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Evaluation of anthrax vaccine safety in 18 to 20 year olds: A first step towards age de-escalation studies in adolescents☆

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ABSTRACT

Background/objectives: Anthrax vaccine adsorbed (AVA, BioThrax®) is recommended for post-exposure prophylaxis administration for the US population in response to large-scale *Bacillus anthracis* spore exposure. However, no information exists on AVA use in children and ethical barriers exist to performing pre-event pediatric AVA studies. A Presidential Ethics Commission proposed a potential pathway for such studies utilizing an age de-escalation process comparing safety and immunogenicity data from 18 to 20 year-olds to older adults and if acceptable proceeding to evaluations in younger adolescents. We conducted exploratory summary re-analyses of existing databases from 18 to 20 year-olds ($n = 74$) compared to adults aged 21 to 29 years ($n = 243$) who participated in four previous US government funded AVA studies.

Methods: Data extracted from studies included elicited local injection-site and systemic adverse events (AEs) following AVA doses given subcutaneously at 0, 2, and 4 weeks. Additionally, proportions of subjects with ≥4-fold antibody rises from baseline to post-second and post-third AVA doses (seroresponse) were obtained.

Results: Rates of any elicited local AEs were not significantly different between younger and older age groups for local events (79.2% vs. 83.8%, $P = 0.120$) or systemic events (45.4% vs. 50.5%, $P = 0.188$). Robust and similar proportions of seroresponses to vaccination were observed in both age groups.

Conclusions: AVA was safe and immunogenic in 18 to 20 year-olds compared to 21 to 29 year-olds. These results provide initial information to anthrax and pediatric specialists if AVA studies in adolescents are required.

Abbreviations: AE, adverse events; AVA, anthrax vaccine adsorbed; BARDA, Biomedical Advanced Research and Development Authority; CDC, Centers for Disease Control and Prevention; CFR, Code of Federal Regulations; ED50, effective dilution resulting in 50% neutralization; ELISA, enzyme linked immunosorbent assay; HHS, Health and Human Services; IgG, immunoglobulin G; IND, investigational new drug; NF50, standardized anthrax toxin 50% neutralizing factor; NPRSB, National Preparedness and Response Science Board; PA, protective antigen; SC, subcutaneous.

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1. Introduction

Bioterrorist attacks using spores derived from *Bacillus anthracis* have been identified as a high priority threat by the United States (US) Department of Homeland Security [1]. This issue was highlighted by bioterrorism-related cases of anthrax illnesses after envelopes containing spores of this organism were sent through the US mail [2]. Accordingly, the US Department of Health and Human Services (HHS) has been charged to address preparedness for such attacks. This preparedness includes providing guidance on the use of post-exposure prophylaxis (PEP) using anthrax vaccine and antibiotics [2]. Anthrax Vaccine Adsorbed (AVA, BioThrax®) manufactured by Emergent BioSolutions Incorporated, was licensed in the US in 1970 for prevention of anthrax in adults aged 18 to 65 years. However, children and pregnant women are special populations for its use [3,4]. AVA is prepared from sterile culture filtrates of the toxigenic, nonencapsulated *B. anthracis* V770-NP1-R grown in a protein-free medium. The final product formulation contains aluminum hydroxide, sodium chloride, benzethonium chloride and formaldehyde [3]. The primary immunogen in AVA is anthrax toxin protective antigen (PA). Anti-PA IgG antibodies are considered to protect against anthrax by neutralizing the *B. anthracis* toxins, inhibiting spore germination, and enhancing phagocytosis and killing of spores by macrophages [5–13].

The current US Advisory Committee on Immunization Practices recommendation for PEP use of AVA is subcutaneous (SC) administration of three doses at 0, 2 and 4 weeks to be initiated within 10 days following an anthrax event [14]. The safety profile of AVA in adults 18–65 years of age is well established [15–22]. There is however, a paucity of data on AVA safety and immunogenicity in special populations, and none in children [23].

In 2011, a HHS interagency tabletop exercise, designated *Dark Zephyr*, was conducted to simulate an anthrax emergency [24]. During this exercise, it was estimated that up to 7.6 million people, of which approximately 25% would be children, could be exposed to *B. anthracis* spores [24]. If such a large-scale event actually happened, the absence of safety and immunogenicity data of AVA in pediatrics may result in concerns about the administration of this vaccine to individuals less than 18 years of age, a situation that could possibly deny children a potentially life-saving prophylactic countermeasure.

During the fall of 2011, the National Biodefense Science Board, now known as the National Preparedness and Response Science Board (NPRSB) was charged with assessing challenges in the use of AVA in the pediatric population in case of a large-scale anthrax emergency [24]. The NPRSB recognized that, in case of mass exposure of a population to *B. anthracis* spores, a FDA approved research investigational new drug protocol would allow the administration of AVA to children using a PEP regimen. However, this effort would require a research team to collect safety and immunogenicity data from these children after each AVA dose during this mass vaccination event. Consequently, the NPRSB noted that this type of post-event evaluation would pose major challenges to first responders, parents and research personnel in terms of mass vaccination of children during a large-scale anthrax spore exposure. Therefore, the NPRSB panel concluded that "HHS should develop a plan for and conduct a pre-event study of AVA in children, to include a research IND. HHS should submit a study protocol to one or more institutional review boards, and comply with the 21 CFR 50.54/45, CFR 46.407 federal review process." [24].

In response to the NPRSB report, the Secretary of HHS requested that the Chair of the Presidential Commission for the Study of Bioethical Issues convene a panel to review the ethical considerations of conducting clinical research studies of medical countermeasures in children. The Secretary went further to ask this panel to specifically include the ethics of conducting a pre-event AVA study in children. The Commission held four public forum meetings that addressed this issue directly and a summary report was issued on March of 2013 [25]. In that report, the Presidential Commission referred to the Code of Federal Regulations (CFR) regarding protections for children involved in research [26].

First, the Commission indicated that pre-event AVA studies could not be conducted in children in the US under 45 CFR 46.405, which specifies that studies above minimal risk require the possibility of direct benefit to the participating child. Second, pediatric studies may be possible using 45 CFR 46.407, which stipulates that a rarely utilized Presidential waiver could be sought if the information gained could possibly benefit children in general even if the study might not benefit the individual child. Finally, the Commission suggested a unique approach that would render a pre-event AVA study to "no more than a minor increase over minimum risk" by using a stepwise, age de-escalation approach. Specifically, the Commission suggested that a pre-event study of individuals 18 to 20 years of age might provide information to substantiate that such a study in 16 to 17 year-olds would involve no more than minimal risk. Consequently, the Commission indicated, with important caveats, that an age de-escalation pathway might be considered under the 45 CFR 46.404, as it poses no more than minimal risk.

In light of this Presidential Commission's unique alternative pathway suggestion, we implemented a retrospective study with an exploratory objective to describe and compare safety and immunogenicity data from healthy individuals aged 18 to 20 years to the same type of data in individuals aged 21 to 29 years who participated in several HHS-sponsored AVA clinical trials. For this study the 'older' age group of 21 to 29 years, albeit somewhat arbitrary, was chosen as the most appropriate age group to compare safety and immunogenicity data to the 18 to 20 year old group for several reasons. First, including data from subjects up to age 65 years would result in a markedly larger and very unbalanced sample size compared to the 18 to 20 year old group. Also, previous data has shown a decrease in antibody responses to AVA as age increases in ten year increments from 18 to 65 year olds [27]. Finally, injection site reactions to AVA significantly decrease with advancing age [20].

2. Methods

2.1. Retrospective studies utilized

This investigation consisted of an exploratory summary reanalysis of existing electronically stored databases from final clinical study reports from four previous HHS-funded studies involving AVA conducted by the US Centers for Disease Control and Prevention (CDC) or funded by Biomedical Advanced Research and Development Authority (BARDA) that took place since the year 2000. Study AVA000, sponsored by CDC, had study arms that involved different AVA intramuscular (IM) or subcutaneous (SC) dosing regimens well beyond 4 weeks to examine issues of general use prophylaxis of AVA not relevant to PEP [27]. Of note, only AVA000 safety and immunogenicity data from subjects who received a full dose of AVA SC at 0, 2 and 4 weeks were included in the present study. In addition, three BARDA-funded AVA PEP studies were included in this report and designated AVA005, AVA006, AVA009 whereby full dose AVA was given SC at 0, 2 and 4 weeks [28–30].

All four studies were selected because (1) enrolled subjects 18 to 20 years of age as well as older subjects; (2) administered full dose AVA (0.5 mL) subcutaneously (SC) for three doses at 0, 2, and 4 weeks; (3) had, at a minimum, individual subject safety data that included virtually identical local and systemic post-vaccination elicited adverse events for 7 days for at least one diary following an AVA administration; and 4) included US Food and Drug