ASSESSING POPULATION-BASED SEROLOGIC IMMUNITY TO TETANUS IN THE UNITED STATES, 2015-2016, AND THE RESULTING PUBLIC HEALTH IMPLICATIONS

by

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ABSTRACT

Tetanus is a vaccine-preventable disease that is otherwise life-threatening. Tetanus is caused by *Clostridium tetani* bacteria found in soil and manure. In unvaccinated persons, tetanus can be fatal, but severity is abated in fully vaccinated persons. In the United States (US), the Advisory Committee on Immunization Practices (ACIP) recommends a three-dose childhood immunization primary series with a tetanus toxoid-containing vaccine for children at 2, 4, and 6 months old to be followed by two booster doses administered between the ages of 15-18 months and 4 to 6 years. ACIP further recommends that adults receive decennial tetanus booster vaccinations at ages 11-12 years.

Serologic data on vaccine-preventable diseases are used to assess the success of immunization programs, the duration of vaccine-induced immunity, and to identify susceptible subpopulations. Recent epidemiological trends in tetanus disease incidence along with results from previous serosurvey, new laboratory findings, and modelling studies suggest a high

prevalence of tetanus seroimmunity in examined populations. These findings impel examination current adult tetanus booster vaccination recommendations.

This observational cross-sectional study analyzed tetanus serum antibody levels collected from 5,910 participants of the National Health and Nutrition Examination Survey (NHANES), 2015-2016 using a microsphere-based multiplex antibody assay (MMACA). The objective was to provide national estimates of tetanus immunity among persons aged six years or older.

Results: Approximately 94% of the US population was seroprotected against tetanus as defined by a protective serum antibody level of ≥0.10 international units per milliliter (IU/mL). However, proportions of seroimmunity declined with advancing age after 60 years. Prevalence of seroimmunity was lower among females than males, and the gap increased with advancing age. Older adults, Hispanic persons, non-Hispanic black persons, divorced, widowed, or separated persons, foreign-born Americans, and those with less than high school education were more likely to be susceptible to tetanus. The population of older adults aged ≥65 years is forecasted to nearly double by 2050. This poses a significant public health challenge as older have a higher burden of tetanus disease from illness, hospitalization, disability, and death. Additional studies are needed to evaluate US adult tetanus booster vaccination recommendations.

INDEX WORDS: Tetanus, seroimmunity, seroprotection, serologic immunity, DTaP, Tdap, decennial booster, tetanus toxoid, tetanus toxoid-containing vaccine, serum antibody levels, vaccination, serosurveys, NHANES, ACIP.

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DEDICATION

I dedicate this work to my parents, Ms. Rachel Ashelley Ollennu and the late Rev. Emmanuel Ohene Bampoe. Thank you for teaching me to dream big and reach for the stars and to serve God and others. You cultivated and nurtured my desire to learn which led to me embarking on this journey - your unwavering love and support have made this possible. I am immensely grateful to be your daughter and I hope you are half as proud of me as I am of you every day.

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CHAPTER 1

INTRODUCTION

Background

Tetanus is a life-threatening, non-communicable, vaccine-preventable disease that affects humans and animals. The disease is caused by a potent neurotoxin produced by spore-forming types of the *Clostridium tetani* bacterium. Tetanus spores are abundant in the environment and have been identified worldwide in human and animal feces, soil, and manure but especially in soil and animal feces (Centers for Disease Control and Prevention, 2011; Khoury & Cahill, 2020; Minh Yen & Thwaites, 2019). *C. tetani* spores are extraordinarily hardy and can withstand air, extreme temperatures, and common disinfectants (Minh Yen & Thwaites, 2019; Thwaites, Beeching, & Newton, 2015). Small doses of tetanus toxin can be lethal in unvaccinated individuals. Once the toxin enters a nerve cell, it cannot be deactivated (Khoury & Cahill, 2020). Natural disasters such as earthquakes, floods, typhoons, and conflicts that lead to the displacement of people and disruption of vaccination programs create ideal conditions for tetanus to thrive (Finkelstein, Teisch, Allen, & Ruiz, 2017).

Infections with tetanus can occur when the wounds of individuals with inadequate protective circulating antibodies against tetanus (low serologic immunity/seroprotection) become contaminated with *C. tetani* spores, and tetanus toxin is transported into the central nervous system of an infected person (Thwaites et al., 2015). The disease commonly develops in weakened and dead tissue through infected burn wounds, animal bites or scratches, fractures, skin gashes, eye injuries, gun-shot wounds, piercings, and other puncture wounds (injection drug

users). Tetanus can develop from the use of unhygienic surgical instruments or through an infected umbilical stump (newborns), unhygienic abortions (obstetric patients), bowel tissue death (surgical patients), infected foot ulcers (diabetic patients) (Khoury & Cahill, 2020). However, there is no noticeable entry wound in about 20% of global tetanus cases (Finkelstein et al., 2017).

Tetanus can occur at any age, and severity is reduced in fully immunized persons (Hammarlund et al., 2016). The incubation period ranges from one day to several months after an injury; however, most cases occur within three days to three weeks after infection. Milder disease cases are associated with an incubation period of ten or more days, while more severe cases often occur in patients with incubation periods within seven days of injury (Roper, Wassilak, Scobie, Ridpath, & Orenstein, 2017). Repeated infections are likely because *C. tetani* bacteria are pervasive in the environment and cannot be destroyed, and because tetanus infection does not provide immunity against future disease. Appropriate wound care and vaccination with a tetanus toxoid-containing vaccine (TTCV) are essential to preventing illness (Khoury & Cahill, 2020; Minh Yen & Thwaites, 2019). Tetanus can also be prevented with hygienic surgical and obstetric practices (Roper et al., 2017).

Types of disease

Tetanus infection can present in three forms: localized, cephalic, and generalized tetanus (Finkelstein et al., 2017). Localized tetanus is rare and characterized by muscle spasms confined to one appendage or body region surrounding an injury site. It is generally mild with less than 1% fatality rate; however, it can progress to generalized tetanus with complications (Roper et al., 2017; World Health Organization, 2017). Cephalic tetanus is also rare and occurs in patients with head lesions or chronic ear infections. It has a short incubation period of 1-2 days after a severe

wound, and 15-30% of those who contract it die. Cephalic tetanus can progress to generalized tetanus (World Health Organization, 2017).

Generalized tetanus is the most common and severe clinical form of the disease and represents approximately 80% of all reported cases globally. Early disease onset is characterized by spasms of the jaw muscles known as trismus or lockjaw (an inability to open one's mouth), which occurs in about 90% of patients. Generalized tetanus is often accompanied by respiratory failure with severe clinical symptoms persisting for 1-4 weeks before declining (Roper et al., 2017). Neonatal tetanus, which arises within the first month of life, is a form of generalized tetanus acquired through an infected umbilical stump (Finkelstein et al., 2017; Roper et al., 2017). Case fatality rates for generalized tetanus range from 25% to 70% in the general population and can approach 100% in advanced older adults (Roper et al., 2017).

Tetanus Epidemiology

Global Tetanus Epidemiology

Tetanus is widespread in several low- and middle-income countries due to low vaccination coverage (Minh Yen & Thwaites, 2019). In 2015, an estimated 79% of global tetanus deaths occurred in South Asia and sub-Saharan Africa, with over 50% of those among neonates. In 2016, tetanus caused an estimated 48,000 to 80,000 deaths worldwide (World Health Organization, 2017). Globally, public health policies to eliminate maternal and neonatal tetanus have significantly reduced disease incidence in the last twenty years. However, twenty-four countries are yet to eliminate maternal and neonatal tetanus. These include Nigeria, Sierra Leone, Guinea, Angola, Afghanistan, Pakistan, Nepal, Bangladesh, Cambodia, and Papua New Guinea, where tetanus remains a leading cause of mortality, with up to 100% death in cases that

do not get medical care and greater than 50% death in cases that receive some hospital care (Minh Yen & Thwaites, 2019; Thwaites et al., 2015).

Conversely, tetanus is rare in high-income countries due to high vaccination coverage. Reported cases are often in people ≥ 60 years old or injection drug users (Minh Yen & Thwaites, 2019). Adults ≥ 65 years, immigrants from countries with less-developed vaccination programs, people with religious or philosophical objections to vaccination, persons with chronic wounds, inadequate tetanus toxoid vaccination (see Appendix 1 for definition of terms), inadequate wound prophylaxis, or diabetes are at greater risk for tetanus infection (Minh Yen & Thwaites, 2019; Roper et al., 2017). Furthermore, persons aged ≥65 years and those under-vaccinated or with inadequate wound prophylaxis are at an elevated risk of dying from the disease (Centers for Disease Control and Prevention, 2011). Older adults are at a greater risk because of the decline in vaccine-induced protection over time and are more likely to be unvaccinated or under-vaccinated. Between 2000-2009, older adult females represented 64% of global tetanus cases with greater disease incidence of 0.42 per 100,000 compared to their male counterparts at 0.38 per 100,000 (Minh Yen & Thwaites, 2019; Roper et al., 2017).

United States Tetanus Epidemiology

Since the introduction of routine immunization with TTCVs in the US in the mid-1940s, the incidence of tetanus has declined by more than 98% and held steady to below 0.01 cases per 100,000 (Liang et al., 2018). Physicians have been required to report all types of tetanus cases to local and state health departments since the inception of national reporting in 1947 to the National Notifiable Diseases Surveillance System (NNDSS), a passive surveillance system (National Center for Immunization and Respiratory Diseases, 2019). The Council of State and Territorial Epidemiologists (CSTE) clinically defines tetanus as “any acute illness with muscle

spasms or hypertonia and diagnosis of tetanus by a local healthcare provider; or death, with tetanus listed on the death certificate as the cause of death or a significant condition contributing to death in the absence of a more likely diagnosis." A clinically compatible case can be classified as probable. There is no definition for confirmed tetanus as there is no diagnostic laboratory test for tetanus (Blain & Tiwari, 2020).

Between 2011 and 2008, 233 cases of tetanus were reported by 45 states. Of the cases for whom outcomes were reported (197 cases), 26 (13.2%) were fatal (Centers for Disease Control and Prevention, 2011). Reported cases ranged from 19-40 each year for an average of 29 cases per year and an average annual incidence of 0.10 per 1 million population. The average annual incidence among persons aged 5-64 years was 0.08 per 1 million whereas in persons aged 65 years and older, it was 0.23 per 1 million population (Centers for Disease Control and Prevention, 2011). Among persons for whom vaccination status was available (92/233 cases), 40.7% had not received any tetanus toxoid vaccines, 28.3% had received a single dose, 5.4% had received 3 doses and 26.1% had received ≥4 doses. Diabetics accounted for 15.4% of 195 patients for whom medical history was known (Centers for Disease Control and Prevention, 2011).

There were 264 tetanus cases and 19 deaths reported between 2009 and 2017. Vaccination status was known for 27% (72/264) of cases; 75% of these were unvaccinated or under-vaccinated with less than 3 doses of tetanus toxoid (Blain & Tiwari, 2020). Persons aged 65 years and older accounted for 23% of cases, those 20-64 years accounted for 64%, and 13% of cases were in persons younger than 20 years. Persons with diabetes accounted for 12% of reported cases and 26% of deaths. All 19 deaths occurred among persons aged 55 years and older (Blain & Tiwari, 2020).

Tetanus Toxoid Vaccines

Tetanus vaccines, also known as tetanus toxoids (TTs), were first produced in 1924 and used broadly among soldiers during World War II. In the US, routine vaccination with a tetanus toxoid was first recommended in 1938 when it became commercially available. They were combined with diphtheria toxoid and a pertussis vaccine in 1948 to create DTP (Offit, 2021). Tetanus incidence in the US has steadily declined partly because of the sustained use of tetanus antitoxin for wound management and the introduction of TTs and TTCVs in the 1930s and 1940s. See Figure 1.1. (Centers for Disease Control and Prevention, 2011; Hammarlund et al., 2016; World Health Organization, 2017). Since they became commercially available, tetanus vaccines have had a long history of safety and led to a considerable reduction in critical disease and a 99% decrease in tetanus-related deaths. Minimal amounts of tetanus toxin can cause infection, but the same volume cannot activate the creation of protective antibody levels. Vaccination is the only way to induce immunity to tetanus toxin (World Health Organization, 2018a).

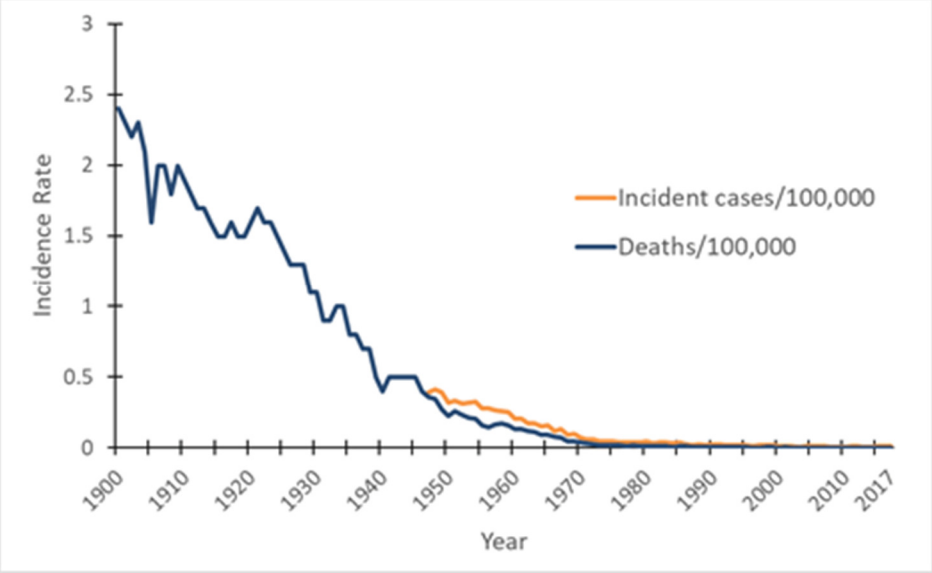

Figure 1.1 Mortality and incidence rates of tetanus reported in the United States, 1900-2017
Source: CDC. Manual for the Surveillance of Vaccine-Preventable Diseases, 2020.

Undesirable side effects from tetanus toxoid vaccination remain a challenge to compliance with vaccine recommendations. An estimated 50%-85% of the combined tetanus and diphtheria vaccine recipients report injection site pain or tenderness, and 25%-30% report swelling (edema) and superficial skin reddening (erythema) (Hammarlund et al., 2016). Previously immunized patients with elevated tetanus immunity levels report a higher incidence of severe reactions. However, anaphylaxis, a severe life-threatening allergic reaction, in recipients is rare and occurs in 1.6 cases per million distributed doses (Hammarlund et al., 2016; World Health Organization, 2017).

Vaccine Recommendations

Globally, WHO issues vaccination recommendations; in 2006, WHO recommended one tetanus booster for adults who enroll in military service, complete their childhood vaccination series, and for females during the first pregnancy (A. M. Slifka, Park, Gao, & Slifka, 2020). In 2017, this guidance was updated to recommend that every individual receive six doses of TTCVs comprising of a three-dose primary series beginning at six weeks and followed by two remaining doses given at a minimum of 4 weeks apart and completed before the 6th month of age; then an additional, three-dose booster series to be administered before adolescence between 12-23 months, 4-7 years, and 9-15 years of age with a minimum of 4 years between doses (World Health Organization, 2018b). Individuals who complete this six-dose primary vaccination series are exempted from additional booster vaccinations in adulthood (A. M. Slifka et al., 2020).

Tetanus Toxoid Vaccine Recommendations in the United States

In the US, the Advisory Committee on Immunization Practices (ACIP) makes and submits annual child, adolescent, and adult vaccination recommendations with input from

subject matter experts from several organizations (see Appendix 2 for complete list) to the CDC director for approval (Advisory Committee on Immunization Practices & Centers for Disease Control and Prevention, 2021). ACIP recommends that children receive a three-dose primary series of a tetanus toxoid-containing vaccine within the first year of life at 2, 4, and 6 months of age, to be followed by a booster dose between 15-18 months and another between 4-6 years. (Centers for Disease Control and Prevention, 2010; Finkelstein et al., 2017; Havers, Cho, Walker, & Hariri, 2020; Khoury & Cahill, 2020; McQuillan, Kruszon-Moran, Deforest, Chu, & Wharton, 2002).

Three combination vaccines are currently used in the US to prevent tetanus (see Table 1.1): (1) diphtheria toxoid, tetanus toxoid, and acellular pertussis (DTaP); (2) tetanus toxoid, a reduced dose of diphtheria, and a reduced dose of pertussis (Tdap); and (3) tetanus toxoid and reduced dose of diphtheria toxoid (Td). DTaP is routinely administered to children under the age of seven, and Tdap and Td to persons seven years and older (Centers for Disease Control and Prevention, 2010; Finkelstein et al., 2017; Khoury & Cahill, 2020)

Table 1.1. US Recommended Pertussis, Diphtheria, and Tetanus Vaccination Schedule- 2020

Vaccine	Age group/ Indication	Recommended schedule
DTaP	2 mos – 6 yrs	Primary (3 doses): 1 dose at ages 2, 4, and 6 mos 1st booster: 1 dose at age 15–18 mos 2nd booster: 1 dose at age 4–6 years
Tdap	11–18 yrs (11-12 yrs preferred)	11–12 yrs: 1 dose 13–18 yrs: 1 dose if not vaccinated previously with Tdap
	≥19 yrs	1 dose if not vaccinated previously with Tdap
	Pregnant women	1 dose with each pregnancy; preferred at 27–36 weeks gestation
Td or Tdap	≥ 11 years	1 dose every 10 yrs for non-pregnant adults after receipt of a single dose of Tdap

Source: (Centers for Disease Control and Prevention, 2018; Havers, Cho, et al., 2020)

A dose of Td or Tdap is recommended every 10 years for people ≥19 years for protection against tetanus and diphtheria, whereas a dose of Tdap is recommended with each pregnancy to provide additional protection to infants against pertussis (Havers, Cho, et al., 2020; Kamiya, Cho, Messonnier, Clark, & Liang, 2016).

Tetanus booster vaccinations were adopted by the US Army, Navy, and Air Force in 1949 and introduced to the civilian population after World War II (Looney, Edsall, Ipsen, & Chasen, 1956). They were recommended every three years for adults in 1955 but changed to once every five years in 1964. By 1996, apprehensions about adverse events from vaccinations administered at short intervals and the availability of additional data on the duration of vaccine-induced immunity prompted re-evaluation and revision of the booster recommendation from every five years to once every ten years (decennial booster) for persons ≥ 6 years where it has remained for the past twenty-five years (Amanna & Slifka, 2020; Hammarlund et al., 2016).

Decennial Tetanus Booster Vaccination

Routine tetanus vaccination recommendations are not uniform among the world's most industrialized and high-income nations, nor are booster recommendations (see Table 1.2.). Some have revised their adult booster dose recommendation(s) to reflect a longer expected duration of protection based on WHO's recommendations or population-based serology study results. For example, Denmark recommends a school-age booster after primary vaccination and subsequent routine boosters at least every twenty years (Roper et al., 2017). The United Kingdom recommends five doses of TTCVs to be administered in infancy, childhood, and adolescence with no further boosters and the administration of tetanus immune globulin (TIG) with wound care when needed. France endorses an age-based schedule recommending adult booster doses at 25, 45, and 65 years of age and then every ten years after that (Roper et al., 2017). The United

States, Canada, and several other countries continue to recommend decennial booster vaccination after ages 11-12 (Hammarlund et al., 2016).

Table 1.2. Recommended Tetanus Vaccination Schedule in Select High-income Countries

Country	*Number of Recommended Childhood Doses*	*Recommended Adult Vaccination*	*Pregnant Women*
Canada	6	Every 10 years	Not specified
France	5	Every 10-20 years (At ages 25, 45, and 65 and every 10 years thereafter)	Not specified
Germany	6	Every 10 years	Not specified
Italy	5	Every 10 years	3rd Trimester
Japan	6	None	Not specified
United Kingdom	5	None	Not specified
United States	6	Every 10 years	3rd Trimester
WHO	6	None	At least 15 days before the end of pregnancy

Source: (A. M. Slifka et al., 2020; World Health Organization, 2018b)

Vaccination Coverage in the United States

Overall, the burden of vaccine-preventable disease is borne by adults ≥19 years than by children ≤12 years, partly because of successful childhood vaccination programs and state pre-enrollment vaccination requirements for school attendance. This burden is even higher among older adults ≥65 years (Centers for Disease Control and Prevention, 2017b). Therefore, vaccinations are recommended over a person's lifespan to mitigate disease risk. The Centers for Disease Control maintains records of vaccination rates for vaccines that are recommended by ACIP through various platforms (Centers for Disease Control and Prevention, 2017b). Data are

collected from different groups within the 50 states and the District of Columbia (DC) via surveys and maintained in databases accessible to the public. The National Immunization Survey (NIS) houses vaccination data on children from birth through 35 months. Vaccination data on kindergarten-aged children are gathered through School Vaccination Assessment Reports required for enrollment (Centers for Disease Control and Prevention, 2016).

The NIS-Teen database collects information on vaccinations given to preteens and teens, and the Behavioral Risk Factor Surveillance System (BRFSS) monitors vaccinations given to adults, including flu vaccinations (Centers for Disease Control and Prevention, 2016). Forty-nine states and DC require DTaP vaccination prior to kindergarten enrollment. During the 2015-2016 school year, median vaccination coverage among kindergarten-aged kids for five doses of DTaP was 94.2%, with twenty states reporting 95% or higher. Less than two percent of parents requested exemptions from the vaccination requirement for religious or philosophical reasons (Seither et al., 2016).

In 2015, overall vaccination rates with a TTCV among adults ≥19 years within the previous 10 years was 62% and dropped to 60.3% among adults ≥18 years in 2016. Adults 65 and older reported vaccination coverage with a TTCV of 57% in 2015 and 48.7% in 2016 (National Center For Immunization and Respiratory Diseases, 2021a; Williams et al., 2017). In a 2017 National Center for Health Statistics (NCHS) data brief on the US vaccination coverage rate among adults aged 65-74, more than half (56.9%) reported receipt of a tetanus vaccine in the preceding 10 years, and males were more likely than females to have received a vaccine (Norris, Vahratian, & Cohen, 2017). Vaccine coverage rates among pregnant females is monitored by the Pregnancy Risk Assessment Monitoring System (PRAMS) (National Center for Immunization and Respiratory Diseases, 2021b).

Problem Statement

Sustaining a long-term antibody response provides vital protective immunity against many pathogens, including tetanus (Amanna, Carlson, & Slifka, 2007). The half-life of antibody responses to tetanus has been estimated to range between 11 years (Amanna et al., 2007) and 14 years (95% CI: 11-17 years) (Hammarlund et al., 2016). These estimates, along with recent well-established evidence from serologic surveys, laboratory and modeling studies in the US and abroad, and the updated WHO guidelines, suggest that tetanus immunity may endure longer than previously estimated (Hammarlund et al., 2016).

Additionally, a recent Slifka et al. (2020) study found no significant difference between tetanus disease incidence in high-income countries with robust booster vaccination schedules compared to countries without (A. M. Slifka et al., 2020). The growing body of evidence has prompted calls by tetanus subject matter experts in the US for a revision to the decennial booster recommendations for persons aged six years and older. However, a decision to keep, modify or discontinue decennial booster recommendations must consider several factors.

First to consider are the most vulnerable population based on age. In 2016, the US population of persons 65 years and older accounted for an estimated 49.2 million people (Roberts, Ogunwole, Blakeslee, & Rabe, 2018). The United States Department of Commerce' Economics and Statistics Administration estimates that by 2056, the population of adults in this age group will become larger than the population under 18 years (United States Census Bureau, 2021). Meanwhile, adult vaccination coverage rates remain low, although the burden of disease among adults from illness, hospitalization, death, and disability is significant. Reasons for the low adult vaccine uptake include patient and provider perceptions about infection risk, vaccine efficacy, clinical value, and economic value (Leidner et al., 2019). Older adults are at a greater

risk of getting tetanus due to declines in vaccine-induced protection over time and because they may be unvaccinated or under-vaccinated. Between 2000 and 2019, 56.8% (25/44) of tetanus deaths reported occurred among older adults ≥80 years (Centers for Disease Control and Prevention, n.d.; Thwaites et al., 2015).

Secondly, treating tetanus is expensive. In 2015, the estimated economic burden attributable to vaccine-preventable diseases related to ten recommended vaccines among US adults aged nineteen and older was $9 billion (Ozawa et al., 2016). Unvaccinated adults accounted for nearly 80% or $7.1 billion of the financial burden. Medications for the treatment of tetanus are high, as high as $605 per patient (Ozawa et al., 2016). The inpatient productivity loss per person of tetanus was $580 compared to $122 for a case of mumps due to extended hospitalizations in adults (Ozawa et al., 2016).

The last US population-based diphtheria and tetanus serosurvey conducted in 2002 using sera from participants of the Third National Health and Nutrition Examination Survey (NHANES III) found that overall, 72% of Americans aged ≥6 years had fully protective levels of tetanus antitoxin measured at >0.15 international units per milliliter (IU/mL) (McQuillan et al., 2002). Among older adults aged ≥70 years, only 31% were seroimmune to tetanus. The study concluded that a substantial proportion of US adults did not have protective antibody levels against diphtheria and tetanus (McQuillan et al., 2002) and, like other studies before it, supported the continuation of ACIP's recommended decennial booster (Khoury & Cahill, 2020; McQuillan et al., 2002; Roper et al., 2017).

Study Purpose

The purpose of this study is to estimate population-level tetanus seroimmunity. The objectives of the study are to (1) estimate population-based seroimmunity to tetanus, (2) analyze

seroimmunity by socio-demographics, military service, parity, and healthcare and (3) identify populations most-at-risk for susceptible tetanus seroimmunity levels.

The study findings will provide more recent scientific evidence on tetanus seroimmunity for consideration by ACIP panelists and workgroup members and inform the larger discussion on whether the decennial tetanus booster vaccination should be amended or discarded.

CHAPTER 2

LITERATURE REVIEW

Tetanus Toxoid-Induced Immunity

According to the Centers for Disease Control and Prevention (2017), immunity to a disease is attained when antibodies, proteins produced by the human body to destroy pathogens or toxins, are present in the body. There are two types of immunity: active and passive (Centers for Disease Control and Prevention, 2017a).

Active immunity, also referred to as natural or acquired immunity occurs when the body is exposed to an antigen and produces an adaptive immune response. It is conferred through infection by a pathogen (natural immunity) or through the delivery of an inactivated or attenuated form of an antigen through vaccination (vaccine-induced or acquired immunity). An adaptive immune response may take days or weeks to form, however, the resulting immunity is long-term and occasionally, lifelong (Baxter, 2007; Centers for Disease Control and Prevention, 2017a). Passive immunity can be attained in one of two ways: (1) when a person receives antibodies not produced by their immune system such as that conferred to newborn babies through the mother's placenta; or (2) when a person receives antibody-containing blood products such as immune globulin. Passive immunity provides immediate protection but unlike active immunity, this immunity is short-lived and often lasts a few weeks or months (Centers for Disease Control and Prevention, 2017a). Long-term antibody response provides essential protective immunity against many antigens making its maintenance vital (Amanna et al., 2007). Blood serum levels are an objective measure of protective antibody and serologic data are used

to evaluate immunization program success and identify vulnerable subpopulations (Gergen et al., 1995; McQuillan et al., 2002). Immunity to tetanus toxin can only be attained through vaccination. Recovery from disease does not confer protective immunity (World Health Organization, 2018a).

Vaccination with a tetanus toxoid-containing vaccine (TTCV) stimulates the creation of antitoxins which can effectively neutralize tetanus toxin produced by an infected wound. The amount of tetanus antitoxin existent in blood serum can be measured using in vivo (occurring inside living organisms in a lab setting) or in vitro (occurring outside the living body or in an artificial environment) laboratory techniques and the minimum level of circulating antitoxin considered to be protective differs depending on the type of laboratory assay used in the measurement (World Health Organization, 2018a).

Neutralization assays (in vivo), measure biologically active antitoxin in blood serum and are regarded as the gold standard method for assessing immune response to tetanus toxin because they are highly sensitive and can detect diminutive amounts of antitoxin such as 0.001 international units per milliliter (IU/mL) of antitoxin. Results in IU/mL are standardized against international reference serum. Passive hemagglutination tests, radioimmunoassay, standard or modified Enzyme-Linked Immunosorbent Assays (ELISAs), and bead-based immunofluorescence assays are some of the in vitro assays used to determine protective tetanus antitoxin levels (World Health Organization, 2018a).

Antitoxin levels $\geq$ 0.01 IU/mL are generally accepted as "protective" and sufficient to prevent disease in humans for tests conducted using neutralization assays, modified ELISAs, or bead-based immunofluorescence assays. Whereas for tests conducted using standard ELISA techniques, antitoxin concentrations of at least 0.1-0.2 IU/mL are considered protective (see table

2.1). Tetanus cases have occurred in people thought to have had "protective" antitoxin levels at or above the defined limits; suggesting maintenance of high antibody or antitoxin levels throughout life is important as protective antitoxin concentration does not always prevent disease from occurring (Roper et al., 2017; World Health Organization, 2018a).

Table 2.1. Tetanus Immunity Titers

Test Type	*Measurement*	*Interpretation/Inference*
In vivo neutralization assay or modified ELISA	> 0.01 IU/mL	Protective antitoxin level
In vitro assay, standard ELISA techniques	≥ 0.1- 0.2 IU/mL	Protective antitoxin level
In vitro assay, standard ELISA techniques	< 0.1 IU/mL	Inadequate protective antitoxin level

(Roper et al., 2017; World Health Organization, 2018a)

Serosurveys and Vaccine Durability

Seroconversion is the production of antibodies in response to an antigen (Merriam-Webster, n.d.-a). All FDA-approved vaccines, except for vaccinia virus-based smallpox vaccines, use seroconversion as a primary endpoint for establishing vaccine immunogenicity, the ability of a vaccine to provoke an immune response in an individual. Conclusive information on vaccine efficacy and protection can be obtained from analysis of serum neutralizing antibody titers generated from vaccines such as tetanus toxin or yellow fever (Amanna & Slifka, 2011). Standardized laboratory techniques such as neutralizing assays, enzyme-linked immunosorbent assays (ELISAs), or in-house assays validated against international serum standards, provide clear and conclusive information on vaccine efficacy and protection (Amanna & Slifka, 2011).

Tetanus and diphtheria vaccines provide a high protective value of 90% - 100% after three or more doses, however, data from cross-sectional serosurveys suggest that this protection wanes with advancing age (Kruszon-Moran, McQuillan, & Chu, 2004); the duration of

protective immunity depends on the magnitude of the serum antibody response and the time it takes for antibody titers to wane to nonprotective levels. WHO and CDC accept a serum antibody level of 0.01 international units per milliliter (IU/mL) as indicative of a minimum level of protective immunity against tetanus using an in vivo neutralization assay (Amanna, Messaoudi, & Slifka, 2008; Amanna & Slifka, 2011; Hammarlund et al., 2016). Serosurveys on tetanus have been conducted in several high-income countries such as the United States, United Kingdom, Denmark, Italy, and Belgium (see Table 2.2). It is important to understand the durability of vaccine-induced immunity and to use that knowledge to guide decisions on the ideal interval spacing for booster vaccinations (Hammarlund et al., 2016).

The Case for Maintaining Decennial Boosters

Gergen et al. (1995) conducted a population-based serologic survey of immunity to tetanus in the United States using data from the Third National Health and Nutrition Examination Survey (NHANES III) conducted from 1988-1994. The researchers found that overall, 69.7% of the US population ≥6 years had protective levels of tetanus antibodies of >0.15 IU/mL (age-adjusted value, 70.3 percent). Immunity differed based on age with respondents between the ages of 6- and 39- years having immunity levels above 80%, however, those levels declined steeply starting at age 40 and steadily until they leveled off at 27.8% in respondents ≥70 years old and among non-Hispanic whites and non-Hispanic blacks. Mexican American respondents had lower rates of immunity at 60% compared to non-Hispanic whites at 72% and non-Hispanic blacks at 68%. Individuals with a history of military service, higher levels of education, or incomes above the poverty level were more likely to have protective antibody levels. Immunity was also higher among males at 79% compared to females at 62% (Gergen et al., 1995).

Table 2.2: Sample Seroprevalence Studies in High-income Countries

Author	Year	Country	Sample Size	Target Population	Survey Design	Assay/cut-off protective immunity	Overall Sero-prevalence
Hammarlund et al.	2016	United States	546	Adults 2002-2008	Cross-sectional	ELISA or double-antigen ELISA; ≥0.01IU/mL	96%
Filia et al.	2014	Italy	3,604	Population based; 0-95 years	Cross sectional	Double-Antigen, time-resolved fluorescence immunoassay (DA-DELFIA); ≥0.1 IU/mL	70.7%
Wagner et al.	2009	United Kingdom	2,697	Population-based. All age groups	Cross-sectional	Multiplex Fluorescent Bead Assay; ≥0.1 IU/mL	89%
Theeten et al.	2006	Belgium	3,974	>40 years old	Cross-sectional	ELISA; >0.16 IU/mL	87.2%
Kruszon-Moran et al.	2004	United States	9,411	Females ≥6 years	Cross-sectional	Solid-phase enzyme immunoassay; >0.15 IU/mL	64%
McQuillan et al.	2002	United States	18,045	US population ≥ 6 years	Cross-sectional	Solid-phase enzyme immunoassay; >0.15 IU/mL	72%
Gergen et al.	1995	United States	10,618	US population ≥6 years	Cross-sectional	Solid-phase enzyme immunoassay; >0.15 IU/mL	69.7%

Source: (Filia et al., 2014; Gerber, 2020; Gergen et al., 1995; Hammarlund et al., 2016; Kruszon-Moran et al., 2004; McQuillan et al., 2002; Theeten et al., 2011; Wagner et al., 2012)

Thus, Gergen et al. concluded that even though effective vaccines against tetanus were readily available, many Americans did not have immunity to tetanus, with the levels lowest among older adults aged 65 years and older. Vaccination rates (96%) and immunity (96%) were correlated among six-year-olds; however, as antibody levels declined over time, 20% of older children between 10-16 years did not have protective antibody levels. Gergen et al. recommended that the primary series of tetanus toxoid be administered to vaccine naïve older adults to rapidly reduce tetanus disease burden in the United States (Gergen et al., 1995).

In a 2002 study "serologic immunity to diphtheria and tetanus in the United States," McQuillan et al. examined NHANES III data from 1988-1994 to provide national estimates of immunity to diphtheria and tetanus by measuring serum antibody levels of 18,045 respondents using a solid-phase enzyme-immunoassay with a lower limit of detection of 0.001 IU/mL. Protective levels of tetanus antitoxin were defined as >0.15 IU/mL using the justification provided in the Gergen et al. study. Overall, this study found that 72% of the US population had protective levels of antibody to tetanus. Prevalence of immunity was significantly lower in Mexican Americans (66%) compared to 74% in both non-Hispanic white and non-Hispanic black persons. Among Americans aged 6-10 years old, 91% had protective levels of tetanus antibody. By age 60, 50% did not have protective antibody levels to tetanus and by age 70 years that proportion had decreased further to approximately 30% (McQuillan et al., 2002).

Overall, more males had protective levels of antibody to tetanus than females and these levels declined swiftly in females after age 40 years. Race was not an independent predictor of immunity among respondents <19 years old. Only 47% of persons aged 20 years or older had levels that were protective against both tetanus and diphtheria (McQuillan et al., 2002). McQuillan et al. concluded that a considerable proportion of American adults did not have

protective antibody levels against diphtheria and tetanus and as such, decennial tetanus and diphtheria toxoid booster doses to adults should be emphasized as standard practice (McQuillan et al., 2002). These findings and conclusions were like those of Gergen et al. (1995).

Kruszon-Moran et al. (2004) conducted a study "tetanus and diphtheria immunity among females in the United States: are recommendations being followed?" to assess the prevalence of tetanus and diphtheria immunity and factors associated with immunity among females in the United States. This study also used NHANES III data and tested sera from 9,411 female respondents aged ≥6 years for diphtheria and tetanus antitoxin using a solid-phase enzyme-immunoassay. Protective levels of tetanus antitoxin were defined as >0.15 IU/mL for all analyses using the same rationale as that of Gergen et al. Prevalence estimates were weighted to represent the US population, account for oversampling of specific demographic groups and non-response to household surveys, and physical examinations (Kruszon-Moran et al., 2004).

Overall, 58% of US females aged ≥20 years who were tested did not have adequate protective levels of tetanus and diphtheria antibodies. Among participants ≥6 years old, 64% were immune to tetanus and seropositivity decreased with age but remained at ≥80% until after 39 years of age before declining significantly. Seroimmunity to tetanus was highest among the youngest female participants aged 6-11 years at 84% but declined more slowly between the ages of 12-39 years to >60%, then sharply to a low of 10% among females ≥60 years. Foreign-born Mexican American females had significantly lower seroimmunity to tetanus than individuals in the other racial/ethnic groups, including US-born Mexican American females. Mexican American females who had access to healthcare and were at or above poverty level had higher tetanus seroimmunity and higher education levels were associated with higher seroimmunity (Kruszon-Moran et al., 2004).

Persons who had routine access to healthcare were less likely to have protective levels of antibodies to both toxins. Birth outside the United States was associated with statistically significant lower seroimmunity. Prior military service was associated with higher seroimmunity to tetanus. Surprisingly, the study found that females who had no history of live births had higher seroimmunity levels than those who had a history of two or more live births and were expected to have had more interactions with the healthcare system. Kruszon-Moran et al. recommended that all physicians, especially obstetricians and gynecologists who may be sole healthcare providers for women, be familiar with and promote the ACIP decennial booster vaccination recommendation to their patients to ensure attainment of higher tetanus seroimmunity (Kruszon-Moran et al., 2004).

The Case for Re-evaluating Tetanus Booster Intervals

Several recent studies have present evidence suggesting current tetanus immunity levels within the US population are adequate and do not require continuation of adult decennial booster vaccination to reduce disease incidence further.

Hammarlund et al. performed a cross-sectional analysis of serum antibody titers in 546 adult subjects recruited from 2002 to 2008 stratified by age or sex with an explicit objective to inform the current debate to continue or discontinue decennial tetanus booster doses. To determine the magnitude and persistence of tetanus-specific antibody responses in present-day populations, the researchers used an enzyme-linked immunosorbent assay (ELISA) or a double-antigen tetanus ELISA and a protective serum antibody titer of ≥0.01 IU/mL to measure levels of immunity. Approximately 99% of persons less than 60 years old and 97% of the overall population had tetanus-specific antibody responses above the protective level of 0.01 IU/mL and

there was no significant difference in tetanus titers between males and females. Older adults ≥ 60 years had an increased likelihood of low seroimmunity to tetanus or diphtheria.

The researchers also examined the half-life of tetanus-specific antibody as a function of time after last vaccination and found that antibody responses to tetanus declined with an estimated half-life of 14 years (95% confidence interval, 11–17 years), with no significant difference between men and women. Their model predicted that 95% of the population in 2016 would remain seroprotected against tetanus for up to 72 years without further booster vaccination. When they applied a half-life of 11 years, obtained by another longitudinal study, their model found 95% of the population would remain seroprotected for 64 years without requiring further vaccination (Hammarlund et al., 2016).

Hammarlund et al. compared the results of their study to those of Gergen, Kruszon-Moran, and McQuillan all of which defined protective tetanus antibody level as ≥0.15 IU/mL and observed that 96% of their population would be protected against tetanus and this estimate was comparable to studies among European Americans and African American military personnel. Similar to previous studies, this study found lower seroimmunity in older adults which they hypothesized was due to (1) older adults at the time of the study being born in the 1920s and 1930s before tetanus vaccines were available in the United States and may not have received their childhood doses, or due to (2) age-related immune aging in which antibody responses decay more rapidly with advanced age (Hammarlund et al., 2016).

Hammarlund et al. concluded that adult booster vaccination with Td every 10 years may no longer be needed to provide protective immunity. They suggested that an age-based vaccination plan of a single Td vaccination at age 30 years and another at age 60 (because most unprotected individuals resided in this group), could replace the existing decennial

recommendation. By their estimation, substituting Tdap for Td at age 30 years would not affect the 1-time dose of Tdap currently recommended for adults and pregnant women would continue to receive Tdap vaccination under this revised plan to protect infants from Bordetella pertussis (Hammarlund et al., 2016).

Slifka et al. (2020), conducted an observational cohort study using WHO case reports from 2001 through 2016 to determine whether decennial boosters were necessary to reduce the incidence of tetanus and diphtheria in high-income countries where both diseases are rare. They compared the incidence of the two diseases in 31 European and North American countries that vaccinate adults every 5–20 years (group 1) to incidence in countries that do not routinely vaccinate adults for tetanus or diphtheria (group 2) and hypothesized that since nearly 95%–97% of reported cases occurred among adults aged >20 years the incidence rate of tetanus would be higher among nonvaccinating countries (group 2) if routine adult booster vaccination were required to maintain immunity, or incidence over time would increase among countries that do not recommend routine adult vaccinations (A. M. Slifka et al., 2020).

In their analysis, Group 1 countries had a tetanus incidence rate of 0.24 tetanus cases/million person-years (95% CI, .23 to .25), compared to Group 2 countries with an incidence rate of 0.27 cases of tetanus/million person-years (95% CI, .25 to .29) (see Table 2.3) (A. M. Slifka et al., 2020). After examining 11.6 billion person-years of data, notwithstanding adult vaccination schedules, both groups had an incidence rate of <1 case of tetanus per three million person-years demonstrating no significant difference in disease risk between countries that do or do not recommend adult tetanus vaccination (P=.52, NBR). Slifka et al. concluded by supporting the WHO 2017 guidance recommending against routine adult tetanus booster vaccination after 6 childhood doses and suggested that if more countries

approved and adopted this policy, healthcare resources could be directed to vulnerable and under-vaccinated populations (A. M. Slifka et al., 2020). This was the first study of its kind and further strengthened the call to re-evaluate current US tetanus booster recommendations.

Table 2.3. Incidence of Tetanus in Relation to Adult Vaccination Schedules

Group Designation	Childhood vaccinations		Adult Vaccinations	Incidence Rate[b] (Per 1,000,000 Person-years)
	No. of Doses	% Vaccination Coverage		
Group 1: North America				
Canada	6	91	Every 10 years	0.09
Mexico	6	97	Every 10 years	0.42
United States	6	95	Every 10 years	0.09
Range	6	91–97	Every 10 years	0.09–0.42
Group 1: Europe[d]				
Austria	5	87	Every 10 years[e]	0.00
Belgium	6	98	Every 10 years	0.13
Bulgaria	7	92	Every 10 years	0.26
Cyprus	6	97	Every 10 years	0.18
Czech Republic	6	96	Every 10–15 years	0.03
Estonia	6	93	Every 10 years	0.23
Finland	5	92	Every 10 years	0.00[f]
France	5	96	Every 10–20 years[g]	0.21
Germany	6	95	Every 10 years	Not reported
Greece	6	99	Every 10 years	0.48
Italy	5	94	Every 10 years	0.85
Latvia	6	98	Every 10 years	0.10
Lithuania	6	94	Every 5–10 years	0.55
Luxembourg	6	99	Every 10 years	0.00
Portugal	6	98	Every 10 years	0.45
Romania	6	89	Every 10 years	0.56
Slovakia	5	96	Every 15 years	0.05
Slovenia	6	94	Every 10 years	1.08
Sweden	5	97	Every 20 years	0.09
Range	5–7	87–99	Every 5–20 years	0 –1.08
Group 2: Europe				
Croatia	7	93	1[h]	1.14
Denmark	4	94	–	0.13
Hungary	6	99	–	0.39
Iceland	5	91	–	0.00
Ireland	5	95	–	0.18
Malta	6	97	–	0.75
The Netherlands	6	95	–	0.10
Poland	6	98	1[h]	0.52
United Kingdom	5	94	-	0.12
Range	4 - 7	91 - 99	-	0 - 1.14

(Source: Incidence of Tetanus and Diphtheria in Relation to Adult Vaccination Schedules (A. M. Slifka et al., 2020)

[a]Coverage in 2016 of infants receiving at least 3 doses of tetanus and diphtheria containing vaccine by age 1 year.
[b]Incidence rates were determined for each country by dividing the cumulative cases reported to the WHO from 2001 through 2016 by the sum of the mid-year populations from 2001 through 2016. Tetanus incidence data from North America group 1, Europe group 1, and Europe group 2 comprised approximately 6.93 billion person-years, 2.73 billionperson-years, and 1.92 billion person-years, respectively.
[c]Recommend individuals aged >60 years receive booster vaccination every 5 years. [f]Finland only reported tetanus incidence in 2015.[g]In 2012, France recommended adult booster vaccinations every 10 years and, by 2014, recommended booster vaccinations every 20 years except that individuals aged >60 years still receive booster vaccinations every 10 years. [h]Recommend 1 booster vaccination at age 18–20 years. Individuals in Croatia aged >60 years also receive 1 booster vaccination. Dashed lines indicate that no routine adult booster vaccinations are recommended.

Cost-Effectiveness of Decennial Booster Vaccinations

A decision to continue or discontinue adult decennial booster recommendations will have economic implications. Between 1988 and 2001, the average direct cost of care for tetanus in the US was an estimated $84,000 (range: $1700 to $925,000 in 2005 dollars) and the estimated total annual cost exceeded $12.6 million with the median cost of hospitalization in California ranging from $166,259 (range: $22,229 to $1,024,672) from 2008 to 2014 (Roper et al., 2017).

Similarly, the cost of vaccines is not negligible. Hammarlund et al. (2016), estimated that substituting tetanus, diphtheria, and acellular pertussis (Tdap) for Td at 30 years of age would translate into substantial healthcare cost savings. In their study, among adults aged 19–64 years, 63%–64% self-reported that they complied with the decennial Td revaccination schedule. With 234 million adults (2010 census), this translates into approximately 150 million adults vaccinated within the last 10 years, or approximately 15 million doses administered per year, which aligns with previous annual estimates of adult Td vaccine doses distributed by the CDC. At $28 per dose per the CDC adult vaccine price list, the adult Td booster vaccination costs $420 million per year. If the current schedule were modified to one requiring booster vaccinations every 30 years, healthcare costs would be reduced by two-thirds, approximately $280 million per year, and lead to over $1 billion in cost savings within 4 years (Hammarlund et al., 2016).

Additional advantages to modifying the adult Td booster vaccination interval include: (1) improved compliance with age-based recommendations and a simplified age-specific vaccination

schedule; (2) improved acceptance of recommendations based on immunological and epidemiological data and current risk-benefit analyses as opposed to compliance with antiquated practice; and (3) reduction in vaccine-associated adverse events from over immunization (Hammarlund et al., 2016).

Summary

Serological surveys demonstrate the potential for appropriately scheduled primary series and boosters to provide high antibody levels to protect individuals against tetanus. Some studies have demonstrated that seroimmunity trends vary by country, age cohort, immunization schedule, military status, country of birth, race, and ethnicity and may change over time. Other studies have suggested that a complete primary vaccination series in addition to boosters late in childhood and adolescence stimulate protective antibody levels well into adulthood, protect females throughout their childbearing years and subsequently protect their newborns (World Health Organization, 2018a). This cross-sectional descriptive study examined NHANES 2015-2016 data to (1) determine current population seroimmunity to tetanus, (2) describe seroimmunity by physical and socio-economic demographics, and (3) identify populations most at risk for low tetanus seroimmunity levels. NHANES data have been used in previous tetanus serosurveys and were appropriate for this study due to their representativeness of the US population.

CHAPTER 3

METHODS

Study Design

Research Design

This cross-sectional descriptive study analyzed secondary data from the National Health and Nutrition Examination Survey (NHANES) 2015-2016, a cross-sectional survey, to determine the seroimmunity to tetanus in the US.

Data Source

The National Health and Nutrition Examination Survey (NHANES)

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional study conducted by Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS) to gather nationally representative data on the health and nutritional status of noninstitutionalized civilian adults and children in the US. NHANES was established in the early 1960s and became a permanent NCHS program in 1999, continuously modifying health and nutrition assessments to align with emerging public health needs (Chen, Clark, Riddles, Mohadjer, & Fakhouri, 2020). NHANES uses a complex stratified multistage probability sampling design to collect data through physical examinations, interviews, and testing of biological samples. In-home interviews comprise demographic, socioeconomic, dietary, and health-related questions while the physical examination component is completed in a Mobile Examination Center (MEC). It consists of medical, dental, and physiological measurements and

laboratory tests managed by qualified medical personnel (National Center for Health Statistics, 2017a).

Blood sera, plasma, urine, and DNA specimens collected from survey participants are stored by NHANES in a biospecimen program and provided to researchers upon request to address future medical, environmental, and public health issues (National Center for Health Statistics, 2021). A request for access to the 2015-2016 stored blood sera was submitted directly on the NHANES biospecimen program website by CDC's Microbial Pathogenesis and Immune Response (MPIR) laboratory, ensuring strict adherence to guidelines outlined in the Federal Register. Once approved, pristine sera (which were frozen immediately upon collection and not put through a freeze-thaw cycle) were released to MPIR for testing using a microsphere-based multiplex antibody assay (MMACA) (National Center for Health Statistics, 2021). Measured tetanus antibody levels were then analyzed and interpreted.

NHANES Data Collection Procedures

Over the past few years, specific NHANES sample designs have evolved to include specifications for clustering, stratification, and oversampling of population subgroups. Since 1999, the primary sample design has comprised multiyear, stratified, clustered four-stage samples, with public-use data released in 2-year cycles. Samples are first extracted from primary sampling units (PSUs), made up of counties, groups of tracts within counties, or combinations of adjacent counties then from segments within PSUs such as census blocks or combinations of blocks. After that, samples are selected from dwelling units (DUs) or households within segments, and lastly, individuals are selected from within the households. PSUs are sampled from all US counties. Screening is conducted at the DU level to identify sampled persons (SPs) based on oversampling criteria (Chen et al., 2020).

Between 2015-2016, NHANES surveyed 30 PSUs, 15 each year (see Appendix 3 for 2015-2016 areas). PSUs can be large or small with as many as 5000 segments or as few as 100 segments in each frame. However, the samples are designed to produce an equal number of samples per PSU. Sample weights are applied to the collected data in three steps: (1) computation of base weights to account for the unequal probabilities of selection for sampling domains; (2) adjustment for survey nonresponse to limit bias; and (3) calibration of weights to the reference population to offset potential coverage differences between the final sample distribution and the target population distribution and to reduce variance in estimates (Chen et al., 2020).

NHANES Survey Participants

Each participant is estimated to represent approximately 65,000 other residents of the US resembling them. Adults 60 years and older are oversampled along with African Americans and Hispanics to produce reliable statistics. Individuals aged ≥16 years are directly interviewed, while adult proxies are used to obtain information on participants <16 years old or those unable to answer. All participants provided written informed consent. Very young participants were excluded from blood sample collection and dental screening. Examinations are age-dependent, with the oldest participants undergoing more extensive tests (Chen et al., 2020; National Center for Health Statistics, 2017a).

Study Sample from NHANES

In 2015-2016, NHANES selected 15,324 participants based on a complex, stratified, multistage probability cluster design sampling plan representative of the US civilian noninstitutionalized population from 15 strata and 30 primary sampling units (PSUs) (See Appendix 3). Of those, 9,971 completed the interview, 9,544 were examined, and 5,910

participants had sufficient sera for testing (see Figure 3.1.). When samples weights were applied, the sample represented 292,736,249 US residents. Information on a wide range of demographic, occupational, and behavior characteristics was collected by interviews conducted in homes and at the examination center. In NHANES 2015-2016 Hispanic persons, non-Hispanic black persons, non-Hispanic Asian persons, non-Hispanic white and other persons at or below 185 percent of the Department of Health and Human Services (HHS) poverty guidelines, and non-Hispanic white and persons ≥80 years were oversampled (National Center for Health Statistics, n.d.). The response rate 61.3% for the interview and 58.7% for those examined at the MEC. Adjustments were made to sample weights to account for non-response (Division of the National Health and Nutrition Examination Surveys, 2018; National Center for Health Statistics, n.d.).

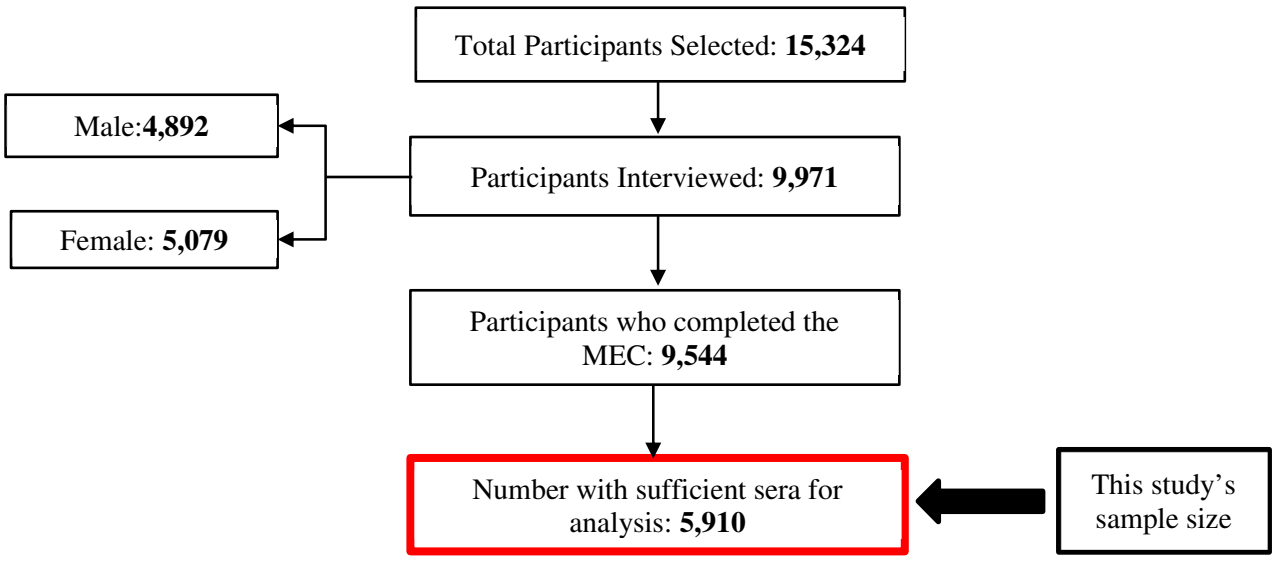

Figure 3.1. NHANES 2015-2016 participant selection flow diagram

Inclusion and Exclusion Criteria

All NHANES 2015-2016 survey participants who had sufficient sera for analysis were included in the study (n=5,910) which automatically excluded respondents who did not complete a physical exam in the Mobile Examination Center (MEC) as no sera was collected from them.

Laboratory Methods

To determine the prevalence of tetanus seroimmunity in the US population, serum samples collected from 5,910 NHANES 2015-2016 participants aged ≥6 years were analyzed and quantified using a microsphere-based multiplex antibody assay (MMACA). The MMACA with tetanus toxin is a newly expanded laboratory method developed by CDC's MPIR laboratory and calibrated to the WHO international Standard of TE-3 for tetanus toxin antibodies (Microbial and Pathogenesis and Immune Response Laboratory, 2017; National Center for Health Statistics, 2017a). Microspheres (beads), were conjugated to tetanus antigen present in the current acellular vaccine formulations, and incorporated into the current 4-plex test (utilizing beads conjugated to Fim, Fha, Prn, and Pt antigens) to create a 5-plex assay to measure tetanus antibody concentrations in IU/mL using a very low amount of capture antigen and sample volume (Microbial and Pathogenesis and Immune Response Laboratory, 2017).

Diluted serum was incubated with tetanus toxoid conjugated Luminex microspheres. Following a series of washes, bound antibody was detected with phycoerythrin (PE) coupled secondary-reporter antibody using the Luminex 200 plate reader (Luminex Corp, Houston, TX). The WHO International Standard Tetanus Immunoglobulin (human), TE-3, used to calibrate the assay was purchased from the National Institute for Biological Standards and Control (NIBSC; UK). The serum concentration of tetanus toxoid antibody was reported in IU/mL. MMACA is a "highly sensitive, specific, accurate and precise rapid test" (National Center for Health Statistics,

2017b). The lowest concentration of anti-tetanus toxin antibodies detectable in human serum for the MMACA assay, also known as the Lower Level of Quantification (LLOQ) was 0.007 IU/mL (National Center for Health Statistics, 2017b).

Data on the minimum protective tetanus antibody thresholds differ significantly based on the type of assay used such as in vivo neutralization, modified Enzyme-Linked Immunosorbent Assays (ELISAs), or bead-based immunofluorescence assays (World Health Organization, 2018a). Regardless, the standard antibody concentration level <0.10 IU/mL is inadequate or susceptible, and ≥0.10 IU/mL is protected (World Health Organization, 2018a); this is the standard used for this study.

Data Measures

This study examined the following independent variables: age, sex, race/ethnicity, education level, marital status, military service, country of birth, poverty level, pregnancy, and access to healthcare, against the dependent variable, tetanus antibody concentration or anti-tetanus IgG concentration.

Tetanus seroimmunity

Tetanus antibody level was measured in international units per milliliter (IU/mL) and classified according to the level of protection provided. While no antibody level provides absolute protection against tetanus, higher levels are commonly ascribed to longer duration and higher clinical protection (Ang, James, & Goh, 2015). A respondent was considered to have protected tetanus antibody levels at ≥0.10 IU/mL and considered susceptible at <0.10 IU/mL (Microbial and Pathogenesis and Immune Response Laboratory, 2017).

Determinants of sero-immunity

Age (RIDAGEYR in NHANES) was measured as age in years at the time of screening, and data analysis only included participants ≥6 years old as sera were not collected on respondents younger than six years. Additionally, children ≤6 years old should have received at least three primary doses of DTaP at 2, 4 and 6 months of age, and their fourth and fifth doses, two boosters, between the ages of 15 and 18 months and 4-6 years (Centers for Disease Control and Prevention, 2018). Three doses of a tetanus toxoid containing-vaccine are thought to offer protective immunity for at least five years (Minh Yen & Thwaites, 2019). For these reasons, participants <6 years old were excluded. To examine seroimmunity levels by age, eleven age (years) categories were created: 6-10, 11-19, 20-29, 30-39, 40-49, 50-59, 60-64, 65-69, 70-74, 75-79, and ≥80 years.

The categories allowed for examination of seroimmunity among children, adolescents, working-age adults, and retired adults. The 6-10-year age group allowed for examination of immunity levels among children who would have received boosters between ages 4 and 6 years, as well as kindergarten-aged children who should have received tetanus vaccinations prior to enrollment in the public/private school system as required by 49 states and the District of Columbia (Seither et al., 2016). The 11-19-year age group provided an opportunity to examine seroimmunity levels among adolescents who should have received a tetanus booster dose between 11-12 years. Young, working-age adults between the ages of 20-29, 30-39, 40-49 and middle-aged working adults between the ages of 50-59, and 60-64 years were classified in groups to assess the impact of education, marriage, parity, military service, and poverty to income ratio on tetanus seroimmunity levels.

Previous studies had noted steep declines in immunity starting at ages 40 and 60 years, therefore it was important to create age groups that clearly demarcated these ages. Four older adult age groups were created 65-69, 70-74, 75-79 and ≥80 years to better assess the prevalence of susceptible tetanus seroimmunity levels among these populations and the rate of decline in protective immunity between these groups as observed in previous studies (Gergen et al., 1995; McQuillan et al., 2002; Wagner et al., 2012).

Race/ethnicity, (RIDRETH3) was self-reported as non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, non-Hispanic Asian, or Other/multiracial. In this study, Mexican American and other Hispanic were combined into "Hispanic," and non-Hispanic Asian and other/multiracial were combined into "Asian/multiracial" to create four distinct race/ethnicity groups: non-Hispanic white (NH white), non-Hispanic black (NH black), Hispanic, and Asian/multiracial. It was critical to separate adult Hispanics as they had been shown to have lower seroimmunity levels in previous studies (Gergen et al., 1995; McQuillan et al., 2002).

The NHANES *ratio of family income to poverty* (INDFMPIR) was calculated by dividing a family or individual's income by the poverty guidelines specific to the survey year. Respondents were required to provide exact income figures rather than ranges therefore, if they reported income as <$20,000 a year or ≥$20,000 a year, their responses were not recorded (National Center for Health Statistics, 2017b). For this study, a poverty ratio of less than 1 was coded as "below the poverty line," whereas ratios ≥1 were coded as "at or above the poverty line." *Education level* (DMDEDUC2) in adults ≥20 years was measured by NHANES 2015-2016 in five categories ranging from less than 9th grade to college graduate or above. In this study, "less than 9th grade" and "9th-11th grade" were combined into one group "less than high

school." Respondents with "high school graduates/GED or equivalent degree" were categorized as "high school graduate," and respondents with "some college or AA degree" or "college graduate or above" were combined into one "post-high school graduate" category for a total of three education level categories (National Center for Health Statistics, 2017b). Serosurvey studies in 1995 and 2002 found US residents living at or above the poverty level more likely to be protected from tetanus and found that seroimmunity increased with increasing level of education (Gergen et al., 1995; McQuillan et al., 2002).

To reduce disclosure risk, *country of birth* (DMDBORN4) was coded as "United States" for those born in the continental US and Washington DC or "Other" for all other countries including US territories. In this study, "Other" was reclassified as "Foreign-born." Military service (DMQMILIZ) was assessed in persons aged ≥17 years and categorized as "ever active" or "never active." Active duty was considered activation for service in the US or a foreign country supporting humanitarian or military operations. These variables were included as previous studies observed lower seroimmunity in Foreign-born Americans and higher seroimmunity among active military personnel (Gergen et al., 1995; McQuillan et al., 2002).

Marital status (DMDMARTL) was assessed for participants 14 years and older; however, data were only released for participants aged 20 years and older to reduce disclosure risk (National Center for Health Statistics, 2017b); and for this study, six original categories were re-grouped into three: "Married" for those married or living with a partner, "divorced, widowed, or separated," and "never married." In a 2016 study, persons who had never been married had higher vaccination coverage (Lu, O'Halloran, Ding, Liang, & Williams, 2016). This study sought to determine if that coverage was reflected in seroimmunity levels across marital groups.

Table 3.1. Study Variables

Variable	Type	Definition	Sample Size	Missing Observations
Dependent Variable				
Tetanus antibody level	Binary	Susceptible	521	0
		Protective	5,389	
Covariates				
Sex	Binary	Male	2,856	0
		Female	3,054	
Age (years)	Categorical Ordinal Continuous	6-10	626	0
		11-19	990	
		20-49	2,082	
		50-64	1,141	
		65-74	611	
		≥75	460	
Race/Ethnicity	Categorical Nominal	Non-Hispanic white	1,965	0
		Non-Hispanic black	1,099	
		Hispanic¶	1,978	
		Asian/multiracial	868	
Education (20+)	Categorical Ordinal	Less than high school	1,015	1,617*
		High school graduate	950	
		Post-high school	2,328	
Marital Status (20+)	Categorical Nominal	Never Married	736	1,616*
		Married	2,647	
		Divorced/Widowed/Separated	911	
Military Service (17+)	Categorical Nominal	Never active	4,164	1,323*
		Ever active	423	
Poverty Index Ratio	Categorical Ordinal	Below poverty level	1,299	535 (9%)
		Above poverty level	4,076	
Country of Birth	Categorical Nominal	Foreign-born	1,599	1
		United States	4,310	
Healthcare Access	Categorical Binary	No	896	0
		Yes	5014	
Parity	Categorical Nominal	Never Pregnant	4179	0
		Ever Pregnant	1731	

¶ Hispanic includes Mexican American & other Hispanic
§ Married includes being married and living with a partner
*Missing values due to eligibility cut-offs for the variable

To examine the relationship between pregnancy and protective immunity, two reproductive health questions, “have you ever been pregnant (RHQ131)” and “how many of your deliveries resulted in a live birth (RHQ171)” were combined into a new variable, *parity* and used as a proxy for vaccination among females who should have received a dose of tetanus toxoid in their third trimester in line with WHO and ACIP recommendations (Centers for Disease Control and Prevention, 2020; World Health Organization, 2017). Females who had ever had live births, miscarriages, stillbirths, tubal pregnancies, or abortions were coded as “ever pregnant” and females who had never had children and men were categorized as “never pregnant.”

Survey respondents were asked if they had a routine place for healthcare (HUQ030). This was re-coded as *healthcare access* and included in the study to determine if healthcare access positively impacted seroimmunity levels. McQuillan et al. (2002) found that persons who had access to routine healthcare were less likely to have protective seroimmunity (McQuillan et al., 2002). All the study measures are listed in Table 3.1.

Data Analysis

Statistical methods

This study analyzed sera from the sample data to obtain estimates of tetanus seroprevalence for the US population. The poverty variable had 535 (9%) missing observations out of the sample size (n=5,910). It was appropriate to proceed with analysis of the poverty variable without additional evaluation or adjustment because the missing observations were less than 10% of the eligible respondents (Division of the National Health and Nutrition Examination Surveys, 2018). Further evaluation or adjustment were also not needed for the education, marital and military status variables as those values were missing due to NHANES’ exclusion of persons

under 17 years for military service and persons under 20 years for marital status and education from the data collection for those variables.

Analyses were completed using SAS/STAT® survey procedures in Statistical Analysis Software (SAS®) 9.4 (Cary, NC) as these procedures appropriately account for the complex NHANES sample design (Division of the National Health and Nutrition Examination Surveys, 2018). The NHANES 2015-2016 demographic (demo_i), healthcare utilization (huq_i), insurance (hiq_i), reproductive health (rhq_i), tetanus antibody serum (sspt_i) data files each with 9,971 observations were downloaded from the CDC/NCHS NHANES site, saved as XPT files, imported, and saved as temporary SAS datasets, and then later as permanent data files. Next the data files were merged into one dataset with 5,911observations and 129 variables for all observations with antibody data, sorted by sequence number (SEQN) and named. All variables of interest were formatted to create a new dataset which contained 5,911 observations and 31 variables. This dataset was used to run all SAS analyses using the PROC SURVEYFREQ and PROC SURVEYLOGISTIC survey procedures.

The PROC SURVEYFREQ, the SAS® procedure most often used to calculate descriptive statistics for categorical variables was used to generate one-, two- and multiple- way frequency and crosstabulation tables (Wells, n.d.). The procedure was used along with the masked variance pseudo-PSU (SDMVPSU), masked variance pseudo-stratum (SDMVSTRA) and the adjusted examination weight (WTSSPT) to compute frequencies, weighted frequencies, standard errors of the weighted frequencies, percent weight in the sample population, and the standard errors of percent for each variable. Row percentages, standard errors, Clopper-Pearson (exact) 95% confidence intervals and *P* values were also calculated using the PROC SURVEYFREQ procedure.

The Rao-Scott chi-square test, a design-adjusted version of the Pearson chi-square test was computed based on the design effect of the proportions to reveal any association between row and column variables and to determine differences between observed and expected frequencies (SAS/STAT(R) 9.2 User's Guide). For one-way tables, Rao-Scott chi-square goodness-of-fit tests adjusted for sample design were provided. For two- or more way tables, design-adjusted tests of independence or no association including the Rao-Scott chi-square test, the Rao-Scott likelihood ratio test, the Wald chi-square test and the Wald log-linear chi-square test were provided (SAS Institute Inc., 2019). Additionally, as recommended by NHANES, a second-order (Satterthwaite) Rao-chi-square test was used to find the approximate distribution of a linear combination of the independent chi-square variables and to test the degrees of freedom of the probability distribution (Division of the National Health and Nutrition Examination Surveys, 2018).

To estimate the standard deviation of the sampling distribution, the Taylor Series Linearization (TSL) was used, as recommended by NHANES, (along with the examination weight, masked variance pseudo-PSU and a masked variance pseudo-stratum) to estimate variance since exact mathematical formulas for variance estimates are not available for complex sample surveys (Chen et al., 2020). The Taylor Series Linearization method is recommended because it generates precise standard estimates and calculates realistic, almost unbiased, and design-consistent estimates of variance. Age standardization of the prevalence estimates was not performed because the population counts were based on the crude (unadjusted) prevalence in the population.

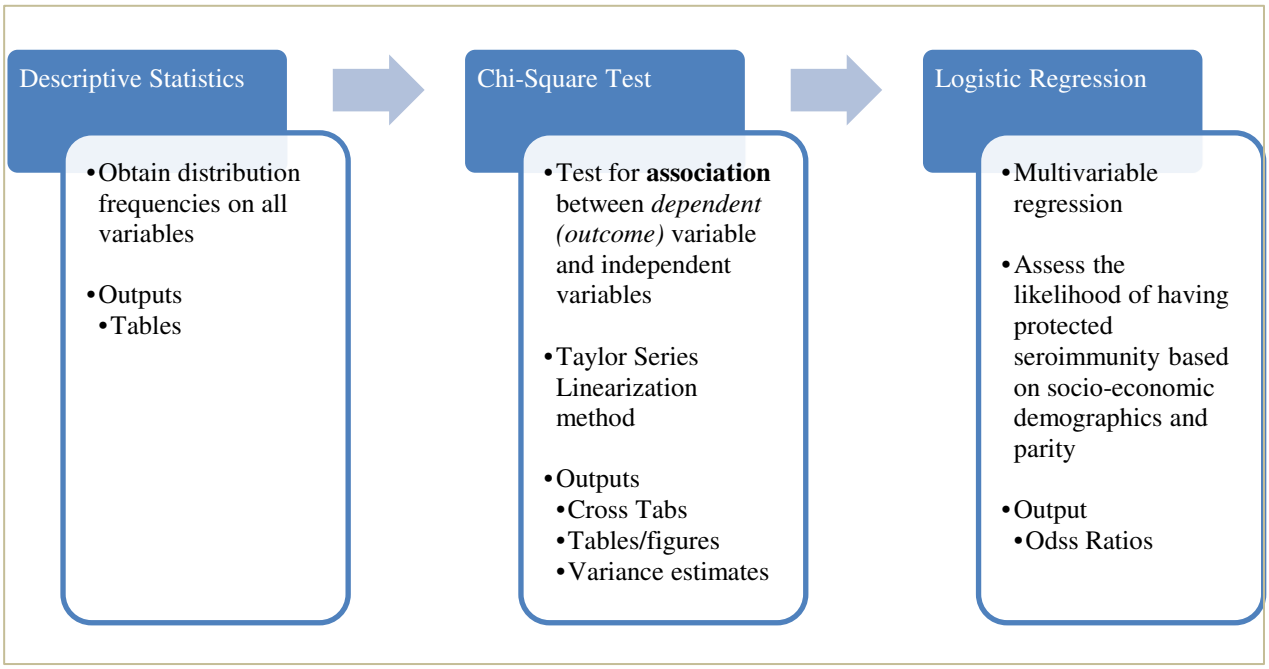

Figure 3.2 Study Data Analysis

Lastly, a multivariable logistic-regression model using the PROC SURVEYLOGISTIC procedure controlling for all variables was ran to (1) assess the relationship of all the regressors (age, sex, race/ethnicity, country of birth, education, marital status, military service, healthcare access, parity and poverty level to the dependent variable, protected tetanus immunity; and (2) to obtain estimates of odds ratios (ORs) and their 95% confidence intervals which were used as good approximations to risk ratios (Kleinbaum & Klein, 2002).

All ten covariates were entered into the model. Odds Ratios between 0 and 1 were considered as less likely to have protected seroimmunity whereas those with values greater than 1 were considered more likely to be protected (Motulsky, 2010). No proportions with fewer than 8 degrees of freedom were reported as they would have produced unreliable estimates and required review and approval for use by an NHANES clearance official (Division of the National

Health and Nutrition Examination Surveys, 2018). Because there were no pre-specified hypotheses tested in this study, no adjustments for multiple comparisons were made.

Ethical Procedures

The National Center for Health Statistics' (NCHS) Research Ethics Review Board (ERB) provided approval for the 2015-2016 NHANES data collection under continuation of protocol #2011-17, effective through October 26, 2017 (National Center for Health Statistics, 2017c). This study was submitted as an amendment to the NHANES survey protocol, approved by NCHS/CDC IRB, and conducted consistent with applicable federal law. The study used de-identified publicly available data that can be downloaded directly from the NCHS website (National Center for Health Statistics, 2017c).

Assumptions

This study made the following assumptions regarding the use of secondary data and serosurvey results: (1) that the 2015-2016 survey was conducted with the rigor afforded all previous and subsequent NHANES surveys, which is well documented in the NHANES procedure manuals, questionnaire instruments, survey methods and analytic guidelines; (2) that NHANES participants answered survey questions honestly; (3) that MPIR laboratory staff who conducted the serosurvey tests used the assay and methodology as recommended; (4) that the presence of tetanus antibody beyond the cut-off value for immunity was evidence of vaccination and protection against tetanus; (5) that based on sampling and weights, the samples included in the 2015-2016 NHANES were nationally representative of the US population, and therefore, the findings of this study can be generalized to the NHANES study population and the population of the US.

Summary

The last population-based serologic survey of immunity to tetanus in the US was conducted in 2002 using NHANES III data. This study population, design and data analysis plan were carefully selected to provide a more recent assessment of seroimmunity to tetanus among the non-institutionalized US population; the results are expected to help evaluate the success of vaccination programs and inform the need for continued decennial booster vaccination recommendations for US adults.

This chapter described the methods used to quantify and analyze tetanus antibody levels from respondents of the NHANES 2015-2016 survey. Participants of this complex survey design were selected using a rigorous methodology from the National Center for Health Statistics. A cross-sectional sample size of 5,910 represented participants ≥6 years old and when weighted, was representative of the non-institutionalized US population. Variables of interest were selected based on previous study findings and appropriate statistical analyses were conducted in SAS® 9.4 (Cary, NC) to test the association and relationship between the dependent variable, tetanus antibody level and selected covariates. Adjustments were made to sample weights to account for non-response. The study was reviewed and approved by the NCHS Ethics Review Board.

CHAPTER 4

RESULTS

This chapter presents the results of a cross-sectional study of tetanus seroimmunity in the United States (US) using a population representative sample from the National Health and Nutrition Examination Survey (NHANES), 2015-2016. The study sought to describe the prevalence of tetanus seroimmunity in the US, explore the differences in seroimmunity across the US population based on sociodemographic (age, sex, race, education, marital status, country of birth, poverty level) characteristics. The study further explored differences in seroimmunity based on military service, health insurance status, and parity, and analyzed the association and odds of seroimmunity by demographics to identify sub-groups more likely to have susceptible seroimmunity. When sample weights were applied, the study sample, of 5,910 persons aged six years and older represented 292,736,249 US residents and was 51% female.

Immunity to Tetanus

Overall Tetanus Immunity and Immunity by Age and Sex

Overall, 93.8% of Americans had protective levels of tetanus immunity (95% CI: 92.85, 94.73). This proportion was remarkably higher than that of the Gergen et al. study (69.7%) and the McQuillan study (72%) (Gergen et al., 1995; McQuillan et al., 2002). See Table 4.1. Age was significantly associated with tetanus immunity (p=<.0001). By age group, protective seroimmunity levels remained at or above 90% between ages 6-74 years before declining steeply to 73.3% among 75-79-year-olds and to 76% among persons aged ≥80 years. Working-age

adults aged 20-29, 40-49 and 50-59 years had the highest proportions of protective immunity [96.8% (95% CI: 95.23, 98.0); 96.78% (95% CI: 94.67, 98.22); and 96.7% (95% CI: 94.37, 98.20)], respectively. Across all age groups, older adults aged 75-79 years and those aged ≥80 years had the highest proportions of susceptible persons at 27% (95%CI: 18.26, 36.65) and 24% (95% CI: 8.6, 20.2) respectively. However, these estimates were somewhat unstable given the large confidence intervals. See Table 4.1 and Figure 4.1.

Immunity was associated with sex (p=.0011). A larger proportion of males (95%) had protective levels of immunity (95% CI: 94.17, 96.14) compared to females [92.5% (95% CI: 91.06, 93.81)]. The proportion of males with protective immunity did not decrease by age at the same rate as it did for females; among males, protective immunity remained high (mean 95%) before declining between ages 75-79 years old to 84.8% (95% CI: 74.48, 92.18). In contrast, among females, protective immunity proportions declined between 65-69 years to 88.5% (95% CI: 80.4, 94.28), before plunging to 64.3% (95% CI: 50.78, 76.32) by age 80. See Figure 4.1.

Immunity by Race and Ethnicity

There was an association between race/ethnicity and immunity (p=.0010). Protective immunity levels across all race/ethnicity groups were at or above 90%. Compared to non-Hispanic white persons, a smaller proportion of Hispanic persons had protective immunity [95.2% (95% CI: 93.94, 96.29) vs. 91% (95% CI: 89.05, 92.41)]. This difference was significant. Males had a higher proportion of seroimmunity across groups, however, the differences were not statistically significant (see Figure 4.2.). While seroimmunity waned in age groups across all races, they declined at a much slower pace among non-Hispanic white persons starting at ages 75-79 years old compared to ages 60-65 years in Hispanic and Asian and multiracial persons. By age 80, non-Hispanic blacks had the lowest proportion of seroimmunity at 59%. See Figure 4.3.

Table 4.1 Estimated Prevalence of Seroimmunity to Tetanus by Demographic Characteristics, United States, 2015-2016

Demographic Characteristic	*Sample Size (Unweighted)*	*Weighted Prevalence ≥0.10 IU/mL* (95% CI)*
Total	**5910**	93.84 (92.85, 94.73)
Sex		
Male	2856	95.23 (94.17 , 96.14)
Female	3054	92.52 (91.06 , 93.81)
Age		
6-10	626	89.99 (85.89 , 93.22)
11-19	990	94.50 (91.67 , 96.59)
20-29	690	96.83 (95.23 , 98.00)
30-39	694	95.70 (93.21 , 97.48)
40-49	698	96.78 (94.67 , 98.22)
50-59	706	96.66 (94.38 , 98.20)
60-64	435	94.20 (59.92 , 97.04)
65-69	347	91.59 (86.76 , 95.08)
70-74	264	91.40 (86.81 , 94.79)
75-79	189	73.28 (63.35 , 81.74)
≥80	271	75.85 (67.67 , 82.84)
Race/Ethnicity		
Non-Hispanic White	1965	95.21 (93.94 , 96.29)
Non-Hispanic Black	1099	93.01 (90.68 , 94.91)
Hispanic	1978	90.83 (89.05 , 92.41)
Asian/Multiracial	868	91.42 (88.81 , 93.60)
Years of Education		
< High school	1015	85.93 (81.49 , 89.65)
High school graduate	950	92.12 (90.88 , 94.61)
Post-high school	2328	96.17 (95.20 , 96.98)
Marital Status		
Married†	2647	94.65 (93.29 , 95.80)
Divorced †	911	90.06 (87.65 , 92.14)
Never married	736	95.83 (93.63 , 97.43)
Military Service		
Ever active	423	99.57 (98.36 , 99.95)
Never active	4164	93.62 (92.47 , 94.64)
Poverty Index		
Below Poverty Level	1299	91.85 (90.22 , 93.28)
At/above Poverty Level	4076	94.51 (93.53 , 95.38)
Country of Birth		
United States	4310	94.98 (94.04 , 95.80)
Other	1599	87.84 (85.02 , 90.30)
Healthcare Access		

Yes	5014	94.05 (92.94 , 95.03)
No	896	92.70 (90.70 , 94.38)
Parity		
Any Pregnancy	1731	92.22 (90.22 , 93.92)
No Pregnancy	4179	94.58 (93.54 , 95.50)

*≥0.10 IU/mL considered "protected" seroimmunity level

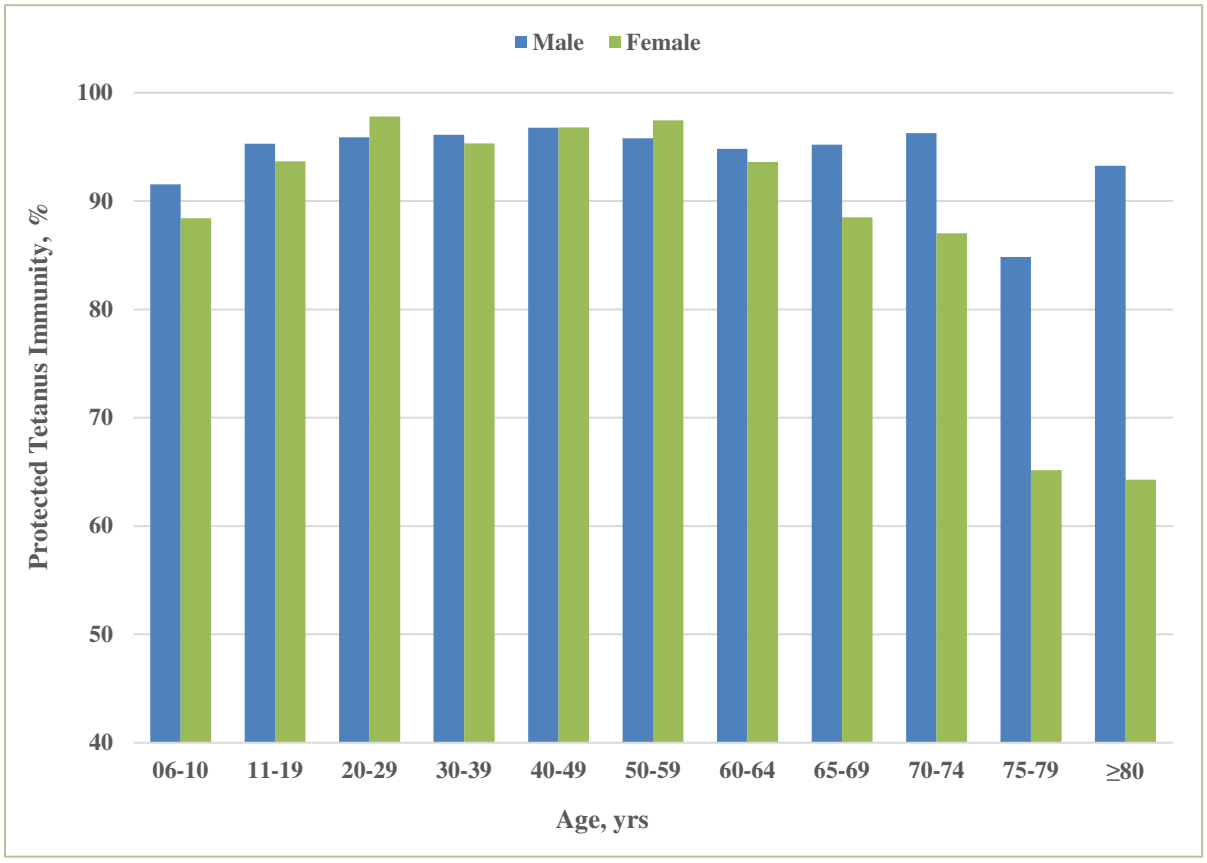

Figure 4.1. Estimated Prevalence of Seroimmunity to Tetanus Immunity by Age and Sex (NHANES, 2015-2016)

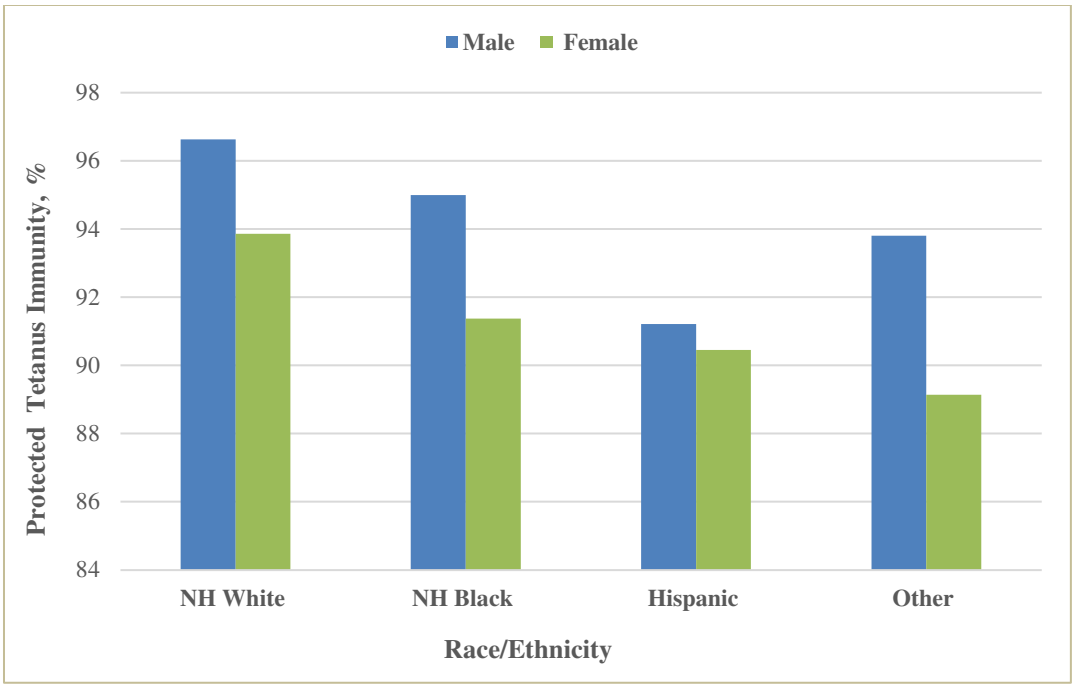

Figure 4.2. Estimated Prevalence of Seroimmunity to Tetanus by Race/Ethnicity and Sex (NHANES, 2015-2016)

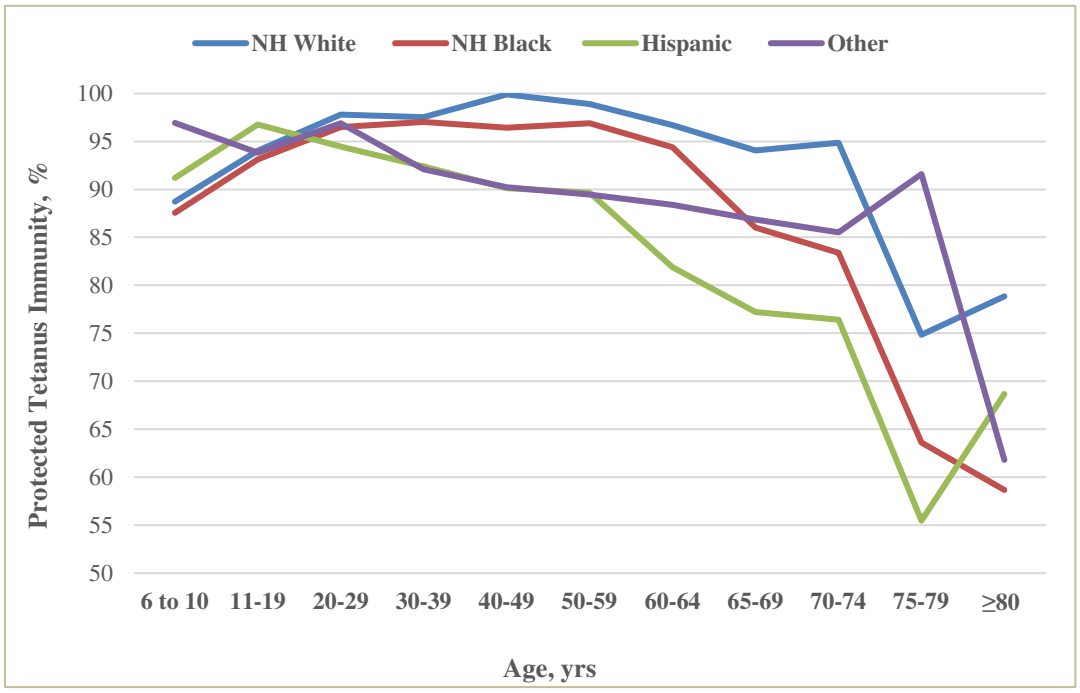

Figure 4.3. Estimated Prevalence of Seroimmunity to Tetanus by Race/Ethnicity and Age (NHANES, 2015-2016)

Immunity by Education, Marital Status, and Parity

There was a highly significant association between years of education and tetanus immunity (p=<.0001). Seroimmunity was lowest among persons with less than high school education 86% (95% CI: 81.49, 89.65) compared to 92.9% (95% CI: 90.88, 94.61) among high school graduates and 96% (95% CI: 95.20, 96.98) among post-high school graduates. Male high school graduates had significantly higher proportions of protective immunity [96% (95% CI: 93.2, 97.9) compared to their female counterparts [89.7% (85.8, 92.8)]. Immunity among females steadily increased as education levels increased. See Figure 4.4.

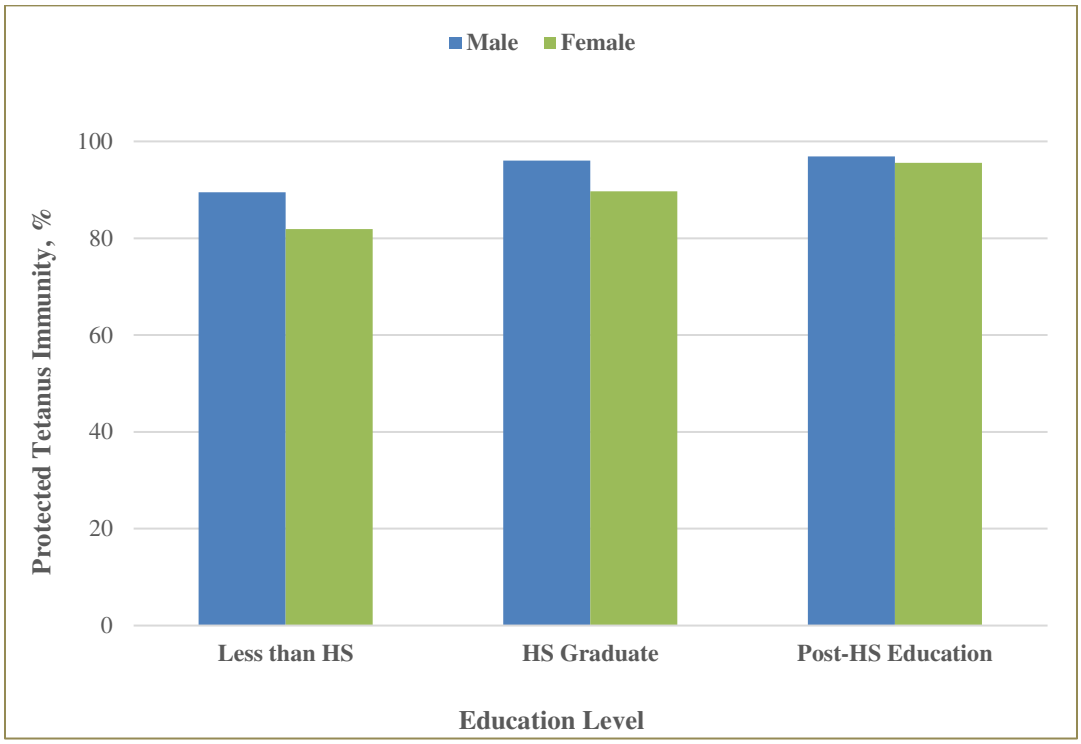

Figure 4.4. Estimated Prevalence of Seroimmunity to Tetanus by Sex and Education Level (NHANES, 2015-2016)

Marital status was associated with tetanus immunity (p=.0001). However, there were no remarkable differences between protective levels of immunity among those who had never

married [95.8% (95% CI: 93.63, 97.43)] and those who were married or living with a partner [94.6% (95% CI: 93.29, 95.80)]. Divorced, widowed, or separated persons had the highest proportion of susceptible persons [9.9% (95% CI: 7.86, 12.35)] double the proportion of married persons [5.4% (95% CI: 4.20, 6.71)] and nearly twice the proportion of susceptible never married persons [4.2% (95% CI: 2.57, 6.37)]. See Figure 4.5.

Pregnancy and immunity were associated (p=.0206). A larger proportion of those who had never been pregnant (sample size included men) had protective levels [95% (95% CI: 93.54, 95.50)] compared to females who had ever been pregnant [92% (95% CI: 90.22 , 93.92)]. However, it was not clear what proportion of the 8% susceptible persons (95% CI: 6.08, 9.78) were pregnant at the time of data collection.

Figure 4.5. Estimated Prevalence of Seroimmunity to Tetanus by Marital Status (NHANES, 2015-2016)

Immunity by Country of Birth, Military Service, Poverty Level, and Healthcare Access

Country of birth was associated with immunity (p=.0001). Seroimmunity was lower in foreign-born persons [88% (95% CI: 85.02, 90.30)] compared to US born persons [95% (95% CI: 94.04, 95.80)]. There was an association between military service and immunity (p=<.0001). Compared to those who had ever served in the military, those who had never served had significantly lower proportions of immunity [99.6% (95% CI: 98.36, 99.95%) vs. 93.6 (95% CI: 92.47, 94.64). The proportion of those who had ever served was less than 10% of the sample size and there were no significant differences in immunity levels between men and females who had ever served [99.5% (95% CI: 98.22, 99.95) vs. 100% (95% CI: 89.11, "-"). Although females had an almost imperceptible edge over their male counterparts, this was not as significant as demonstrated by previous studies (Gergen et al., 1995). Having a routine place of healthcare was not significantly associated with protective tetanus immunity (p=0.1641).

Multivariable Regression Results

The adjusted odds ratios (aOR) of protective tetanus immunity were generated from a multivariable logistic regression after controlling for age, sex, race/ethnicity, education, marital status, military service, country of birth, healthcare access, and parity. Females had statistically significantly lower odds (aOR=0.62, 95% CI: 0.48, 0.79) of having protective immunity compared to men. Persons ≤64 years of age had higher odds of having protective immunity compared to persons ≥65 years of age. The odds of having protective immunity decreased with age over the age of 65 years with the oldest older adults likely to have protective immunity to tetanus [(65-69-year-olds: aOR=0.36, 95% CI: 0.20, 0.63); (70-74-year-olds aOR=0.35, 95% CI: 0.19, 0.65); (75-79-year-olds aOR= 0.09, 95% CI: 0.06, 0.14); and ≥80-year-olds: aOR=0.10, 95% CI: 0.05, 0.20].

Table 4.2 Multivariable Regression Model for Protective Immunity

Demographic Characteristic	*Adjusted Odds Ratio*	*95% Wald Confidence Limits*
Sex		
Male	1.00	Ref
Female	0.62	0.48 , 0.79
Age		
20-29	1.00	Ref
6 to 10	0.29	0.18 , 0.48
11 to 19	0.56	0.32 , 0.99
30-39	0.73	0.41 , 1.31
40-49	0.98	0.50 , 1.93
50-59	0.95	0.49 , 1.85
60-64	0.53	0.26 , 1.08
65-69	0.36	0.20 , 0.63
70-74	0.35	0.19 , 0.65
75-79	0.09	0.06 , 0.14
>= 80	0.10	0.05 , 0.20
Race		
Non-Hispanic white	1.00	Ref
Non-Hispanic black	0.67	0.48 , 0.93
Hispanic	0.50	0.35 , 0.70
Other	0.54	0.35 , 0.83
Education		
Post-High School Graduate	1.00	Ref
Less than High School	0.24	0.16 , 0.38
High School Graduate	0.52	0.39 , 0.70
Marital Status		
Married	1.00	Ref
Never Married	1.30	0.84 , 2.02
Divorced/Widowed/Separated	0.51	0.36 , 0.72
Military		
Ever Active	1.00	Ref
Never Active	0.06	0.02 , 0.18
Country		
US-Born	1.00	Ref
Other	0.38	0.28 , 0.52
Poverty		
At/above Poverty Line	1.00	Ref
Below Poverty Line	0.65	0.52 , 0.82
Parity		
Ever Pregnant	1.00	Ref
Never Pregnant	1.47	1.09 , 1.98
Routine Place for Healthcare Access		
Yes	1.00	Ref
No	0.80	0.59 , 1.10

Compared to non-Hispanic White persons, other races were significantly less likely to have protective tetanus immunity. The odds of having protective immunity among Hispanic persons was lower (aOR=0.50, 95% CI: 0.35, 0.70) compared to non-Hispanic white persons (aOR=0.54, 95% CI: 0.35, 0.83). Non-Hispanic blacks were less likely to have seroimmunity (aOR=0.67, 95% CI: 0.48, 0.93) compared to non-Hispanic whites. Protective tetanus immunity increased with attainment of higher education levels.

Americans with less than a high school education were less likely to have protective tetanus immunity [aOR=0.24, 95% CI: 0.16, 0.38) compared to high school graduates and post-high school graduates. Similarly, high school graduates were less likely to have protective immunity (aOR=0.52, 95% CI: 0.39, 0.70; p=.0002) compared to post-high school graduates. Divorced, widowed, or separated persons had lower odds of protective immunity [aOR=0.51, 95% CI: 0.36, 0.72] compared to married persons. Americans who had never served in the military were less likely (aOR=0.06, 95% CI: 0.02, 0.18) than those who had ever served to be protected.

Foreign-born persons had significantly lower odds of having seroimmunity (aOR=0.38, 95% CI: 0.28, 0.52) compared to US-born nationals. Persons below the poverty line were less likely than those at or above the line to have protective immunity (aOR=0.65, 95% CI: 0.52, 0.82). Persons who had never been pregnant were 1.47 times (aOR=1.47, 95% CI: 1.09, 1.98) as likely to have protected immunity than those had ever been pregnant. Having a routine place of healthcare, having never been married, and being between ages 11-19 and 30-64 years were not significantly associated with having protective immunity to tetanus.

Summary

The study findings were presented in this chapter. The results facilitated summarization of demographic and socio-economic characteristics of the US population and provided tetanus seroimmunity estimates among the non-institutionalized US population. The statistical analyses conducted allowed interpretations and inferences to be made about the data. Overall, protective tetanus seroimmunity was high among the US population and males had higher proportions of protective immunity than females. By age group, protective seroimmunity levels remained at or above 90% between ages 6-74 years before declining steeply among 75-79-year-olds and oldest old adults aged ≥80 years. Immunity waned among females at a faster rate compared to men. Persons with less than a high school education had higher proportions of susceptibility compared to high school and post-high school graduates. Access to a routine place of healthcare was not associated with having protective immunity. Chapter 5 will provide a discussion of the findings, the study limitations, and immediate and future public health implications.

CHAPTER 5

CONCLUSIONS, RECOMMENDATIONS AND PUBLIC HEALTH IMPLICATIONS

Study Summary

This cross-sectional descriptive study used data from the 2015-2016 National Health and Nutrition Examination Survey (NHANES) to determine the US population seroimmunity to tetanus; describe tetanus seroimmunity by socio-demographics, military service, parity, and healthcare status; and identify susceptible populations to low seroimmunity within the US population. This chapter discusses the study findings, public health implications and recommendations for future studies.

Discussion

Overall, a higher proportion of the US population had protective immunity to tetanus (94%) than were reported by previous serosurveys that had analyzed NHANES data. It is important to note that the definition of protective immunity and the laboratory assays used in the calculation of tetanus titers from those studies differed from the assay used in this study. Additionally, some of those studies defined protective immunity as tetanus antibody titers ≥0.15 IU/mL, unlike ≥0.10 IU/mL in this study, which may have underestimated the proportions of protected persons in their study (Hammarlund et al., 2016). Data on minimum protective tetanus antibody thresholds differ significantly based on the type of assay (World Health Organization, 2018a). The standard antibody concentration level of <0.10 IU/mL as inadequate or susceptible,

and ≥0.10 IU/mL as protected was used for this study because of the MMACA (World Health Organization, 2018a).

Vaccination with a three-dose primary series (at 2, 4, and 6 months old in the US), two boosters (between 15-18 months, and 4-6 years in the US) and one booster every ten years is regarded as a highly efficient tetanus prevention strategy which provides up to 95% of protection to vaccine recipients (Borella-Venturini et al., 2017). Forty-nine states and the District of Columbia (DC) require DTaP vaccination prior to kindergarten enrollment. During the 2015-2016 school year, median vaccination coverage among kindergarten-aged kids for five doses of DTaP was 94.2% with twenty states reporting 95% or higher (Seither et al., 2016). Despite this report, a concerning 10% (95% CI: 8.0 , 17.27) of children between the ages of 6-10 years who should have received a three-dose primary series and two boosters of DTaP, were susceptible with tetanus immunity levels <0.10 IU/mL in this study suggesting that vaccination coverage rates for this group may be overestimated. While most cases of tetanus in the US occur among unvaccinated adults (Gergen et al., 1995), other reasons may exist for this divergence in the estimated proportions of protected persons.

Among teens 11-19 years old, the proportion of protective immunity identified in this study [97% (95% CI: 94.5, 96.1)] was remarkably higher than rates of reported receipt of one or more doses of Tdap vaccination among 13-17- year-olds in 2015, 86% (95% CI: 85.4, 87.3) and 88% (95% CI: 87.1, 88.9) in 2016 (Walker et al., 2017). The higher immunity in this group may be due to receipt of the first recommended Tdap booster vaccine between the ages of 11 and 12 years. Immunity from this booster may have extended into three age groups between 20-49 years which had high protective immunity averaging 96%. Gergen et al. suggested that higher immunity among males in the working-age adult group may be indicative of a higher likelihood

of accidents which would result in increased engagement with the healthcare system and likely receipt of tetanus vaccination boosters (Gergen et al., 1995). It is also likely that seroimmunity is higher among this group due to high male participation in military service and subsequent vaccination requirements.

This study validated the finding from previous studies that immunity waned among older adults (Gergen et al., 1995). The decline was more gradual in males starting at age 75 years compared to a sharper decline in immunity among females starting at age 65 years as demonstrated in Chapter 4. This decline is evident in reported vaccination coverage among US adults. In 2015, overall vaccination rates among adults ≥19 years who reported receipt of any tetanus-containing vaccine within the previous 10 years was 62% and dropped to 60.3% among adults ≥18 years in 2016. Among adults aged 65 years and older, the reported vaccination coverage with a TTCV was 57% in 2015 and 48.7% in 2016 (National Center For Immunization and Respiratory Diseases, 2021a; Williams et al., 2017).

A 2017 National Center for Health Statistics (NCHS) data brief on the US vaccination coverage rate among adults aged 65-74 years, where more than half (56.9%) reported receipt of a tetanus vaccine in the preceding 10 years with males more likely than females to have received a vaccine (Norris et al., 2017) provides a plausible explanation for the lower immunity among older adults observed in this study and others. Lastly, the lower immunity observed in older adults could be a function of immune senescence where antibody responses deteriorate quickly with advancing age (Hammarlund et al., 2016). Efforts to vaccinate adults 65 years and older ought to be strengthened to increase immunity within this group.

Across race/ethnicity, there were no significant differences in proportions of protective immunity between non-Hispanic whites and non-Hispanic blacks; however, non-Hispanic whites

had significantly higher proportions of immunity (95%) compared to 91% among Hispanics and Asian/multiracial persons. It is likely that the proportion of susceptible Hispanic and Asian/multiracial persons were foreign-born and may have had limited access to routine childhood immunization programs prior to emigration to the US. Kruszon-Moran et al. saw a difference in proportions of seroimmunity among US-born Mexican American females and foreign-born Mexican American females (Kruszon-Moran et al., 2004). Race/ethnicity and country of birth were not further stratified by age, insurance, or poverty level in this study; therefore, we speculate on the cause of this difference in seroimmunity between US-born and foreign-born persons based on our knowledge that routine immunization programs are not as robust in other countries as they are in the US (Roper et al., 2017; World Health Organization, 2018a). It is also likely that these respondents may have received their primary series in their native countries but were unable to obtain booster vaccination in the US due to challenges related to emigration and assimilation.

While proportions of seroimmunity among persons at/above the poverty level or with access to a routine place of health were high at 95% and 94% respectively, a noteworthy proportion of persons within these populations were susceptible to tetanus confirming what was observed in the McQuillan study that these economic indicators, expected to empower healthcare seeking behavior did not translate into 100% compliance with recommended immunization schedules (McQuillan et al., 2002). When education is used as a proxy for socioeconomic status, advanced education may be correlated with protective immunity as seroimmunity increased with increasing education level and was lowest among those with less than a high school education.

The proportion of protective immunity among those who had ever been pregnant (92%) was much higher than the reported 2015 Tdap vaccination coverage rate (53%) among

females≥18 years who had had a *recent* live birth as reported by the Pregnancy Risk Assessment Monitoring System (PRAMS) and higher than the 72.3% coverage reported for 2016 by all participating PRAMS sites (National Center for Immunization and Respiratory Diseases, 2021b). This difference is most likely because this study assessed immunity levels among females who had not only *ever* had a live birth, but also may have had miscarriages, stillbirths, tubal pregnancies, or abortions with the expectation that they would have received Tdap booster vaccinations at the third trimester pre-natal visit, thereby assuming all pregnancies remained viable through the third trimester. It was expected that women who had never had a live birth would have lower immunity compared to those who had had live births, however, the "never pregnant" group included males who had consistently higher immunity across most demographics compared to females (see Appendix 6). Therefore, the recorded value for "never pregnant" may not be a true reflection of immunity among women who have never had a live birth.

The data in this study indicate that overall, proportions of protective tetanus immunity remained at or above 90% across all studied variables except among foreign-born Americans (88%), those with less than a high school education (86%) and 6-10-year-olds (88%). No significant differences were noted in proportions of protective tetanus immunity among those with access to routine place of healthcare compared to those who did not.

Public Health Implications

Tetanus Incidence 2000-2017

Between the years 2001 and 2008, there were 233 tetanus cases reported to the National Notifiable Disease Surveillance System (NNDSS). Tetanus prevalence was 0.10 cases per

million in the general population but higher at 0.23 cases per million for persons aged 65 years and older during this period. Older adults 65 years and older made up 30.5% of cases (Centers for Disease Control and Prevention, 2011). Among persons for whom outcomes were available (197 cases), the case fatality rate was 13.2% overall but 31.3% among persons aged ≥65 years. Cases were nearly two times higher among Hispanic persons compared to non-Hispanic persons. During that 8-year period, thirty-seven (40.2%) of ninety-two patients for whom vaccination records were available had not been vaccinated. Males accounted for 59.2% of all cases while persons with diabetes made up 15.4% during this period (Centers for Disease Control and Prevention, 2011).

From 2009 through 2017, 264 cases were reported to the National Notifiable Disease Surveillance System (NNDSS). Thirteen percent (13%) of these were among persons ≤19 years old, 64% occurred in working-age adults between 20 and 64 years old, and 23% occurred in persons 65 years and older. Persons with diabetes accounted for 12% of all cases. Nineteen deaths, all of which occurred in persons older than 55 years of age, were reported during this period. Diabetics accounted 26% of deaths (Blain & Tiwari, 2020). Tetanus incidence as described between 2000 and 2017 demonstrates that unvaccinated persons, diabetics, working-aged adults, and older adults are susceptible to tetanus, and older adults are more likely to die from it.

Vulnerable Persons and Vaccination Coverage

The US population is forecasted to grow gradually, however, the population of older adults is projected to nearly double by 2050 growing from 43 million in 2012 to 84 million; Suggesting that by 2030, 1 in five Americans will be 65 years or older (Ewert, 2015). According to the US Census Bureau, there were more people aged 65 years and older in the 2010 census

than in any other census and population growth among this group increased at 15.1%, (5.3 million) a rate faster than the total US population growth rate at 9.7% and this growth was across the 50 states except for Rhode Island. In contrast, between 1990 and 2000 the total population grew by 13.2% and 12% among those 65 years and older (Werner, 2011). Compared to males, females had longer life expectancy and lower mortality with advancing age into older adulthood. Among the oldest-old adults, 85-89-year-olds made up the largest proportion and those 90-94 years experienced a growth in the 2010 census; this growth was across all 50 states. Additionally, in 2010, 1 in every 5,786 persons was 100 years or older and there were more females in this group compared to males (Werner, 2011).

The population of persons 65-and-older grew by 34.2% between 2010 and 2020; and 1 in 5 persons in Maine, Florida, West Virginia and Vermont were 65 years and older in 2019 (United States Census Bureau, 2020). The population of US adults 65 and older is projected to be 21% of the total population by 2050, and exceed the population of persons 18 years and younger by 2056 (Ewert, 2015). Persons 65-74 years are projected to represent 45% of the older adult population ≥65, 75-84-year-olds are expected to be 34%, and those ≥85 years are expected to be 21% by 2060 (Ewert, 2015).

Older adults are more susceptible to disease and the burden of more severe disease from illness, hospitalization, death, and disability among them is considerable, however, vaccination coverage rates for several recommended adult vaccinations remain low among this population. Coverage varies by sex, age, race/ethnicity, and family income (Leidner et al., 2019; Norris et al., 2017). In a 2015 report based on the National Health Interview Survey (NHIS), only 56.9% of adults ≥65 and older reported having received a tetanus vaccine in the past 10 years and non-Hispanic white adults had higher coverage rates compared to non-Hispanic black and Hispanic

adults. Rates were also lower in persons below the poverty line. Males were more likely than females to have received a vaccine and 65-74-year-olds were more likely to have received a vaccine than persons 85 years and older (Norris et al., 2017). Reasons for the low vaccination rates include perceptions about risks, clinical value and economic value held by providers, inadequate education about risks, transportation issues, poverty, citizenship status, physician failure to recommend vaccines (Alliance for Aging Research, 2015).

By 2060, the population of Hispanic persons of any race is projected to reach 30.6% of the total population. Non-Hispanic black persons 13.2% and Non-Hispanic Asian persons, 7.9%, multiracial persons are expected to make up 4.8% of the total population. All race groups examined in this study, except non-Hispanic white persons, had higher odd of susceptibility to tetanus. These groups represent significant proportions of the US population and the reasons for this susceptibility should be studied.

Expensive Treatment

Many adults are unvaccinated although vaccines save thousands of lives each year in the US. Needless costs to individuals and the society from low vaccination uptake include deaths and disabilities, economic losses from doctors' visits, hospitalizations and lost income (Ozawa et al., 2016). The treatment of unvaccinated children of parents with philosophic or religious objections to vaccination can also be expensive. In 2017, an unvaccinated 6-year-old boy from Oregon was hospitalized for two months with tetanus and almost died, after sustaining an injury while playing on his parents' farm. The case was the first pediatric tetanus case in Oregon in over 30 years. He received an emergency dose of tetanus vaccine while in the hospital and survived. Not including the air ambulance and inpatient rehabilitation, his care cost nearly one

million dollars. His parents refused a second dose of tetanus and all other recommended childhood vaccines (Mervosh, 2019).

Ozawa et al. (2016), estimated the US economic burden from ten vaccine-preventable diseases attributable to adults 19 years and older in a single year, 2015. Unvaccinated persons were responsible for nearly 80% or $7.1 billion of the financial burden (Ozawa et al., 2016).

Improving perceptions about the value of vaccines and increasing adult immunization uptake may result in economic benefit (Ozawa et al., 2016). Modifications to the decennial booster schedule may substantially impact healthcare costs associated with tetanus vaccinations which could add up to $420 million per year (Hammarlund et al., 2016).

Adverse Events

A decision by ACIP to change decennial booster recommendations to a longer time frame may reduce the number of adverse events (AEs) associated with Tdap vaccinations among older adults ≥65 years old and perhaps increase compliance to the recommendations among this age group. A 2020 study on the number of Tdap-related AEs reported between September 2010 – December 2018 to the Vaccine Adverse Event Reporting System (VAERS) among adults ≥65 years was 1,798 of which 104 (6%) were considered serious. Adverse events ranged from injection site erythema (26%; n=468), injection site pain (19%; n=335), injection site swelling (18%; n=329), and erythema (18%; n=321). Seven deaths were identified, none attributed to receipt of Tdap. Serious non-fatal AEs reported included nervous system disorders (35.1%; n=34) and infections and infestations (n=18.6%; n=18) (Haber et al., 2020).

Tetanus is fatal in un- and under-vaccinated persons. Females, 6–10-year-olds, persons older than 60 years, Americans of Hispanic descent, foreign-born Americans, persons with less than a high school education and persons below the poverty line had higher odds of low

seroimmunity in this study. Identifying and recommending an appropriate tetanus booster vaccination schedule to cover all vulnerable persons and to ensure enduring protective immunity is critical.

Vaccine Decision Making in the United States

The Advisory Committee on Immunization Practices (ACIP) was formed in 1964, before which there had been limited federal involvement in the establishment of immunization recommendations for civilians and no formal process for instituting national immunization policy (Walton, Orenstein, & Pickering, 2015). New ACIP recommendations or substantial revisions to existing recommendations are made using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) an evidence-based, Evidence to Decision (EtD) or Evidence to Recommendation (EtR) framework which was adopted by ACIP in October 2010. See Figure 5.1. (Centers for Disease Control and Prevention, 2012).

EtD/EtR frameworks contain three main phases from evidence to decision: formulate the question; develop evidence-informed assessments; and derive conclusions. An exact list of criteria is deployed to complete these phases (Moberg et al., 2018). Evidence submitted for evaluation and consideration in the formulation of recommendations, go through several steps with ACIP workgroup members and panelists. Recommendations are classified into three categories A, B and “no recommendation” as demonstrated in Table 5.1. below (Ahmed, 2013b).

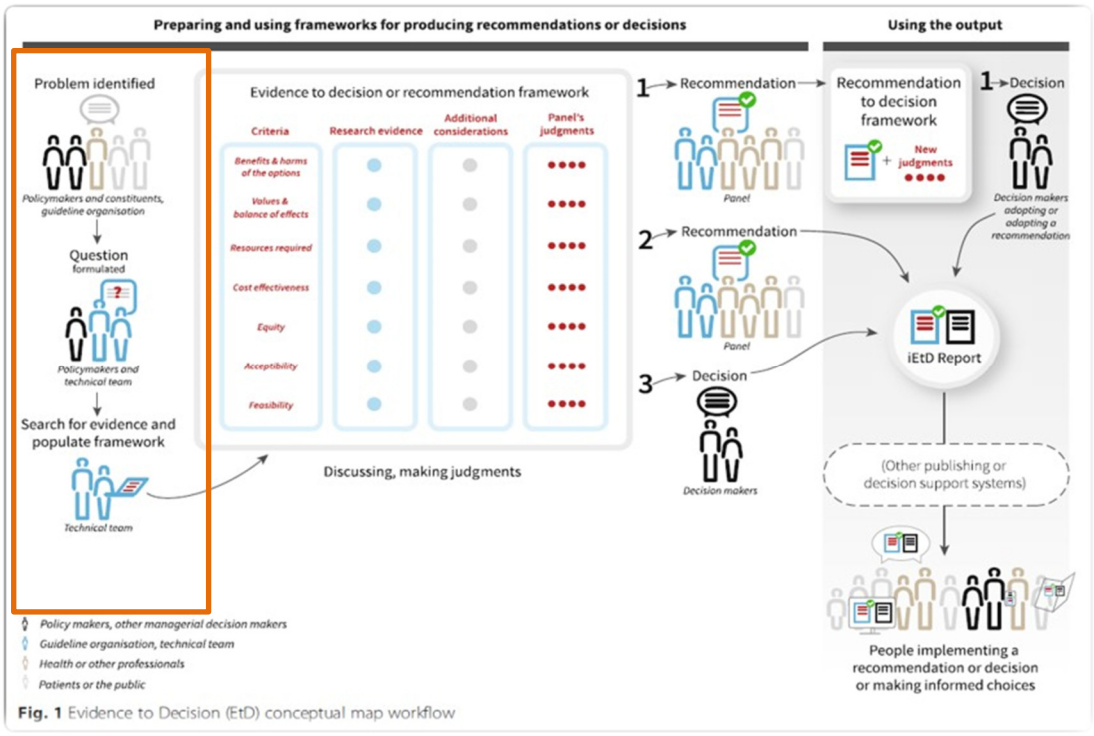

Figure 5.1 The GRADE EtR Framework for Health System and Public Health
Source: (Moberg et al., 2018)

Table 5.1. ACIP Recommendation Categories

Category	*Definition*
A	Recommendation that applies to all persons in an age- or risk-based group. Category A recommendations include the words *recommend*, *recommend against*, *should*, and *should not.*
B	Recommendation for individual clinical decision making. Category B recommendations include the words *may* and *suggest against*.
No recommendation	In some instances, it is possible that the ACIP may decide not to make a recommendation if additional information is needed.

Source: ACIP Handbook for Developing Evidence Based Recommendations (Ahmed, 2013b)

GRADE Evidence to Recommendation (EtR) Framework Steps

ACIP uses the Evidence to Recommendation (EtR) framework to convey considerations and judgments made by workgroup members during formulation to arrive at new or significantly

revised ACIP recommendations for vaccination (Lee, Carr, Group, & Group, 2018). The EtR framework facilitates the movement from evidence to decision and offers transparency on the effect of additional factors on deliberations when considering a recommendation (Lee et al., 2018). Use of the framework requires a meticulous review of eleven critical steps highlighted in Figure 5.2. These steps are grouped under seven umbrellas: problem, benefits and harms, values, acceptability, resource use, equity, and feasibility.

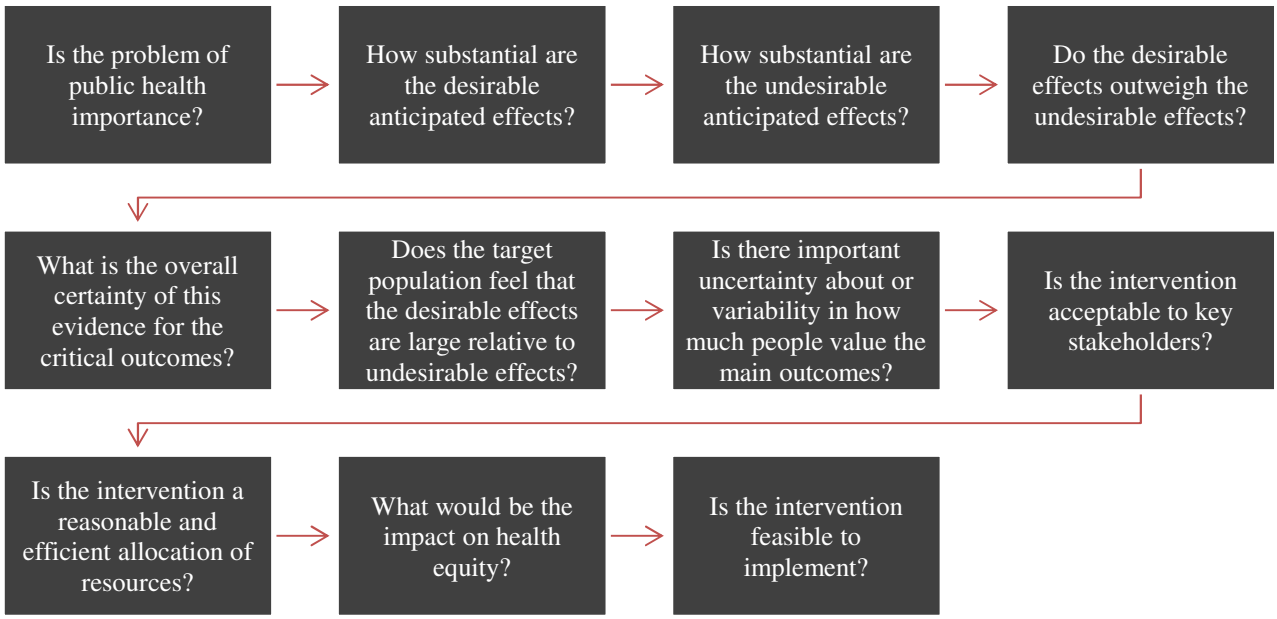

Figure 5.2 The ACIP Evidence to Recommendation Framework Steps (EtR)

Problem

The EtR review process begins with whether the problem is of public health importance and ends with whether the intervention is feasible to implement. A question addressing the population, intervention, comparison, and outcomes (PICO) of interest, for example, "should the recommended timing of tetanus booster vaccination in adults be maintained or modified?" will be presented to ACIP workgroup members for consideration. Members will determine the inclusion and exclusion criteria for literature review, and the types of scientific and non-scientific

evidence that should be reviewed and assessed. To initiate the EtR, they will make a judgment on whether the problem is of public health importance by voting "no," "probably no," "probably yes," and "yes," "varies" or "don't know" (Ahmed, 2013a). See appendix 5 for complete list of options. This study's results, discussion and summarized literature findings provide enough evidence to indicate the public health significance of waning seroimmunity among persons aged 65 years and older, and low proportions of seroimmunity among females, persons of Hispanic descent, foreign-born Americans, persons with less than a high school education and persons below the poverty line.

Benefits and Harms

Four criteria are reviewed to evaluate the harms and benefits of a new or revised recommendation. First, members assess the harms and benefits of the policy question to decide how substantial the desirable anticipated effects are. This element requires a description of the magnitude of the beneficial effects of vaccination on individuals, and on the population while considering baseline benefit similarity across subgroups, as well as any indirect effects. A final judgment of "minimal," "small," "moderate," "large," "varied," or "don't know" will be made on the risk level (Advisory Committee on Immunization Practices, 2018). This study's findings and available literature on tetanus seroimmunity provide evidence that can be used to satisfy this criterion.

Second, workgroup members assess the scale of undesirable anticipated effects. In this step, they consider whether there will be undesirable effects of a new or revised tetanus booster recommendation on individuals (e.g., adverse events following immunization) or the population. This assessment determines if there is baseline risk across subgroups and if there should be separate recommendations for subgroups based on harms. A final judgment of "minimal,"

"small," "moderate," "large," "varied," or "don't know" will be made on this criterion (Advisory Committee on Immunization Practices, 2018). This study and others have provided adequate evidence on subgroups susceptible to low tetanus seroimmunity such as females, persons aged 65 years and older, Hispanic Americans and foreign-born Americans that can be used to weigh undesirable anticipated effects.

Next, an appraisal of the desirable effects against the undesirable effects is made to determine if the benefits outweigh the harms. In this step, a description of the balance of benefits of a new or revised recommendation with possible harms at the individual and population level is provided and discussed. Final judgment options include "favors intervention," "favors comparison," "favors both," "favors neither," and "unclear" (Advisory Committee on Immunization Practices, 2018). This study did not provide enough evidence to aid this determination. Findings from other studies and available literature will have to be reviewed to make a judgement in this step.

Lastly, an assessment on the overall certainty of the submitted evidence on two critical outcomes: effectiveness of the intervention; and safety of the intervention will be made using comprehensive indices provided in the ACIP Handbook for Developing Evidence-Based Recommendations (Advisory Committee on Immunization Practices, 2018). Final judgments on the effectiveness and safety of a new or revised recommendation will include "no included studies," "very low," "low," "moderate," or "high" to indicate the quality of evidence reviewed (Advisory Committee on Immunization Practices, 2018). Additional study findings or literature review must be conducted to support this criterion because this study did not provide substantial evidence on certainty of the effectiveness and safety of a new or revised booster vaccination recommendation.

Values

In assessing the value of a new or revised recommendation, workgroup members will answer two questions, does the target population feel that the desirable effects outweigh the undesirable effects, and is there "important uncertainty about variability in how much people value the anticipated outcomes?" (Advisory Committee on Immunization Practices, 2018). Both value assessments require input from the target population. Studies on perceptions about vaccination and on the benefits, harms, and costs of vaccination among older adults and other identified susceptible sub-groups would be critical to review for these criteria. This study did not provide evidence that can be used to assess these criteria; and although studies on adult perceptions of the overall benefits, costs, and harms of vaccination exist, additional studies specific to perceptions about tetanus among the identified susceptible groups would be helpful to address this criterion.

Acceptability, Resource Use, Equity, and Feasibility

Another step considered by workgroup members is the acceptability of a new or revised booster vaccination recommendation to key stakeholders. Stakeholder acceptability of a new or revised recommendation based on ethical, programmatic, and financial implications among others will be considered. A final judgement of "no," "probably no," "uncertain," "probably yes," "yes," or "varies" will be made on the question, "is the intervention acceptable to key stakeholders?" (Advisory Committee on Immunization Practices, 2018). Stakeholder opinions on the question will need to be obtained through other sources such as surveys, focus groups, literature reviews to satisfy this criterion as this study did not solicit input from key stakeholders.

Additionally, workgroup members determine if recommending a new or revised tetanus booster vaccination schedule would be a reasonable and efficient allocation of resources or not by voting "no," "probably no," "uncertain," "probably yes," or "yes." Summary findings of cost-effectiveness analyses (CEAs) of such as recommendation on the target population will be reviewed at this stage to include base case results, a sensitivity range, and any other significant findings (Advisory Committee on Immunization Practices, 2018). A CEA was not conducted as part of this study, therefore, findings from other studies would have to be included to evaluate this criterion.

To evaluate the impact of a new or revised booster recommendation on health equity, workgroup members review summary findings from literature reviews tackling issues of health inequity or disadvantaged groups. They then judge whether the health equity impact is "reduced," "probably reduced," "probably no impact," "probably increased," "increased," "varies," or "don't know"(Advisory Committee on Immunization Practices, 2018).

Lastly, members will evaluate any barriers to implementing a new or revised booster vaccination schedule. They will decide "no," "probably no," "probably yes," "yes," "varies," or "don't know" on whether the intervention is feasible to implement using a provided Implementation Considerations Checklist (Advisory Committee on Immunization Practices, 2018). Information from this study is likely to be used in making this determination.

Balance of Consequences

ACIP workgroup members will also review the balance of consequences by concluding if (1) undesirable consequences *clearly outweigh* desirable consequences in most settings; (2) undesirable consequences *probably* outweigh desirable consequences in most settings; (3) the balance between desirable and undesirable consequences *is closely balanced* or *uncertain*; (4)

desirable consequences *probably outweigh* undesirable consequences in most settings; (5) desirable consequences *clearly outweigh* undesirable consequences in most settings; or (6) there is insufficient evidence to determine the balance of consequences (Advisory Committee on Immunization Practices, 2018).

After this determination, they assess whether there is sufficient evidence to move forward with a recommendation by voting "yes" or "no," and offer policy options for ACIP's consideration: (A) we do not recommend the intervention. The intervention may be used within FDA licensed indications; (B) we recommend the intervention for individuals based on clinical decision-making; or (C) we recommend the intervention. They also include draft language for the recommendation for ACIP's consideration. This step concludes the workgroup's work and initiates that of the ACIP voting members. Voting members would select one of the three final recommendations (A, B or C) presented by workgroup members and outline any noteworthy additional considerations (e.g., aspects related to implementation, monitoring and evaluation, research priorities, etc.) to conclude the EtR framework.

Opportunities for Future Research

Studies are needed in several areas to facilitate the arrival at a decision to revise or develop new tetanus booster vaccine recommendations. This study found that overall, the proportion of US residents in 2015-2016 with protective tetanus seroimmunity was high. However, lower reported vaccination coverage rates from the same period suggest that this immunity may not solely be predicated on receipt of decennial booster vaccination but may be indicative of longer-term, enduring vaccine-induced immunity or other factors. Supporting evidence on the duration of vaccine-induced immunity from Hammarlund et al. (2016) and Slifka et al. (2014) were presented in this study, however, results of other studies on the subject

matter may need to be reviewed for consideration in the decision-making process (Hammarlund et al., 2016; M. K. Slifka & Amanna, 2014).

Furthermore, despite the overall high proportions of protective immunity in the US, certain subpopulations including females, persons aged 65 years and older, persons of Hispanic descent, persons with less than a high school education, divorced/widowed/separated persons, and foreign-born Americans had higher odds of susceptibility to tetanus. Further studies on these groups to determine the root cause of this lower seroimmunity would be helpful. Additionally, studies to understand perceptions on the benefits and harms of vaccination among these subgroups would be critical to completing the EtR framework and arriving at a recommendation.

Current tetanus-toxoid containing vaccines used in the US for routine and booster vaccinations are combination vaccines that contain protective agents against diphtheria and pertussis (Havers, Moro, Hunter, Hariri, & Bernstein, 2020). Thus, any new or revised tetanus booster vaccination recommendations must include assessments of diphtheria and pertussis serosurvey findings.

Cost effectiveness analyses must also be conducted on possible alternatives to provide a comprehensive outlook on the feasibility of a new or revised recommendation. A decision on the spacing of tetanus boosters would benefit from input from the findings of these studies. A thorough appraisal of the benefits and harms of France's age-based schedule may provide critical insights that would benefit ACIP's decision-making (see Table 2.2). Lastly, it would be useful to conduct a side-by-side comparison of vaccination coverage data from the National Immunization Survey (NIS), NIS-Teen, and the National Health Interview Survey (NHIS) with the results of this serosurvey to ascertain the true effect of tetanus booster vaccination on seroimmunity.

Study Limitations and Delimitations

A strength of this study was the sample size and diversity of participants. These attributes enhanced the probability that the study population was representative of the US general population and methods like those used in this study have been used to conduct previous seroprevalence studies (Gergen et al., 1995; Kruszon-Moran et al., 2004; McQuillan et al., 2002). NHANES studies are used in epidemiological studies to determine significant disease prevalence and risk factors and health sciences research to facilitate the design and implementation of public health programs and services, the development of evidence-based public health policy, and the expansion of health knowledge for the nation because of their representative nature (Chen et al., 2020). Use of the Taylor Series Linearization method generated precise standard estimates and calculated realistic, almost unbiased, and design-consistent estimates of variance (Division of the National Health and Nutrition Examination Surveys, 2018).

However, there were important limitations. NHANES recommends that two or more survey cycles be combined to obtain more accurate and stable estimates. This study used a single 2-year NHANES cycle data and may have generated unstable estimates. Furthermore, these findings cannot be generalized to the institutionalized adult population in prisons, mental institutions, and the military (Division of the National Health and Nutrition Examination Surveys, 2018). Another limitation was the use of odds ratios in this analysis which may have overestimated risk ratios (Tamhane, Westfall, Burkholder, & Cutter, 2017).

Cross-sectional serosurveys capture a snapshot of immunity. Lastly, immunization status and history of tetanus was not assessed in the 2015-2016 cycle of NHANES thus, time since last vaccination could not be determined, the number of tetanus doses received could not be determined, and durability of protection could not be assessed for the US population in this

study. This study had an omitted variable bias because vaccination, a vital variable was not included in the multivariable logistic regression model (Barreto & Howland, 2005). Future studies that attempt to determine the effect of tetanus vaccination on seroimmunity using NHANES and NIS or NHIS data, and or studies on the persistence of vaccine-induced immunity in older adults may be more beneficial.

Conclusion

Several studies have been conducted globally to determine the persistence of tetanus immunity and the appropriate intervals for tetanus booster vaccination dosing. Evidence from other high-income countries with low incidence of tetanus suggest that decennial boosters may no longer be needed and vaccine immunology experts in the US have called for a revision of the requirement for decennial boosters (Hammarlund et al., 2016; A. M. Slifka et al., 2020). This study indicated that overall, a high proportion of the US population has protective immunity against tetanus toxin; however, females, Hispanic Americans, foreign-born Americans, persons with less than a high school education, and persons below the poverty line were at increased risk of susceptibility; additionally, immunity waned with age and the decline was higher among older adults aged ≥65 years, and steeper among females- demonstrating the need for targeted immunization efforts among older adults and the other identified at-risk sub-populations. The results of this study may be used as supporting evidence for consideration by ACIP panels in their assessment of the need for decennial boosters using the EtR framework.

Until a decision is made by ACIP to revise current booster recommendations, federal, state, local, non-profit and private organization efforts to promote vaccination among older adults and the other identified subgroups must continue to include: education on the benefits and importance of vaccination; facilitation and support of diverse vaccination sites such as medical

homes and pharmacies etc.; provision of transportation to vaccination sites; and encouragement of physicians to offer vaccines to eligible patients and enroll in programs that allow direct billing of Medicare Part D plans to prevent beneficiaries from paying out of pocket costs (Alliance for Aging Research, 2015). This cross-sectional descriptive study depicted tetanus seroimmunity in the non-institutionalized US population aged ≥6 years and provided evidence to be considered in the revision or development of new tetanus booster vaccination recommendations by ACIP

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APPENDICES

Appendix 1: Definition of Terms

The following public health definitions were used to describe frequently used terms and those related to tetanus, tetanus vaccination and serologic immunity:

ACIP: The United Sates Advisory Committee on Immunization Practices, a federal advisory committee that develops written recommendations for use of vaccines licensed by the Food and Drug Administration (FDA) for the U.S. civilian population (Walton et al., 2015).

Active Immunity: Occurs when the body is exposed to an antigen and produces an adaptive immune response. It is also referred to as natural or acquired immunity (Centers for Disease Control and Prevention, 2017a).

***Antibodies*:** Proteins produced by the body to neutralize or destroy toxins or pathogens (Centers for Disease Control and Prevention, 2017a).

ELISA: Enzyme-linked immunosorbent assay. A plate-based technique designed for detecting and quantifying soluble substances such as peptides, proteins, antibodies, and hormones (Thermo Fisher Scientific, n.d.).

Immunity: Protection from an infectious disease (Centers for Disease Control and Prevention, 2017a).

Immunization: The process by which a person becomes protected against a disease through vaccination. Immunization is often interchanged with vaccination or inoculation (Centers for Disease Control and Prevention, 2017a).

Tetanus toxoid*:* Tetanus toxin is inactivated by formaldehyde to produce tetanus toxoid which can be used as a single-antigen vaccine or in combination with other vaccine-preventable diseases vaccines (World Health Organization, 2018a).

NHANES: The National Health and Nutrition Examination Survey is a program of studies designed to assess the health and nutritional status of adults and children in the United States (National Center for Health Statistics, 2017b).

Passive Immunity**:** Refers to when a person is given antibodies to a disease rather than producing them through his or her own immune system (Centers for Disease Control and Prevention, 2017a).

Serology*:* The scientific study of blood serum, especially regarding its immunological reactions and properties; the testing of blood serum to detect the presence of antibodies against a specific antigen (Merriam-Webster, n.d.-b).

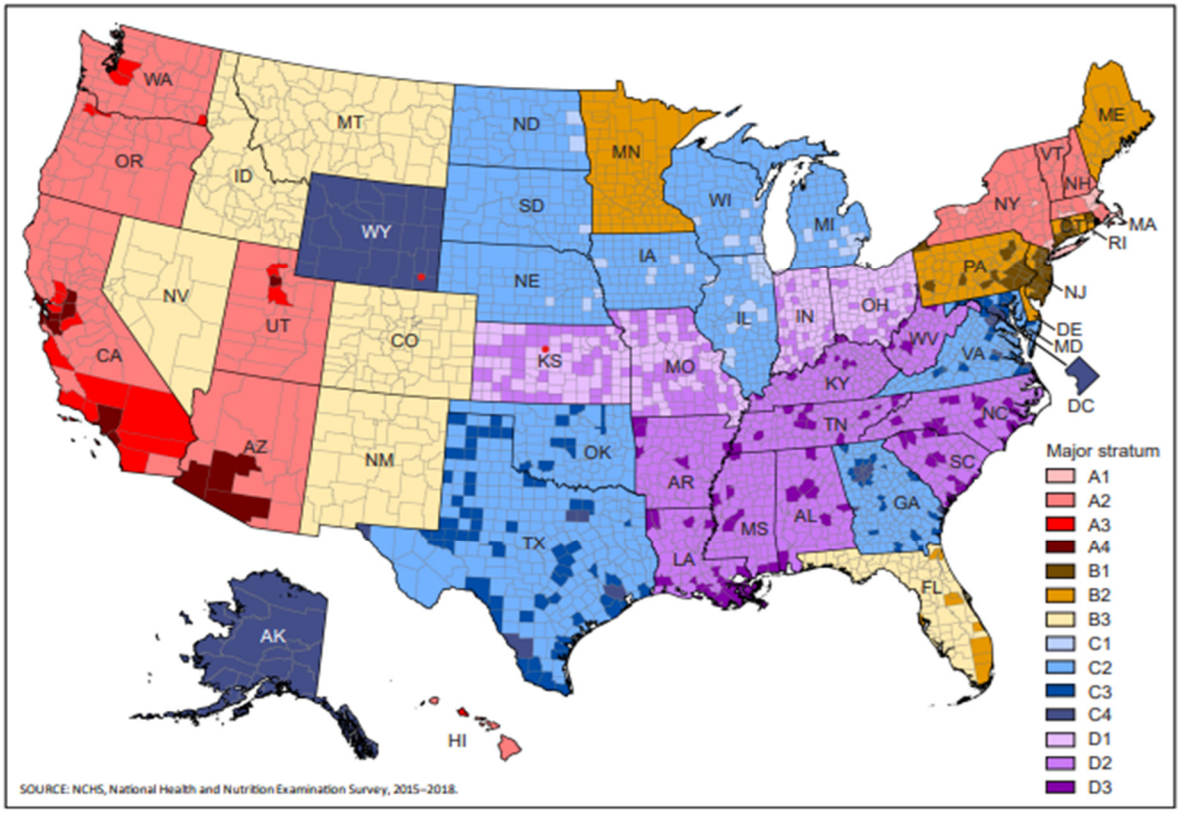
Vaccine**:** A product that stimulates a person's immune system to produce antibodies to a specific disease, protecting the person from that disease (Centers for Disease Control and Prevention, 2017a).

Vaccination**:** The act of introducing a vaccine into the body to produce immunity to a specific disease (Centers for Disease Control and Prevention, 2017a).

Appendix 2: ACIP Membership Table as of October 2017

Group	*No.*	*Description of members*
Voting members	14	Subject matter experts in vaccinology, immunology, pediatrics, internal medicine, nursing, family medicine, virology, public health, infectious diseases, and/or preventive medicine.
	1	Consumer rep provides perspectives on social/community aspects of vaccination.
Ex officio members (non-voting) *Individuals in the roles listed or their designees*	8	• Director, Division of Vaccine Injury Compensation, Bureau of Health Professions, Health Resources and Services Administration • Deputy Director for Scientific Activities, Office of the Assistant Secretary of Defense for Health Affairs, Department of Defense • Under Secretary for Health, Department of Veterans Affairs • Director, Center for Biologics Evaluation and Research, FDA • Director, Center for Medicaid and State Operations, CMMS • Director, Division of Microbiology, and Infectious Diseases, NIAID, NIH • Director, Indian Health Service • Director, National Vaccine Program Office, HHS
Liaison representatives from professional organizations (non-voting)	31	Participating organizations: • American Academy of Family Physicians • American Academy of Pediatrics • American Academy of Physician Assistants • American College Health Association • American College of Nurse-Midwives • American College of Obstetricians and Gynecologists • American College of Physicians • American Geriatrics Society • America's Health Insurance Plans • American Medical Association • American Nurses Association • American Osteopathic Association • American Pharmacists Association • Association of Immunization Managers • Association for Prevention Teaching and Research • Association of State and Territorial Health Officials • Biotechnology Industry Organization • Council of State and Territorial Epidemiologists • Canadian National Advisory Committee on Immunization • Infectious Diseases Society of America • National Association of County and City Health Official • National Association for Pediatric Nurse Practitioners • National Foundation for Infectious Diseases • National Immunization Council and Child Health Program, Mexico • National Medical Association • National Vaccine Advisory Committee • Pediatric Infectious Diseases Society • Pharmaceutical Research Manufacturers of America • Society for Adolescent Health and Medicine • Society for Healthcare Epidemiology of America

Appendix 3: Primary Sampling of Unit major strata, NHANES, 2015-2018



Major stratum	Primary sampling unit description
A1	State Group A with less than 8.6% of the population living in rural areas in the Northeast
A2	State Group A with 8.6% or more of the population living in rural areas in the Northeast, or with 10.5% or more of the population living in rural areas in the West
A3	State Group A with 3.1% to less than 10.5% of the population living in rural areas in the West
A4	State Group A with less than 3.1% of the population living in rural areas in the West
B1	State Group B with less than 24.6% of the population living in rural areas in the Northeast
B2	State Group B with 24.6% or more of the population living in rural areas in the Northeast or the Midwest, or with less than 3.4% of the population living in rural areas in the South
B3	State Group B with 3.4% or more of the population living in rural areas in the South or the West

Major stratum	Primary sampling unit description
C1	State Group C with less than 17.5% of the population living in rural areas in the Midwest
C2	State Group C with 17.5% or more of the population living in rural areas in the Midwest, or with 29.5% or more of the population living in rural areas in the South
C3	State Group C with 4.5% to less than 29.5% of the population living in rural areas in the South
C4	State Group C with less than 4.5% of the population living in rural areas in the South or the West
D1	State Group D with less than 69.2% of the population living in rural areas in the Midwest
D2	State Group D with 69.2% or more of the population living in rural areas in the Midwest, or with 28.5% or more of the population living in rural areas in the South
D3	State Group D with less than 28.5% of the population living in rural areas in the South

Appendix 4. List of Acronyms

Acronym	*Meaning*
ACIP	Advisory Committee on Immunization Practices
aOR	Adjusted Odds Ratios from a multivariable logistic regression.
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
DC	District of Columbia
DNA	Deoxyribonucleic Acid
DTaP	Diphtheria Tetanus acellular Pertussis Vaccine
DTP	Diphtheria Tetanus Pertussis Vaccine
ELISA	Enzyme-Linked Immunosorbent Assays
EtD	Evidence to Decision Framework
EtR	Evidence to Recommendation Framework
FDA	United States Food and Drug Administration
Fha	Filamentous hemagglutinin
Fim	Bordetella pertussis fimbriae
GED	General Education Development
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HHS	Department of Health and Human Services
HS	High School
IU/mL	international units per milliliter
LLOQ	Lower Level of Quantification
MEC	Mobile Examination Center
MMACA	microsphere-based multiplex antibody assay
MMWR	Morbidity and Mortality Weekly Report
MPIR	Microbial Pathogenesis and Immune Response
NCHS	National Center for Health Statistics
NH	Non-Hispanic
NHANES	National Health and Nutrition Examination Survey
NIBSC	National Institute for Biological Standards and Control
PE	phycoerythrin
PICO	Population Intervention Comparison Outcome
PRAMS	Pregnancy Risk Assessment Monitoring System
Prn	Pertactin
PSU	primary sampling units
SAS	Statistical Analysis Software (SAS®)
Td	Tetanus and Diphtheria Vaccine
Tdap	Tetanus toxoid, diphtheria toxoid, acellular pertussis vaccine
TT	Tetanus Toxoid
TTCV	Tetanus Toxoid-Containing Vaccine
UGA	University of Georgia
UK	United Kingdom
US	United States
WHO	World Health Organization

Appendix 5: ACIP Evidence to Recommendations Framework

ACIP Evidence to Recommendations Framework

Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework.The question should be precise and identify the specific intervention, comparison, and outcome, as well as the target population and the setting (specific subpopulations) in PICO format. **Population:** Target population for the vaccine (e.g., age range, sex, immune status, pregnancy) **Intervention:** Vaccination (if applicable, dosage and schedule) **Comparison(s):** No Vaccination/Standard of care/An existing vaccine/Other prevention option **Outcome:** Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)			
Background: The addressed PICO question should be described in detail, and important background information for understanding the questionand why a recommendation or decision is needed should be briefly provided. If a recommendation is preferential or represents off-label use, this should be indicated. *Include sample language: Additional background information supporting the ACIP recommendations on the use of xxx vaccine can be found inthe relevant publication of the recommendation referenced on the ACIP website.*			
	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	**Is the problem of public health importance?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide available scientific evidence on the burden of disease, preferably within the target population for the recommendation. If no published evidence is available, provide expert judgment on the public health priority considerations.	Identify any additional public health priority considerations, including consideration of disparities.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	**How substantial are the desirable anticipated effects?** o Minimal o Small o Moderate o Large o Varies o Don't know	Describe the magnitude of the beneficial effects of vaccination on individual (vaccine effectiveness, duration of protection) and population (herd immunity) levels.	Take into consideration: Is the baseline benefit similar across subgroups (by age, gender, pregnancy orlactation status, occupation [i.e.,healthcareworkers], immune status, race, SES, and other groups)? Are there indirect effects that should beconsidered (e.g., herd immunity)?
	How substantial are the undesirable anticipated effects? o Minimal o Small o Moderate o Large o Varies o Don't know	Are there undesirable effects of the vaccine, either on the individual (e.g., adverse events following immunization) or population (e.g., age-shift of disease, serotype replacement) levels?	Take into consideration: Is the baseline risk for harm similar across subgroups (see above)? Should there be separate recommendationsfor subgroups based on harms?
	Do the desirable effects outweigh the undesirable effects? o Favors intervention o Favors comparison o Favors both o Favors neither o Varies o Don't know	Describe the balance of benefits of the vaccine with possible harms (individual and population level).	

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	What is the overall certainty of this evidence for the critical outcomes? *Effectiveness of the intervention* o No studies found o 4 (very low) o 3 (low) o 2 (moderate) o 1 (high) *Safety of the intervention* o No studies found o 4 (very low) o 3 (low) o 2 (moderate) o 1 (high)	Please refer to GRADE evidence profiles for a detailed assessment of the certainty of the evidence. For more information, please see the ACIP Handbook for Developing Evidence-Based Recommendations.	If GRADE was not used to evaluate the certainty of evidence, please provide justification and the method and outcome ofany other tools used to evaluate the body of evidence relevant to the critical outcomes.
VALUES	**Does the target population feel that the desirable effects are large relative to undesirable effects?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide any available evidence on target population values & preferences related to vaccination and comparative health benefitsand risks. Describe the source of these estimates.	Are values and preferences for relevant outcomes measured? Are the benefits, harms and costs of vaccination valued differently by different subgroups? If the target group doesn't value the intervention or attributes little value to the harms and benefits, consider whether potential education measures are needed.

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
	Is there important uncertainty about or variability in how much people value themain outcomes? o Important uncertainty or variability o Probably important uncertainty or variability o Probably not important uncertainty or variability o No important uncertainty or variability o No known undesirable outcomes	Please provide available data used to determine the relative importance that the target population attributes to the desirable and the undesirable outcomes related to the intervention as well as the comparison.	Describe the source of variability, if any. Are there methods for determining valuessatisfactory for this recommendation? If not, systematic assessment of the values and preferences of the target group may be considered.
ACCEPTABILITY	**Is the intervention acceptable to keystakeholders?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide assessment of whether intervention would be acceptable to stakeholders (ethically, programmatically, financially, etc.)	
RESOURCE	**Is the intervention a reasonable andefficient allocation of resources?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Provide a summary of cost-effectiveness analyses (CEAs) of the vaccine in the target population. Include base case results and a sensitivity range. Include any other notable findings, for example, specific policy-relevant scenarios.	Overall findings: Summarize the findingsfrom available CEAs, including major differences in baseline assumptions. Uncertainty: Does the analysis capture the full range of uncertainty? For example, are the findings from the uncertainty of evidence analysis, identified earlier in this document (the EtR Framework), appropriately represented in the methods ofthe CEAs? Multiple assessments: Are there multiple CEAs? If so, what are the major differencesin methods and results?

	WORK GROUP JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
EQUITY	**What would be the impact on healthequity?** o Reduced o Probably reduced o Probably no impact o Probably increased o Increased o Varies o Don't know	Summarize the findings from a review of the literature addressing issues of health inequities or groups who may be disadvantaged.	Consider from the evidence or guideline panel: • Are there any groups or settings that might be disadvantaged concerning the problem or options that are considered? • Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings? • Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings? • Are there important considerationsthat should be made when implementing the intervention (option) to ensure that inequities are reduced, if possible,and that they are not increased?
FEASIBILITY	**Is the intervention feasible to implement?** o No o Probably no o Probably yes o Yes o Varies o Don't know	Are there any barriers to implementation?	Please refer to the Implementation Considerations checklist.

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences
Is there sufficient information to move forward with a recommendation? Yes ○ No ○						

Policy options for ACIP consideration	ACIP does not recommend the intervention* *Intervention may be used withinFDA licensed indications	ACIP recommends the interventionfor individuals based on shared clinical decision-making	ACIP recommends the intervention
Draft recommendation (text)	Please provide the draft recommendations proposed to ACIP.		
Additional considerations (optional)	Please outline any significant additional considerations (e.g., aspects related to implementation, monitoring andevaluation, research priorities, etc.).		

Final deliberation and decision by the ACIP

Final ACIP recommendation	ACIP does not recommend theintervention* *Intervention may be used within FDA licensed indications	ACIP recommends the intervention for individuals based on shared clinical decision-making	ACIP recommends the intervention
Additional ACIP considerations	Wording as accepted in the guide		

Appendix 6. Estimated Prevalence of Seroimmunity to Tetanus by Demographic Characteristics Stratified by Sex, United States, 2015-2016

Demographic Characteristic	*MALE*	*FEMALE*
	Weighted Prevalence ≥0.10 IU/mL (95% CI)	**Weighted Prevalence ≥0.10 IU/mL (95% CI)**
Age		
6 – 10	91.5 (85.2 , 95.8)	88.4 (83.0 , 92.6)
11 – 19	95.3 (92.0 , 97.5	93.7 (89.9 , 96.4)
20 – 29	95.9 (92.6 , 98.0)	97.8 (95.7 , 99.0)
30 – 39	96.1 (93.4 , 98.0)	95.3 (92.0 , 97.6)
40 – 49	96.8 (93.7 , 98.6)	96.8 (94.5 , 98.3)
50 – 59	95.8 (91.8 , 98.2)	97.4 (95.3 , 98.8)
60 – 64	94.8 (89.0 , 98.1)	93.6 (87.5 , 97.3)
65 – 69	95.2 (88.2 , 98.7)	88.5 (80.0 , 94.3)
70 – 74	96.3 (91.8 , 98.7)	87.0 (79.5 , 92.6)
75 – 79	84.8 (74.5 , 92.2)	65.2 (50.4 , 78.0)
≥ 80	93.3 (87.6 , 96.9)	64.3 (50.8 , 76.3)
Race/Ethnicity		
Non-Hispanic white	96.6 (95.0 , 97.8)	93.9 (92.0 , 95.4)
Non-Hispanic black	95.0 (92.6 , 96.8)	91.4 (88.5 , 93.7)
Hispanic	91.2 (89.2 , 93.0)	90.5 (87.5 , 92.9)
Other	93.8 (91.0 , 95.9)	89.1 (85.6 , 92.0)
Country of Birth		
United States	96.5 (95.3 , 97.4)	93.6 (92.3 , 94.7)
Other	88.9 (85.6 , 91.6)	86.8 (83.4 , 89.8)
Poverty Level		
Below Poverty Line	92.7 (89.8 , 95.0)	91.1 (88.8 , 93.1)
At/Above Poverty Line	95.9 (95.0 , 96.8)	93.1 (91.7 , 94.4)
Education 20+		
Less than High School	89.5 (84.8 , 93.2)	81.9 (75.5 , 87.2)
High School Graduate	96.0 (93.2 , 97.9)	89.7 (85.8 , 92.8)
Post-High School Education	96.9 (95.3 , 98.0)	95.6 (93.9 , 96.9)
Military Service 17+		
Ever Active	99.5 (98.2 , 100)	100 (89.0 , “,”)
Never Active	94.7 (93.4 , 95.8)	92.6 (90.2 , 94.2)