Estimating the Number of Measles-Susceptible Children and Adolescents in the United States Using Data From the National Immunization Survey–Teen (NIS-Teen)

Robert A. Bednarczyk*, Walter A. Orenstein, and Saad B. Omer

* Correspondence to Dr. Robert A. Bednarczyk, CNR 7019, Mailstop 1518-002-7BB, Hubert Department of Global Health, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322 (e-mail: rbednar@emory.edu).

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Despite high measles vaccination rates in the United States, imported measles cases have led to outbreaks in the United States. These outbreaks have not led to sustained measles transmission; however, with each birth cohort of children not fully vaccinated against measles, measles-susceptible individuals accumulate in the population. The total number of measles-susceptible children and adolescents in the United States is unknown. We used age-specific measles vaccination data from the National Immunization Survey–Teen (2008–2013) to estimate the number of measles-susceptible children aged 17 years or younger, accounting for vaccine effectiveness, infant protection from maternal antibodies, and loss of immunity following childhood cancer treatment. Approximately 12.5% of US children and adolescents are susceptible to measles, with the highest levels of susceptibility being observed in children aged 3 years or younger (24.7% are susceptible to measles). In sensitivity analyses, we found that a sustained decrease in measles vaccination coverage from 91.9% (2013 level) to 90.0% (2009 level) would add nearly 1.2 million susceptible children and adolescents (thus making 14.2% of those aged 17 years or younger susceptible to measles). This reemphasizes the need for high measles vaccination coverage to support population-level immunity and prevent reestablishment of indigenous measles transmission in the United States.

disease susceptibility; immunization; measles; measles-mumps-rubella vaccine

In the United States, uptake of childhood measles, mumps, and rubella (MMR) vaccine is generally high. In 2013, 91.9% of children aged 19–35 months had received at least 1 dose of MMR vaccine (1), and 94.7% of children entering kindergarten had received 2 doses (2). However, even with high MMR vaccine coverage, the United States continues to experience measles outbreaks as a result of imported measles cases. During the period 2013–2014, there were 34 measles outbreaks in the United States (3). None of these outbreaks to date has led to reestablishment of indigenous measles transmission (i.e., sustained transmission of a measles strain for >1 year within the United States). Nevertheless, as long as measles remains endemic in Europe, Asia, and Africa (4–7), the United States is at risk of continued importations and, if immunity levels are not sustained, reestablishment of indigenous transmission.

With the general absence of measles disease in the United States, measles immunity among the population occurs primarily as a result of immunization. However, not all children from each year’s birth cohort are fully immunized as they progress through childhood and adolescence. As new birth cohorts emerge with children who are not fully immunized, there is then an accumulation of measles-susceptible children, with each new group of susceptible children adding to those already in the population. Additionally, estimates of childhood MMR vaccine coverage do not fully account for unprotected individuals who 1) are too young to receive MMR, 2) have received MMR but not until later childhood or adolescence, 3) may have altered immunity following cancer therapy or other forms of immunosuppression, or 4) did not have a protective immune response to vaccination. To our knowledge, there has not been a rigorous quantitative
assessing the total number of measles-susceptible children and adolescents (aged 17 years or younger) in the United States or the overall proportion of susceptible children and adolescents relates to the conventionally accepted, population-level measles herd immunity threshold of 92%–95% (8), under the imperfect assumption that this immunity threshold must be achieved across all age cohorts. Hence, there is a need to look at the overall accumulation of measles-susceptible individuals, rather than focusing solely on snapshots within a given age range.

Generating an estimate of the total number of measles-susceptible children in the United States will aid in evidence-based planning for measles outbreaks in the context of a highly immunized population. Additionally, it can better assess the way population-level immunity compares with the herd immunity threshold for measles, which can underscore the importance of maintaining and increasing immunization coverage in the United States. We used data from the National Immunization Survey (NIS–Teen) to estimate the total number of children aged 17 years or younger in the United States who were susceptible to measles infection.

METHODS

Analytical data sets

All analyses were conducted using data from the NIS–Teen, available from the Centers for Disease Control and Prevention in Atlanta, Georgia (9). The NIS-Teen is an annual, nationally representative survey using household surveys of parents of adolescents (13–17 years of age) and provider verification of vaccination to estimate US vaccine coverage. In the NIS-Teen, measles vaccination history and age at receipt of each MMR dose are collected and verified with health-care providers. Analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina), using PROC SURVEYFREQ with appropriate sample weighting to maintain internal consistency for the estimates. For example, a child aged 17 years would have had up to 17 years to receive measles-containing vaccine (MCV); thus, the NIS-Teen age-specific vaccine-uptake proportion for each age, up to 17 years, would be considered. For children under 1 year of age, for example, only vaccine uptake for children under 1 year of age would be considered. These annual age-specific estimates were generated for 18 birth cohorts to account for children through 17 years of age.

After we estimated the number and proportion of children who received MCV at each age, we found that the NIS-Teen data for the receipt of the first MMR dose by the third birthday (87.2%) was lower than the average childhood NIS coverage for children born during the same time frame (90.4%) (11–19). To account for this early childhood difference, we adjusted the estimate of first-dose MMR-vaccine uptake by the third birthday from the NIS-Teen to the average childhood NIS coverage (adjustment ratio, 90.4/87.2 = 1.04). To account for children and adolescents who were not fully protected after vaccination, we applied estimates of measles vaccine effectiveness (93% after 1 dose; 97% after 2 doses) to all age-specific MCV coverage proportions (20). Because measles incidence has been so low in the United States for 2 decades, we assumed that all measles immunity was due to vaccination.

Measles antibodies can be transferred transplacentally, and while evidence of maternal antibody interference with measles vaccination during infancy has led to the recommendation for vaccination at 12 months of age (4, 20), a synthesis of the current evidence indicated that vaccine-induced maternal antibodies may provide protection through approximately 6 months of age (21–24). We accounted for this protection by assuming that half of infants younger than 1 year of age would be protected by maternal antibodies. With the current US recommendation (20) for first measles vaccination between 12 and 15 months of age, established after findings of a shorter duration of maternal protection when mothers have predominantly vaccine-induced immunity (25–28), we made the decision not to model the potential of interference from maternal antibodies.

Cancer treatments have been shown to reduce circulating measles antibody titers to levels below protective levels in approximately 25% of children undergoing therapy, suggesting an increase in susceptibility (29, 30). The incidence of cancer in children aged 19 years or younger in the United States is approximately 1 in 285 (31). We prorated the number of children susceptible to cancer by the number of years available for cancer development, and we assumed that 50% of children with a cancer diagnosis would undergo cancer therapy and that 25% (29, 30) of treated children would have resultant losses in measles immunity.

Sensitivity analysis assumptions and variable estimates

Sensitivity analyses were conducted with variation in estimates for 1) vaccine coverage, 2) vaccine effectiveness, and 3) duration of maternal antibody protection. MCV coverage in the United States has remained consistent since the mid-1990s, but the potential exists for vaccine hesitancy to lead to decreased vaccine coverage. We based this sensitivity analysis on the assumption of a modest,
sustained decrease in vaccine coverage for children from the 2013 NIS estimate (91.9%) (1) to the 2012 NIS estimate (90.1%) (32), a relative decrease of 2%. We multiplied all age-specific vaccine coverage estimates by 0.98 to account for this decrease in immunization coverage.

Because conventional estimates of measles vaccine effectiveness (VE) are based on assessments of a variety of studies, we computed estimates based on slightly reduced VE (93% to 92% for 1 dose of measles-containing vaccine (MCV)) and 96% to 96% for 2 MCV doses).

Given the large contribution of measles-susceptible children under 1 year of age, we also examined the change in estimates of susceptibility with the assumption that maternal antibody protection lasts up to 10 months of age. Due to the relatively small number of children vaccinated prior to 1 year of age and the recommendation for revaccination of infants vaccinated prior to 1 year of age for international travel (20), there would be minimal long-term susceptibility of infants vaccinated in the presence of maternal antibodies, due to the potential for revaccination with additional MCV doses.

**Measles immunity and susceptibility calculations**

For each age group, for all children and adolescents aged 17 years or younger (inclusive), and for children for whom 2

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**Figure 1.** Age-specific measles susceptibility in the United States, estimated using 2008–2013 National Immunization Survey–Teen data. Dark gray shading represents the proportion of US children and adolescents susceptible to measles; the segment of each figure not shaded dark gray represents the proportion of US children and adolescents who are immune to measles. A) Baseline model. B) Model assuming decreased vaccine effectiveness of 92% (1 dose of measles-containing vaccine (MCV)) and 96% (2 doses of MCV). C) Model assuming a decrease in MCV coverage to 98% of current levels.
MCV doses are recommended (ages 4–17 years), we computed the numbers and proportions of children who were considered immune and not immune to measles, according to the stated assumptions. Using the commonly accepted population-level herd immunity threshold of 92% (4) as a guide, we used the operational definition of age group–specific immunity of 92% as a benchmark for comparison. All benchmark comparisons throughout this study are relative to this operational definition. Individual age group immunity above or below this benchmark does not yield population-level immunity due to age-specific differentials in potential for measles infection; however, it does provide a point of reference for comparison of historical data and future evaluations of measles susceptibility, and it is widely used by immunization programs to inform policy interventions. The same methodology was used to compute the proportion of measles-susceptible children and adolescents using varied assumptions for sensitivity analyses.

Geographic distribution of unvaccinated adolescents

To evaluate the geographic distribution of measles-susceptible individuals, we used the 2013 NIS-Teen to estimate the total number of adolescents aged 13–17 years in each state who had not received a first dose of MMR. This metric was chosen because state-level estimates of age-specific MMR vaccine receipt from the NIS-Teen were not stable enough to compute estimates of susceptible populations as was done for national data.

Because this analysis used existing, previously collected, and freely available public data, this study was considered to be non–human subjects research and did not require institutional review board approval.

RESULTS

Baseline model results

Among 18 cumulative birth cohorts, with a total of 69,856,092 children and adolescents aged 17 years or younger, we estimated there to be 8,714,275 (12.5%) children and adolescents who were not immune to measles. This population-level immunity estimate was driven largely by age—24.7% of children aged 3 years or younger (3,837,835 of 15,523,576 children) were not immune to measles, while 9.0% of children and adolescents aged 4–17 years (4,876,439 of 54,332,516 children and adolescents) were not immune to measles. Even among older adolescents, who had the longest period to be vaccinated (ages 13–17 years), more than 1.5 million were not immune to measles (n = 1,529,902; 7.9% of adolescents aged 13–17 years), although this is within the operational definition of the immunity threshold for measles prevention (Figure 1A).

Sensitivity analysis results

A 1-percentage-point decrease in MCV VE for both first MCV dose (from 93% VE to 92% VE) and second MCV dose (from 97% to 96%) yielded 9,330,809 (13.4%) children and adolescents aged 17 years or younger who were susceptible to measles. Although the proportion of children immune to measles is greater than 90% for those aged 10 years or older, this small deviation in VE can add over half a million children to the susceptible category (Figure 1B).

A prolonged period of a 2% relative decrease in MCV coverage among children and adolescents would correspond to the addition of nearly 1.2 million susceptible children (9,898,302 children aged ≤17 years susceptible to measles—14.2% of this population). Among children aged 4–17 years, 10.8% would be susceptible to measles, and no age group through 17 years of age would reach the operational threshold of 92% immunity (Figure 1C). Over 17 years, these additional susceptible children would accumulate slowly, by approximately 70,000 additional susceptible children and adolescents per year. However, with a consistent accumulation in this fashion, there would be a steady decline in the proportion immune to measles, from 87.5% to 85.8% (Figure 2).
Figure 3. State-specific prevalence proportion (A) and number of children aged 13–17 years (B) who had received zero doses of measles-containing vaccine, National Immunization Survey–Teen, 2013.
Assuming an increase in protection due to maternal antibodies, the total number and proportion of susceptible children and adolescents aged 17 years or younger would drop to 7,420,643 (10.6% of children and adolescents), with the increase in protection being seen only in infants.

**Geographic distribution of adolescents unvaccinated against measles**

In 2013, 4.5% of adolescents aged 13–17 years (n = 941,134) had not received any doses of MMR. In 10 states and the District of Columbia, at least 6% of adolescents aged 13–17 years had received zero MMR doses (Figure 3A). In each of 14 states, over 20,000 adolescents had received zero MMR doses (Figure 3B). Absolute numbers of adolescents who received zero MMR doses were highest in the states with the largest populations. Six states (Arizona, California, Missouri, North Carolina, Texas, and Utah) each had at least 20,000 unvaccinated adolescents, with at least 6% of their adolescents being unvaccinated with MMR. In these 6 states, there were a total of 458,358 adolescents aged 13–17 years who had received zero MMR doses.

**DISCUSSION**

To our knowledge, this was the first population-based quantitative assessment of the cumulative number of children in the United States who are susceptible to measles, with direct comparisons of population-level susceptibility with the herd immunity threshold. Our finding that the overall immunity levels in school-aged children appeared to be near or higher than the operational immunity benchmark of 92% (8) provides some support to the observation that indigenous measles transmission has been eliminated in the United States since 2000 (33). Nevertheless, with approximately 8.7 million children aged 17 years or younger who are susceptible to measles, there is a potential for large measles outbreaks even in the context of generally high vaccination coverage (1, 2). Many susceptible children are under 1 year of age—too young to be vaccinated (34) and at the greatest risk of complications from measles (35). Even assuming that infants are fully protected by maternal antibodies through 10 months of age, there are still nearly 650,000 infants at risk of measles infection. This highlights the need for consistently maintained high levels of immunity in the population, through high vaccine coverage, to protect these infants.

The conventionally accepted herd immunity threshold of 92%–95% is based on a population average. With a wide variety of intermixing factors at play (e.g., age-specific immunity levels, geographic heterogeneity of intentionally unimmunized individuals, population density, international travel to measles-endemic countries), herd immunity thresholds may be different for various subpopulations. These dynamics are driven, to a greater extent, by intermixing factors in an era of generally high MCV coverage, particularly as they relate to geographic distribution of intentionally unvaccinated individuals (36), and can be associated with measles transmission to nonimmune individuals (37). Despite potentially high measles susceptibility in younger children, we see little sustained post-importation transmission in this group, suggesting that without large-scale transmission in older age groups, the force of infection (i.e., the rate at which susceptible individuals become infected, accounting for number of susceptible persons and level of exposure) in this age group in the United States may be relatively low (38, 39). Notably, it has been estimated that herd immunity requirements needed to terminate transmission in preschool populations appear to be lower than those for older children, due to lower levels of exposure and contact between children during early childhood (38). Future research is needed to refine and extend these findings with a greater understanding of the role of these demographic and mixing dynamics (especially age and geographic distribution of vaccine exemptors) in measles transmission.

Using estimates to assess the proportion of protected individuals, rather than just overall immunization coverage, may be beneficial in monitoring population-level risk from measles outbreaks. While, in our conservative baseline model, the age-specific proportion protected did not exceed the operational immunity thresholds (40, 41) until 13 years of age, the proportion immune to measles was still over 90% among those aged 6 years or older. This is still compatible with sustained elimination of indigenous transmission because age-specific infection is highest around 10 years of age (39); with greater immunity and only sporadic measles importations affecting adolescents, there may be less opportunity for measles to spread to children aged 6–12 years given the relatively low numbers of measles-infected individuals in the United States following imported cases.

Our analyses were conducted using a consistent birth cohort size, corresponding to the smallest annual birth cohort among the years in which NIS-Teen-eligible children were born (3,880,894 births in 1997) (10). This would have resulted in a conservative absolute estimate of the number of susceptible individuals born during this period. Had we used a different cohort size, the overall proportion of susceptible children would have remained the same, although the absolute number of susceptible children would have been larger.

While we used the average age-specific MMR vaccination rates from the 2008 through 2013 NIS-Teen surveys, we felt confident in this choice given the low variability in these coverage estimates. There were some differences in the childhood NIS and NIS-Teen estimates of first-dose MMR vaccination prior to the third birthday; these surveys use different sampling frames and source populations, which may have different rates of in- and out-migration. Each iteration of the NIS-Teen encompasses a wider range of birth years; therefore, it is not unexpected to see differences such as this. There are approximately 2.9 million children under 3 years of age who may be susceptible to measles. However, given differences in population mixing for infants and young children relative to older children and adolescents, it has been shown that a lower herd immunity threshold may be sufficient to prevent widespread outbreaks among these younger children (38).

The United States has not had reestablishment of indigenous measles for more than 14 years despite repeated importations. Although the overall population of school-aged children does have an estimated immunity level at or in excess of traditional herd immunity thresholds calculated for measles, other influences may also be present. Reports of measles lead to extensive outbreak-control activities, which
may be playing an important role (3, 42–45). Thus, we cannot feel fully secure that transmission will not be reestablished, particularly because there are susceptible persons who could sustain transmission (46), including clusters of children who have not been vaccinated against measles, among whom there is an increased risk of measles outbreaks (47). Additionally, our analysis assuming a relatively small decrease in immunization coverage showed that childhood population-level immunity would be reduced to levels below the operational threshold of 92%. It is critical not only to maintain current MCV coverage but to actively seek to increase MCV coverage to ensure adequate immunity in the population. This is particularly important because our estimates are national-level estimates and do not account for state- and community-level heterogeneity in measles vaccine coverage and measles immunity among children and adolescents. With the gradual accumulation of measles-susceptible children and adolescents described here leading to the failure of any age group to reach 92% immunity, the risks of related measles outbreaks are magnified, particularly in older adolescents, who may have a greater opportunity for measles exposure.

The geographic distribution we observed with regard to adolescents who received zero MMR doses indicates that even within the large proportion of children nationally who are susceptible to measles, there are areas where measles susceptibility may be greater. Additional review of state-level childhood and adolescent MMR coverage will help policymakers and emergency planners prepare for future measles outbreaks. Additional modeling is needed, at both the national and state levels, to understand accumulated measles susceptibility in the full US population beyond children aged 17 years or younger.

This study has some limitations. First, we based our estimates of age at first-dose MMR receipt on data from the NIS-Teen. There is currently no national survey that addresses vaccination for all children and adolescents between 4 and 12 years of age, so we used the NIS-Teen to evaluate vaccination at all ages through 17 years. We mitigated some of the potential biases from evaluating childhood vaccination coverage using data on adolescents by using provider-verified data for age at first MMR dose and applying a correction factor to adjust NIS-Teen estimates for early childhood vaccination to be more similar to childhood NIS estimates. Future studies using population-based immunization information systems can help validate these findings related to adolescents’ childhood MMR receipt.

Second, while we tested our assumptions on maternal antibody protection through sensitivity analyses, there is uncertainty over the level of protection provided to infants by maternal antibodies. Our assumption—that only half of children under 1 year of age would be fully protected by maternal antibodies (21–24)—was evaluated through sensitivity analyses, and while increased protection through 10 months of age reduced the overall total number of susceptible individuals in the childhood and adolescent population, it did not alter the accumulation of susceptible persons over time for children through 17 years of age. Additional research is needed to understand the dynamics of measles protection in infancy, prior to the routine recommendation for childhood measles vaccination.

Finally, there are 2 limitations regarding children who may have lost immunity due to immunosuppressive therapies. We could not estimate the proportion of children with cancer diagnoses who underwent cancer treatment that could have altered their measles immunity status. However, with an estimated 122,555 children in our total cohort diagnosed with cancer (31), children with cancer represented a small proportion of the total (0.18%); removal of these children from the susceptible pool did not alter our overall estimates of susceptibility. Additionally, we did not account for children who may have had an altered immune response due to immunosuppressive therapy for other conditions (e.g., immune suppression following organ transplantation). With an average of 1,700 annual organ transplants among children aged 17 years or younger in the United States (48), there would be little change in our estimates, given our hypothesized cohort of over 69 million children and adolescents. However, these cases would serve only to decrease the number of children and adolescents who were immune to measles, further pushing our estimates closer to, or below, the operational measles immunity threshold of 92%.

In conclusion, the overall level of immunity to measles is generally at or higher than the operational threshold of 92%. This is compatible with the experience to date that, despite substantial numbers of importations, endemic measles transmission has not been reestablished. Nevertheless, a substantial number of children and adolescents aged 17 years or younger in the United States are susceptible to measles, with some clustering raising concerns that endemic measles transmission could be reestablished despite the overall high level of immunity. Sustained minor decreases in MCV uptake can also result in children having greater susceptibility to measles. These estimates underscore the need to help public health professionals plan for future immunization programs and potential measles outbreaks and to maintain appropriate levels of immunity in the population to prevent widespread transmission of this highly infectious disease.

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Author affiliations: Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia (Robert A. Bednarczyk, Saad B. Omer); Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, Georgia (Robert A. Bednarczyk, Saad B. Omer); Emory Vaccine Center, Emory University, Atlanta, Georgia (Robert A. Bednarczyk, Walter A. Orenstein, Saad B. Omer); Division of Infectious Diseases, Department of Medicine, School of Medicine, Emory University, Atlanta, Georgia (Walter A. Orenstein); and Department of Pediatrics, School of Medicine, Emory University, Atlanta, Georgia (Saad B. Omer).

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National Immunization Survey—Teen data sets from 2008–2013 are available from the Centers for Disease Control and Prevention in Atlanta, Georgia (http://www.cdc.gov/nchs/nis/data_files_teen.htm).

All analyses, interpretations, or conclusions reached are those of the authors and not of the National Center for Health Statistics, which is responsible only for the initial data.

Conflict of interest: none declared.

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