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Latex Content in the Anthrax Vaccine Absorbed

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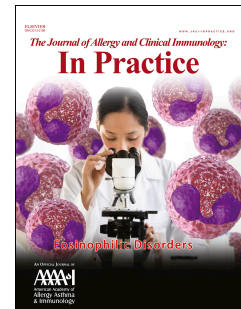
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Clinical Implications

The Anthrax Vaccine Absorbed does not contain detectable levels of the natural rubber latex allergens Hev b 1, 3, 5 and 6.02. These data provide evidence for further prospective research into the safety of vaccinating latex allergic patients.

Natural rubber latex (NRL) hypersensitivity reactions are well characterized events with symptoms ranging from mild local cutaneous reactions to life-threatening anaphylaxis.¹ Some vaccines, including the anthrax vaccine absorbed (AVA), contain NRL in their vial stoppers. This poses concern for triggering hypersensitivity reactions in latex allergic individuals.² Anthrax has been used on rare occasions as a biological weapon around the world for over a century. In 1970, a protein-based human anthrax vaccine was licensed as part of a vaccination program for U.S. military personnel.^{3,4} AVA is a cell-free filtrate of an avirulent, nonencapsulated strain of *Bacillus anthracis*. The final product contains the 83 kDa protective antigen protein, ≤ 2.4 mg aluminum hydroxide (equivalent to 0.83 mg of aluminum) per 0.5 ml dose, 25 mcg/ml benzethonium chloride and 100 mcg/ml formaldehyde, added as preservatives.⁵ Currently AVA is FDA approved for pre and post-exposure prophylaxis in adults 18-65 years old at high risk for exposure to anthrax.² For pre-exposure prophylaxis the vaccine is typically given intramuscular (IM), whereas for post-exposure prophylaxis it is administered subcutaneous (SQ) as this results in higher antibody concentrations by week 4 than the IM route.⁶ Active duty military personnel at risk of exposure through the threat of bioterrorism make up the vast majority of the population who currently receive AVA. According to the Adverse reactions to vaccine practice parameter 2012 update, if a person has a history of a severe anaphylactic allergy to latex, then vaccines supplied in vials or syringes should be avoided.⁷ Providing protection against anthrax through vaccination of high risk active duty military members with a history of latex allergy, presents potential challenges and safety concerns.

There have been a few rare reports of possible immediate hypersensitivity reactions after immunization with vaccines which contain latex packaging in recipients with a history of a latex allergy. In most instances, specific studies to confirm latex as the cause of the reaction have not been performed.^{8,9} Interestingly, only one vaccine anaphylactic reaction attributed to latex has been documented in the

literature. This occurred after a hepatitis B vaccination in 1995. The authors suggest that vaccine contamination happened when the needle was passed through the NRL vial stopper when the vaccine was drawn. On re-vaccination, where the vaccine was drawn using a glass syringe from a vial with the stopper removed, there was no reaction.¹⁰ AVA only comes in a 5ml multiple-dose vial that contains ten 0.5 ml doses. Repeated puncture of the vial, theoretically increases the risk of the vaccine solution coming into contact with the NRL stopper, and, in turn, increases the potential risk for hypersensitivity reactions. No previous studies enumerating latex content in the AVA have been published.

The goal of our study was to quantify the NRL content present in AVA. Hev b 1,3,5, and 6.02 allergens were used as a screen for NRL content; they are the only commercially available latex allergens with an ELISA assay. The ELISA assay used in the study was manufactured by Icosagen. The assay's limit of detection for Hev b 1 and 3 was 10ng/ml, while the limit of detection for Hev b 5 and 6.02 was 5 ng/ml. A total of 3 vaccines with different lot numbers were examined. The first vaccine was tested after being inverted for 6 months so as to make certain that vaccine solution was in contact with the rubber stopper. All other conditions mimicked package storage. Then two new anthrax vaccines were tested. Next, using a 20- gauge needle, the two new vaccines were punctured thirty times, with inversion of the vaccine between each puncture in order to ensure solution contact with the vial stopper. Thirty punctures were performed which would far exceed the number of punctures for real world use.

Results are presented in table I. These data demonstrate undetectable Hev b 1,3,5 and 6.02 content among all three anthrax vaccines tested. Neither the rubber stopper contact with the vaccine solution for 6 months, or repeated rubber stopper puncturing, had an effect on the outcome of the vaccines tested. This study provides the first known data quantifying NRL content in AVA. There are four

limitations to our study that should be addressed. First, due to vaccine supply, only three lots were tested, but it should be noted that results were consistent and reproducible between all lot numbers. Second, although we tested all commercially available latex allergens, all known NRL allergens were not tested. Third the latex threshold dose to elicit a systemic reaction is not reported in the literature, however this study provides evidence that if latex is present in the vaccine solution it is less than 10 ng/ml and is unlikely to be clinically relevant. Lastly, given that AVA can be given both IM and SQ, there is a theoretical increased risk for reaction with IM dosing due to increased blood supply at the site of injection. In the future, SQ dosing of latex allergic patients may be a suitable alternative.

In conclusion, our study revealed undetectable levels of the NRL allergens Hev b 1, 3, 5, and 6.02 in all tested anthrax vaccines.

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TABLE I. Latex allergen content in AVA (measured by ELISA)

AVA Lot number	Hev b 1	Hev b 3	Hev b 5	Hev b 6.02
AV570A	<10 ng/ml limit of detection	<10 ng/ml limit of detection	<5 ng/ml limit of detection	<5 ng/ml limit of detection
6 months of inversion				
FAV623A Pre/Post puncture	<10 ng/ml limit of detection	<10 ng/ml limit of detection	<5 ng/ml limit of detection	<5 ng/ml limit of detection
FAV625A Pre/ Post puncture	<10 ng/ml limit of detection	<10 ng/ml limit of detection	<5 ng/ml limit of detection	<5 ng/ml limit of detection

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