under a non-research IND could begin while IRB approval was obtained for collecting blood specimens and symptom data under the research IND (which would be classified as research under HHS regulations). Local health officials would need to understand the reasoning behind this approach, which may require an “official” public determination by OHRP.

⁵⁸ An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA. Available at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/default.htm.

Appendix 12. Considerations About the Parental Permission Process for Administering AVA to Children

The parental permission process serves as the “informed consent process” for children (who, as minors, cannot provide informed consent for themselves). It assumes that a parent or legal guardian has been given sufficient information about the risks and benefits of their child's participation in a clinical trial, and adequate time to consider the information before being asked to make an informed decision. The parental permission process also assumes that the circumstances are such that the parent's decision is voluntary. Parental permission must be documented in writing.

- (1) **Content and process of obtaining parental permission for children to receive AVA.** The information about AVA that would be provided to parents, who (as adults) could receive AVA under an EUA, would be identical to the information provided to parents whose children would receive AVA under a research IND or a non-research IND. The parental signature is required for a child to participate in the non-research IND and research IND.
- (2) **Anticipated difficulty in obtaining parental permission before or during an anthrax emergency.** Under any circumstances, it would be difficult for some parents to consent to the administration of AVA to their children. Currently, no data are available to assure parents that AVA would be safe or immunogenic. However, parental permission would be equally informed and voluntary if AVA were administered before or after an anthrax attack, or under a research IND or a non-research IND. Requesting and obtaining parental permission in the setting of an anthrax event would be similar to the informed consent obtained from adults seeking vaccination. In fact, because antibiotics would be administered first as PEP, should an anthrax emergency occur, parents could delay their decision whether or not to allow their children to receive AVA PEP, which would allow time for additional consideration.
- (3) **How parental permission could be obtained during an anthrax emergency.** On the assumption that individuals (including parents) seeking immunization would be standing in lines while waiting for PEP, this time could be used to provide information about AVA. The information (in multiple languages) could be provided in written form, or displayed in video format on television monitors in the waiting area. Ideally, when a parent gets to the head of the line, he or she could simply be asked whether they have any questions, and then sign a permission form for their child to receive AVA.

Appendix 13. Public Readiness and Emergency Preparedness (PREP) Act

The PREP Act is an important vehicle in that it lays out the immunity from liability of the USG and others and it authorizes compensation for eligible individuals who sustain serious injuries as the direct result of the administration or use of a medical countermeasure. The PREP Act authorizes the Secretary of HHS to issue a declaration (a “PREP Act declaration”) that provides immunity from tort liability (except for willful misconduct) for claims of loss relating to administration or use of countermeasures to diseases, threats and conditions determined by the Secretary to constitute a present, or credible risk of a future public health emergency to entities and individuals involved in the development, manufacture, testing, distribution, administration, and use of such countermeasures. [Public Law (PL) 109-148, Dec 30, 2005, available at www.hrsa.gov/gethealthcare/conditions/countermeasurescomp/covered_countermeasures_and_prep_act.pdf. Public Health Service (PHS) Act Section 319F-3; Section 319F-4, 42 U.S.C. §247d-6d, §247d-6e. See also Support Anti-terrorism by Fostering Effective Technologies [SAFE-T] Act, within the Homeland Security Act of 2002, PL 107-296.]

A PREP Act declaration provides immunity from tort liability, and is different from, and not dependent on, other emergency declarations. The PREP Act also authorizes an emergency fund in the United States Treasury to provide compensation for injuries directly caused by administration or use of a countermeasure covered by the Secretary’s declaration.

Immunity under the PREP Act becomes available when the Secretary issues a declaration, beginning on the effective date or other triggering event stated in the declaration.

A countermeasure covered under a PREP Act declaration may be:

- A qualified pandemic or epidemic product or
- A security countermeasure.

Covered countermeasures are products approved, cleared, or licensed under the Federal Food, Drug, and Cosmetic Act (FFDCA) or the PHS Act, or authorized for investigational use or under EUA.

As noted, the PREP Act authorizes a compensation fund to provide “timely, uniform, and adequate compensation to eligible individuals for covered injuries directly caused by” a covered countermeasure administered or used pursuant to a Secretarial declaration. Requests for compensation must be filed within one year of administration or use.

Additional information may be found at the following websites:

Anthrax countermeasures are currently covered by a PREP Act declaration, available at edocket.access.gpo.gov/2008/E8-23547.htm.

HRSA's Countermeasures Injury Compensation Program (CICP) provides compensation to eligible individuals for certain injuries incurred from administration or use of countermeasures covered by PREP Act declarations at www.hrsa.gov/gethealthcare/conditions/countermeasurescomp.

General information about the PREP Act is available at publichealthemergency.hhs.gov/Preparedness/legal/prepact/Pages/prepqa.aspx.

Appendix 14. Estimated Time Required to Administer AVA Under an EUA Versus an IND

Table D (next page) indicates that the estimated amount of time required to administer AVA under an EUA versus an IND is approximately the same.

A comparison of selected activities in offering an injectable medical countermeasure (MCM) at a point of administration under an EUA or under a non-research IND appears in Table D. The scenarios are based on anticipated events in administering vaccinations, and all times indicated are estimates. Additional time would be needed for individuals with impaired or non-English communication skills. This structure assumes that parents would take more time to read and consider an informed consent form than an EUA fact sheet. The cumulative time estimates are described from the perspective of the individual in line to consider and potentially receive the MCM. It is not from the perspective of the clinic administrator who might be measuring throughput. Some activities could be conducted in group sessions to make the process more efficient; hence, processing of groups (e.g., 1000 people) would not require 1,000 times the estimate for administering AVA to an individual.

TABLE D. Estimated Time Required to Administer AVA Under an EUA Versus an IND

| Selected Activities | Time per Activity | Cumulative Time Elapsed, Estimated (H : MM) | |
|--|-------------------|---|--------------|
| | | EUA Scenario | IND Scenario |
| A. Initial On-Site Activities | | | |
| | Start | 0:00 | 0:00 |
| A1. Interactive education for individuals, parents, and legal guardians | 15-20 min | 0:15 | 0:20 |
| A2a. IND: Individual or parent or legal guardian reads the Informed Consent Form | 15 min | | 0:35* |
| A2b. EUA: Individual or parent or legal guardian reads or receives the content of the Fact Sheet for Recipients (* may occur before clinic visit, if Fact Sheets distributed in advance, or it may occur in large group settings.) | 20 min | 0:35* | |
| A3. Questions and answers, then individual decision to accept or decline product. For IND, additional time needed to witness consent, archive documents. | 5-10 min | 0:40 | 0:45 |
| A4. Healthcare worker interviews individual or parent or legal guardian to complete initial portions of the clinical record form (e.g., intake information, patient demographics, other information required by specific situation). Forms may differ for EUA vs. IND, but similar effort expected. | 15 min | 0:55 | 1:00 |
| B. Medical Countermeasure (MCM) Administration | | | |
| B1. Individual receives vaccination or other injectable product | 5 min | 1:00 | 1:05 |
| C. Post-Administration Observation Period (~15-minute period to watch for allergic reaction) | | | |
| C1. Time also can be used to repeat educational information, follow-up instructions, reminders about subsequent doses, information on how to self-monitor for adverse events, and how to report this information to health authorities | 15 min | 1:15 | 1:20 |
| C2a. IND: Complete balance of clinical record form (as applicable to visit) | 5 min | | 1:25 |
| C2b. EUA: Complete EUA data collection (as applicable to conditions of the EUA) | 5 min | 1:20 | |
| Estimated differential in total clinic visit time | | Baseline | + 5min |
| D. Other Activities and Potential Requirements for Clinic Personnel | | | |
| D1. Healthcare workers review the IND (P) and/or EUA Fact Sheet for Healthcare Providers (FS) | | YES (FS) | YES (P) |
| D2. Verbal translation of IND Informed Consent (IC) Form or EUA Fact Sheet for Recipients (FS), if necessary (written translation not available) | | YES (FS) | YES (IC) |
| D3. Training for clinic personnel on clinic-based adverse event reporting procedures (eg, relevant forms, routing) | | YES | YES |
| D4. Training for clinic personnel on product inventory, accountability, disposal processes and records – potential reporting to CDC/FDA | | YES | YES |
| D5. Submission of protocol documents to local institutional review board (IRB), if required, if subject to local IRB approval | | | YES |
| D6. Completion of Statement of Investigator form and submission of form and Curriculum Vitae to CDC | | | YES |

Appendix 15. List of Acronyms

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| AAP | American Academy of Pediatrics |
| ACIP | Advisory Committee for Immunization Practices |
| ASPR | Assistant Secretary for Preparedness and Response |
| AV WG | Anthrax Vaccine (AV) Working Group (WG) |
| AVA | Anthrax Vaccine Adsorbed |
| BARDA | Biomedical Advanced Research and Development Authority |
| CDC | Centers for Disease Control and Prevention |
| CFR | Code of Federal Regulations |
| CICP | Countermeasures Injury Compensation Program |
| DHS | U.S. Department of Homeland Security |
| DoD | U.S. Department of Defense |
| EF | Edema Factor |
| EUA | Emergency Use Authorization |
| FDA | Food and Drug Administration |
| FFDCA | Federal Food, Drug, and Cosmetic Act |
| FS | Fact Sheet |
| FWA | Federal wide Assurance |
| HHS | U.S. Department of Health and Human Services |
| HRSA | Health Resources and Services Administration |
| IC | Informed Consent |
| IDE | Investigational Device Exemptions |
| IM | Intramuscular |
| IND | Investigational New Drug Application |
| IOM | Institute of Medicine |
| IRB | Institutional Review Board |
| LF | Lethal Factor |
| MCM | Medical Countermeasure |
| MMWR | Morbidity and Mortality Weekly Report |
| NBSB | National Biodefense Science Board |
| NHP | Non-Human Primate |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIH | National Institutes of Health |
| OHRP | Office for Human Research Protections |
| OMB | Office of Management and Budget |
| P | Protocol |
| PA | Protective Antigen |
| PAC | Pediatric Advisory Committee |
| PAHPA | Pandemic and All-Hazards Preparedness Act |
| PEP | Post-Exposure Prophylaxis |
| PHERRB | Public Health Emergency Research Review Board |
| PHS | Public Health Service |
| PL | Public Law |
| PODs | Points of Distribution |
| PREP Act | Public Readiness and Emergency Preparedness Act |
| SACHRP | Secretary's Advisory Committee on Human Research Protections |
| SARS | Severe Acute Respiratory Syndrome |
| SC | Subcutaneous |

| | |
|---------|---|
| SNS | Strategic National Stockpile |
| STTL PH | State, Territorial, Tribal, and Local Public Health |
| USC | United States Code |
| USG | United States Government |
| VAERS | Vaccine Adverse Event Reporting System |