



Cross-species prediction of human survival probabilities for accelerated anthrax vaccine absorbed (AVA) regimens and the potential for vaccine and antibiotic dose sparing



G.V. Stark^{a,*}, G.S. Sivko^a, M. VanRaden^b, J. Schiffer^c, K.L. Taylor^b, J.A. Hewitt^b, C.P. Quinn^c, E.O. Nuzum^b

^a Battelle Memorial Institute, Columbus, OH 43201, USA

^b Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, Bethesda, MD 20892-9825, USA

^c Centers for Disease Control and Prevention, Atlanta, GA 30329-4027, USA

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ABSTRACT

Anthrax vaccine adsorbed (AVA, BioThrax) was recently approved by the Food and Drug Administration (FDA) for a post-exposure prophylaxis (PEP) indication in adults 18–65 years of age. The schedule is three doses administered subcutaneous (SC) at 2-week intervals (0, 2, and 4 weeks), in conjunction with a 60-day course of antimicrobials. The Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) developed an animal model to support assessment of a shortened antimicrobial PEP duration following *Bacillus anthracis* exposure. A nonhuman primate (NHP) study was completed to evaluate the efficacy of a two dose anthrax vaccine absorbed (AVA) schedule (0, 2 weeks) aerosol challenged with high levels of *B. anthracis* spores at week 4– the time point at which humans would receive the third vaccination of the approved PEP schedule. Here we use logistic regression models to combine the survival data from the NHP study along with serum anthrax lethal toxin neutralizing activity (TNA) and anti-PA IgG measured by enzyme linked immunosorbent assay (ELISA) data to perform a cross-species analysis to estimate survival probabilities in vaccinated human populations at this time interval (week 4 of the PEP schedule). The bridging analysis demonstrated that high levels of NHP protection also yield high predicted probability of human survival just 2 weeks after the second dose of vaccine with the full or half antigen dose regimen. The absolute difference in probability of human survival between the full and half antigen dose was estimated to be at most approximately 20%, indicating that more investigation of the half-antigen dose for vaccine dose sparing strategies may be warranted.

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1. Introduction

Anthrax vaccine absorbed (AVA, BioThrax®) is the only FDA approved vaccine for prevention of anthrax in humans. The pre-exposure prophylaxis (PrEP) schedule for AVA is a priming series of 3 intramuscular (IM) injections (0, 1, 6 months) with boosters at 12 and 18 months, and annually thereafter for those at continued risk of infection [1]. In 2015, under the ‘animal rule’, FDA also approved a post-exposure prophylaxis (PEP) indication for AVA in adults 18–65 years of age. The schedule is three doses administered subcutaneous (SC) at 2-week intervals (0, 2, and 4 weeks), in conjunction with a 60-day course of antimicrobials [2–4]. In a 2010 FDA meeting, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) agreed on the use of PrEP animal

model to establish protective antibody levels at relevant time points in support of the PEP indication [5]. These protective levels may be used to bridge to humans [6].

In 2014, the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) announced an intention to develop an animal model to support assessment of a shortened antimicrobial PEP duration following *Bacillus anthracis* exposure [7]. The resulting study evaluated short term efficacy of a two dose AVA schedule (0, 2 weeks) in nonhuman primates (NHP) challenged with high levels of *B. anthracis* spores at week 4. In addition, to evaluate multifold expansion of the current anthrax vaccine stockpile, the PHEMCE established a human clinical trial of two-dose AVA regimens (0, 2 weeks or 0, 4 weeks) with the full antigen dose and a three-dose regimen (0, 2, 4 weeks) with full and half the standard antigen amount [8]. The objective of that study was to determine the safety and immunogenicity of reduced or divided doses of vaccine.

* Corresponding author at: 505 King Ave., Columbus, OH 43201, USA.

E-mail address: starkg@battelle.org (G.V. Stark).

The primary immunogen in AVA is anthrax toxin protective antigen (PA). Serological analyses of anthrax vaccines include serum anthrax lethal toxin neutralizing activity (TNA) and anti-PA IgG measured by enzyme linked immunosorbent assay (ELISA). These measures of humoral immune response have been established as correlates of protection (COP) in animal models [6,9–12]. These COP have been used as a modeling tool with NHP survival data to predict the probability of survival in vaccinated human populations [13,14]. The cross-species modeling to estimate the probability of survival for anthrax vaccines in humans is necessary because clinical infection studies are impractical and ethically infeasible [5,13,15].

Here we report on a cross-species analysis between the accelerated two-dose NHP study data [16] and the human immunogenicity trial [8]. The primary objective of the analysis was to investigate the predicted probabilities of survival in humans at Day 28 receiving a full-dose or half-dose of AVA at only the 0 and 2 week time points of the accelerated PEP regimen (0, 2, and 4 weeks) when extrapolated from NHP data on a matching schedule. The immune response data from both studies and the survival data from the NHP study were used to generate predicted survival probabilities in humans receiving two doses (0, 2 weeks) of the full or half antigen dose accelerated AVA regimens. These data may assist in estimating the predicted probability of survival in humans of the half-dose regimen relative to the full-dose regimen. A half-dose regimen may provide significant increases in vaccination coverage during a large scale emergency when the demand for AVA may exceed availability.

2. Materials and methods

2.1. Vaccine

The human clinical trial and non-clinical study both used the same lot of AVA (FAV392A). Sterile saline was used as a diluent to generate the dilutions specified for the non-clinical study.

2.2. Non-clinical test system

The animal study is described in detail by Sivko [16]. In brief, 48 cynomolgus macaques (24 males and 24 females) were assigned to one of 5 AVA dose groups, which ranged from 1:3 to 1:243 dilutions of the human dose or to receive saline only. Animals were vaccinated intramuscularly (IM) on Days 0 and 14 and then aerosol challenged with *B. anthracis* Ames strain spores on Day 28. The design for the non-clinical study is presented in Table 1. Following challenge, animals were observed for survival through the morning of Day 56. Prior to challenge, blood was collected for anti-PA IgG ELISA and TNA (NF₅₀ and ED₅₀) on Days 0, 14, 21, and 28. The limit of detection (LOD) for the NHP assays were 1.6 µg/mL, 0.074, and 37 for anti-PA IgG, TNA NF₅₀, and TNA ED₅₀, respectively. The study was conducted with oversight from the Institutional Animal Care and Use Committee.

2.3. Immunogenicity and safety human clinical trial

The results of the human clinical trial have been detailed by Bernstein et al. [8]. The study design for the clinical trial is presented in Table 2. Subjects were scheduled to have blood samples drawn for anti-PA IgG ELISA and TNA (NF₅₀ and ED₅₀) testing on Days 0, 7, 14, 21, and 28. The LOD for the human assays were 0.855 µg/mL, 0.059, and 26 for anti-PA IgG, TNA NF₅₀, and TNA ED₅₀, respectively. Additional details and results are available at Clinicaltrials.gov NCT01641991.

2.4. Statistical methods

From the human clinical trial, only the groups vaccinated on Days 0 and 14 (Table 2; Arms A, C, and D) were included in the analysis. Since Arms A and C had the same vaccination schedule and dose up to this point, they were combined into a single group for this analysis. In addition, the analysis only included human humoral immune response data up to and including the Day 28

Table 1
Pre-clinical study design and survival data.

Group	AVA [®] vaccine lot	AVA [®] vaccine dilution (IM)	Number of animals	Vaccination days	Challenge day	Number of survivors (Percent)
5	FAV392A	1:3	8	0 and 14	28	7 (88)
1		1:9	8			8 (100)
4		1:27	9			9 (100)
3		1:81	9			6 (67)
2		1:243	8			2 (25)
6	Saline control		6			0 (0)

IM – Intramuscular.

Table 2
Clinical trial study design.

Study arm	Number of subjects in per protocol population	Vaccine	Vaccination schedule ^a			
			Day 0 SC (mL)	Day 14 SC (mL)	Day 28 SC (mL)	6 Months IM (mL)
A	67	Full-Dose AVA	0.50	0.50	NA	0.50
B	59	Full-Dose AVA	0.50	NA	0.50	0.50
C	59	Full-Dose AVA	0.50	0.50	0.50	0.50
D	60	Half-Dose AVA	0.25	0.25	0.25	0.50
Total	245					

SC – Subcutaneous.

IM – Intramuscular.

NA – Not applicable.

^a Only data through Day 28 included in analysis.

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