Rubella Immunity Levels in the United States Population: Has the Threshold of Viral Elimination Been Reached?

Terri B. Hyde, Deanna Kruszon-Moran, Geraldine M. McQuillan, Cynthia Cossen, Bagher Forghani, and Susan E. Reef

After the 1989–1991 rubella resurgence, rubella vaccination efforts targeted children and women of childbearing age. Utilizing National Health and Nutrition Examination Survey data collected during 1988–1994 and 1999–2004, we assessed whether US levels of rubella seropositivity are consistent with rubella elimination and whether changes are consistent with immunization efforts. Serum samples with rubella antibody levels ≥10 IU tested by rubella immunoglobulin G enzyme immunoassay were considered to be positive. In 1999–2004, the overall age-adjusted rubella seropositivity level was 91.3% (95% confidence interval [CI], 90.5%–92.1%), a significant increase from 88.1% (95% CI, 86.9%–89.1%) in 1988–1994 (P < .001). Among children, seropositivity was highest in children 6–11 years of age (96.2%), followed by adolescents 12–19 years of age (93.7%). Both groups showed significant increases in immunity levels, in comparison with those in 1988–1994 (P < .001). Among adults, seropositivity among women increased (from 88.9% to 91.5%; P = .015), and there was no change among men (from 87.8% to 88.0%; P = .84). In 1999–2004, population rubella immunity levels were at or above the modeled threshold for elimination of rubella virus transmission. Increases in immunity levels are consistent with vaccination efforts.

In contrast to the prevaccine era, when hundreds of thousands of cases of rubella were reported annually [1, 2], surveillance data since 2001 show <25 cases of rubella and <4 cases of congenital rubella syndrome (CRS) per year. In cases in which the disease has been imported from abroad, little or no subsequent spread has been documented in the United States since 2001. Such patterns suggest that high rubella immunity levels may prevent ongoing rubella virus transmission in the United States [3, 4].

Models based on the epidemiological profile of disease in the United States in the prevaccine era suggest that population immunity must be >87.5% to interrupt rubella virus transmission [5]; this level of immunity may represent a threshold for disease elimination. Vaccination rates among preschool and school-entering children are extensively and regularly surveyed [6–9]. Among older children and adults, rubella immunization surveys are difficult, in part because such age groups often lack records of their childhood vaccinations. Serosurveys may provide the best insights into the rubella immunity status of these groups, particularly persons of childbearing age (15–45 years) for whom prevention of rubella virus infection during pregnancy is the primary objective of the rubella immunization program. In contrast to the indirect evidence of coverage surveys, serosurveys have the advantage of documenting immunity directly, but they have the disadvantage of not distinguishing between vaccine- and disease-induced immunity.

In 1988–1994, during which time >3500 rubella and
>100 CRS cases were reported [10], the population-based National Health and Nutrition Examination Survey (NHANES) indicated that overall immunity to rubella was at a level high enough to eliminate endemic rubella. However, large population subgroups had immunity levels below the elimination threshold [11]. Of greatest concern, those in childbearing age groups had the lowest immunity levels, placing them at increased risk for having children with CRS. Since then, major rubella vaccination efforts have been directed at ensuring that all school-age children receive 2 doses of rubella vaccine and that rubella-susceptible women of childbearing age are vaccinated.

With rubella and CRS disease incidence now at historically low levels, we decided to reexamine rubella immunity levels among US school-age and adult populations to determine (1) whether immunity levels exceed the threshold of elimination, both overall and among groups previously identified with relatively low levels of immunity and (2) whether changes in patterns of immunity compared with 1988–1994 were consistent with immunization efforts during the intervening period, rather than with viral circulation.

**METHODS**

**Survey design and participants.** The NHANES is conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention (CDC), to provide national statistics on the health and nutritional status of the noninstitutionalized civilian population through household interviews, standardized physical examinations, and the collection of biological samples in special mobile examination centers [12]. The procedures followed to select the sample (a stratified, multistage, probability cluster design) and conduct the interviews and examinations have been described elsewhere [13, 14]. The present report is based on NHANES III (1988–1994) and the first 6 years of the continuous NHANES (1999–2004). African Americans and Mexican Americans were oversampled in all years (1988–1994 and 1999–2004). NHANES 1999–2004 also included oversampling of low-income persons and adolescents 12–19 years of age.

**Laboratory testing.** Serum samples were available for testing for rubella antibodies for persons 6 years of age and older in NHANES III and persons 6–49 years of age in NHANES 1999–2004. The laboratory methods used have been reported elsewhere [11]. The same laboratory and indirect EIA were used for rubella IgG antibody testing in NHANES III and NHANES 1999–2004 [15]. Briefly, the absorbance of rubella viral antigen (AG) and the absorbance of the nonspecific (NS) control antigen were used to calculate the value AG minus NS (AG−NS). To determine the IU equivalent of this measure, a regression analysis was performed, and a standard curve was calculated using the duplicate AG−NS values for the 10-IU, 40-IU, and 100-IU standards and their squares. Values ≥10 IU were considered to indicate seropositivity.

**Statistical analysis.** We limited the analyses to persons 6–49 years of age and examined age at time of survey (using the NHANES standard age groupings of 6–11, 12–19, 20–29, 30–39, and 40–49 years) and by variables previously examined in NHANES III [11]. Race/ethnicity was defined as self-reported non-Hispanic white, non-Hispanic black, or Mexican American. The sample size was not sufficient to stratify by other racial and ethnic groups; however, these groups were included in overall estimates. Prevalence estimates were weighted to represent the US population, to account for oversampling in specific demographic subgroups, and for nonresponse to the household survey and physical examinations. Prevalence estimates for NHANES III (1988–1994) and NHANES 1999–2004 were compared, both unadjusted and age adjusted to the 2000 US population by the direct method. Age-adjusted estimates were reported when seroprevalence was compared across surveys for the entire population (6–49 years of age). Although age-adjusted seroprevalence among adults, in particular for NHANES III, were somewhat higher than unadjusted estimates because of the age distribution of the standard population used, differences did not impact conclusions drawn when comparing across surveys. Therefore, reported results for youth (6–19 years of age) and adult (20–49 years of age) population subgroups were not age adjusted, to provide the actual population estimate for that subgroup for the survey period. SE estimates were calculated using the Taylor series linearization method in SUDAAN, to account for the complex sample design [14]. Collett’s method for calculating exact CIs was used to calculate 95% CIs [16, 17]. A t statistic with the combined SE was used to test differences in prevalence between NHANES III and NHANES 1999–2004. P values <.05 were considered to be significant. Analysis focused on persons 6–19 years of age, who were the target of school immunization efforts, and on persons 20–49 years of age, among whom women were the target of childbearing-age immunization efforts. We compared levels of seropositivity across the 2 survey periods for the total population and among specific population subgroups. The specific population subgroups examined were chosen on the basis of the findings of the 1988–1994 survey and included males and females, racial/ethnic groups, Mexican Americans born inside or outside of the United States, and persons below, at, or above the poverty level.

**RESULTS**

**Study population: 1988–1994.** Of the 18,332 persons 6–49 years of age who were interviewed for NHANES III, 17,120 (93%) underwent physical examinations, and 14,393 (79% of those interviewed) had serum tested for antibodies to rubella.
Among those examined, the percentage of persons with serum tested was lowest in the youngest age group (6–11 years, 60%), but there was no other consistent trend with age (range among the remaining age groups, 90%–94%). The percentage of persons with serum tested was also lower among non-Hispanic white persons (79%) than among non-Hispanic black persons (85%) or Mexican Americans (89%) ($P < .001$) and was lower among persons born in the United States (83%) than among those born outside the United States (91%) ($P < .001$). The percentage of persons with serum tested did not vary by sex ($P = .072$) or poverty index ($P = .099$).

**Study population: 1999–2004.** Of the 18,433 persons 6–49 years of age who were interviewed in NHANES 1999–2004, 17,672 (96%) underwent a physical examination, and 16,049 (87% of those interviewed) had serum tested for antibodies to rubella virus. The percentage of persons with serum tested among those examined was somewhat lower among non-Hispanic black persons (89%) than among non-Hispanic white persons (91%) or Mexican Americans (92%) ($P < .001$) and among those born in the United States than among those born outside the United States (90% vs. 92%) ($P = .006$). The percentage of persons with serum tested among those examined was lowest in the youngest age group (6–11 years, 83%), but no other consistent trends with age were observed (range among the remaining age groups, 91%–95%). The percentage of persons with serum tested did not appear to vary by sex ($P = .51$) or poverty index ($P = .46$).

**Rubella IgG seropositivity overall.** Overall, in 1999–2004, age-adjusted rubella IgG seropositivity in the US population 6–49 years of age was 91.3% (95% CI, 90.5%–92.1%), a significant increase compared with 1988–1994, when seropositivity was 88.1% (95% CI, 86.9%–89.1%) ($P < .001$) (figure 1). This overall increase was attributable to increases among persons 6–29 years of age, whereas no significant increase was seen in persons 30–49 years of age. All age groups in 1999–2004 were at or above the modeled threshold of elimination, as were both sexes and each racial/ethnic group examined. When compared with estimates from 1988–1994, levels of rubella immunity in 1999–2004 increased significantly for all racial/ethnic groups and for both males and females.

**Rubella seropositivity among youth 6–19 years of age.** Immunity levels in the school-age population increased from 86.4% (95% CI, 84.1%–88.4%) in 1988–1994 to 94.7% (95% CI, 93.9%–95.5%) in 1999–2004 ($P < .001$) (figure 2). By 1999–2004, children in all strata examined had immunity levels above the modeled threshold of elimination (range, 93.5%–98.8%), and each showed a significant increase compared with 1988–1994 (range, 4.5%–11.9%). Children 6–11 years of age had the highest levels of rubella seropositivity (96.2% [95% CI, 95.0%–97.2%]) of any age group in the general population for 1999–2004, but...
adolescents 12–19 years of age had the greatest increase in immunity level compared with 1988–1994, from 82.6% (95% CI, 79.3%–85.5%) to 93.7% (95% CI, 92.6%–94.6%) (P < .001). Among Mexican American children, rubella seropositivity increased 4.7% for those born outside the United States (from 91.2% [95% CI, 88.1%–93.8%] to 95.9% [95% CI, 93.9%–97.3%]; P = .01) and 11.8% for those born in the United States (from 83.6% [95% CI, 80.9%–86.0%] to 95.4% [95% CI, 94.3%–96.4%]; P < .001).

Rubella seropositivity among adults 20–49 years of age. Immunity levels in the adult population increased from 88.4% (95% CI, 87.0%–89.6%) in 1988–1994 to 89.8% (95% CI, 88.6%–90.9%) in 1999–2004 (P = .107) (figure 3). By 1999–2004, all but 1 subgroup examined had immunity levels above the modeled threshold of elimination (range, 87.9%–92.1%; except for US-born Mexican American adults 20–49 years of age, 85.9% [95% CI, 82.5%–88.9%]). Four groups showed statistically significant increases compared with 1988–1994: women (from 88.9% [95% CI, 87.5%–90.2%] to 91.5% [95% CI, 89.9%–92.9%]; P = .015), persons 20–29 years of age (from 84.6% [95% CI, 82.2%–86.7%] to 89.4% [95% CI, 88.1%–90.7%]; P < .001), and non–US-born Mexican Americans (from 88.7% [95% CI, 87.0%–90.3%] to 91.5% [95% CI, 89.3%–93.4%]; P = .040).

DISCUSSION

In summary, rubella immunity levels for 1999–2004 were above the postulated threshold of elimination in the US population overall and in all but 1 subgroup examined. In contrast to 1988–1994, rubella seropositivity across the US population became more uniform. The increases in rubella seropositivity from the 1988–1994 study period were most marked in groups targeted by immunization programs: school-age children of both sexes and women of childbearing age. In contrast, no significant change in immunity was seen among persons who were not the target of immunization efforts: adult males and persons born in the prevaccine era (born before 1957). These data support the hypothesis that the low current incidence of reported rubella disease reflect vaccine-induced elimination of viral transmission in the United States.

Of particular note, the relatively low levels of rubella immunity seen in women of childbearing age in 1988–1994 were increased to the point at which age-specific immunity levels in the 1999–2004 population were uniformly high. Part of this improvement appears to represent the aging of a well-vaccinated school population of both sexes into young adulthood, and part represents specific efforts to vaccinate susceptible women of childbearing age, as demonstrated by the increase in immunity among women but not men. Since the primary objective of any rubella vaccination program is to prevent CRS, this specific improvement in childbearing-age immunity may represent an achievement second only to raising overall immunity beyond the postulated viral transmission threshold.

By 1999–2004, school-age children in the United States had very high levels of rubella seropositivity (94.7% overall), with children 6–11 years of age having the highest levels of any age group (adult or child) and adolescents 12–19 years of age achieving the greatest increase in comparison with 1988–1994. Immunity levels rose markedly among Mexican American children born in the United States and somewhat less among those born in Mexico. These changes are consistent with widespread implementation of a 2-dose requirement for school entry in the United States, as well as the initiation of childhood rubella vaccination in Mexico in 1989 [18].

This study has a number of limitations. Among persons interviewed for NHANES, serum samples were not available for 21% in 1988–1994 and 13% in 1999–2004. Data were not available for children <6 years of age in either survey. Provider-validated vaccination information was not available for analysis;
hence, the relationship between immunity changes and vaccination programs is circumstantial. The proposed elimination threshold of 87.5% immunity is based on modeling from the prevaccine era and may not apply to current conditions. Although rubella immunity level estimates among adults 20–49 years of age from NHANES 1999–2004 for most demographic subgroups met or were greater than the modeled 87.5% threshold (except adult US-born Mexican Americans [85.9%]), the lower 95% confidence limit for certain adult subgroups did not meet the modeled 87.5% threshold. The adult subgroups in which the lower 95% confidence limit did not meet the modeled 87.5% threshold included those 30–39 years of age (lower confidence limit, 86.1%), males (lower confidence limit, 86.5%), adult US-born Mexican Americans (lower confidence limit, 82.5%), and those living below the poverty level (lower confidence limit, 85.4%).

Epidemiological and vaccination coverage data [10, 19] are consistent with our findings that immunity levels in the United States have been raised to the point that sustained virus transmission has been prevented. However, nearly 10% of women of child-bearing age were rubella seronegative in 1999–2004, placing their children at risk for CRS. Furthermore, relatively small decreases in vaccination levels among children may be manifested in increases in CRS decades later. Since 75% of the world’s children live in countries without national rubella vaccination programs, the threat of viral reintroduction to the United States could be high. Only maintenance of high vaccine-induced immunity levels in the United States can ensure that rubella elimination is not a transient event.

Acknowledgments

We thank Mary McCauley and Charles LeBaron for review and editing of the manuscript.

Financial support. Centers for Disease Control and Prevention.

Supplement sponsorship. This article was published as part of a supplement entitled “The Evidence for the Elimination of Rubella and Congenital Rubella Syndrome in the United States: A Public Health Achievement,” sponsored by the Centers for Disease Control and Prevention.

Potential conflicts of interest. All authors: no conflicts.

References

2. Williams NM, Preblud SR. Rubella and congenital rubella surveillance, 1983. MMWR CDC Surveill Summ 1984; 33:15S–10S.