PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2008; **17**: 1060–1067
Published online 10 September 2008 in Wiley InterScience (www.interscience.wiley.com) **DOI**: 10.1002/pds.1657

ORIGINAL REPORT

Evaluation of body mass index, pre-vaccination serum progesterone levels and anti-anthrax protective antigen immunoglobulin G on injection site adverse events following anthrax vaccination in women

Yujia Zhang PhD[1†], Stacey W. Martin MSc[2†], Charles E. Rose Jr PhD[2], Raymond E. Biagini PhD[3], Laura H. Franzke PhD, MPH[4], Jerry P. Smith PhD[3], Deborah L. Sammons BS[3], Shirley A. Robertson[3] and Michael M. McNeil MD, MPH[2*]

[1]*Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[2]*Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[3]*National Institute of Occupational Safety and Health, Centers for Disease Control and Prevention, Atlanta, GA, USA*
[4]*Division of Alliance Management, National Center for Public Health Informatics, Centers for Disease Control and Prevention, Atlanta, GA, USA*

SUMMARY

Background In 2002, CDC initiated the Anthrax Vaccination Program (AVP) to provide voluntary pre-exposure anthrax vaccination for individuals at high risk for exposure to *Bacillus anthracis* spores. The AVP offered an opportunity to investigate hypothesized reasons for a reported gender difference in injection site adverse events (AEs) following anthrax vaccine adsorbed (AVA).

Objectives To evaluate in women the impact of body mass index (BMI), pre-vaccination serum progesterone levels, and pre-vaccination anti-anthrax protective antigen immunoglobulin G concentrations (anti-PA IgG) on the occurrence of AEs following subcutaneous AVA vaccination.

Methods Participants' BMI was determined at enrollment. Also, pre-vaccination blood samples were assayed for serum progesterone and anti-PA IgG. Post-vaccination solicited AEs were recorded by participants using a 4-day diary card.

Results Obese group had an elevated risk for arm soreness. Decreased pre-vaccination serum progesterone level was associated with arm swelling. Increased pre-vaccination anti-PA IgG was associated with itching on the arm; and within the obese group, was associated with arm swelling, lump or knot, redness, soreness, and warmth.

Conclusions In AVA vaccinated women, obesity was associated with arm soreness and decreased pre-vaccination serum progesterone levels were associated with increased rate of arm swelling. Increased pre-vaccination anti-PA IgG may be associated with an increased frequency of itching on the arm, and in obese women, may increase the occurrence of arm swelling, lump or knot, redness, and warmth. Administering AVA according to a woman's menstrual phase may reduce the occurrence of certain injection site reactions. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — injection site adverse events; body mass index; pre-vaccination serum progesterone levels; pre-vaccination anti-anthrax protective antigen immunoglobulin G

Received 8 January 2008; Revised 14 July 2008; Accepted 5 August 2008

* Correspondence to: M. M. McNeil, CDC, MS C-25, Atlanta, GA 30333, USA. E-mail: mmm2@cdc.gov
† Yujia Zhang and Stacey W. Martin contributed equally to this article.

INTRODUCTION

Currently, anthrax vaccine adsorbed (AVA) is the only licensed human anthrax vaccine available in the United States. The approved regimen of AVA consists of a six-shot priming series, administered subcutaneously over the upper deltoid at 0, 2, and 4 weeks, 6, 12, and 18 months, followed by annual boosters.[1] Concerns about the safety of AVA arose in 1998 after the Department of Defense (DOD) initiated a program to provide AVA to all active duty and reservist U.S. service members.[2]

In 2002, an Institute of Medicine (IOM) review reported that AVA was reasonably safe and noted a gender difference (female predominance) in the occurrence of injection site reactions, although the etiology of this finding was unknown.[3] This gender difference was first reported by military investigators.[4–6] In a 1999 mandate, policy makers directed CDC to address this gender difference.[7]

A female predominance for injection site adverse events (AEs) has also been demonstrated with many other vaccines.[8] Data from the Vaccine Adverse Event Reporting System (VAERS) provide indirect evidence of a possible role for sex hormones; there is a female predominance among reports of vaccine associated AEs for those aged ≥ 10 years,[9] which may correspond with menarche in girls. Whether sex hormones represent a primary mechanism for heightened reactogenicity in women, or contribute through secondary effects [e.g., a difference in body mass index (BMI) or deltoid fat pad thickness between men and women and/or gender specific immune responses] is unclear.

A localized type III or Arthus reaction is another possible mechanism for heightened reactogenicity to AVA in women. These type III reactions have been reported to occur at the injection site of vaccines containing tetanus or diphtheria toxoids after reimmunization in the presence of high circulating IgG antibody.[10–13] These reactions develop over 6–12 hours when pre-vaccination antibody in the serum and antigen in the vaccine may form antigen–antibody complexes which deposit in the walls of blood vessels in the tissues and are characterized by pain, swelling, induration, and edema occurring at the injection site. Thus, the gender difference in AVA reactogenicity may be associated with a gender specific difference in immune responsiveness which itself may or may not involve circulating sex hormone levels.

In 2002, the Anthrax Vaccination Program (AVP) provided voluntary pre-exposure anthrax vaccinations for workers who were considered to be at high risk for occupational exposure to *Bacillus anthracis*.[14] This program provided an opportunity to investigate potential risk factors and the biologic basis for injection site reactogenicity in women. This observational study evaluated our *a priori* hypotheses that hormonal phase [pre-vaccination (with AVA) serum progesterone level] and pre-vaccination serum anti-PA IgG concentration had a potential effect on injection site reactions reported by women during the first 4 days following each AVA dose. We tested for a potential interaction between these two parameters and also each individually with BMI calculated on participants at the time of their enrollment.

METHODS

Study population

The study population comprised pre-menopausal, non-pregnant women who consented to receive AVA through the AVP. AVP eligibility requirements are described elsewhere.[14] Pre-menopausal was defined as having self-reported regular menses during the 12-month period prior to enrollment.

Study procedures

At enrollment, each participant was interviewed, provided with study educational materials, signed an informed consent form, and completed a brief demographic and medical history questionnaire. Immediately prior to receipt of each AVA dose, the study nurse obtained a follow-up menstrual history and collected a 10 ml blood sample. The blood specimens were centrifuged and processed on site and sent for immediate serum progesterone testing. A frozen serum aliquot from each pre-AVA blood draw was later assayed for anti-PA IgG concentration.

Following each AVA dose, participants were given a diary card and instructed to report AEs they experienced during the first 4 days after vaccination (including the vaccination day). Solicited injection site AEs included arm movement limitation, arm swelling, bruise, itching on the arm, lump or knot, redness, soreness, and warmth. Participants were also asked to assign a severity rating to all AEs according to the following criteria: mild—does not interfere with routine activities, moderate—interferes with routine activities, severe—unable to perform routine activities.

BMI was computed using the participant's body weight and height recorded at their enrollment visit. The BMI categories previously defined by the CDC

DOI: 10.1002/pds

are: (1) underweight (BMI < 18.5), (2) normal (BMI between 18.5 and 24.9), (3) overweight (BMI between 25 and 29.9), and (4) obese (BMI ≥ 30).[15] After conducting a preliminary analysis, it was found that the obese category was uniquely different with respect to our outcomes when compared to the other categories. As a result, BMI categories were reduced to a dichotomous variable: non-obese (BMI < 30) and obese (BMI ≥ 30) for the final analysis.

Serum progesterone concentration was assayed using the ADVIA Centaur® Progesterone Assay, which is a competitive immunoassay using direct chemiluminescent technologies.[16] The values of serum progesterone concentration provided by the testing laboratory were 0.2–1.4 and 3.3–26.0 ng/ml for follicular phase and luteal phase, respectively. Since progestin compounds in pharmacologic contraceptives limit the secretion of naturally occurring progesterone by acting on the pituitary gland to decrease the secretion of follicle-stimulating hormone and luteinizing hormone at mid-cycle, determination of these participants' natural progesterone level may be complicated. Thus, participants reporting use of pharmacological contraceptives were excluded from the analysis.

Pre-vaccination serum anti-PA IgG was measured using a fluorescent covalent microsphere immunoassay (FCMIA) as previously reported.[17,18]

Statistical analysis

Binary outcomes were defined as the presence or absence of individual injection site AEs during the 4-day period following each AVA dose. The potential risk factors we investigated included BMI, pre-vaccination serum progesterone (ranged from 0.11 to 27.63 ng/ml with a mean value 3.33 ng/ml and used as a continuous variable in analysis), and pre-vaccination anti-PA IgG concentration. Anti-PA IgG concentrations ranged from 0.92 μg/ml (the laboratory assay cutoff for 'non-detectable') to 404 μg/ml and the majority (>90%) were values less than 100 μg/ml. To correct for skewness in the serum progesterone and anti-PA IgG concentration, we transformed these results using a $\log_{10}$ scale. Linearity of these continuous variables was evaluated using quartile plots and Box-Tidwell transformations. The $\log_{10}$ transformed serum progesterone values were < 0.15 for the follicular phase and from 0.52 to 1.41 for the luteal phase.

Multivariable logistic models were fit to obtain adjusted estimates of the odds ratio (OR). The following covariates were evaluated: BMI, $\log_{10}$ pre-vaccination progesterone, $\log_{10}$ pre-vaccination anti-PA IgG concentration, age, and race. Participants' age (ranged from 22 to 56 years) was treated as a categorical variable. Initially, age was grouped in four 10-year intervals: 18–24, 25–34, 35–44, and $\geq$45 years; however for our analysis, we eliminated the youngest category and included the three individuals (22, 23, 24 years) together with those in the 25–34 year interval as one 18–34 year category (Table 1). All two way interactions between potential risk factors were examined in preliminary model fits; however, only the interaction between BMI and $\log_{10}$ pre-vaccination anti-PA IgG concentration was found to be significant in the models of arm swelling, itching on the arm, lump or knot, redness, and warmth and thus retained in their final models. p-Values < 0.05 were considered statistically significant. The generalized estimating equation (GEE) approach was employed in modeling, and the exchangeable working correlation structure was used to address the correlation inherent from repeated measurements in parameter estimates and the AVA dose number was used to specify the order of repeated measurements within participants. Given the exploratory nature of this analysis, adjustments for multiple comparisons were not made.

The study was initially delayed in order to obtain Institutional Review Board approval. This necessary delay resulted in an unbalanced sample distribution across the dosing schedule; this was addressed using a weighted model. The weights were defined as the inverse of the particular vaccine dose's selection probability, that is, the proportion of the diary cards for that dose to the number of diary cards overall. SAS® version 9.1 (SAS Institute, Inc., Cary, NC) was used for our analysis.

Table 1. Demographics for 128 participants included in our analysis

Characteristic	Number of women (%)
Age in years (at enrollment)	
18–34	36 (28.1)
35–44	44 (34.4)
≥45	48 (37.5)
Race	
Black	19 (14.8)
Other	11 (8.6)
White	98 (76.6)
BMI (at enrollment)	
Non-obese (BMI < 30)	86 (67.2)
Obese (BMI≥30)	42 (32.8)

DOI: 10.1002/pds

Table 2. Reported solicited injection site AEs by BMI group

Injection site adverse event	Number reported as mild or moderate (%)		Number reported as severe* (%)	
	Non-obese*	Obese**	Non-obese*	Obese**
Soreness	250 (84.5)	79 (88.8)	8 (2.7)	6 (6.7)
Lump or knot	240 (81.1)	77 (86.5)	5 (1.7)	2 (2.3)
Redness	234 (79.1)	77 (86.5)	3 (1.0)	1 (1.1)
Arm swelling	226 (76.4)	64 (71.9)	3 (1.0)	2 (2.3)
Itching on the arm	197 (66.6)	70 (78.7)	0 (0.0)	1 (1.1)
Warmth	191 (64.5)	65 (73.0)	1 (0.3)	1 (1.1)
Arm motion limitation	88 (29.7)	31 (34.8)	4 (1.4)	1 (1.1)
Bruise	60 (20.3)	19 (21.4)	0 (0.0)	0 (0.0)

*The total diary cards from non-obese group = 296.
**The total diary cards from obese group = 89.

RESULTS

Our study enrolled 165 participants who completed a total of 532 diary cards. Included in our analytic dataset was information from 385 diary cards submitted by 128 participants who at their dose/visit had no recent history of pharmacologic contraceptive use. For the 385 diary cards included in the analysis, 43, 35, 38, 111, 87, and 71 followed vaccine doses 1, 2, 3, 4, 5, and 6, respectively.

We found the average pre-vaccination anti-PA IgG concentration (μg/ml) varied by dose: dose 1 (undetectable); dose 2 (undetectable); dose 3 (36.0, 95% CI 18.0, 54.0); dose 4 (9.5, 95% CI 7.2, 11.7); dose 5 (69.1, 95% CI 52.8, 85.3); and dose 6 (71.3, 95% CI 57.9, 84.6).

Table 1 summarizes participants' demographics by age category, race, and BMI group. The distribution by participants' age groups was similar with a slight predominance in those aged ≥45 years. The participants were predominantly white (76.6%) and approximately one-third of participants (32.8%) were in the obese (BMI≥30) group.

Table 2 presents the occurrence of solicited AEs. The most frequently reported solicited injection site AE was injection site soreness (89.1%).

Table 3 summarizes the results from the unadjusted and adjusted logistic models of arm movement limitation, bruise, and soreness and these analyses found that the obese group had an elevated risk for arm soreness (adjusted OR 3.58; 95% CI 1.21, 10.55). Tables 4 and 5 summarize the results from the unadjusted and adjusted logistic models of the other injection site AEs and these analyses found that decreased pre-vaccination progesterone level was associated with an increased frequency of arm swelling (adjusted OR 1.66; 95% CI 1.10, 2.49). Within the obese group (BMI ≥ 30), high pre-vaccination anti-PA IgG concentration was associated with an increased frequency of arm swelling (adjusted OR 3.31; 95% CI 1.41, 7.77), itching on the arm (adjusted OR 4.83; 95% CI 1.62, 14.42), lump or knot (adjusted OR 3.73; 95% CI 1.26, 11.04), redness (adjusted OR 3.81; 95% CI 1.33, 10.87), and warmth (adjusted OR 2.35; 95% CI 1.35, 4.09). Within the non-obese group, pre-vaccination anti-PA IgG concentration was associated with an increased frequency of itching on the arm (adjusted OR 1.48; 95% CI 1.08, 2.02).

DISCUSSION

To the best of our knowledge, this is the first report to present associations between BMI, pre-vaccination serum progesterone level and pre-vaccination IgG concentration, and AEs experienced by female vaccine recipients. This study suggests that obese women may experience elevated arm soreness and a depressed pre-vaccination serum progesterone level may increase a woman's odds of experiencing injection site arm swelling. Additionally, our results suggest that a high anti-PA IgG concentration at the time of vaccination may increase a woman's odds for experiencing itching on the arm, and in obese women, may increase the odds for experiencing arm swelling, lump or knot, redness, and warmth.

Both serum estrogen and progesterone levels vary during a woman's menstrual cycle, which is divided into two phases: follicular (estrogen dominant) and

DOI: 10.1002/pds

Table 3. Unadjusted odds ratios and adjusted odds ratios by age and race for selected covariates by solicited injection site AEs without significant interaction between pre-vaccination anti-PA IgG and BMI group

	Arm movement limitation		Bruise		Soreness	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Log_{10} pre-vaccination serum progesterone (one unit decrease)	1.40 (0.86, 2.30)	1.43 (0.86, 2.40)	1.40 (0.84, 2.33)	1.44 (0.86, 2.41)	1.66 (0.80, 3.44)	1.85 (0.84, 4.05)
Log_{10} pre-vaccination anti-PA IgG (one unit increase)	0.81 (0.63, 1.05)	0.78 (0.59, 1.04)	0.74 (0.54, 1.01)	0.75 (0.55, 1.02)	0.75 (0.53, 1.06)	0.69 (0.46, 1.02)
BMI group						
Other	Reference	Reference	Reference	Reference	Reference	Reference
Obese	1.33 (0.58, 3.07)	1.72 (0.70, 4.18)	1.01 (0.48, 2.13)	1.18 (0.55, 2.55)	3.98 (1.16, 13.63)	3.58 (1.21, 10.55)

Table 4. Unadjusted odds ratios and adjusted odds ratios by age and race for covariate pre-vaccination serum progesterone by solicited injection site AEs with significant interaction between pre-vaccination anti-PA IgG and BMI group

	Arm swelling		Itching on the arm		Lump or knot	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Log_{10} pre-vaccination serum progesterone (one unit decrease)	1.64 (1.10, 2.45)	1.66 (1.10, 2.49)	1.27 (0.88, 1.83)	1.24 (0.85, 1.83)	1.40 (0.79, 2.47)	1.41 (0.76, 2.61)

	Redness		Warmth	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Log_{10} pre-vaccination serum progesterone (one unit decrease)	0.89 (0.53, 1.50)	0.90 (0.52, 1.54)	0.86 (0.55, 1.35)	0.87 (0.55, 1.37)

DOI: 10.1002/pds

Table 5. Unadjusted odds ratios and adjusted odds ratios by age and race for covariate pre-vaccination anti-PA IgG stratified by BMI group for solicited injection site AEs in Table 4

	Arm swelling		Itching on the arm		Lump or knot	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Log_{10} pre-vaccination anti-PA IgG (one unit increase) for obese women	2.05 (1.09, 3.83)	3.31 (1.41, 7.77)	3.97 (1.59, 9.93)	4.83 (1.62, 14.42)	3.06 (1.31, 7.16)	3.73 (1.26, 11.04)
Log_{10} pre-vaccination anti-PA IgG (one unit increase) for non-obese women	1.29 (0.93, 1.79)	1.16 (0.81, 1.66)	1.47 (1.09, 1.96)	1.48 (1.08, 2.02)	1.18 (0.84, 1.66)	1.17 (0.80, 1.70)
	Redness				Warmth	
	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)			Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Log_{10} pre-vaccination anti-PA IgG (one unit increase) for obese women	2.99 (1.19, 7.52)	3.81 (1.33, 10.87)			2.07 (1.22, 3.53)	2.35 (1.35, 4.09)
Log_{10} pre-vaccination anti-PA IgG (one unit increase) for non-obese women	0.98 (0.72, 1.32)	0.96 (0.68, 1.36)			1.14 (0.89, 1.47)	1.13 (0.87, 1.48)

luteal (progesterone dominant). Unlike serum estrogen which remains at moderate or high concentrations throughout the cycle, serum progesterone is at very low or undetectable levels during the follicular phase and following ovulation rapidly increases to peak at the end of the luteal phase. Progesterone has been shown for human beings and animals (mice) to depress antibody production whereas estrogen increases the B-cell response *in vivo* and *in vitro*.[19,20] Thus, AVA administered subcutaneously when the serum progesterone level is low could result in enhanced antibody production and anti-PA IgG response and manifest as a localized type III or Arthus reaction with increased arm swelling. Using our estimated ORs and the cutoffs of serum progesterone provided by the testing laboratory we expect about a one unit difference between the two menstrual phases in log_{10} transformed serum progesterone level and estimate that the odds for experiencing arm swelling would be 66% higher if AVA is administered subcutaneously during a woman's follicular menstrual phase when progesterone levels are depressed. Sex hormones have also been involved in a spectrum of immune responses such as thymocyte function, cytokine and monokine production, lymphocyte proliferation, and the expression of adhesion molecules and HLA-class II receptors.[20]

Increased anti-PA IgG concentration at the time of vaccination was associated with itching on the arm. Furthermore, we found for obese women that increased pre-vaccination anti-PA IgG concentration was associated with injection site arm swelling, lump or knot, redness, and warmth. For example, we evaluated obese subjects according to whether their dose 5 pre-vaccination anti-PA IgG was low (<average pre-vaccination anti-PA IgG) or high (>average pre-vaccination anti-PA IgG). We found an average 15.5 μg/ml (log_{10} transformed anti-PA IgG value of 1.2) for the low group and 141.3 μg/ml (log_{10} transformed anti-PA IgG value of 2.2) for the high group. Thus, obese subjects in the high group had about a one unit increment in their log_{10} transformed anti-PA IgG which equates to about a 3.3 higher odds of experiencing injection site arm swelling compared to the low group. While the exact physiological reasons for this finding remains to be elucidated, we speculate that vaccination into adipose tissue, which has poorer circulation than muscle, and lacks the appropriate cells to initiate the immune response, may cause delayed antigenic processing by macrophages increasing the likelihood of AVA injection site reactions. Additionally, injection of AVA subcutaneously in an obese woman's arm introduces antigen

DOI: 10.1002/pds

directly into a complex pro-inflammatory milieu which could contribute to our findings.[21–23]

Poland *et al*.[24] measured the thickness of the deltoid fat pad of the arm in 220 adults (healthcare workers presenting for hepatitis B immunization) using high frequency ultrasonography. These researchers found women had significantly more subcutaneous fat overlying the deltoid muscle than men and subcutaneous injections have been reported associated with more injection site AEs.[25–29] In addition, Pittman *et al*.[4] reported that in women, the incidence of erythema, induration, and subcutaneous nodules were significantly reduced when AVA was administered by the intramuscular route compared to the standard subcutaneous route. These and other findings suggest the need for a study comparing intramuscular and subcutaneous AVA administration to potentially reduce injection site reactions.

There are several limitations which may influence the interpretation of our results. The participants were volunteers enrolled in a program to vaccinate high-risk civilian workers. Therefore, the study population is not representative of all U.S. women or women in the military who continue to be mandated to receive AVA. In this study, we excluded 37 women who had a recent history of pharmacologic contraceptive use. Although the frequency of injection site AEs reported by these women and the distribution of their pre-vaccination IgG concentrations were similar to those of the women we included, there was a higher proportion of younger aged women (56.8 *vs.* 28.1%) and a higher proportion of non-obese subjects (81.1 *vs.* 67.2%) thus this exclusion may have introduced some bias in our analysis. Since all study participants received AVA, there were no unvaccinated controls in whom to assess the background occurrence of injection site AEs. Also, BMI for our participants was obtained only at the time of their enrollment and possible fluctuations in BMI during the course of the study were not measured. We did not measure other female sex hormones, in particular serum estrogens, which may potentially have an effect on injection site AEs. Finally, our study was limited to the assessment of pre-AVA anti-PA IgG as a potential risk factor for AEs and no serum was obtained for post vaccination anti-PA IgG concentrations from our participants.

While our results are interesting, limitations including the observational nature of the study and its small sample size make further confirmation of our findings important. An evaluation of serum progesterone levels in women may be revealing in the evaluation of other vaccines which have a demonstrated gender differential. However, these preliminary results suggest that administering AVA according to a woman's menstrual phase may reduce the occurrence of certain injection site reactions.

DISCLAIMERS

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Mention of a product or company name does not infer endorsement by the Centers for Disease Control and Prevention. The content and conclusions of this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

The protocol for this study was approved by an Institutional Review Board of the Centers for Disease Control and Prevention.

None of the authors has conflicts of interest to declare.

ACKNOWLEDGEMENTS

The authors would like to thank the many volunteers who made this study possible. Also, we thank Lanaya Peterson (Logistics Health, Inc.) for her assistance with the study survey and Aaron Aranas for managing

KEY POINTS

- Prior studies have indicated that women typically experience more injection site AEs than men following subcutaneous AVA vaccination.
- To the best of our knowledge, this is the first report to present associations between BMI, pre-vaccination serum progesterone level and pre-vaccination IgG concentration, and AEs experienced by female vaccine recipients.
- Obesity may be a potential risk factor for arm soreness in women.
- Decreased pre-vaccination serum progesterone level in women may be a potential risk factor for arm swelling.
- Increased pre-vaccination anti-PA IgG in women may be a potential risk factor for itching on the arm.
- Increased pre-vaccination anti-PA IgG in obese women may be a potential risk factor for arm swelling, lump or knot, redness, and warmth.
- Administering AVA according to a woman's menstrual phase may reduce the occurrence of certain injection site reactions.

DOI: 10.1002/pds

the database. This work was supported in part by an interagency agreement between NIOSH and NIEHS (Y1-ES-0001—Clinical Immunotoxicity).

REFERENCES

1. Anthrax Vaccine Adsorbed (BIOTHRAX™) Package Insert. 2002; Manufactured by Bioport Corporation, Lansing Michigan, US Lic. No. 1260.
2. Lange JL, Lesikar SE, Rubertone MV, Brundage JF. Comprehensive systemic surveillance for adverse events of anthrax vaccine absorbed, US Armed Forces 1998–2000. *Vaccine* 2003; **21**: 1620–1628.
3. Institute of Medicine. *The anthrax vaccine. Is it safe? Does it work*? National Academy Press: Washington DC, 2002.
4. Pittman PR, Kim-Ahn G, Pifat DY, *et al*. Anthrax vaccine: Immunogenicity and safety of a dose-reduction, route-change comparison study in humans. *Vaccine* 2002; **20**: 1412–1420.
5. Pittman PR, Gibbs PH, Cannon TL, Friedlander AM. Anthrax vaccine: Short-term safety experience in humans. *Vaccine* 2001; **20**: 972–978.
6. Hoffman K, Costello C, Menich M, Grabenstein JD, Engler RJ. Using a structured medical note for determining the safety profile of anthrax vaccine for US soldiers in Korea. *Vaccine* 2003; **21**: 4399–4409.
7. Institute of Medicine. *An Assessment of the CDC Anthrax Vaccine Safety and Efficacy Research Program*. National Academy Press: Washington DC, 2002.
8. McNeil MM, Chiang IS, Wheeling JT, Zhang Y. Short-term reactogenicity and gender effect of anthrax vaccine: Analysis of a 1967–1972 study and review of the 1955–2005 medical literature. *Pharmacoepidemiol Drug Saf* 2007; **16**: 259–274.
9. Braun MM, Ellenberg SS. Descriptive epidemiology of adverse events after immunization: Reports to the Vaccine Adverse Event Reporting System (VAERS), 1991–1994. *J Pediatr* 1997; **131**: 529–535.
10. Facktor MA, Bernstein RA, Fireman P. Hypersensitivity to tetanus toxoid. *J Allergy Clin Immunol* 1973; **52**: 1–12.
11. Ponvert C, Scheinmann P. Vaccine allergy and pseudo-allergy. *Eur J Dermatol* 2003; **13**: 10–15.
12. Institute of Medicine. *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality*. National Academy Press: Washington, DC, 1994.
13. CDC. Preventing tetanus, diphtheria, and pertussis among adolescents: Use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. *MMWR* 2006; **55**: 1–49.
14. Fowler GL, Baggs JM, Weintraub ES, Martin SW, McNeil MM, Gust DA. Factors influencing laboratory workers' decisions to accept or decline anthrax vaccine adsorbed (AVA): Results of a decision-making study in CDC's Anthrax Vaccination Program. *Pharmacoepidemiol Drug Saf* 2006; **15**: 880–888.
15. BMI—Body Mass Index: About BMI for Adults, Centers for Disease Control and Prevention: http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/about_adult_BMI.htm (accessed June 26, 2007).
16. ADVIA, Centaur, ReadyPack, and ACS: 180. Bayer Corporation, 1998.
17. Biagini RE, Sammons DL, Smith JP, *et al*. Determination of serum IgG antibodies to *Bacillus anthracis* protective antigen in environmental sampling workers using a fluorescent covalent microsphere immunoassay. *Occup Environ Med* 2004; **61**: 703–708.
18. Biagini RE, Sammons DL, Smith JP, *et al*. Comparison of a multiplexed fluorescent covalent microsphere immunoassay and an enzyme-linked immunosorbent assay for measurement of human immunoglobulin G antibodies to anthrax toxins. *Clin Diag Lab Immunol* 2004; **11**: 50–55.
19. Ahmed SA, Hissong BD, Verthelyi D, Donner K, Becker K, Karpuzoglu-Sahin E. Gender and risk of autoimmune diseases: Possible role of estrogenic compounds. *Environ Health Perspect* 1999; **107**: 681–686.
20. Da Silva JAP. Sex hormones and glucosteroids: Interactions with immune system. *Ann NY Acad Sci* 1999; **876**: 102–117.
21. Wellen KE, Hotamisligil GS. Inflammation, stress and diabetes. *J Clin Invest* 2005; **115**: 1111–1119.
22. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; **112**: 1796–1808.
23. Xu H, Barnes GT, Yang Q, *et al*. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003; **112**: 1821–1830.
24. Poland GA, Borrud A, Jacobson RM, *et al*. Determination of deltoid fat pad thickness: Implications for needle length in adult immunization. *JAMA* 1997; **277**: 1709–1711.
25. Zuckerman JN. The importance of injecting vaccines into muscle. Different patients need different needle sizes. *BMJ* 2000; **321**: 1237–1238.
26. Ipp MM, Gold R, Goldbach M, *et al*. Adverse reactions to diphtheria, tetanus, pertussis-polio vaccination at18 months of age: Effect of injection site and needle length. *Pediatrics* 1989; **83**: 679–682.
27. American Academy of Pediatrics. *Report of the committee on infectious diseases* (24th edn). AAP: Washington, 1997.
28. Michaels L, Poole RW. Injection granuloma of the buttock. *Can Med Assoc J* 1970; **102**: 626–628.
29. Haramati N, Lorans R, Lutwin M, Kaleya RN. Injection granulomas: Intramuscle or intrafat? *Arch Fam Med* 1994; **3**: 146–148.

DOI: 10.1002/pds