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Historical perspective of measles control in the United States

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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Abstract

Historical perspective of measles control in the United States

By Araceli Mariana Gomez Estevez

Measles is a highly contagious disease with significant childhood mortality slated for regional elimination and eventual eradication. Maintenance and assessment of local measles elimination is challenging in face of continued importations of the disease. In the present study, we quantify measles transmissibility in the United Sates from 1985 to 2015, by estimation of the effective reproduction number (R_E) (the average number of secondary cases generated by a case). Four mathematical methods to estimate R_E were applied to national surveillance data to ascertain when measles elimination was achieved in the United States. Analysis shows that since 1997, R_E point estimates by all methods were below the threshold value of 1; the minimum to sustain endemic transmission. Thereafter, year-to-year variability in the values of R_E and an increase in transmissibility in recent years were noted with all methods. Fluctuations in R_E show an inverse proportion pattern with vaccination rates, and R_E values below 1 correlated with a measles incidence of 1 case per million population. Our findings suggest that elimination of endemic measles transmission was attained in 1997 in the United States, and maintained, and emphasize the primacy of high measles vaccination coverage throughout the population to limit measles transmission.

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Table of Contents

Historical perspective of measles control in the United States

Gomez Estevez Araceli Mariana, MD, MPH candidate.

Measles is a highly contagious viral disease that can lead to severe complications and death. It remains an important cause of mortality worldwide with an estimated 134,200 deaths annually (Patel et al., 2016) and accounts for a staggering 52% of deaths among children 5 years of age or less (CMC, 2016). Due to the availability of a highly effective vaccine that confers life-long immunity, and given that the measles virus has no animal reservoir and is serologically monotypic, measles is a candidate for world eradication. (William, & Moss, et al., 2016). Following the 2010 Global Vaccine Action Plan to increase routine measles vaccine coverage and reduce the incidence and mortality of measles globally, the World Health Assembly (WHA) had set the ambitious goal to eliminate measles from four World Health Organization (WHO) regions by 2015. Although significant progress was made from 2000 through 2015, including the prevention of an estimated 20.3 million measles deaths and a decline in measles incidence of 75% (from 146 to 36 cases per 1 million population), elimination milestones have not been reached, and reductions in incidence and mortality has slowed down (Patel et al., 2016).

The elimination of endemic measles transmission requires adequate vaccine delivery infrastructure, effective policies that promote high vaccination coverage, high-quality surveillance systems, and coordinated efforts within and between countries. In 2016, the Americas was the first region in the world to be declared measles free (Mitchel, 2017) and the United States attained and has sustained elimination since at least 2000 -- the year elimination was declared (Papania et al., 2014). Characterizing the experiences and lessons learned with the achievement of measles elimination in these countries is important and could inform policies and strategies for measles control in endemic settings or in counties nearing elimination.

In the present study we use historical measles data from the United Sates from the period of 1985 through 2015, to quantify temporal trends in measles transmissibility. Our primary objectives were to: (1) pinpoint when elimination was achieved in the US and to correlate the achievement of elimination to the policies that were in place at the time, (2) compare the attainment of measles elimination and measles transmissibility to reported incidence rates and coverage levels, and (3) quantify recent increases in measles transmissibility.

METHODS

We analyzed de-identified physical and electronic data of confirmed measles cases reported by local and state health department to the National Center for Immunization and Respiratory diseases (NCIRD) at the Centers for Disease Control and Prevention (CDC) during the period 1985 through 2015. We assessed measles transmissibility by estimation of the effective reproduction number, R_E, the average number of secondary cases generated by each case. Elimination of endemic measles, defined as the lack of sustained transmission of the virus in a defined geographical area for 12 months or longer, is attained by maintaining low levels of susceptibility in the population through high vaccination coverage. Measles elimination can be assessed by estimation of R_E; when R_E is <1, on average, each measles case generates less than one case; transmission tends to wane, measles spread eventually stops, and elimination has been achieved (De Serres, Gay, & Farrington, 2000). Four mathematical methods to estimate R_E were applied to national measles surveillance data. The first method estimates R_E as 1-P, where P is the proportion of cases that are imported, and is based on the geometric progression of cases expected each generation given a value of R_E. The second and third methods estimate the expected distribution of outbreak sizes and durations, respectively, based on branching processes, given a value of R_E. Observed data are then fit to the modeled distributions to estimate R_E (De Serres et al, 2004). The fourth method uses a Bayesian approach to probabilistically reconstruct transmission trees by use of incidence data and the distribution of serial intervals (time between onset of symptoms in one case and onset of symptoms in a secondary case) (Wallinga et al., 2004). Details on the derivation of these formulas are available elsewhere (De Serres, Gay, & Farrington, 2000) (Cori et al, 2013) (Wallinga et al., 2004). Several important assumptions of the methods need to be considered. The first three methods assume that endemic transmission of measles has stopped (i.e., that elimination has been achieved), and that chains of transmission are finite; point estimates of R_E based on these methods will therefore always be <1. Applying these methods prior to elimination, however, would show R_E estimates to be close to 1 and upper confidence limits may cross 1, thereby allowing for the exclusion of endemic transmission. Because the number of secondary cases arising from each importation, and the size and the duration of outbreaks, may be affected by control measures, the first three methods may underestimate R_E in settings where public health interventions are vigorously instituted. Since this is the case in the US, we use the last method to estimate the reproduction number of the index case $R_{E(index)}$, the first case in each transmission chain, in order to evaluate measles transmissibility early during outbreaks, before public health interventions were likely to be in place. Finally, these methods also assume random mixing, which may not be satisfied in a setting where baseline vaccination levels are high and outbreaks occur in defined pockets of under-immunization. However, this assumption does not preclude an evaluation of trends in transmissibility over time. In addition, the last method, which measures contagiousness in each transmission chain, is not bound by this assumption, and allows for evaluation of transmissibility in heterogeneous subpopulations.

R_E was estimated for each year from 1985 through 2015 (the range of years covered depended on nature of data available for each of the methods). First, we ascertain when measles elimination was achieved in the US, and associate transmissibility to the vaccination policies that were in place at the time. Second, we correlate estimates of R_E to reported measles incidence rates to assess whether an incidence rate of <1 case per million, considered as one of the lines of evidence of lack of indigenous measles transmission, is a good indicator of measles elimination. Finally, estimates of R_E were correlated to measles-mumps-rubella (MMR) vaccine coverage levels to evaluate whether changes in coverage at the national level could explain changes in measles transmissibility. Yearly incidence rates (IR) were calculated by dividing the annual number of reported US case-patients by corresponding US population estimates. Data from the National Immunization Survey were used to examine national rates of 1-dose measles vaccination coverage among children 19-35 months of age from 2001 through 2014 (NIS, 2016), the only full years for which data were available.

Analyses was performed in R version 3.0.2. (R: A language and environment for statistical computing; R Core Team, Vienna, Austria).

RESULTS

Measles vaccination coverage for children 19 to 35 months old has remained at or above 90% since 1996 with yearly variability (range 89.8% to 93%) (Figure 1). The annual reported incidence of measles varied between 1.2 to 93 cases per million population between 1985 and 1996, and has remained below 1 case per million population, every year, since 1997, except in 2014 when the incidence was 2.08 per million population (Figure 2).

Estimates of R_E for measles in the United States during 1985–2015 were significantly less than 1 with each of the first three methods. However, point estimates and the upper limit of the confidence interval of R_E, as estimated from the proportion of cases imported (Method 1) and $R_{E(index)}$ based on observed dates of symptom onset and the distribution of the serial interval (Method 4), were close to or above 1 until 1996 (Figures 3-6). It is not until 1997 that all methods show point estimates below 1. Overall, annual values were generally smaller when R_E was estimated from the distribution of chain sizes (Method 2) and the distribution of chain durations (Method 3).

Year-to-year variation in the values of R_E and $R_{E(index)}$ were noted for all estimation methods across study years, yet, consistently across methods, R_E and $R_{E(index)}$ estimates were generally higher in recent post-elimination years when compared with previous post-elimination years (i.e., after measles was declared eliminated in 2000) (Figure 3-6). Of note, $R_{E(index)}$ point estimates were at or above 1 in 2005, 2013, and 2015, and the upper limit of the confidence interval for $R_{E(index)}$ crossed 1 in 2008, 2009, and 2014 (Figure 6).

R_E and $R_{E(index)}$ were inversely associated with 1-dose measles vaccination coverage among children 19-35 months in the United States (Figure 7); R^2 was 0.09 for all methods combined (*p*-value=0.008). R_E and $R_{E(index)}$ were also associated to the reported incidence of measles in the United States, particularly for R_E as estimated from the proportion of cases imported (Method 1), and $R_{E(index)}$ (Method 4); point estimates closer to the threshold value R_E =1 correlated with incidence rates near and above an incidence of 1 case per million population (Figure 8). Overall, mean R_E and $R_{E(index)}$ values were 0.51 (range, 0.21 to 1.16) and 0.88 (range, 0.57 to 2.01) when the incidence was below and above 1 case per million population, respectively.

DISCUSSION

The basic reproduction number, R_0, which describes the transmissibility of a disease in a totally susceptible population, is estimated to be 12-18 for measles virus, the highest of all known infectious diseases (Nelson 2014). In the present study, annual R_E estimations were used to better understand the impact of measles control policies in the United States. The elimination of indigenous measles transmission in the US was declared in 2000, based on several pieces of evidence suggesting limited transmission in the years prior to 2000 (including low incidence, limited size and duration of outbreaks, lack of an endemic virus strain, and high population immunity) (Papania et al., 2004). Our analysis by all four of these modelling methods convincingly show R_E to be below the threshold of 1 starting in 1997 which is consistent with a similar assessment of US national surveillance data for the years 1997-1999 by Gay et al (2004). Although a prior analysis of US measles data for 1995-1997 by De Serres et al. (2000) concluded that endemic transmission had been eliminated by those years cautious interpretations is warranted. Their upper confidence limits of the R_E estimates are not far below the elimination threshold and, given the data we present, the point estimate of $R_{E(index)}$ for 1995 exceeded 1 indicating transmissibility above the threshold before public health responses.

Several key strategies for measles control in the United States evolved in the late 1980s and early 1990s that led to the elimination of measles. By 1980, state legislatures across the country had enacted laws that required proof of immunization as a condition of school entry or attendance (Johnson, Sardell, & Richards, 2000). This increased 1-dose measles vaccination coverage and further reduced measles incidence. During the 1980s, a few thousand measles cases were still being reported each year. These measles outbreaks were occurring mainly among school-aged children who had received 1 dose of measles vaccine and prompted the switch to a 2-dose measles vaccine schedule in 1989 (Estrebel et al., 2004). From 1989 through 1991, another measles epidemic in the United States resulted in several tens of thousands of cases of measles and hundreds of deaths. During the resurgence, more than half of the children who had measles were unvaccinated children in inner city areas. As a result, congress created the Vaccines for Children (VFC) program in 1994, to fund vaccine purchases for poor underinsured children. Finally, in 1991, the Pan American Health Organization (PAHO) established the measles elimination initiative (De Serres, & Gay, 2000) and by 1994, the Ministers of Health of all the member countries in the Americas set the goal for global measles elimination by 2000 (Estrebel et al., 2004). These initiatives had a significant impact on cases in the United States by significantly reducing the risk of importations from Latin America; by 2000, only 40 importations/year were reported to occur from the Americas.

Interestingly, we document the interruption of sustained measles transmission when 1-dose measles vaccination coverage levels were just over 90% among children 19 to 35 months of age, and when 2-dose measles vaccination coverage levels were 67.8% among adolescents 13 to 15 years of age (McCauley et al 2008), and that elimination has been sustained with 1-dose measles vaccination coverage levels ranging between 90%-93%. These coverage levels translate to immunity levels below the theoretical herd-immunity threshold (i.e., the population immunity level needed to interrupt transmission) which for measles is estimated at 92% to 94% (Orenstain, & Seib, 2014). These findings emphasize the importance of heterogeneity in both contact rates and immunity for measles transmissibility (Glasser, et al., 2016). Because of these same factors, outbreaks continue to occur in subpopulations even when overall immunity levels exceed the herd-immunity threshold. Thus policies supporting coverage levels exceeding 95% are warranted. We also demonstrate an inverse relationship between measles vaccination coverage and measles transmissibility; combining all methods, we show that ~9% of the variation in transmissibility may be explained by the variation in measles vaccination coverage. This was somewhat unexpected given that measles coverage rates at the national level are not thought to reveal vulnerabilities in defined under-immunized communities and because the coverage we assessed represents a small segment of the age range. Although cautious interpretations is necessary, in elimination settings, where measles epidemiology is characterized by limited spread among non-immune persons (Durrheim, Crowcroft, & Strebel, 2014) this finding emphasizes the primacy of high measles vaccination coverage in limiting measles spread.

Considerable variability was noted in estimates of R_E and $R_{E(index)}$ after elimination was achieved in the United States. Yet, consistently across methods, we saw higher annual estimates of R_E and $R_{E(index)}$ in more recent post-elimination years when compared to earlier post-elimination years. The upper confidence limits of R_E as estimated from the proportion of cases imported and from the distribution of outbreak sizes were close to 1 in 2014 and 2015, and point estimates of $R_{E(index)}$ were near or above 1 in 2013 through 2015. This is a potentially concerning trend which warrants continued monitoring through high-quality surveillance and highlights the importance of maintaining high levels of vaccination across the population. Importantly, given that national vaccination coverage has remained high, these recent increases in transmissibility likely reflect increased susceptibility and transmission after introductions in certain subpopulations only. Emphasizing the importance of remaining vigilant of measles to help expedite containment strategies, particularly in areas with known clusters of vulnerability.

The increase in R_E observed in post-elimination trends is due to large outbreaks taking place among vulnerable subpopulations. As an example, the largest outbreak (383 cases) observed in our analysis from 1993 to 2015, occurred in 2014 in an Amish Community in Ohio, where 89% of the cases were unvaccinated and vaccination rates in affected Amish households was an estimated 14%. In this outbreak, almost no spread was reported to the general non-Amish community, where NIS estimated measles coverage at 88%, suggesting that the vaccine was decidedly effective in containing spread. (Gastanaduy et al, 2016) Similarly, in early 2015, from January 4 to April 2, 159 measles cases were reported in the United States, of which 80% were unvaccinated or had an unknown vaccination status. (Clemmons et al, 2015) Finally, as early as 1999, studies have shown that exemptors from mandated school immunization requirements, a proxy measure for lack of vaccination, are at increased risk of contracting measles, and, furthermore, that the greater proportion of vaccine eligible children who are exempted, the larger the effect in the general population assuming random mixing (Salmon et al, 1999).

One of the lines of evidence towards having achieved measles elimination, as defined by the World Health Organization (WHO), is an incidence rate of <1 reported cases per million population annually. Our results showing a strong correlation between incidence above 1 case/million and R_E point estimates closer to the threshold value R_E =1 and support the notion that this WHO target is a good indicator of measles control. Yet, incidence rates higher than 1 case/million may be misleading as they can occur despite elimination being maintained, for example, when the population denominator of a country is small relative to the number of importations (Durrheim, Crowcroft, & Strebel, 2014) or when sizeable outbreaks occur in defined pockets of under-immunization (Heywood, 2009). This phenomenon was evident in Australia in 2006, a year in which measles incidence was reported as 6 cases per million (Heywood, 2009). Over half of the reported cases that year occurred in a specific unvaccinated population attending a spiritual gathering. Similarly, in 2014 in the US, the measles incidence was 2.08 cases per million, yet one measles outbreak in a highly unvaccinated Amish population accounted for close to 60% of cases that year, and endemic transmission of measles did not occur.

Several limitations of this analysis should be considered. First, estimates of R_E by the first three methods are under the assumption of homogeneity in immunity and contact rates. In the US, however, increases in transmissibility likely reflect clusters of undervaccination rather than more homogenous susceptibility as suggested by the fourth method. In this regard, temporal changes in transmissibility may occur by chance, for example, measles being introduced into larger pockets of under-immunization populations in more recent years; thus continued monitoring is warranted. National measles immunization data only assessed coverage of a small segment of the population and do not reflect heterogeneity in coverage at the local levels so we were unable to fully quantify the impact of vaccination rates on measles transmissibility. Because R_E estimates are truncated at the critical value of 1, and because $R_{E(index)}$ could only be estimated for a number of years, we could also not fully assess the relationship between elimination and an incidence of 1 case per million population. Finally, the possibility of reporting changes should be considered, in particular the data quality and completeness for the earlier years, although sustained surveillance adequacy has been documented and measles is a nationally-notifiable disease.

By examining R_E in the United States over the years, we found that elimination of endemic transmission of measles was likely achieved in 1997, and that it has been maintained ever since. The conditions that led to elimination included a 2-dose measles vaccination schedule; the allocation of federal funds for vaccine purchase which closed immunity gaps; state legislation making immunizations a requisite for school attendance; and the development of high-quality surveillance systems and strong outbreak response to measles cases. Although elimination was attained when 90% of children between 18 and 36 months were immunized against measles, immunization policies aimed to achieve 95% measles vaccine coverage levels are warranted to address outbreaks amongst growing under & unvaccinated sub-populations. The suggested increases in transmissibility in recent years may point to increased susceptibility in these subpopulations. Our findings emphasize the importance of maintaining high and broad measles vaccination coverage, of continued monitoring of measles transmissibility in the US, of remaining vigilant of measles to expedite containment strategies, and of supporting other nations in their elimination efforts for eventual eradication.

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Feliz cumpleaños papi.

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FIGURES

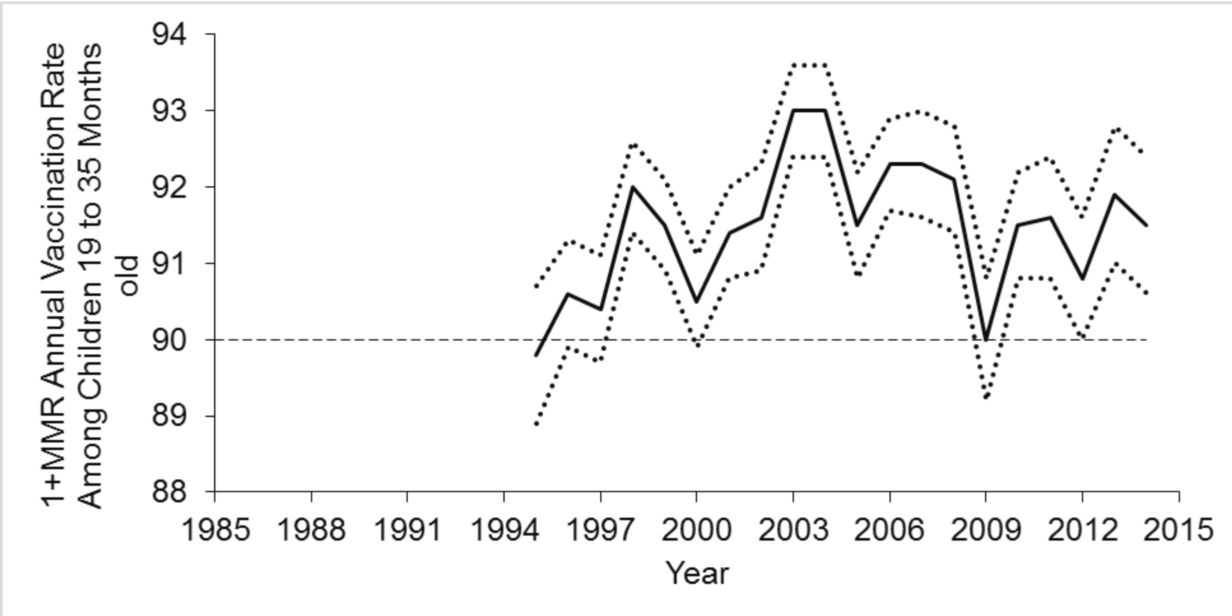

Figure 1. Annual MMR vaccination coverage in the United States, 1995 to 2014. The dark line indicated the annual measles vaccination coverage for children 19 to 35 months old and the dotted line indicates the 95% confidence Interval; the dashed line indicates a vaccination coverage of 90%.

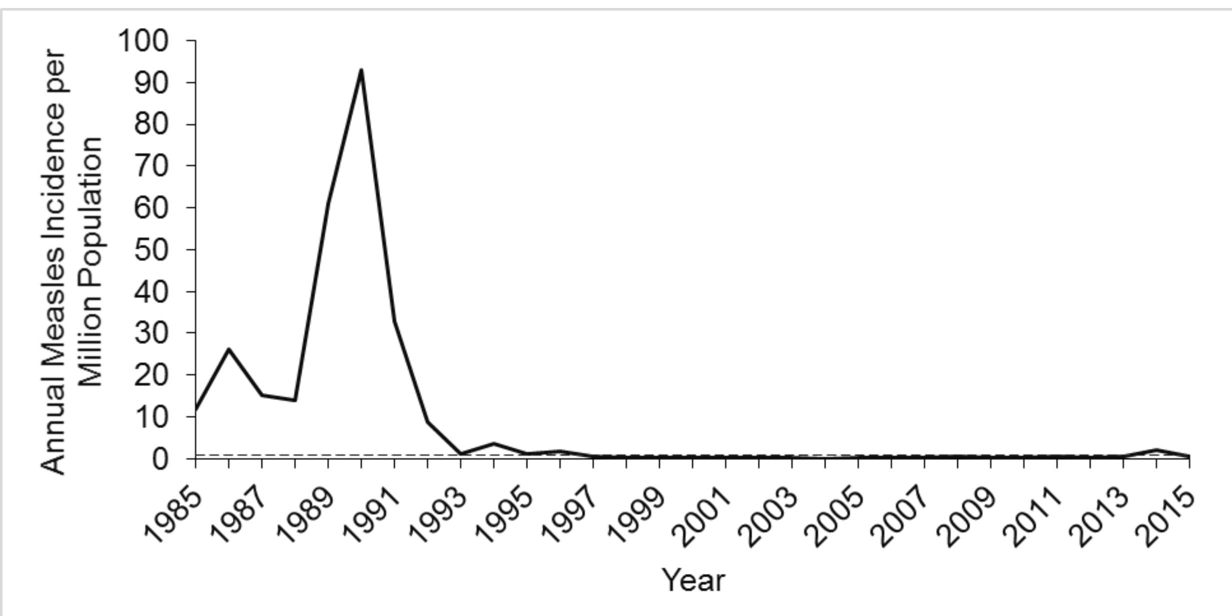

Figure 2. Annual measles incidence in the United States, 1985 to 2015. The dark line indicated the annual measles incidence per million population and the dashed line indicates an incidence of

1 case per million population; an annual incidence of <1 case/million is one of the lines of evidence of the absence of indigenous measles transmission.

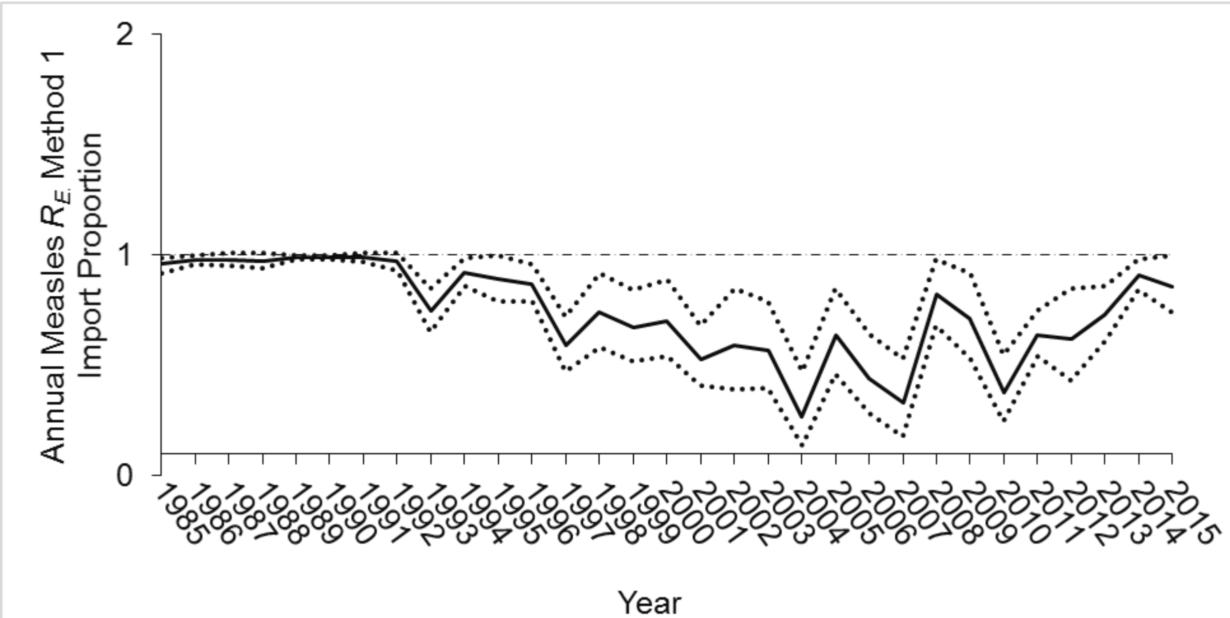

Figure 3. Annual estimates of the net or effective reproduction number, *R*, in the United States, 1985 to 2015, based on the proportion of cases imported. The dotted line indicates the 95% confidence interval around the *R* estimate, and the dashed line indicates the threshold value *R*=1.

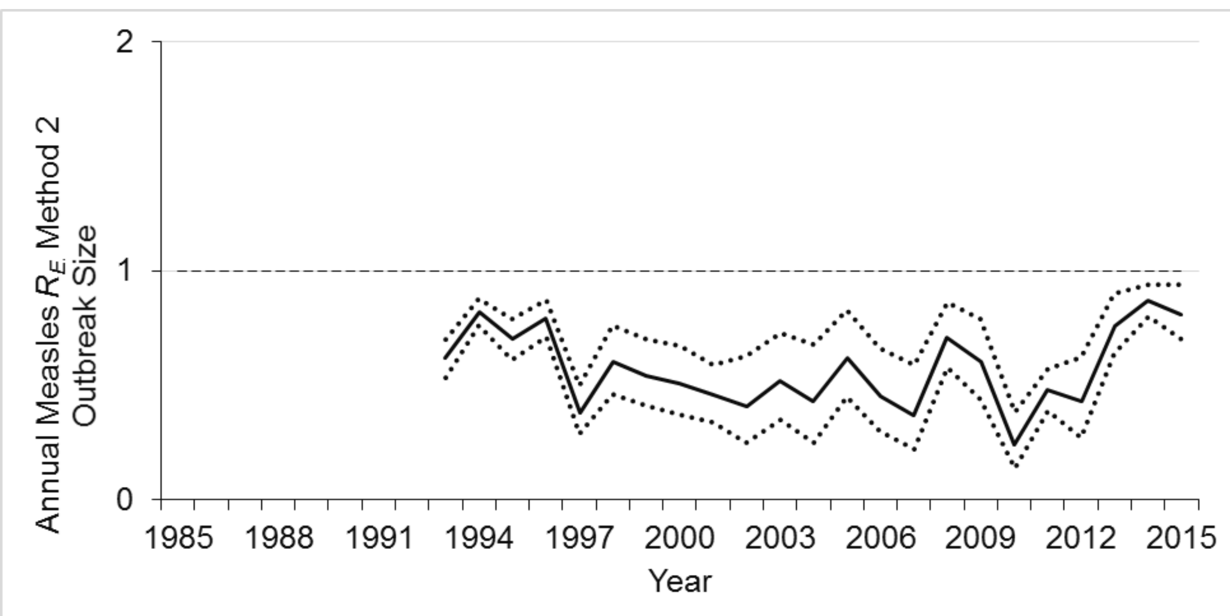

Figure 4. Annual estimates of the net or effective reproduction number, *R*, in the United States, 1985 to 2015, based on the distribution of outbreak sizes. The dotted line indicates the 95% confidence interval around the *R* estimate, and the dashed line indicates the threshold value *R*=1.

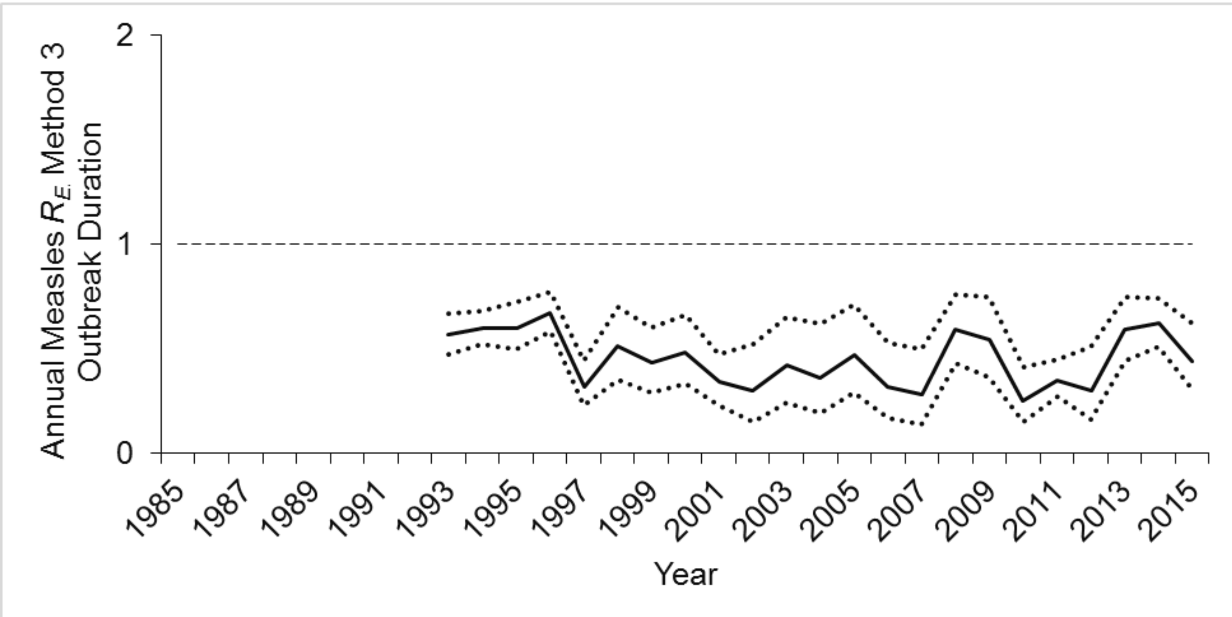

Figure 5. Annual estimates of the net or effective reproduction number, *R*, in the United States, 1985 to 2015, based on the distribution of outbreak durations. The dotted line indicates the 95% confidence interval around the *R* estimate, and the dashed line indicates the threshold value *R*=1.

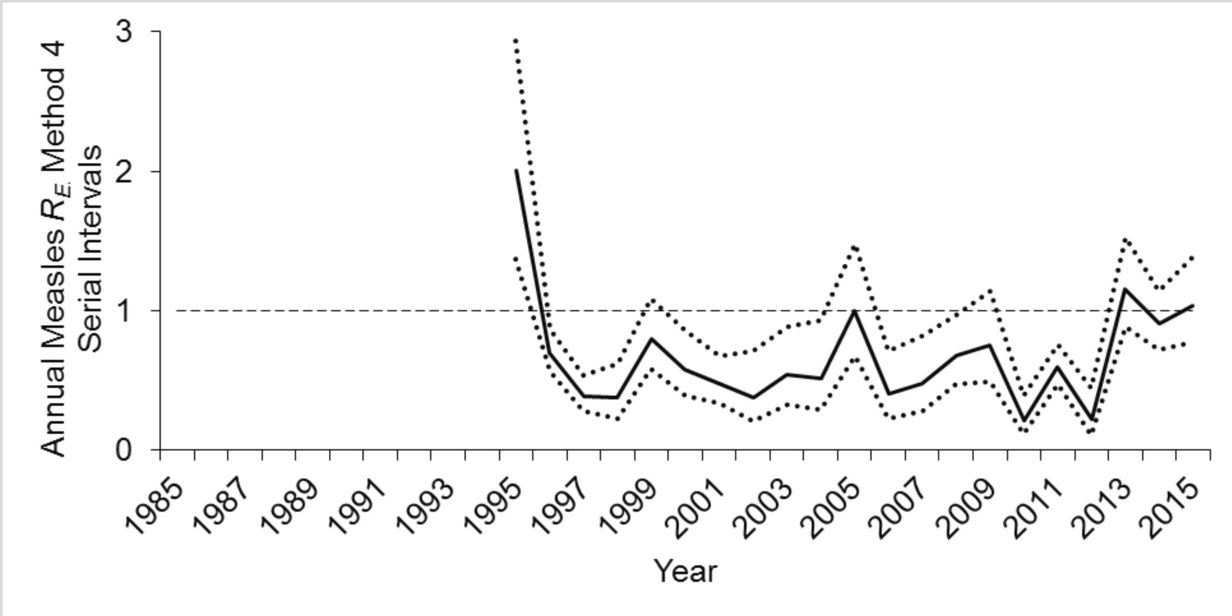

Figure 6. Annual estimates of the net or effective reproduction number, *R*, in the United States, 1985 to 2015, based on the distribution of serial intervals. The dotted line indicates the 95% confidence interval around the *R* estimate, and the dashed line indicates the threshold value *R*=1.

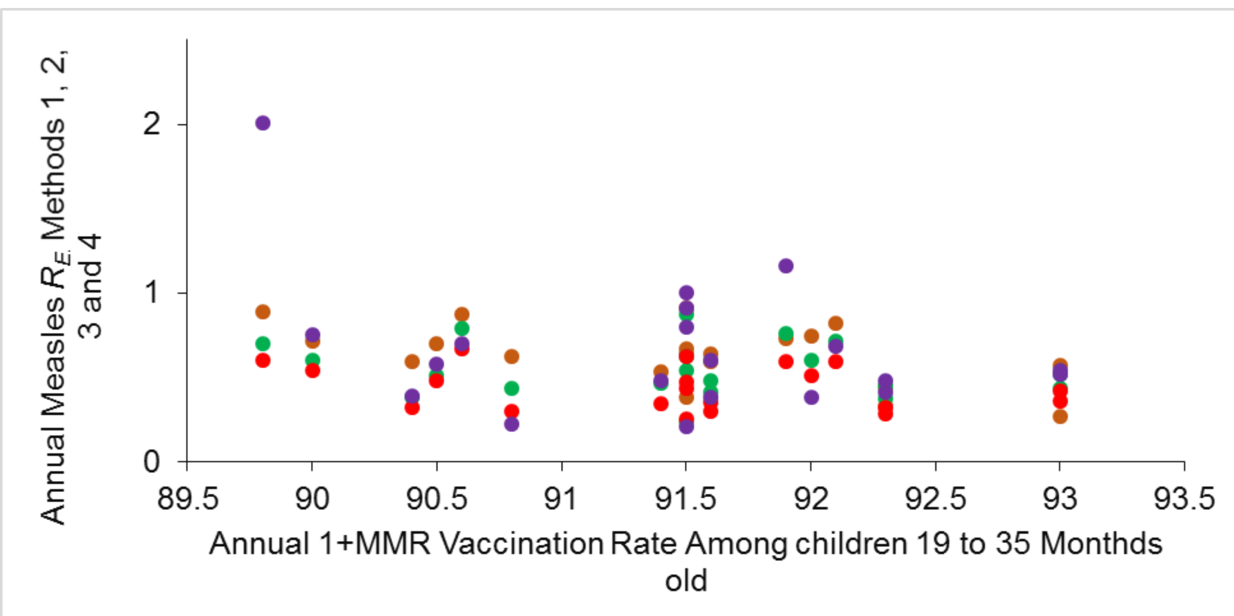

Figure 7. Scatter plot of the net or effective reproduction number, *R*, and MMR vaccination coverage, in the United States, 1995 to 2014. *R* is based on the proportion of cases imported and

coverage data is 1-dose measles vaccination coverage among children 19-35 months of age from the National Immunization Survey. R^2=0.088, F=7.42, P-value=0.008.

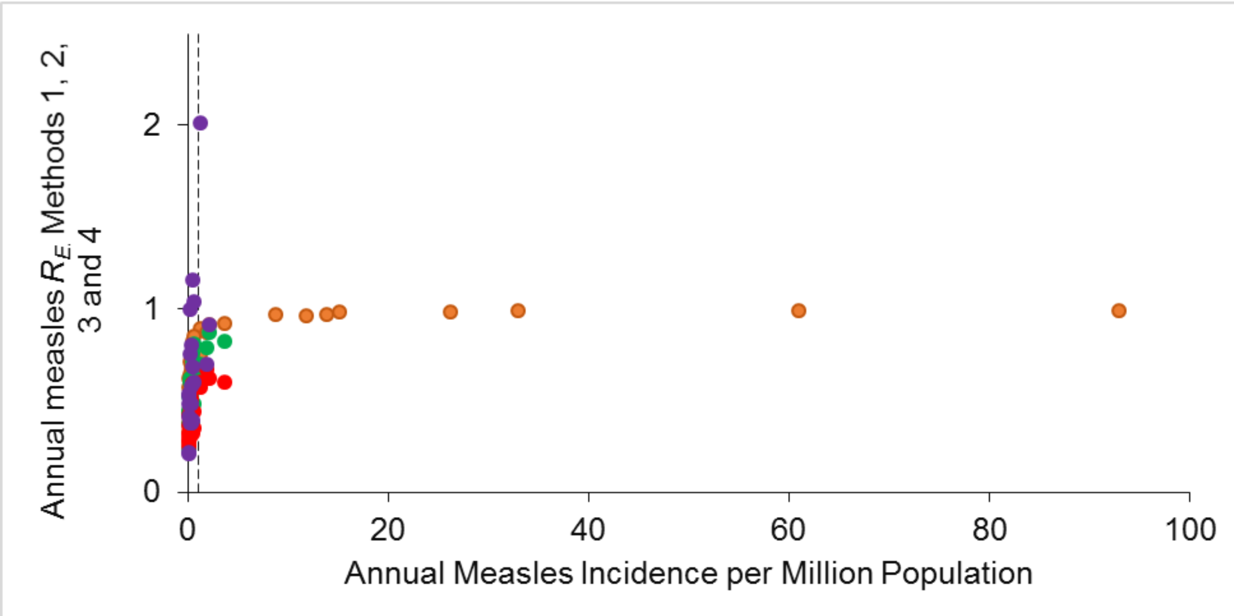

Figure 8. Scatter plot of the net or effective reproduction number, *R*, and measles incidence in the United States. *R* is based on the proportion of cases imported.