Serologic Immunity to Diphtheria and Tetanus in the United States

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Background: Serologic data on diseases that are preventable by vaccine are useful to evaluate the success of immunization programs and to identify susceptible subgroups.

Objective: To provide national estimates of immunity to diphtheria and tetanus by measurement of serum antibody levels.

Design: Examination of data from the Third National Health and Nutrition Examination Survey, a representative cross-sectional sample of the U.S. population.

Setting: 89 randomly selected locations throughout the United States.

Participants: 18,045 persons 6 years of age or older who were examined from 1988 to 1994.

Measurements: Serum samples obtained at a single time point were tested for diphtheria and tetanus antitoxin.

Results: Overall, 60.5% of Americans 6 years of age or older had fully protective levels of diphtheria antibody (≥0.10 IU/mL) and 72.3% had protective levels of tetanus antibody (>0.15 IU/mL). Ninety-one percent of Americans 6 to 11 years of age had protective levels of both diphtheria and tetanus antibody; this proportion decreased to approximately 30% among persons 70 years of age (29.5% for diphtheria and 31.0% for tetanus). Adult Mexican-Americans were slightly less likely to have protective levels of antibody to both toxins. Only 47% of persons 20 years of age or older had levels that were protective against both diseases, and only 63% of adults who were protected against tetanus were also protected against diphtheria.

Conclusions: A substantial proportion of adults in the United States do not have antibody levels that are protective against diphtheria and tetanus. In addition, although the recommended vaccine is a combination of tetanus and diphtheria, only 63% of adults with protective antibody to tetanus also had protective antibody to diphtheria.


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ican. Persons who did not choose one of these categories were classified as “other” and were analyzed with the total population. The poverty-index ratio was calculated by dividing total family income by the poverty threshold index, adjusted for family size at year of interview. Residence in a county with a population equal to or greater than 1 million was defined as metropolitan residence. Residence in all other counties (including rural areas) was defined as nonmetropolitan. Data on years of education, marital status, occupation, and military service were analyzed for study participants 20 years of age or older. Participants were considered to have access to care if they indicated that they usually visited a particular clinic, health center, or physician’s office when they were sick or for routine care. If a participant said that he or she usually saw one particular health professional or physician, he or she was categorized as having access to both a clinic and a physician.

**Laboratory Methods**

Serum samples were obtained once when each participant was examined.

**Diphtheria Antitoxin**

Antibody levels to diphtheria toxin were determined by a neutralization assay in Vero monkey kidney cells by using a modification of the procedure described by Miyamura and colleagues (6, 7). The serum samples from NHANES were run singly with 20% duplication. Diphtheria antitoxin titers were converted to IU/L after standardization with reference serum specimens provided by the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, by using a standard technique (8). The lowest level of detection for the diphtheria assay was 0.0038 IU/mL, and the upper limit of detection was 5.6 and 8.0 IU/mL on different runs of the assay. An antibody concentration of 0.10 IU/mL or greater was considered a fully protective level (9, 10).

**Tetanus Antitoxin**

Tetanus antitoxin was measured by using a solid-phase enzyme immunoassay (Immulon 1, Dynatech, Chantilly, Virginia) with a lower limit of detection of 0.001 IU/mL. This method is described in detail elsewhere (11, 12). For all our analyses, protective levels of tetanus antitoxin were defined as greater than 0.15 IU/mL; the rationale for considering this cutoff protective is discussed elsewhere (11, 13).

**Response Rates**

All analyses were restricted to persons 6 years of age or older who had sufficient serum specimen for both assays. A total of 30,930 persons 6 years of age or older were selected for the study, and 23,527 (76%) were examined. Of those examined, 18,045 (77%) had a sufficient serum specimen for both tetanus and diphtheria testing. Persons 70 years of age or older had the lowest rates of available serum (69%). No differences by sex were observed, but response rates were lower for non-Hispanic blacks (74%) than for non-Hispanic whites and Mexican-Americans (78%). Careful evaluation using data from the home interview (91.6% completed the interview) detected no systematic selection bias due to nonresponse in the examination data. The results are therefore representative of the U.S. population.

**Statistical Analysis**

Prevalence estimates were weighted to represent the total U.S. population and to account for oversampling and nonresponse to the household interview and physical examination (14, 15). Standard errors were calculated by using SUDAAN (Research Triangle Institute, Research Triangle Park, North Carolina) (16), a family of statistical procedures for analysis of data from complex sample surveys. For comparisons between subgroups
of NHANES III, data were age-adjusted to the 1980 U.S. population by using the direct method (17).

To screen for possible predictors of seropositivity, differences in seroprevalence were evaluated without correction for multiple comparisons by examining the 95% CIs for the seroprevalence values generated by SUDAAN. $P$ values were calculated by using a univariate $t$-statistic obtained from a general linear contrast procedure in SUDAAN.

**RESULTS**

**Immunity to Diphtheria**

Only 60.5% of the sample had protective levels of diphtheria antibody (Table). Mexican-Americans were 5% to 9% less likely than other racial or ethnic groups to have protective levels of antibody. The percentage of men with protective antibody to diphtheria decreased with increasing age, and only 30% of male participants 60 to 69 years of age were protected (Figure 1). Fewer women than men had protective levels of antibody, and the percentage of protected women also decreased with age (Figure 1).

When antibody levels were examined by race/ethnicity and age, a similar decrease in the proportion of protected persons was observed among non-Hispanic white persons and black persons until 49 years of age (Figure 2). Among black persons older than 50 years of age, the proportion of those with protective levels of antibody remained stable at approximately 40%. Mexican-Americans had a lower prevalence of protective antibody compared with non-Hispanic white persons and black persons for each 10-year age group from 20 to 49 years of age ($P < 0.001$). After 59 years of age, white persons had a lower prevalence of protective antibody levels than did non-Hispanic black persons and Mexican-Americans ($P < 0.001$).

**Immunity to Tetanus**

Seventy-two percent of the sample had protective levels of antibody to tetanus (Table). Mexican-Americans were 8% less likely than white or black persons to have protective levels of antibody ($P < 0.001$).

The disparity between men and women with protective levels of antibody was greater for tetanus than for diphtheria: Seventeen percent more men than women had protective levels of antibody to tetanus ($P < 0.001$). The proportion of men with protective levels of antibody to tetanus did not decrease by age at the same rate as for diphtheria (Figure 1). At 70 years of age, 45% of men had protective antibody to tetanus. In contrast, the percentage of women with protective levels of tetanus antibody decreased rapidly after 40 years of age. By 70 years of age, only 21% of women had protective levels.

As was seen with diphtheria antibody, protective

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**Figure 1.** Age-specific prevalence of immunity to tetanus and diphtheria by sex, Third National Health and Nutrition Examination Survey, 1988–1994.
levels of antibody to tetanus differed little by race/ethnicity until after 19 years of age (Figure 3). A smaller percentage ($P_{/H11349} \leq 0.05$) of Mexican-Americans in each 10-year group from 20 to 49 years of age had protective antibody. White persons 50 to 69 years of age were significantly more likely than black persons or Mexican-Americans to have protective levels of tetanus antibody.

**Demographic Predictors of Protective Antibody to Diphtheria and Tetanus**

Examination of the association of demographic variables with protective levels of antibody to diphtheria and tetanus revealed several contrasting patterns (Table). At each increasing level of education, a higher percentage of participants had protective antibody to both toxins. In contrast, persons living at or above the poverty level were less likely to be protected from diphtheria. Persons who had a routine source of medical care and a regular physician were less likely to have protective levels of antibody to both toxins.

Birth outside the United States was associated with decreased prevalence of protective levels of antibody to both toxins, but this association was statistically significant only for tetanus antibody ($P = 0.07$ for diphtheria; $P_{/H11021} \leq 0.01$ vs. reference group. $P_{/H14067} \leq 0.05$ vs. reference group.

### Table. Prevalence of Immunity to Diphtheria and Tetanus by Demographic Characteristics, Third National Health and Nutrition Examination Survey, 1988–1994

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Total Tested*</th>
<th>Diphtheria-Immune Participants (95% CI)</th>
<th>Tetanus-Immune Participants (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18 045</td>
<td>60.5 (58.3–62.8)</td>
<td>72.3 (70.6–73.9)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white†</td>
<td>6907</td>
<td>59.5 (56.7–62.4)</td>
<td>73.8 (71.9–75.8)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>5158</td>
<td>64.2 (62.3–66.2)‡§</td>
<td>73.7 (71.4–76.1)‡§</td>
</tr>
<tr>
<td>Mexican-American</td>
<td>5245</td>
<td>55.0 (52.9–57.2)</td>
<td>65.7 (63.9–67.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8634</td>
<td>64.1 (61.5–66.8)‡</td>
<td>81.0 (79.4–82.6)‡</td>
</tr>
<tr>
<td>Female</td>
<td>9411</td>
<td>57.0 (54.7–59.4)</td>
<td>63.9 (61.9–65.9)</td>
</tr>
<tr>
<td>Poverty index</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Below poverty level</td>
<td>4340</td>
<td>65.2 (62.6–67.9)‡</td>
<td>71.7 (68.8–74.7)</td>
</tr>
<tr>
<td>At or above poverty level</td>
<td>12 027</td>
<td>60.2 (57.8–62.6)</td>
<td>73.3 (71.7–75.0)</td>
</tr>
<tr>
<td>Population density</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metropolitan (≥1 million)</td>
<td>9165</td>
<td>60.9 (58.4–63.6)</td>
<td>72.4 (70.1–74.8)</td>
</tr>
<tr>
<td>Nonmetropolitan (&lt;1 million)</td>
<td>8880</td>
<td>60.0 (56.1–64.2)</td>
<td>72.1 (69.5–74.8)</td>
</tr>
<tr>
<td>U.S. region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northeast†</td>
<td>2524</td>
<td>56.2 (50.4–62.5)</td>
<td>68.1 (65.1–71.3)</td>
</tr>
<tr>
<td>South</td>
<td>7331</td>
<td>61.2 (58.2–64.4)</td>
<td>73.9 (71.3–76.6)‡</td>
</tr>
<tr>
<td>Midwest</td>
<td>3569</td>
<td>59.2 (55.1–63.7)</td>
<td>71.9 (69.3–74.6)</td>
</tr>
<tr>
<td>West</td>
<td>4621</td>
<td>65.2 (60.8–69.9)</td>
<td>74.4 (69.7–79.4)‖</td>
</tr>
<tr>
<td>Country of birth</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>14 666</td>
<td>61.0 (58.6–63.5)</td>
<td>75.2 (73.6–76.9)‡</td>
</tr>
<tr>
<td>Other</td>
<td>3327</td>
<td>56.7 (52.9–60.8)</td>
<td>51.4 (48.0–55.1)</td>
</tr>
<tr>
<td>Years of education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No school or elementary school</td>
<td>3225</td>
<td>44.0 (40.5–47.7)‡</td>
<td>41.7 (39.0–44.5)‡</td>
</tr>
<tr>
<td>Some high school</td>
<td>2626</td>
<td>54.0 (49.1–59.4)‡</td>
<td>68.5 (65.9–71.2)‡</td>
</tr>
<tr>
<td>High school graduate</td>
<td>4325</td>
<td>52.9 (50.5–55.5)‡</td>
<td>70.1 (68.0–72.3)‡</td>
</tr>
<tr>
<td>College†</td>
<td>3896</td>
<td>61.4 (58.4–64.6)</td>
<td>77.4 (75.1–79.8)</td>
</tr>
<tr>
<td>Military service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever in military</td>
<td>2080</td>
<td>50.3 (46.6–54.3)</td>
<td>82.7 (80.5–85.0)‖</td>
</tr>
<tr>
<td>Never in military</td>
<td>12 004</td>
<td>56.5 (54.1–59.1)‡</td>
<td>67.3 (65.5–69.1)</td>
</tr>
<tr>
<td>Access to care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither clinic nor physician</td>
<td>3835</td>
<td>64.1 (60.8–67.6)‡</td>
<td>75.0 (72.4–77.7)‡</td>
</tr>
<tr>
<td>Clinic</td>
<td>2641</td>
<td>66.5 (63.6–69.5)‡</td>
<td>77.9 (74.4–81.5)‡</td>
</tr>
<tr>
<td>Clinic and physician†</td>
<td>11 560</td>
<td>58.3 (55.9–60.8)</td>
<td>70.4 (68.6–72.2)</td>
</tr>
</tbody>
</table>

* Total includes participants who selected “other” for race/ethnicity.
† Reference group.
‡ $P < 0.01$ vs. reference group.
§ $P < 0.01$ for non-Hispanic black persons vs. Mexican-American persons.
‖ $P < 0.05$ vs. reference group.
When we restricted the analysis to persons 20 years of age or older, Mexican-American adults born outside the United States were less likely than those born in the United States to have levels of protective antibody to diphtheria (35.8% vs. 55.0%; \( P < 0.001 \)) or tetanus (37.6% vs. 67.4%; \( P < 0.001 \)). Previous military service was associated with a higher prevalence of protective antibody to tetanus (\( P < 0.001 \)) but a lower prevalence of protective antibody to diphtheria (\( P = 0.001 \)).

Only 46.6% (95% CI, 44.0% to 49.2%) of adults had protective antibody to both diseases. Because we observed disparities in the proportion of persons with protective levels of tetanus and diphtheria antibody after adolescence, we performed an analysis to determine characteristics of persons 20 years of age or older who had protective antibody to tetanus but not diphtheria. After adjustment for age, only 63% of adults who had protective levels of tetanus antibody also had protective levels of diphtheria antibody. No demographic or economic factor explained this lack of immunity.

**DISCUSSION**

Although diphtheria and tetanus are now rare diseases in the United States, analysis of serum specimens from participants in NHANES III demonstrates that a substantial proportion of the U.S. population lacks protective levels of diphtheria and tetanus antibodies. Previous analysis of data from the first phase of the survey (1988 to 1991) demonstrated low levels of protective tetanus antibody in elderly persons (11). Although fewer than 50 cases of tetanus are reported each year, the incidence is highest among persons 60 years of age or older (18). These gaps were even more evident with diphtheria: Only 30% of persons 60 years of age or older had protective levels of antibody.

Only 49 cases of diphtheria were reported in the United States from 1980 to 1999. However, although the disease is now rare, *Corynebacterium diphtheriae* continues to circulate in certain communities. In 1996, multiple strains of *C. diphtheriae* were documented in a Native American community in South Dakota. These strains were found to be closely related to strains iden-
identified in the same area from 1979 to 1983, suggesting ongoing endemic circulation (19).

Among children 6 to 11 years of age, the proportions of those with protective levels of tetanus and diphtheria antibody were high. This finding reflects high coverage by childhood immunization and the requirement in most states that a booster dose of vaccine be given at 4 to 6 years of age, before enrollment in school. The proportion of those with protective levels decreased to around 80% (78.9% for diphtheria and 81.4% for tetanus) among adolescents 12 to 19 years of age. In 1996, the ACIP recommended that the first booster dose of adult formulation tetanus and diphtheria toxoids be administered at 11 or 12 years of age (20). Implementation of this recommendation should prevent the decrease in immunity among adolescents.

Differences by race/ethnicity were not seen in children and were observed primarily among Mexican-Americans 20 to 49 years of age who were born outside the United States. The latter group had significantly lower levels of protective antibody to both toxins, which probably reflects absence of routine childhood immunization.

The conflicting relationship between economic indicators and protective levels of tetanus and diphtheria antibody suggest that income and access to medical care did not ensure compliance with the ACIP adult immunization recommendation of a tetanus and diphtheria toxoid booster every 10 years throughout life (1, 20, 21).

Data from NHANES III also suggest that a routine source of health care did not guarantee that a person would be offered the recommended immunizations. In fact, those who reported such a source of care were less likely to have protective levels of antibody. These data reinforce concerns that over time, diphtheria and tetanus antitoxin levels fall below optimal protective levels. Administration of booster doses of tetanus and diphtheria toxoid to adults every 10 years needs to be reinforced as standard practice (20, 21).

By 60 years of age, 50% of the sample did not have protective antibody levels to tetanus and 62% did not have protective levels to diphtheria. This discrepancy between tetanus and diphtheria becomes evident at 20 years of age and was more pronounced in men, who were consistently more likely to have protective antibody to tetanus. Although few cases of tetanus are reported among people who received a primary vaccine series, seropositivity decreases with increasing age. El-

Figure 3. Age- and race/ethnicity-specific prevalence of immunity to tetanus, Third National Health and Nutrition Examination Survey, 1988–1994.
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References


