Vaccine 33 (2015) 3709–3716

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Bridging non-human primate correlates of protection to reassess the Anthrax Vaccine Adsorbed booster schedule in humans

Jarad M. Schiffer[a,*], Ligong Chen[b,1], Shannon Dalton[b,2], Nancy A. Niemuth[c], Carol L. Sabourin[c], Conrad P. Quinn[a]

[a] Centers for Disease Control and Prevention (CDC), Atlanta, GA 30333, United States
[b] Atlanta Research and Education Foundation (AREF), Decatur, GA 30033, United States
[c] Battelle, 505 King Avenue, Columbus, OH 43210, United States

ARTICLE INFO

*Article history:*
Received 26 March 2015
Received in revised form 14 May 2015
Accepted 29 May 2015
Available online 10 June 2015

*Keywords:*
*Bacillus anthracis*
Anthrax
Anthrax Vaccine Adsorbed
AVA
Biothrax
Correlates of protection
Clinical trial
Non-clinical trial
Animal model

ABSTRACT

Anthrax Vaccine Adsorbed (AVA, BioThrax®) is approved for use in humans as a priming series of 3 intramuscular (i.m.) injections (0, 1, 6 months; 3-IM) with boosters at 12 and 18 months, and annually thereafter for those at continued risk of infection. A reduction in AVA booster frequency would lessen the burden of vaccination, reduce the cumulative frequency of vaccine associated adverse events and potentially expand vaccine coverage by requiring fewer doses per schedule. Because human inhalation anthrax studies are neither feasible nor ethical, AVA efficacy estimates are determined using cross-species bridging of immune correlates of protection (COP) identified in animal models. We have previously reported that the AVA 3-IM priming series provided high levels of protection in non-human primates (NHP) against inhalation anthrax for up to 4 years after the first vaccination. Penalized logistic regressions of those NHP immunological data identified that anti-protective antigen (anti-PA) IgG concentration measured just prior to infectious challenge was the most accurate single COP.

In the present analysis, cross-species logistic regression models of this COP were used to predict probability of survival during a 43 month study in humans receiving the current 3-dose priming and 4 boosters (12, 18, 30 and 42 months; 7-IM) and reduced schedules with boosters at months 18 and 42 only (5-IM), or at month 42 only (4-IM). All models predicted high survival probabilities for the reduced schedules from 7 to 43 months. The predicted survival probabilities for the reduced schedules were 86.8% (4-IM) and 95.8% (5-IM) at month 42 when antibody levels were lowest. The data indicated that 4-IM and 5-IM are both viable alternatives to the current AVA pre-exposure prophylaxis schedule.



## 1. Introduction

The US licensed anthrax vaccine adsorbed (AVA, BioThrax®) was approved in 1970 for prevention of anthrax in humans [1–3]. The primary immunogen in AVA is anthrax toxin protective antigen (PA) [4]. The 1970 regimen for AVA was a subcutaneous (s.c.) six-dose primary schedule at 0, 0.5, 1, 6, 12 and 18 months with subsequent annual boosters. In May 2012, the US Food and Drug Administration (FDA) approved a revised AVA schedule with an intramuscular (i.m.) three-dose primary schedule at months 0, 1, 6 (3-IM), with boosters at months 12 and 18 followed by annual boosters for those at continued risk of infection (http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm304758.htm). The public health impact of these changes resides in the significant reduction in the frequency, severity and duration of local adverse events with i.m. administration, the elimination of the injection at week 2 and

*Abbreviations:* AE, adverse events; AUC, area under the receiving operator characteristic curve; AVA, Anthrax Vaccine Adsorbed; AVRP, Anthrax Vaccine Research Program; CDC, Centers for Disease Control and Prevention; COP, correlates of protection; ED50, effective dilution for 50% neutralization; FDA, Food and Drug Administration; GCP, Good Clinical Practices; IACUC, Institutional Animal Care and Use Committee; i.m., intramuscular; IND, Investigational New Drug; LLOD, lower limit of detection; LLOQ, lower limit of quantification; NHP, non-human primate; PA, protective antigen; s.c., subcutaneous; TNA, toxin neutralization activity; VE, vaccine effectiveness.

* Corresponding author at: MS-D01, 1600 Clifton Road NE, Atlanta, GA 30329-4027, United States. Tel.: +1 404 639 0894; fax: +1 404 639 4139.
*E-mail address:* jschiffer@cdc.gov (J.M. Schiffer).
[1] Current address: Department of Epidemiology, University of Alabama at Birmingham, LHL 440, 1720 2nd Ave South, Birmingham, AL 35294, United States.
[2] Current address: 4805 Ruby Forrest Drive, Stone Mountain, GA 30083, United States.

http://dx.doi.org/10.1016/j.vaccine.2015.05.091

immunological protection acquired with the administration of the third dose at month 6 rather than after the sixth dose at month 18. Nonetheless, the AVA booster schedule retains a relatively high burden of injections compared to many other vaccines [5,6].

Studies by Pittman and coworkers have demonstrated that increasing the intervals between doses of AVA can increase the antibody response to booster vaccinations [6–8]. Similar conclusions were reported in the CDC Anthrax Vaccine Research Program (AVRP) phase 4 human clinical trial [3,9]. The CDC AVRP demonstrated that study participants receiving the 3-IM priming series with boosters at months 18 and 42 (5-IM) or only at month 42 (4-IM) developed significantly higher levels of anti-PA antibodies at months 19 (5-IM group) and 43 (4-IM and 5-IM groups) compared to those receiving annual boosters (7-IM). These differences were particularly striking in the group receiving only the month 42 booster (4-IM), which achieved post-boost antibody concentrations twice as high as the original licensed 8-SC schedule (433.2 μg/mL vs. 216.8 μg/mL). These data in humans indicated that immunological priming by AVA was long-lasting and robust with the ability to produce a high magnitude anamnestic response up to at least 3 years after 3-IM priming [9].

The 3-IM priming schedule without boosters has also been demonstrated to provide long term protection up to 4 years in rhesus macaques [10]. Chen et al. subsequently applied penalized logistic regression models to the NHP humoral and cellular immunological response profiles to select the most predictive immune correlates of protection (COP) [11]. The most accurate single COP was the serum anti-protective antigen (anti-PA) IgG concentration at the time of infectious challenge. Additional COP with good predictive power included peak anti-PA IgG concentrations and lethal toxin neutralization activity (TNA) titers at month 7, and dual-correlate models that combined one peak measurement (anti-PA IgG or TNA ED50) and anti-PA IgG at challenge [11]. The COP are considered pivotal for cross-species predictions of anthrax vaccine efficacy in humans where clinical efficacy studies are impractical and ethically infeasible ([12,13], http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm239733.htm).

The objective of the current report was to determine the feasibility of reduced AVA booster schedules in humans. We describe bridging of the NHP anti-PA IgG and TNA ED50 COP to the CDC AVRP human study data using logistic regression models to generate predicted survival probabilities provided by annual and reduced booster schedules [13]. Distinct from the previous non-inferiority analysis of peak responses to vaccination, this study provides a specific focus on determining survival probabilities during the periods of receding and lowest antibody levels between the completion of the priming series and the subsequent booster vaccinations. This is the first report of a bridging analysis between the CDC nonhuman primate correlates of protection data with the CDC AVRP human clinical trial.

## 2. Materials and methods

### 2.1. Human and NHP data sets

Study schedules for humans and NHP are summarized in Table 1. The human data sets were from the CDC AVRP clinical trial comprising 1563 human participants as previously reported [9]. Three study arms (7-IM, 5-IM, and 4-IM, Table 1) received i.m. priming doses at 0, 1 month, and 6 months, matching the NHP cohort schedule. After completion of priming, the study groups received annual or alternate booster schedules: 7-IM received the complete schedule of boosters at month 12, 18, 30 and 42; 5-IM received booster doses at months 18 and 42; and 4-IM received a single booster at month 42. Serum anti-PA IgG antibodies were quantified in all participants that were According to Protocol (ATP) for immunogenicity [9]. TNA ED50 was obtained for a subset of approximately 46% of the ATP participants. The study was sponsored by CDC under an Investigational New Drug (IND) application, was approved by the human investigations committees at participating clinical sites and at CDC, and was conducted according to the International Conference on Harmonization Good Clinical Practices (GCP) (www.clinicaltrials.gov; NCT00119067).

The NHP study has been reported in detail by Quinn et al. [10] and Chen et al. [11]. Chen et al. identified serum anti-PA IgG concentrations at the time of challenge (last) as the most accurate immunological COP for 3-IM priming in rhesus macaques. Additional correlates with good predictive power included peak anti-PA IgG concentrations and lethal toxin neutralization activity (TNA) titers at month 7 (peak), and dual-correlate models that combined one peak measurement (anti-PA IgG or TNA ED50) and last anti-PA IgG [11].

### 2.2. Bridging from NHP to humans

The method for bridging a non-human COP to predict survival probability in humans was described by Fay et al. [13] and Kohberger et al. [14] and in http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/

**Table 1**
Schedule of intramuscular vaccination for The Human and NHP Study Groups in the AVRP Study.

| | Primary series (months) | Booster schedule (months) | Study group | Month 0 | Month 0.5 | Month 1 | Month 6 | Month 12 | Month 18 | Month 30 | Month 42 | Month 52 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Human | 0, 1, 6 | 12, 18, 30, 42 | 7-IM | AVA | Saline | AVA | AVA | AVA | AVA | AVA | AVA | N/A |
| | 0, 1, 6 | 18, 42 | 5-IM | AVA | Saline | AVA | AVA | Saline | AVA | Saline | AVA | N/A |
| | 0, 1, 6 | 42 | 4-IM | AVA | Saline | AVA | AVA | Saline | Saline | Saline | AVA | N/A |
| NHP | 0, 1, 6 | None | Human dose | AVA | No injection | AVA | AVA | No injection | No injection | Challenge (subset) | No injection | Challenge |
| | | | 1:5 | AVA | No injection | AVA | AVA | No injection | No injection | Challenge (subset) | No injection | Challenge |
| | | | 1:10 | AVA | No injection | AVA | AVA | Challenge (subset) | No injection | Challenge (subset) | No injection | Challenge |
| | | | 1:20 | AVA | No injection | AVA | AVA | Challenge (subset) | No injection | Challenge | NA | NA |
| | | | 1:40 | AVA | No injection | AVA | AVA | Challenge | NA | NA | NA | NA |

The human and NHP studies have been described in detail previously [9,10]. At each time point, humans received either a full dose of AVA or a saline placebo. NHP received diluted doses of AVA (undiluted, 1/5, 1/10, 1/20 or 1/40) at months 0, 1 and 6. Subsets of NHP were challenged at months 12, 30 and 52 [10,11].