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## Original Contribution

# Birth Defects among Infants Born to Women Who Received Anthrax Vaccine in Pregnancy

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In response to bioterrorism threats, anthrax vaccine has been used by the US military and considered for civilian use. Concerns exist about the potential for adverse reproductive health effects among vaccine recipients. This retrospective cohort evaluated birth defects, in relation to maternal anthrax vaccination, among all infants born to US military service women between 1998 and 2004. Department of Defense databases defined maternal vaccination and infant diagnoses; multivariable regression models described potential associations between anthrax vaccination and birth defects in liveborn infants. Among 115,169 infants born to military women during this period, 37,140 were born to women ever vaccinated against anthrax, and 3,465 were born to women vaccinated in the first trimester of pregnancy. Birth defects were slightly more common in first trimester-exposed infants (odds ratio = 1.18, 95% confidence interval: 0.997, 1.41) when compared with infants of women vaccinated outside of the first trimester, but this association was statistically significant only when alternative referent groups were used. Although the small observed association may be unlikely to represent a causal relation between vaccination in early pregnancy and birth defects, this information should be considered when making decisions about administering anthrax vaccine to pregnant women.

anthrax vaccines; congenital abnormalities; immunization; military personnel; reproductive history; women's health

Abbreviation: ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification.

World events have prompted grave concern about the use of infectious agents for political terrorism. In 2001, bioterrorists exposed civilians to *Bacillus anthracis* spores through the US postal system, causing five deaths, several disease cases, and many subclinical exposures (1, 2). There is potential for much more extensive morbidity and mortality if weaponized anthrax were aerosolized over a large population. Health officials have provided guidance on responding to anthrax exposure (3, 4), and there has been some public outcry to provide anthrax vaccine to large numbers of civilians (5). Effective prevention or response to anthrax threats might require very high vaccine coverage of populations at risk (6–8).

Currently available anthrax vaccine is produced from formalin-treated, attenuated anthrax bacilli. The vaccine has been licensed by the US Food and Drug Administration since 1970 and was originally used to protect persons whose occupation put them at risk of anthrax. Recognizing the potential threat of anthrax in biowarfare, the US military provided anthrax vaccine to several thousand service members during the Gulf War of 1990–1991, but tracking of vaccinations was less than optimal (9). In 1997, the Department of Defense

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developed a plan to vaccinate all military members against anthrax over the course of several years and to systematically track vaccination (10). Supply and logistic challenges limited the broad application of the original vaccine plan, and the policy was later revised to require anthrax vaccination only for those deploying to certain regions outside of the United States. Pregnancy has remained one of the few medical reasons under which military members may be exempt from anthrax vaccination.

Many professionals, military and civilian, have expressed concern about the potential adverse health effects of anthrax vaccination (11, 12). Much subsequent research has been undertaken to confirm the safety of anthrax vaccine (13–15). Still, reproductive health effects are among the most troublesome and difficult problems to assess. Limited studies have not established reproductive health problems after anthrax vaccination (16, 17), but no studies have evaluated exposure during pregnancy. Although anthrax vaccine was never intentionally administered to pregnant women, exposures occurred when pregnancy was not recognized at the time of vaccination.

Because the US military administered anthrax vaccine to more than 1 million healthy young adults between 1998 and 2004, the Department of Defense is in a unique position to provide valuable information about its experience with immunization (18). The availability of a relatively new military-wide vaccine database (19), in addition to well-established databases on health-care utilization (20), makes such analyses possible. This investigation was undertaken to identify the cohort of military women inadvertently vaccinated during pregnancy and to evaluate birth defects among their infants as one important reproductive health outcome.

## MATERIALS AND METHODS

All liveborn infants with identifiable data born between January 1, 1998, and December 31, 2004, to women serving in the US military were defined through the Department of Defense Birth and Infant Health Registry (21). Infants born to families in which the father was in the military but the mother was civilian were not included in these analyses. The system captures electronic data on virtually all Department of Defense livebirths worldwide, in both military and civilian facilities, and all available health-care encounters, inpatient and outpatient, for infants in the first year of life. Birth defects are defined by nationally accepted diagnostic codes from the *International Classification for Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), as detailed by the National Birth Defects Prevention Network (22). Registry data are routinely validated by review of a sample of birth defect cases (21) with criteria established by the Metropolitan Atlanta Congenital Defects Program (23). For this study, additional confirmation of birth defects diagnoses was performed by a dysmorphologist (C.A.M.), who reviewed available medical records of infants with a birth defect code who were born in 1998 and 1999 and included in the primary analysis. This review was performed to evaluate potential systematic errors in the coding of defects; the reviewer had no knowledge of the timing of the maternal vaccine exposures related to these cases (24).

Anthrax vaccination data were obtained from the central electronic database maintained by the Department of Defense. Data include dates and location of each vaccine dose given to military members, as well as identifying and demographic information. Anthrax vaccination data may include up to six doses in the primary series, as well as annual booster doses. Vaccination data from the electronic database were compared with data contained in the hard-copy medical records of a subset of women whose records were archived after they left military service (19, 24).

Infants were classified by maternal exposure to anthrax vaccination and the timing of such exposure in relation to the first trimester, defined as the first 14 weeks of pregnancy. The first trimester was determined by gestational age at delivery in the medical record (5,569 cases) when available. For cases without gestational age defined at delivery, ICD-9-CM codes were used to distinguish preterm (ICD-9-CM code 765.1), extreme preterm (ICD-9-CM code 765.0), and full-term births. Full-term, preterm, and extreme preterm infants were considered exposed to anthrax vaccine in the first trimester of pregnancy if there was a record of maternal vaccination between 196 and 294 days (28–42 weeks), 161 and 259 days (23–37 weeks), and 98 and 196 days (14–28 weeks) before birth, respectively. Although anthrax vaccine doses may have been received before, during, and after pregnancy, vaccination categories were defined as mutually exclusive, such that first trimester vaccination took precedence, followed by second or third trimester exposure, prepregnancy vaccination, and postpregnancy vaccination.

The prevalence of birth defects diagnosed in the first year of life was calculated. Multivariable analyses were performed to assess the relation between birth defects and all independent variables, including maternal anthrax vaccination, infant's gestational age, plurality (singleton or multiple), infant's gender, maternal age, race/ethnicity, marital status, military service branch (Army, Navy, Air Force, or Marine Corps), and military rank (enlisted or officer). Regression diagnostics were performed to assess possible collinearity among variables. Multivariable logistic regression models were used to estimate the adjusted odds and 95 percent confidence intervals of birth defects among infants with the exposures of concern. The models used generalized estimating equations to account for correlated outcomes among multiple births; such births included siblings from different pregnancies as well as twins (25). All analyses were performed by using SAS, version 8.0, software (SAS Institute, Inc., Cary, North Carolina).

The primary, a priori model assessed the odds of birth defects among infants exposed to anthrax vaccine in the first trimester compared with infants of all other vaccinated women. Other vaccinated women were used as the comparison group because of concerns that never-vaccinated women might be less comparable, perhaps less healthy, because they were waived from being ready for deployment (26, 27). Alternative models were developed to assess the odds of birth defects among all infants in anthrax-vaccinated groups compared with each other and compared with infants

born to never-vaccinated women. In addition, sensitivity analyses were performed on the exposure window, moving the first trimester period of concern up to 3 weeks before and 3 weeks after the presumed onset of the ovulatory cycle of pregnancy. Finally, dose-response was evaluated in an alternative model that included those with two or more doses of anthrax vaccinations received in the first trimester of pregnancy.

The dysmorphologist reviewed all defect cases born to vaccinated mothers to ascertain if patterns or clusters of birth defects were apparent. The prevalence of specific defects in first trimester-exposed infants was compared with that of infants of other vaccinated women in separate regression models, adjusting for all available independent variables.

This research, performed under Naval Health Research Center institutional review board-approved protocol 31272, has been conducted in compliance with all applicable US Federal Regulations governing the protection of human subjects in research.

## RESULTS

Among 115,169 infants born to 95,595 military women during 1998–2004, analyses revealed that 3,465 infants were born to women who received anthrax vaccine during the first trimester of pregnancy (table 1). Of these, 938 infants were exposed to more than one dose during the first trimester. There were 33,675 infants born to women who received anthrax vaccine outside of the first trimester. Of these, 663 infants appeared exposed in late pregnancy, 14,306 infants' mothers were vaccinated before pregnancy, and 18,706 infants' mothers were vaccinated only after giving birth. Finally, 78,029 infants were born to military women who had no record of receiving anthrax vaccine.

Original hardcopy medical records were reviewed for 11,271 of the 95,595 women who gave birth during the study period, and the anthrax vaccination information in these records was compared with that contained in the electronic database. Hardcopy records were available from a national archive after women left military service; therefore, the 11,271 records did not represent a random sample but were more likely from women who gave birth earlier in the observation period and left military service soon after. A total of 1,318 women had anthrax vaccination in their medical records, and 1,158 had anthrax vaccination recorded in the electronic database. When compared with those of medical records, the specificity of electronic data was 97.5 percent, and the sensitivity was 61.5 percent for correctly identifying vaccine recipients. Among women whose vaccination date was recorded in both their medical record and in the electronic database, the recorded dates agreed to within 2 days for 87 percent of records.

Validation of birth defect diagnoses was pursued by use of hardcopy records of infants from vaccinated mothers. A total of 115 complete records were available and reviewed, and these included 133 birth defect diagnoses. The dysmorphologist validated 91 (68 percent) of the individual defects; most invalid diagnoses represented suspected birth defects that were subsequently ruled out, prematurity related, or minor anomalies; cases with invalid diagnoses were excluded from all analyses. Patent ductus arteriosus and congenital hip dislocation represented the majority of invalid diagnoses; 23 of 32 cases (72 percent) of patent ductus arteriosus were invalid, and nine of 14 cases (64 percent) of congenital hip dislocation were invalid. Because of these findings, cases of isolated patent ductus arteriosus and cases of isolated congenital hip dislocation were not considered major defects in the primary analysis.

The birth and demographic characteristics of all infants are shown in table 1. Infants exposed to first trimester anthrax vaccination were slightly less likely to be born preterm, compared with infants born to other vaccinated women (7.6 vs. 8.9 percent, respectively) (Pearson's chi-square $p = 0.01$). No statistically significant differences were observed between exposure groups with regard to multiple births or infant's gender. Never-vaccinated mothers differed from vaccinated mothers, however, in that never-vaccinated women tended to be older, of White race/ethnicity, married, serving in the Air Force or Navy, and of officer rank.

A total of 162 infants (4.7 percent) exposed to maternal anthrax vaccine in the first trimester had at least one major birth defect diagnosed in the first year of life. Among infants born to women vaccinated outside of the first trimester, 4.2 percent had birth defects. Table 2 shows the results, including odds ratios and 95 percent confidence intervals, of saturated multivariable regression analysis of the primary, a priori model. Variables that were statistically significantly associated with birth defects included preterm birth, male infant's gender, and maternal age over 35 years. When logistic regression was performed on a model reduced by manual, stepwise, backwards elimination of variables, the findings related to maternal vaccination and birth defects were unchanged.

In alternative models, infants born to women vaccinated only postpregnancy and infants born to never-vaccinated women were considered the referent groups. Infants born to women in other vaccinated groups were compared with these referent groups, and adjusted odds of birth defects are shown in table 3. Infants exposed to maternal anthrax vaccine in the first trimester were at slightly increased odds of birth defects in these alternative models (odds ratio = 1.20, 95 percent confidence interval: 1.02, 1.42, when the referent group was defined as infants born to never-vaccinated women).

When sensitivity analyses were performed, varying the definition of the window of exposure, odds ratios associated with first-trimester exposure did not vary substantially from the a priori model (detailed results not shown). When vaccine dose-response was evaluated in an alternative model, infants exposed to two or more maternal anthrax vaccine doses in the first trimester did not have a significantly increased risk of birth defects (adjusted odds ratio = 1.19, 95 percent confidence interval: 0.86, 1.63).

Specific types of birth defects among infants exposed to maternal anthrax vaccine in the first trimester were compared with those among infants born to other vaccinated women. Multivariable regression analyses were performed for all defects with five or more cases in both the exposed

**TABLE 1. Characteristics of births to US military women, 1998–2004, by maternal anthrax vaccination exposure**

| Variable | Never vaccinated* ($n = 78,029$) | | Prepregnancy vaccination* ($n = 14,306$) | | First trimester vaccination* ($n = 3,465$) | | Second or third trimester vaccination* ($n = 663$) | | Postpregnancy vaccination* ($n = 18,706$) | | Total ($n = 115,169$) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % | No. | % | No. | % | |
| Infants with birth defects† | 3,145 | 4.03 | 652 | 4.56 | 162 | 4.68 | 25 | 3.77 | 720 | 3.85 | 4,704 |
| Gestational age | | | | | | | | | | | |
| Full term | 71,296 | 91.37 | 12,931 | 90.39 | 3,201 | 92.38 | 608 | 91.70 | 17,133 | 91.59 | 105,169 |
| Preterm‡ | 5,678 | 7.28 | 1,118 | 7.81 | 226 | 6.52 | 51 | 7.69 | 1,354 | 7.24 | 8,427 |
| Extreme preterm‡ | 1,055 | 1.35 | 257 | 1.80 | 38 | 1.10 | 4 | 0.60 | 219 | 1.17 | 1,573 |
| Infant's birth status | | | | | | | | | | | |
| Singleton | 75,867 | 97.23 | 13,839 | 96.74 | 3,390 | 97.84 | 651 | 98.19 | 18,182 | 97.20 | 111,929 |
| Multiple | 2,162 | 2.77 | 467 | 3.26 | 75 | 2.16 | 12 | 1.81 | 524 | 2.80 | 3,240 |
| Infant's gender | | | | | | | | | | | |
| Female | 38,460 | 49.29 | 6,961 | 48.66 | 1,685 | 48.63 | 314 | 47.36 | 9,226 | 49.32 | 56,646 |
| Male | 39,569 | 50.71 | 7,345 | 51.34 | 1,780 | 51.37 | 349 | 52.64 | 9,480 | 50.68 | 58,523 |
| Maternal age, years | | | | | | | | | | | |
| Younger than 35 | 72,587 | 93.03 | 13,380 | 93.53 | 3,347 | 96.59 | 642 | 96.83 | 17,875 | 95.56 | 107,831 |
| 35 or older | 5,442 | 6.97 | 926 | 6.47 | 118 | 3.41 | 21 | 3.17 | 831 | 4.44 | 7,338 |
| Maternal race/ethnicity | | | | | | | | | | | |
| White | 41,359 | 53.00 | 6,415 | 44.84 | 1,452 | 41.90 | 294 | 44.34 | 7,927 | 42.38 | 57,447 |
| Black | 23,465 | 30.07 | 5,033 | 35.18 | 1,282 | 37.00 | 212 | 31.98 | 7,407 | 39.60 | 37,399 |
| Hispanic | 6,990 | 8.96 | 1,603 | 11.21 | 417 | 12.03 | 76 | 11.46 | 1,883 | 10.07 | 10,969 |
| Asian | 2,754 | 3.53 | 566 | 3.96 | 136 | 3.92 | 24 | 3.62 | 769 | 4.11 | 4,249 |
| Other/unknown | 3,461 | 4.44 | 689 | 4.82 | 178 | 5.14 | 57 | 8.60 | 720 | 3.85 | 5,105 |
| Maternal marital status | | | | | | | | | | | |
| Married | 51,558 | 66.08 | 9,355 | 65.39 | 1,926 | 55.58 | 399 | 60.18 | 11,661 | 62.34 | 74,899 |
| Unmarried | 26,471 | 33.92 | 4,951 | 34.61 | 1,539 | 44.42 | 264 | 39.82 | 7,045 | 37.66 | 40,270 |
| Maternal branch of service | | | | | | | | | | | |
| Army | 25,179 | 32.27 | 5,556 | 38.84 | 1,754 | 50.62 | 304 | 45.85 | 8,684 | 46.42 | 41,477 |
| Navy | 22,608 | 28.97 | 3,382 | 23.64 | 507 | 14.63 | 106 | 15.99 | 3,428 | 18.33 | 30,031 |
| Marine Corps | 4,357 | 5.58 | 1,292 | 9.03 | 392 | 11.31 | 145 | 21.87 | 1,188 | 6.35 | 7,374 |
| Air Force | 23,586 | 30.23 | 4,052 | 28.32 | 792 | 22.86 | 98 | 14.78 | 5,160 | 27.58 | 33,688 |
| Other/unknown | 2,299 | 2.95 | 24 | 0.17 | 20 | 0.58 | 10 | 1.51 | 246 | 1.32 | 2,599 |
| Maternal rank | | | | | | | | | | | |
| Enlisted | 67,892 | 87.01 | 13,009 | 90.93 | 3,267 | 94.29 | 623 | 93.97 | 17,062 | 91.21 | 101,853 |
| Officer | 10,137 | 12.99 | 1,297 | 9.07 | 198 | 5.71 | 40 | 6.03 | 1,644 | 8.79 | 13,316 |
| Maternal military status | | | | | | | | | | | |
| Regular | 65,338 | 83.74 | 12,710 | 88.84 | 3,078 | 88.83 | 606 | 91.40 | 17,064 | 91.22 | 98,796 |
| Reserve/other | 12,691 | 16.26 | 1,596 | 11.16 | 387 | 11.17 | 57 | 8.60 | 1,642 | 8.78 | 16,373 |

* Vaccination categories are mutually exclusive such that first trimester vaccination takes precedence, followed by second or third trimester vaccination, prepregnancy vaccination, and postpregnancy vaccination.

† Excluding all cases of patent ductus arteriosus and congenital hip dislocation.

‡ Preterm infants were defined as 28–37 weeks' gestational age at birth or as *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM), code 765.1 when not confirmed with actual record. Extreme preterm infants were defined as less than 28 weeks' gestational age at birth or as ICD-9-CM code 765.0 when not confirmed with actual record.

and referent groups (table 4). Fifty-eight exposed infants had atrial septal defect, representing a statistically significant increase from the referent group. If preterm infants with isolated atrial septal defect were excluded from analyses, the association was no longer statistically significant. Similarly, statistical significance related to any individual defect, including atrial septal defect, was not found if adjustment for multiple comparisons was applied.

**TABLE 2. Adjusted* odds of birth defects among infants of US military women who received anthrax vaccine, 1998–2004**

| Variable | No birth defect | | Birth defect† | | Odds ratio | 95% confidence interval |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | | |
| Vaccination timing | | | | | | |
| Outside first trimester‡ | 32,278 | 95.85 | 1,397 | 4.15 | | |
| First trimester | 3,303 | 95.32 | 162 | 4.68 | 1.18 | 0.997, 1.41 |
| Gestational age | | | | | | |
| Full term‡ | 32,732 | 96.63 | 1,141 | 3.37 | | |
| Preterm or extreme preterm | 2,849 | 87.21 | 418 | 12.79 | 4.37 | 3.86, 4.94 |
| Infant's birth status | | | | | | |
| Singleton‡ | 34,576 | 95.88 | 1,486 | 4.12 | | |
| Multiple | 1,005 | 93.23 | 73 | 6.77 | 0.74 | 0.55, 1.00 |
| Infant's gender | | | | | | |
| Female‡ | 17,545 | 96.48 | 641 | 3.52 | | |
| Male | 18,036 | 95.16 | 918 | 4.84 | 1.39 | 1.25, 1.54 |
| Maternal age, years | | | | | | |
| Younger than 35‡ | 33,802 | 95.91 | 1,442 | 4.09 | | |
| 35 or older | 1,779 | 93.83 | 117 | 6.17 | 1.51 | 1.23, 1.87 |
| Maternal race/ethnicity | | | | | | |
| White‡ | 15,438 | 95.96 | 650 | 4.04 | | |
| Black | 13,318 | 95.58 | 616 | 4.42 | 1.01 | 0.89, 1.14 |
| Other | 6,825 | 95.88 | 293 | 4.12 | 1.00 | 0.86, 1.16 |
| Maternal marital status | | | | | | |
| Married‡ | 22,394 | 95.94 | 947 | 4.06 | | |
| Unmarried | 13,187 | 95.56 | 612 | 4.44 | 1.06 | 0.95, 1.19 |
| Maternal branch of service | | | | | | |
| Army‡ | 15,625 | 95.87 | 673 | 4.13 | | |
| Air Force | 9,692 | 95.94 | 410 | 4.06 | 1.05 | 0.92, 1.20 |
| Navy | 7,075 | 95.31 | 348 | 4.69 | 1.15 | 1.00, 1.32 |
| Marine Corps | 2,902 | 96.19 | 115 | 3.81 | 0.97 | 0.79, 1.19 |
| Other | 287 | 95.67 | 13 | 4.33 | 1.11 | 0.62, 1.98 |
| Maternal rank | | | | | | |
| Enlisted‡ | 32,534 | 95.80 | 1,427 | 4.20 | | |
| Officer | 3,047 | 95.85 | 132 | 4.15 | 0.94 | 0.75, 1.19 |
| Maternal military status | | | | | | |
| Regular‡ | 32,049 | 95.79 | 1,409 | 4.21 | | |
| Reserve/other | 3,532 | 95.93 | 150 | 4.07 | 0.96 | 0.78, 1.17 |

* Adjusted for all the variables listed in the table.
† Excluding all cases of patent ductus arteriosus and congenital hip dislocation.
‡ Referent group.

## DISCUSSION

We found that infants born to women who received anthrax vaccine in the first trimester of pregnancy had a slightly higher prevalence of birth defects than did infants born to women vaccinated outside of the first trimester. This finding was not statistically significant in the primary model and was statistically significant only when alternative referent groups were used.

When considering whether this association may be causative, researchers should consider some important limitations. Electronic records were the primary means of identifying maternal anthrax vaccination, infants' births, and birth defect diagnoses. Although extensive measures were undertaken to validate electronic records with actual medical records and expert review, not all entries could be validated. It is possible that some exposures or diagnoses were misclassified in these analyses. Electronic vaccination

**TABLE 3. Comparison of primary and alternative models, with the adjusted* odds of birth defects† among infants of US military women, by maternal anthrax vaccination status, 1998–2004**

| Exposure group | Odds ratio | 95% confidence interval |
|---|---|---|
| *Vaccination outside of first trimester, primary model (referent group)* | | |
| First trimester vaccinated | 1.18 | 0.997, 1.41 |
| *Vaccination postpregnancy (referent group)* | | |
| First trimester vaccinated | 1.20 | 1.005, 1.43 |
| Prepregnancy vaccinated‡ | 1.09 | 0.98, 1.22 |
| Late-pregnancy vaccinated | 0.86 | 0.58, 1.27 |
| *Never vaccinated (referent group)* | | |
| First trimester vaccinated | 1.20 | 1.02, 1.42 |
| Prepregnancy vaccinated‡ | 1.08 | 0.99, 1.17 |
| Late-pregnancy vaccinated | 0.86 | 0.59, 1.26 |
| Postpregnancy vaccinated | 1.02 | 0.95, 1.10 |
| Ever vaccinated | 1.05 | 0.98, 1.12 |

* Models adjusted for infant's birth status (singleton or multiple), infant's gender, maternal age, race/ethnicity, marital status, military service branch, rank, and military service status.

† Excluding all cases of patent ductus arteriosus and congenital hip dislocation.

‡ Analyses of prepregnancy vaccination were based on 1999–2004 birth cohorts; 1998 births were excluded because such infants would have almost no opportunity for prepregnancy maternal vaccination.

records were only 61.5 percent sensitive in identifying all vaccine recipients in a sample of women from early in the observation period. The timing of vaccination, however, was very accurate when recorded in electronic records. This was an important consideration in limiting the analysis to only infants born to vaccinated women and using the timing of vaccination as the critical variable. There was no evidence that birth defects, as defined in these analyses, were differentially misclassified in either the first trimester-exposed or the other vaccinated groups.

Despite potential data challenges, it may be considered provocative that infants exposed to maternal anthrax vaccine in early pregnancy appeared to have a higher prevalence of birth defects. The association observed was small but relatively consistent across a number of alternative models and sensitivity analyses. Findings were not explained by simple confounding of available demographic variables, which were adjusted in multivariable analyses. It is possible, however, that women vaccinated in early pregnancy differed from other women in important but less tangible ways. Inadvertent vaccination may be associated with late recognition of pregnancy, and late recognition of pregnancy has been associated with a small increased risk for a number of birth defects (28). One possible mechanism for such an association is that later-recognized pregnancies are also at higher risk for inadvertent exposure to tobacco, alcohol, medications, and environmental teratogens. It was not possible to evaluate such exposures in this study. If late-recognized pregnancies are at higher risk of problems, then infants exposed in the second or third trimester or exposed to two or more anthrax vaccine doses in utero may represent the latest-recognized pregnancies, and they might be expected to have the highest prevalence of birth defects; however, this was not suggested in our analyses. Later-recognized pregnancies in military members may result in receipt of multiple vaccinations in preparation for deployment, especially in recent years. Although the current analyses were limited to maternal anthrax vaccination, other analyses of maternal smallpox vaccination have shown similar results (29).

There is little information available to support biologic plausibility of anthrax vaccine as being teratogenic. No maternal vaccination has been established as causing birth defects, and inactivated vaccines are usually considered safe in pregnancy (30–33). Even inadvertent use of live virus vaccines in pregnant women is rarely associated with teratogenic effects (34–37). In fact, there is some animal evidence that nonspecific stimulation of the maternal immune system may be associated with a decreased risk of birth defects in offspring (38, 39).

It is interesting to note that infants exposed to maternal anthrax vaccine in the first trimester had a significantly higher risk of defects when compared with infants of never-vaccinated women in alternative modeling. Because vaccination is associated with military deployment, never-vaccinated women appeared demographically different from vaccinated women (table 1). Never-vaccinated women may include a higher proportion of older women and women with health problems that may limit their military readiness (26, 27). One of the potential strengths of these analyses was the ability to use more appropriate comparison groups, that is, infants born to women who were eligible for anthrax vaccination but not vaccinated in early pregnancy.

The finding of a slightly higher prevalence of certain defects, in particular, atrial septal defect, among first trimester-exposed infants merits further consideration. Confidence limits were presented without statistical adjustment for multiple comparisons; with such adjustment, the confidence interval would have included one. In addition, statistical significance of the atrial septal defect association was not found when preterm infants with isolated atrial septal defects were excluded from analyses. This alternate model for atrial septal defects may be more appropriate because the ICD-9-CM code for atrial septal defect includes patent foramen ovale, an obligatory opening in the atrial septum in the fetus (40). The Metropolitan Atlanta Congenital Defects Program, on which we based our validation study, excludes patent foramen ovales in all preterm infants and full-term infants up to 6 weeks of life because of the likelihood of persistence of the structure and the known difficulty of differentiating atrial septal defects from patent foramen ovales in the newborn period (23, 41). Although this study had limited statistical power to evaluate relatively rare birth defects, overall, no strong or consistent associations were observed between maternal vaccination and specific defects or patterns of defects in infants.

Further research on the health effects of anthrax vaccine and other immunizations should continue to focus on the full spectrum of reproductive health outcomes, in both men

**TABLE 4. Adjusted odds of selected birth defects among infants of US military women who received anthrax vaccine, 1998–2004**

| Defect category | ICD-9-CM* codes | First trimester vaccination of 3,465 infants | | Outside of first trimester vaccination of 33,675 infants | | Odds ratio† | 95% confidence interval† |
|---|---|---|---|---|---|---|---|
| | | No. | % | No. | % | | |
| Hydrocephalus without spina bifida | 742.3 without 741.0, 741.9 | 5 | 0.14 | 39 | 0.12 | 1.34 | 0.52, 3.44 |
| Microcephalus | 742.1 | 7 | 0.20 | 38 | 0.11 | 1.86 | 0.82, 4.24 |
| Ventricular septal defect | 745.4 | 31 | 0.89 | 241 | 0.72 | 1.27 | 0.87, 1.86 |
| Atrial septal defect‡ | 745.5 | 58 | 1.67 | 446 | 1.32 | 1.38 | 1.04, 1.82 |
| Pulmonary valve atresia or stenosis | 746.01, 746.02 | 9 | 0.26 | 124 | 0.37 | 0.74 | 0.38, 1.46 |
| Cleft palate or lip | 749.0, 749.1, 749.2 | 6 | 0.17 | 59 | 0.18 | 0.97 | 0.42, 2.27 |
| Pyloric stenosis | 537.0, 750.5 | 15 | 0.43 | 100 | 0.30 | 1.41 | 0.81, 2.45 |
| Obstructive genitourinary defects | 753.2, 753.6 | 11 | 0.32 | 121 | 0.36 | 0.89 | 0.48, 1.66 |
| Hypospadias and epispadias§ | 752.61, 752.62 | 18 | 1.01 | 191 | 1.11 | 0.94 | 0.56, 1.56 |
| Trisomies | 758.0, 758.1, 758.2 | 7 | 0.20 | 48 | 0.14 | 1.63 | 0.67, 4.00 |

* ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification.
† Adjusted odds ratios and 95% confidence intervals from multivariable models.
‡ Of the atrial septal defect cases, 304 were isolated anomalies. The remainder ($n = 200$) were diagnosed with other anomalies as well.
§ Analysis restricted to male infants.

and women, beyond birth defects (16, 17). Pregnancy losses, although not associated with maternal immunizations in general (30–37), are particularly challenging to evaluate well in observational epidemiologic studies. Other metrics among livebirths may represent part of the spectrum of reproductive health effects and even be used as indirect measures of higher-than-expected rates of pregnancy loss in a population. These metrics include the rate of full-term delivery and the male:female sex ratio of liveborn infants (42, 43). Neither of these measures was significantly reduced among the exposed population in the present study, suggesting no challenges with pregnancy loss after exposure to anthrax vaccine in utero. Future evaluations, especially using active follow-up, such as that within the Smallpox Vaccine in Pregnancy Registry (37, 44), may better evaluate outcomes such as pregnancy loss.

Research that may be just as important to vaccine recipients and policymakers is assessment of the reproductive risk of vaccinations given to women, or men, before conception. Note that these analyses found no evidence that prepregnancy maternal anthrax vaccination is associated with an increased risk for birth defects. Future studies may assess a wider range of preconception reproductive health concerns. Studies of possible reproductive health effects in animal models also would be helpful.

In summary, we found that maternal anthrax vaccination in the first trimester of pregnancy was associated with a small increased prevalence of birth defects in infants, which was not statistically significant when compared with that of infants born to women vaccinated outside of pregnancy. Women vaccinated prepregnancy or in late pregnancy did not appear to be at increased risk of having an infant with a birth defect, compared with never-vaccinated women. There are several possible explanations for any observed association with first trimester exposures not being causal and, in fact, the degree of association observed here might be expected in any cohort of late-recognized pregnancies. Nonetheless, a causative association cannot be completely ruled out. Although these findings may be reassuring to women who are inadvertently vaccinated in pregnancy, they also suggest that women with no known exposure to inhalational anthrax should continue to avoid anthrax vaccination during pregnancy.

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