Tetanus and diphtheria immunity among females in the United States: Are recommendations being followed?

Deanna M. Kruszon-Moran, MS,* Geraldine M. McQuillan, PhD,* Susan Y. Chu, PhD, MSPHb

Division of Health and Nutrition Examination Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md,* and the Office of the Director, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Ga.b

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Objective: The purpose of this study was to examine prevalence and factors associated with tetanus and diphtheria immunity among women in the United States.

Study design: Sera from 9411 female participants from the third National Health and Nutrition Examination Survey were tested for diphtheria and tetanus antitoxin. Interview information for adult women was analyzed to examine associations with immunity.

Results: Fifty-seven percent of the female subjects who were ≥6 years old were positive for diphtheria, and 64% of the female subjects for tetanus antitoxin. Among women ≥20 years old, only 41% of the women were protected against both antigens. Older age, birth outside the United States, and less education was associated with lower immunity. Markers for contact with the health care system were not related to higher immunity.

Conclusion: More than one half of US women ≥20 years old who were tested were not protected fully against diphtheria and tetanus. All physicians, including obstetricians and gynecologists who may be the sole medical providers for women, should be familiar with the current Advisory Committee on Immunization Practices recommendations regarding tetanus and diphtheria toxoid booster vaccines.

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seropositivity among women to both these vaccine-preventable diseases. This study offered the opportunity to examine in more detail whether current recommendations are being followed, whether there are possible predictors of seroprevalence among women, and whether new strategies must be designed that ensure adequate vaccination coverage that are targeted to providers of primary care for women, especially obstetric and gynecology practitioners.

**Material and methods**

**Survey design and data collection**

NHANES III was 1 of a series of cross-sectional national surveys that were conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) to provide national statistics on the health and nutritional status of the noninstitutionalized civilian population through household interviews, standardized physical examinations, and the collection of blood samples in special mobile examination centers. The NHANES III sampling plan was based on a complex, stratified, multistage probability cluster design from which a sample representative of the US civilian noninstitutionalized population was selected. The NHANES III sample included approximately 40,000 persons aged ≥ 2 months from 89 randomly selected locations throughout the United States. Persons over age 60 years, Mexican American individuals, and non-Hispanic black individuals were over-sampled. The survey research protocol was reviewed and approved by a CDC institutional review board.

Information on a wide range of demographic, occupational, and behavior characteristics was collected by interviews that were conducted in homes and at the examination center. Race/ethnicity was self-reported as non-Hispanic white, non-Hispanic black, or Mexican American; individuals who did not self-select 1 of these categories were classified as “other” and analyzed with the total population. The poverty index ratio was calculated by the division of the total family income by the poverty threshold that was adjusted for family size for the year of the interview; values below 1 were considered below the poverty line. Education was measured as the last year of school that was completed and grouped into 4 levels (no school or elementary school, some high school, high school completed, some college). As a marker for access to care, we combined responses to questions about whether a participant could identify a particular clinic, health center, or doctor’s office as a source of routine care and whether the participant usually saw 1 particular health professional or doctor. A history of live births was categorized as 0, 1, or ≥2 reported live births.

**Laboratory methods**

**Diphtheria antitoxin**

Antibody levels to diphtheria toxin were determined by a neutralization assay in VERO monkey kidney cells, with a modification of the procedure described by Miyamura et al and Deforest et al. Assays were done in 96-well microtiter plates, with doubling serum dilutions. Diphtheria antitoxin titers were converted to international units per milliliter after standardization with reference sera (provided by the Center for Biologics Evaluation Research, US Food and Drug Administration) using a standard technique. The lowest level of detection for the diphtheria assay was 0.0038 IU/mL, and the upper limit was 5.6 IU/mL and 8.0 IU/mL on different runs of the assay. In this study, the antibody concentration of > 0.10 IU/mL, defined as a fully protective level, was used as our cutoff for immunity.

**Tetanus antitoxin**

Tetanus antitoxin was measured with a solid phase enzyme-immunoassay. Enzyme-immunoassay plates (Immulon I; Dynatech, Chantilly, Va) were coated with tetanus toxoid by incubation with tetanus toxoid (0.1 limit of flocculation unit per well; Wyeth-Ayerst Laboratories, Marietta, Pa) that was diluted in 0.25 mol/L sodium carbonate/bicarbonate buffer, pH 9.6. This method is described in detail elsewhere. For all analyses, protective levels of tetanus antitoxin were defined as > 0.15 IU/mL. The rationale for this cutoff as being protective has been published previously.

**Sample size and response rates**

Our analyses were done in 2 parts. First, we determined the age-specific prevalence of antibody to tetanus and diphtheria in the sera collected from female patients who were aged ≥ 6 years in NHANES III. Second, we examined risk factors for susceptibility to these diseases among women aged ≥ 20 years to identify possible areas for intervention that would be most applicable to adult women.

There were 16,123 female participants aged ≥ 6 years in NHANES III; of those, 13,527 participants were interviewed (83.9%), and 12,399 participants (76.9%) also underwent a physical examination. Sera were available from 9411 female participants aged ≥ 6 years for diphtheria and tetanus antitoxin testing (75.9% of those participants who were examined). The availability of sera did not vary greatly by demographic factors but was somewhat lower among the youngest female participants (71.0% of those examined aged 6-11 years) and oldest female participants (67.4% of those examined aged > 70 years, range was 76.6%-80.4% for all age groups among those examined aged 12-69 years). For the risk factor analysis, we used sera and interview data that were collected from 6957 women (76.7% of those examined) who were aged ≥ 20 years.
Statistical methods
Prevalence estimates were weighted to represent the US population, to account for the over sampling of specific demographic subgroups, and to account for nonresponse to the household survey and physical examinations.14,15 Estimates and standard errors were calculated with SUDAAN,16 a family of statistical procedures for survey data analysis that accounts for sample weights and complex sample design. Prevalence estimates were age-adjusted by the direct method.17 To screen for possible predictors of seropositivity, differences in seroprevalence were evaluated by examining 95% confidence intervals that were calculated with a t-statistic, without correction for multiple comparisons. Probability values were generated with a univariate t-statistic from a general linear contrast procedure in SUDAAN. Logistic modeling was conducted on the total population, separately for the 3 racial/ethnic groups (non-Hispanic white, non-Hispanic black, and Mexican American), and for both foreign-born and US-born Mexican American groups. Those individuals who were classified in the “other” race/ethnic group were not included in the logistic models but were included in the estimates that were given for the total population.

Results
Among female participants ≥6 years old, 57% were immune to diphtheria; 64% were immune to tetanus, and 48% were immune to both. Diphtheria seropositivity decreased notably with age; among women ≥60 years old, only 27% were seropositive (Figure 1). Teta-
nus seropositivity also decreased with age but remained at ≥80% until after age 39 years, when the decline became more significant. As with diphtheria, women ≥60 years old had the lowest level of immunity, with only 23% being seropositive at that age (Figure 1). Correspondingly, seropositivity to both diphtheria and tetanus was highest among the youngest female participants (84% of the 6- to 11-year-old participants were seropositive); it declined more slowly between the ages of 12 to 39 years (>60%), then it decreased steeply to a low of
10% seropositivity for both antigens among women aged ≥60 years (Figure 1).

Seropositivity to diphtheria and tetanus was compared by racial/ethnic subgroup and because immunization practices differ among countries, Mexican American female participants who were born inside the United States were also compared with those who were born outside the United States (Figures 2 and 3). The place of birth comparison could be performed only among the Mexican American population because the numbers of foreign born among non-Hispanic white and black female participants were too small to produce stable age-specific estimates. For diphtheria (Figure 2), there was little difference in seropositivity among the 4 subgroups for girls aged 6 to 11 years and for women aged 50 to 59 years. However, among women of childbearing age (12-49 years old), Mexican American women who were born outside the United States had substantially lower seropositivity to diphtheria than the other racial/ethnic subgroups (P < .01 for women in all 4 age groups, except P = .07 when comparing US-born with non-US-born Mexican American women who were aged 40-49 years). Interestingly, although non-Hispanic white women had significantly higher diphtheria seropositivity at ages 30 to 39 years, by age ≥50 years, non-Hispanic white women had the lowest levels of protection of all racial/ethnic groups. Similarly for tetanus, differences among the subgroups were minor for the youngest (those aged 6-11 years and those aged 12-19 years) and oldest (≥60 years) female patients, but across age groups from 20 to 59 years, foreign-born Mexican American women had significantly lower seropositivity to tetanus than individuals in the other racial/ethnic groups, including US-born Mexican American women (P < .001).

To examine for possible risk factors that were related to seropositivity, age-adjusted estimates for women ≥20 years of age were presented for various sociodemographic and health care access variables separately for each racial/ethnic group (Tables I and II). As demonstrated in the previous figures, diphtheria and tetanus seropositivity was higher among Mexican American women who were born in the United States than those born outside the United States (P < .001 for both). Similarly, being at or above poverty level and having the ability to identify a regular source of care were associated with diphtheria and tetanus seropositivity among Mexican American women, but these associations were not clear among the other racial/ethnic subgroups. More consistent among all race/ethnic groups was generally higher seropositivity levels with higher education. Unexpectedly, those with a history of ≥2 births, presumably

<table>
<thead>
<tr>
<th>Table I</th>
<th>Age-adjusted diphtheria antitoxin seropositivity for women aged ≥20 years by race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Sample size (n)</td>
</tr>
<tr>
<td>Total</td>
<td>6957</td>
</tr>
<tr>
<td>Poverty index</td>
<td></td>
</tr>
<tr>
<td>Below</td>
<td>1566</td>
</tr>
<tr>
<td>At or above¹</td>
<td>4699</td>
</tr>
<tr>
<td>Education</td>
<td></td>
</tr>
<tr>
<td>No school/elementary only</td>
<td>1529</td>
</tr>
<tr>
<td>Some high school</td>
<td>1110</td>
</tr>
<tr>
<td>High school completed</td>
<td>2323</td>
</tr>
<tr>
<td>Some college¹</td>
<td>1959</td>
</tr>
<tr>
<td>Birth origin</td>
<td></td>
</tr>
<tr>
<td>US born</td>
<td>5553</td>
</tr>
<tr>
<td>Not US born¹</td>
<td>1388</td>
</tr>
<tr>
<td>Access to care identified</td>
<td></td>
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<tr>
<td>Both clinic and provider</td>
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<tr>
<td>Clinic only</td>
<td>889</td>
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<tr>
<td>Neither¹</td>
<td>1134</td>
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<tr>
<td>History of live births</td>
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<tr>
<td>≥2</td>
<td>4412</td>
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<tr>
<td>1</td>
<td>1116</td>
</tr>
<tr>
<td>0¹</td>
<td>1256</td>
</tr>
</tbody>
</table>

* Those classified in the “Other” race/ethnic group were included in the total population only.
¹ Reference group.
³ P value < .05 for t-statistic, for differences in estimate from the reference group for each individual risk factor.
¹ Prevalence estimate and standard error were unreliable because too few sample persons were represented in this subgroup.
women who would have more contact with the health system, had lower seropositivity to diphtheria and tetanus than those with no history of a live birth. This association was found among the total population of non-Hispanic white and Mexican American women, but not among non-Hispanic black women.

Multivariate modeling adjusting for age, race/ethnicity, and foreign birth in the total population and stratification on race/ethnicity and foreign birth (for Mexican American participants only) validated many of these univariate findings (results not shown). Higher education remained the most important predictor of increased immunity to diphtheria and tetanus for the total population and non-Hispanic white participants, and foreign birth and education remained important predictors of immunity to both these diseases for Mexican American participants only. This association was found among the total population of US women aged ≥20 years. Data from the CDC’s Behavioral Risk Factor Surveillance System and the National Health Interview Survey support these findings, which show that the proportion of persons who report the receipt of tetanus toxoid during the previous 10 years decreased substantially with age and that, in all age groups, men were more likely to report receipt of tetanus toxoid compared with women. We found that only 51% and 58% of US women aged ≥20 years have protective levels of antibody to diphtheria and tetanus, respectively, with protective levels falling dramatically as women age.

**Comment**

Data from NHANES III were analyzed to provide population-based estimates of seropositivity for both diphtheria and tetanus antitoxin among women in the United States. Despite recommendations by the ACIP, previous analyses of NHANES III data showed a lack of immunity to these diseases in the US population with increasing age and a greater decline among women as compared with men. Data from the CDC’s Behavioral Risk Factor Surveillance System and the National Health Interview Survey support these findings, which show that the proportion of persons who report the receipt of tetanus toxoid during the previous 10 years decreased substantially with age and that, in all age groups, men were more likely to report receipt of tetanus toxoid compared with women. We found that only 51% and 58% of US women aged ≥20 years have protective levels of antibody to diphtheria and tetanus, respectively, with protective levels falling dramatically as women age.

It is well-known that many women seek primary care from their obstetrician and gynecologist. Data from the
National Ambulatory Medical Care Survey showed the second most frequent reason for a visit to a gynecologist for women aged ≥15 years was for a general medical examination and that women aged 15 to 44 years sought care with a gynecologist for their general medical examination 4 times more often than a general family practitioner and 12 times more often than an internist. A study of program residency requirements by Seltzer et al. showed that obstetricians and gynecologists are being educated in preventive primary health care for women, which includes immunization services; in another survey, 85% of obstetricians and gynecologists felt screening for vaccine-preventable diseases was not outside the scope of their practice. Despite this, we found no consistent association between greater seropositivity to diphtheria and tetanus and a history of ≥2 births or the ability to identify a regular source of care, both of which are markers for access to care. This suggests that increased contacts with the health care system (whether a regular primary care physician, obstetrician, or gynecologist) did not increase the chances of getting the recommended tetanus-diptheria toxoid booster. In a survey of American College of Obstetrics/Gynecology members, more than one half of the responding physicians considered themselves primary care providers, but only 10% of the respondents offered all major vaccines that are recommended to women who are pregnant or after delivery, and only 32% of the respondents offered the recommended tetanus-diptheria toxoid booster.

The protective efficacy of both diphtheria and tetanus toxoid after 3 or more doses is high (90%-100%); although for both, serosusceptibility increases with advancing age. Although only 2 cases of diphtheria and 37 cases of tetanus (14 in individuals aged >60 years) were reported in the United States in 2001, the re-emergence of diphtheria in the Newly Independent States of the former Soviet Union demonstrates that adults become susceptible to diseases that are preventable by vaccines that produce less than lifelong immunity. The ACIP recommendation for adults to receive a 10-year booster dose of tetanus-diptheria toxoid will ensure protective levels to achieve adequate population immunity. Obstetricians and gynecologists who may be the sole primary care provider for these women should be familiar with current ACIP adult vaccination schedules so that they can provide opportunities for vaccination when necessary.

References
