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

**September 2011**

## Executive Summary

In the event that anthrax spores are released in the United States, the current plan of the U.S. Government (USG) is to ensure that anthrax vaccine absorbed (AVA) is made available to all children and adults.<sup>1</sup> In this emergency scenario, AVA would be used in combination with antibiotics to prevent the development of infection and illness following exposure to anthrax spores, a form of therapy termed “post-exposure prophylaxis” (PEP).<sup>2</sup> Antibiotics would offer prompt (but temporary) protection against infection, and vaccination would offer prolonged protection after a few doses. However, a complex array of scientific, medical, ethical, legal, regulatory, and administrative issues complicates the use of AVA PEP. 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 the U.S. Department of Health and Human Services (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.<sup>3</sup>

The USG has stockpiled AVA as a key component of PEP following an anthrax attack. Since the 2001 anthrax attacks, federal and local officials from many U.S. communities have conducted exercises to test the USG response following a hypothetical terrorist attack using *B. anthracis* spores as a biological weapon. 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,

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

<sup>2</sup> 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 <http://www.who.int/hiv/topics/prophylaxis/en/>

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

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particularly children under the age of 18, who comprise 25 percent of the U.S. population.<sup>4,5</sup>

To develop this report, NBSB decided to focus on children 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 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 Working Group (AV WG) on July 7, 2011, the HHS Assistant Secretary of 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.”

Given the lack of data about the safety or immunogenicity of AVA (for pre- or post-exposure prophylaxis) in children, a key question HHS is addressing is whether to try to conduct a research study of AVA in children now, before a public health emergency occurs. The question is not straightforward because of ethical, legal, and societal questions and constraints. A fundamental issue is that no one wants to subject children to any risks that are unnecessary, and any vaccination carries certain risks, however small when compared to the risks associated with developing disease. 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

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<sup>4</sup> The Dark Zephyr Exercise scenario was based on an intentional, large-scale outdoor release of *B. anthracis* 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 the 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. 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.

<sup>5</sup> U.S. Bureau of the Census, "USA QuickFacts from the US Census Bureau," available at <http://quickfacts.census.gov/qfd/states/00000.html>

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AVA post-exposure.<sup>6</sup> 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.<sup>7</sup> The vaccine is not licensed for use as PEP for any age group.<sup>8</sup>

However, if the Secretary of HHS declares a public health emergency following the intentional release of anthrax, the FDA can issue an emergency use authorization (EUA) that allows adults (individuals 18 years and older) to receive AVA as prophylaxis on a voluntary basis. At present, the only way children could receive AVA for any reason—before or after exposure to anthrax—is if the FDA approves an investigational new drug (IND) protocol, 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 protocol for children).

In addition to these regulatory disparities governing the administration of AVA, there is concern that the vaccine should not be offered to the pediatric population without knowing it is safe and capable of inducing antibodies against the bacteria (that is, immunogenic). The need for 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 benefit to the vaccinated child at the time of the study or in the future.

Given these complexities, the ASPR asked the NBSB to consider whether the USG should take this opportunity to increase national preparedness by conducting clinical trials with AVA in children prior to a public health emergency. In her letter to the Chair

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<sup>6</sup>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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf).

<sup>7</sup> 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, but that could be employed if the Secretary of HHS declares a public health emergency.

<sup>8</sup> Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, [www.biothrax.com](http://www.biothrax.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.

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of the NBSB on April 27, 2011, 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 under 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 request, the NBSB formed a working group that held meetings and workshops to solicit input from academic scientists, physicians and other healthcare providers, and representatives from professional pediatric organizations, and federal professionals (from stakeholder agencies) to hear their views and discuss the issues. As a result, the working group has developed the following background information and responses to the four questions posed above.

## BACKGROUND INFORMATION

- The licensed indication of Anthrax Vaccine Adsorbed (AVA) is for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in persons 18 – 65 years of age at high risk of exposure. AVA is not licensed for use as part of a therapeutic regimen following exposure to anthrax bacteria or spores. In the United States, AVA is used to protect military and at-risk laboratory personnel. The vaccine is not FDA licensed for PEP in any age group.<sup>9</sup>
- Data about the clinical use of AVA have been published in multiple clinical trials and epidemiologic studies, and laboratory investigations. Published reports include dozens of follow-up studies of millions of vaccinated military personnel.<sup>10</sup> 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.”<sup>11</sup> 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.<sup>12</sup>

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<sup>9</sup> Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, [www.biothrax.com](http://www.biothrax.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](http://www.anthrax.mil).

<sup>10</sup> This information is based on multiple studies and reports: (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](http://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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf)

<sup>11</sup> 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](http://www.nap.edu/catalog/10310.html).

<sup>12</sup> (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

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- 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. During a public health emergency declared by the Secretary of HHS, the vaccine could be administered intramuscularly to children under an IND. Antibiotic treatment is considered standard of care and a significant component of PEP if an individual is exposed to *B. anthracis*. According to ACIP guidelines, PEP includes the administration of both antimicrobial agents and vaccine.<sup>13</sup>
- ACIP recommends the administration of three doses of AVA as the vaccine component of PEP, because it has been shown in NHPs that late germination of the anthrax spores can *occur after* an antibiotic regimen is completed. Vaccination with AVA protected NHPs against bacteria that emerged due to late germination of anthrax spores, but this effect has not been studied in humans for ethical reasons.<sup>14</sup>
- ACIP recommends the FDA-licensed 60-day course of antimicrobials for post-exposure use in adults. 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.<sup>15</sup> Although antimicrobials such as ciprofloxacin or

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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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf). (4) Prescribing information. BioThrax. Emergent BioSolutions, Lansing, MI, www.biothrax.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](http://www.anthrax.mil).

<sup>13</sup> 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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf)

<sup>14</sup> (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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf).

<sup>15</sup> 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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf)

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doxycycline are typically not administered to children, the severity of anthrax is sufficient that treatment with these antimicrobials is warranted and recommended for children who have been exposed to aerosolized *B. anthracis* spores. Amoxicillin is preferred for antimicrobial PEP in children when susceptibility testing indicates that the *B. anthracis* isolate involved is susceptible to penicillin.<sup>16</sup>

- If the Secretary of HHS declares a public health emergency, the FDA can issue an Emergency Use Authorization (EUA) to allow the use of an unapproved medical product or the unapproved use of an approved product.<sup>17</sup> 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; therefore, AVA can be used in adults under an EUA for an unapproved use (e.g., with a 3-dose post-exposure regimen).
- Any use of children as subjects in any type of research requires additional protections beyond those afforded to adults who volunteer to be the human subjects of research.<sup>18</sup> 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.<sup>19</sup>

### **Proposed plan for PEP following exposure to *B. anthracis***

As indicated above, the current USG 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 under these emergency conditions is entirely voluntary, and – for individuals under the age of 18 – would require

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<sup>16</sup>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](http://www.cdc.gov/mmwr/PDF/rr/rr5906.pdf)

<sup>17</sup> 21 USC 360bbb-3. For more information, see [www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm](http://www.fda.gov/EmergencyPreparedness/Counterterrorism/ucm182568.htm)

<sup>18</sup> (1) 21 CFR 50, subpart D. (2) 45 CFR 46, subpart D.

<sup>19</sup> National Bioethics Advisory Commission (NBAC), “Ethical and Policy Issues in Research Involving Human Participants.” Vol. II, Bethesda, MD. August 2001. Accessed 9 September 2011. <http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.67.7929&rep=rep1&type=pdf#page=209>.

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informed consent from a parent or legal guardian under the current IND mechanism intended for providing AVA PEP to children.

The ACIP recommends a 60-day course of antimicrobial agents as a component of PEP. However, a 2003 National Advisory Committee on Children and Terrorism determined that children under age nine could not reliably be administered the antimicrobial agents as an anthrax countermeasure in tablet form. HHS is working to identify a means to rapidly reconstitute antibiotic countermeasures that does not compromise palatability. Although this was not a major focus of the NBSB working group or a charge to the Board, the Board supports the ongoing efforts to develop palatable, effective antibiotics for children under age nine that can be stored in the SNS.

HHS now faces a critical question about the post-exposure use of AVA in children. One of the reasons why this question is so critical is all of the AVA that will be used during an emergency event is presently under HHS control in the SNS. The use of AVA will be subject to the U.S. laws and the strict interpretation of the Code of Federal Regulations.

***What is the best way to gain some assurance about the safety and immunogenicity of AVA in children?*** HHS is considering two approaches. Both approaches would conduct protocols under a research IND. The major difference would be the timing of when the studies are conducted, before or after another public health emergency involving the release of anthrax. The first approach is to do a research study in children ***before another anthrax emergency occurs***. This would involve enrolling children in a research protocol, with parental consent, and testing its immunogenicity by using the same dosing regimen that would be used for adult PEP. The second approach would also involve enrolling children in a research protocol, with parental consent, and evaluate the safety and immunogenicity of AVA PEP ***during the response to an anthrax emergency***.

### **Conduct of Clinical Trials**

Typically in product development, 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 methodology that generates data that guide a determination of the optimal dosing regimen for each age group or special population.

Standard procedures and approaches for evaluating new medical products include a protocol review and approval by institutional review board (IRBs), the establishment of 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

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serious adverse events or unusual or unsuspected reactions critical to assuring safety of volunteers who participate in the trial. Well designed clinical trials minimize risk in every way possible, so that risks to individuals who participate are minimal and acceptable to an IRB.

The FDA and the National Institute for Allergy and Infectious Diseases (NIAID), National Institutes for Health (NIH), in consultation with external clinical pediatric clinical trial experts have considered an approach to learn about the safety and immunogenicity of AVA in children prior to a public health emergency involving the release of *B. anthracis*. A study to evaluate the immunogenicity of AVA PEP would be conducted in adults first. If the adult protocol for AVA PEP demonstrates its immunogenicity, the USG would likely develop a proposal to evaluate the adult AVA PEP regimen for use in children. The protocol for testing AVA in the pediatric population would be designed to evaluate AVA PEP in sequential studies beginning with the oldest group first and, based on the outcome, to test the vaccine in younger age groups. The Safety Monitoring Committee would be asked to review the data before proceeding to enroll the next younger age group.

In summary, as part of preparedness planning for an event involving *B. anthracis*, the present post-event response would include administering AVA PEP under an EUA for adults 18 years and older, and a non-research IND for children younger than 18 years of age. A research IND protocol conducted (either before or during a response to an anthrax emergency) to gather data on the safety and immunogenicity of AVA PEP in children may support an EUA rather than a research IND for administering AVA PEP for children.

### **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 individuals, including adults who want the vaccine and children whose parents or legal guardians consent. In this emergency situation, AVA PEP could be administered to millions of children at a dose and frequency 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 IND research protocol designed to obtain definitive data that can be used to guide the administration of AVA PEP by age group, prior to its widespread use in children.

In general, the primary objective of clinical trials in a pre-event 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 dose of vaccine for children less 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 in children pre-event versus after an event?**

**Pre-Event Evaluation of AVA PEP**

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

- (1) Vaccination carries some risk.

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

- (1) Children who have been immunized might be protected from anthrax infection and disease, should they be exposed.
- (2) In the event of a public health emergency, the U.S. pediatric population could then receive a dose of AVA PEP that has been demonstrated to be safe and immunogenic.
- (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; studies would be conducted in a controlled setting to reduce the likelihood of errors (that could result due to the haste that will likely occur during an emergency).
- (5) Conducting pre-event trials of AVA PEP may afford the USG the opportunity to shorten the duration of antimicrobial use with concurrent receipt of AVA, depending on the results of AVA safety and immunogenicity studies.

- (6) The route (intramuscular [IM] or subcutaneous) of administration of AVA for PEP to children under a research IND protocol is under discussion. AVA is licensed for pre-exposure administration for adults in five doses given IM with annual boosters.

### **Post-Event Evaluation of AVA PEP**

#### **The risks of administering AVA PEP to children under a research IND protocol post-event (meaning there is an imminent threat from exposure to *B. anthracis*).**

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 to the pediatric population is incurred from not testing AVA PEP prior to such a public health emergency.

- (1) In the absence of safety and immunogenicity data, AVA PEP would be administered to children, with parental consent under a non-research IND, following ACIP recommendations. In contrast to the expected response to AVA in adults (i.e., that it would protect against infection and disease), children could be at serious risk of adverse events following administration of AVA, due to the absence of any data on safety and immunogenicity in the pediatric population. The PREP Act would ensure liability and medical compensation.<sup>20</sup>
- (2) If a public health emergency involving the release of anthrax occurs, the response of the USG including federal, state and local agencies; healthcare providers; decision makers involved in such a national response; adults, parents, and legal guardians is likely to be complicated and rushed, and the implementation of a research IND protocol post-event would need to be integrated into an already complex and difficult series of decisions and actions.

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<sup>20</sup>(1) Anthrax countermeasures are currently covered by a PREP Act declaration, available at <http://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 <http://www.hrsa.gov/gethealthcare/conditions/countermeasurescomp> (3) General information about the PREP Act is available at <http://publichealthemergency.hhs.gov/Preparedness/legal/prepact/Pages/prepqa.aspx>

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- (3) The current USG plan for obtaining information about the safety and immunogenicity of AVA administered during or after an emergency is to enroll volunteers who have agreed to receive the vaccine (under the non-research IND protocol recommended by the ACIP) in a separate, post-event research IND protocol. This post-event research IND protocol would be designed to study adverse events and antibody responses in children. However, because all children enrolled in the two protocols would receive AVA PEP, there would not be a valid control group for obtaining definitive data on vaccine safety or the immunogenicity of different dosing regimens for different age groups, and the post-event study would therefore be observational. Data gathered under these circumstances might not be useful for guiding other immunizations related to the current or a future event in which children were exposed to *B. anthracis*.

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, that is, we may not be able to distinguish side effects/adverse effects of an antibiotic from that of the AVA vaccine.

### **The benefit of administering AVA PEP to children under a research IND protocol post-event (meaning there is an 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 consent to enroll their children in this non-research IND protocol also can consider enrolling their children in a post-event research IND protocol.

- (1) Some potential direct benefit to children enrolled in a post-event research IND protocol could 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 whether the vaccine was immunogenic, and therefore have some expectation of being protected against *B. anthracis* in the event of future exposures.

Preparation for a national and potentially global threat from the use of *B. anthracis* spores by a terrorist (or group of 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 the

paramount challenge the USG will face during such an event. The NBSB recommendation is designed to mitigate that challenge.

**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 (EUA)?**

The challenges of conducting a definitive study post event or during an event are summarized in 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. 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 protocol and the research IND protocol. It also will be necessary to provide a hotline (or similar resource) that parents can contact to answer any questions they might have.

Challenges include, but are not limited to, logistical concerns, communications, and operational issues for administering a vaccine under a research IND protocol during an emergency event when all children have the opportunity to receive vaccine under a non-research IND protocol. The content of the message is critical. How do public health officials communicate to the parents what they are doing and why in a short period of time and during a crisis? How do public health officials explain to parents that by enrolling their child 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.

**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 USG plan is to ensure that AVA PEP, in combination with antibiotics, is made available to all children

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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.

***The USG should 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 USG 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 and the risk the vaccine could pose. 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 what risks their children might face. To further complicate matters, while parents are still trying to ponder the risks to their children and agreeing to the administration of AVA under the non-research IND protocol they will be asked if they would like to enroll in their child in a research IND protocol.

Any printed, visual, or audio media intended for public communication must be reviewed and vetted by all relevant USG departments and agencies, emergency responders, state and local health officials, and the public. It also should be field-tested for comprehensiveness and clarity.

***HHS must have in place two well-vetted and pre-approved, post-event protocols for administering AVA PEP to children.*** The first protocol is a ***non-research IND*** under which the vaccine would be administered to all children whose parents want them to receive the vaccine, should an anthrax emergency occur. The protocol was developed by CDC, and is under review by FDA. The second protocol is a ***research IND*** protocol designed to gather sufficient data for determining the safety and immunogenicity AVA PEP in individuals younger than 18 years of age. These data also may be used to support the use of AVA PEP under an EUA, should a subsequent anthrax attack occur. The data gathered in this post-event, research IND protocol 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 protocol is under development.

Both protocols, the non-research IND and the research IND, need to be approved by the FDA and an appropriate Institutional Review Board. The non-research IND protocol for administering AVA PEP to all children whose parents provide consent would be part of the emergency response. The research IND protocol would be in conjunction with the

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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 before an anthrax emergency occurs to all federal and state public health authorities to allow integration into national, state, and local preparedness planning. Another issue that needs to be addressed is prioritization, i.e., who should receive vaccines first.

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 plan for administering antibiotics also should be clearly understood and processes defined by all public health authorities.

#### **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?**

The mission of HHS is to protect public health, including children, who represent nearly 25 percent of the U.S. population. New policies under consideration by HHS need to be shared with local and state health officials, other public health authorities, parents, the general public, all healthcare institutions and providers.

Over the years, CDC has been a critical USG resource for teaching risk communication about 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 disseminate information about urgent health issues. HHS should leverage its 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.

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### OPTIONS CONSIDERED BY THE NBSB

*OPTION 1 - Conduct a **pre-event** research IND protocol:* The USG should develop a pre-event, research IND protocol 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. (The Safety Monitoring Committee 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, consent documents, and recruiting documents. These materials would be submitted to an IRB, with the expectation that the protocol would be subjected to the review and approval process outlined in 21 CFR 50.54 / 45 CFR 46.407.

The results of this pre-event, research IND protocol should yield important information about the safety and immunogenicity of age-appropriate doses of AVA PEP in children, and also could be considered by FDA as support for making AVA PEP available to children under an EUA, rather than an 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.

*OPTION 2 – Conduct a **post-event** research IND protocol:* In the event of a public health emergency involving the release of *B. anthracis* bacteria or spores, the USG plan is to follow current ACIP recommendations to administer AVA PEP and antibiotics to children, with parental consent, under a post-event, non-research IND protocol. In addition to this post-event, non-research IND protocol, the USG also could offer children, with parental consent, the opportunity to participate in a research IND protocol to gather some safety and immunogenicity data about AVA PEP. Data from this post-event study would likely not be of the same quality as data gleaned from a pre-event study, but might be sufficient to learn something about the safety and immunogenicity of AVA PEP, adverse events, and possibly, to adjust the dosage. This research protocol also is under development.

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### DISCUSSION

The AV WG and the NBSB deliberated 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. Also lacking is a strategy 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 in children, it is necessary to address the ethical concern that children are unable to give informed consent. 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 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. The clinical trial planned by NIH is intended by design to minimize risks and provide benefit to study participants, while producing information needed to guide appropriate use in a post-event scenario.

Administering an untested vaccine to large numbers of children under 18 years of age poses a risk. The Board accepts the USG threat analysis and recognizes that the dissemination of *B. anthracis* is a threat to the U.S. population including its 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 immunogenic 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 research subjects; (3) weighed the possibility of not being able to accomplish 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 gain the safety and immunogenic data about AVA PEP in children prior to an anthrax event.

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### RECOMMENDATION

The NBSB makes this recommendation in light of the current USG plan to follow the ACIP recommendations for use of AVA for PEP following exposure to *B. anthracis* spores. This recommendation should be revisited if new anthrax vaccines or other therapeutic countermeasures become available.<sup>21</sup>

The USG should develop a plan for a pre-event study to include a full protocol (the full protocol should outline the data points that need to be collected and why – clear goals, number of subjects to make sure the data is statistically reliable), communication package, consent documents, and recruiting documents. Submit the protocol to an IRB, fully expecting it to go through the 21 CFR 50.54 / 45 CFR 46.407 process. This study may provide sufficient data to support AVA PEP moving from an IND to an EUA status.

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<sup>21</sup> 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 <http://www.hhs.gov/news> September 15, 2011). The vaccine being developed under the new contract 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 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.

New anthrax vaccines are being developed and new formulations AVA examined. “BARDA currently supports the advanced development of three other next-generation anthrax vaccines known as recombinant protein antigen (rPA)-based vaccines, as well as development of a new formulation of the currently licensed anthrax vaccine, Anthrax Vaccine Adsorbed (AVA), that may require less antigen (the active vaccine ingredient) and fewer doses to be effective.

In addition, BARDA previously funded the development and acquisition of two anthrax antitoxin drugs that reside in the Strategic National Stockpile. These drugs could be authorized for use in an emergency. BARDA continues to support the late-stage development of these drugs toward full approval by the FDA.