Open Forum Infectious Diseases
MAJOR ARTICLE

# Heterogeneity Between States in the Health and Economic Impact of Measles Immunization in the United States

**Angel Paternina-Caicedo,[1] Julia Driessen,[1] Mark Roberts,[1] and Willem Gijsbert van Panhuis[2]**

Departments of [1]Health Policy and Management and [2]Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania

***Background.*** Vaccines have been used successfully for disease elimination programs in many countries. Evidence on the impact of vaccination programs can support decision-making among medical practitioners and policy makers to improve immunization rates. We estimated the health and economic impact of measles vaccination for each of the 48 contiguous states and the District of Columbia since 1964.

***Methods.*** For each state, we fitted multiple time-series models to prevaccination data and used the best-fitting model to predict counterfactual cases that would have occurred in the absence of vaccination. We then subtracted observed from counterfactual measles cases, deaths, and related costs to estimate the impact of vaccination.

***Results.*** We estimated that 149 million children were vaccinated against measles in the United States between 1964 and 2014, at a cost of $12.2 billion, and that vaccination prevented 29.8 million cases, 32 000 deaths, and $25.8 billion in societal costs. The impact exceeded the national average in 70% of Western and Northeastern states, compared with only 24% of Southern and Midwestern states.

***Conclusions.*** The significant health and economic benefit of measles vaccination in the United States should encourage continued investments to sustain and expand vaccination programs globally.

**Keywords.** measles; measles vaccine; vaccine impact.

Measles vaccination is one of the most successful public health programs worldwide and has prevented an estimated 17.1 million deaths between 2000 and 2014. In the United States alone, vaccination has prevented an estimated 0.5–3.8 million measles cases per year [1–4]. Despite a declaration of measles elimination in the United States in 2000, vaccine hesitancy and reintroductions of the virus have led to continued outbreaks [5, 6]. At least 40% of measles cases in the United States from 18 outbreaks that occurred between 2000 and 2015 were unvaccinated [7]. In 2017, Minnesota experienced its largest measles outbreak since 1990, 79 cases occurred in a community where vaccination rates had dropped to 42% [8].

Vaccine regulations can vary between states, leading to heterogeneity in vaccination coverage rates and in the risk of disease outbreaks. For example, California and Vermont have recently enacted legislation to end personal belief exemptions [9], and Pennsylvania reduced the time allowed for children to get vaccinated to 5 days from school entry, from 8 months previously [10]. Several studies have assessed the epidemiological and economic impact of measles vaccination in the United States at the national level [1–4], but information about the heterogeneity of impact between states is limited.

We estimated the number of cases and deaths prevented, and cost savings, by measles vaccination for each state since the introduction of this vaccine in 1964.

## METHODS

### Data Sources

Project Tycho is a repository for disease surveillance data that contains data for all notifiable diseases in the United States that have been reported provisionally by states to the Centers for Disease Control and Prevention (CDC) on a weekly basis since 1888. Measles cases were available from Project Tycho for 1931–1992, and we used measles cases reported by annual CDC surveillance summaries for 1993–2014 [11]. We excluded Hawaii and Alaska because these states were not included in the national surveillance system until the 1950s. We found that 32% of weekly Project Tycho data were missing, mostly between 1980 and 1992, when case counts were low [1]. Without imputation, nationally aggregated Project Tycho data overestimated CDC national data for some years that had both sources available. We imputed missing weekly Project Tycho counts for each

Received 19 April 2018; editorial decision 30 May 2018; accepted 13 June 2018

Previous presentations. MIDAS Meeting, Atlanta, May, 2017. The Health and Economic Impact of Measles Immunization in the United States: A State-Level Analysis From 1931 to 2014.

Correspondence: W. G. van Panhuis, MD, PhD, 130 De Soto Street, Office A737, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261 (wilbert.van.panhuis@pitt.edu).

**Open Forum Infectious Diseases®**



DOI: 10.1093/ofid/ofy137

state with the average of counts for the preceding and following weeks for which data were available (linear imputation). Our imputed Project Tycho counts likely overestimated CDC data in the vaccination period and would lead to conservative estimates of vaccine impact.

We collected the annual number of measles deaths from the National Vital Statistics System (NVSS) for 1961–2014 and from US vital mortality statistics reports [12] for 1931–1960.

We used national-level cost data for all-cause and measles-specific hospitalization in 1995 [2] and state-specific cost data for all-cause hospitalization between 1969 and 2014 [13, 14] to estimate the direct health care costs of measles disease. We used the health care inflation rate to impute missing cost data between 1931 and 2014. We assumed a higher cost of measles hospitalization and measles-related encephalitis compared with nonhospitalized measles. We used the probability of measles hospitalization as reported by CDC surveillance [15] and the probability of measles-related encephalitis from Zhou et al. [2]. We used state-specific annual income data between 1931 and 2014, as reported by the Bureau of Economic Analysis [16], to estimate indirect costs of measles.

Nationwide coverage data for the measles, mumps, rubella (MMR) vaccine were available for all years between 1931 and 2014, except between 1986 and 1990 (these missing data years were imputed using linear interpolation) [17]. State-specific vaccination coverage rates for 1 dose of the MMR vaccine were available from the National Immunization Survey (NIS) for the years between 1995 and 2014 [18]. In the absence of 2-dose coverage data from NIS, we assumed that 1-dose coverage reported in the NIS was similar to 2-dose coverage. We used the ratio of national and state-specific vaccination coverage rates during the years for which both were available to estimate state-specific vaccination coverage rates for the years 1964–1994 (Supplementary Figure 1). We used the cost per vaccination dose for commercial entities to estimate the cost of vaccination (Supplementary Table 1). In the absence of more detailed information, we assumed that commercial vaccine prices would be representative of the cost of vaccines and also of vaccine delivery in the United States, given that most US vaccines are purchased at discounted prices. Previous studies also used commercial pricing to represent the cost of vaccination [19–21]. We provide additional details about the study methodology in Supplementary Text.

#### Estimation of Counterfactual Cases

We used a time-series autoregressive integrated moving average (ARIMA) model to estimate the counterfactual number of cases and deaths that would have occurred in the absence of vaccination between 1964 and 2014. We separately estimated counterfactual cases and deaths. ARIMA models represent autocorrelation, seasonal patterns, and trends over time and have been used previously to model infectious disease time-series data [22]. Previous studies have used prevaccination data to estimate counterfactual case counts during the vaccination period using a variety of counterfactual models [1, 22, 23]. A vaccine impact model based on prevaccination data compares a population with a vaccination program (vaccination period) with a population without a vaccination program (prevaccination period), and thus estimates an overall impact of the vaccine that includes the direct and indirect (ie, herd immunity) effects of the vaccine [24].

For each state, we fitted 72 different ARIMA models to the first 20 years of the prevaccination data using time as the independent variable and measles incidence rates as the dependent variable (1931–1950). We used each model to predict (out of sample) the last 10 years of the prevaccination data (1951–1960) using time as the independent variable. The 72 ARIMA models comprised every combination of: (1) 6 specifications of the autoregressive component (0–5), (2) 2 specifications of the difference component (0–1), and (3) 6 specifications of the moving average component (0–5). We defined the best model for each state as the model with the lowest mean squared error between the observed and predicted values for the 1951–1960 testing period (Supplementary Table 2 and Supplementary Figures 2 and 3). We then fitted the best model for each state to data from the entire prevaccination period (1931–1960) and predicted the counterfactual case incidence or death rates. We used the lower and upper bounds of the ARIMA 80% confidence interval as the lower and upper uncertainty bounds for counterfactual estimates (Supplementary Figures 4 and 5). The ARIMA confidence interval became wider over time as predictions for years far from the prevaccination period were less certain vs years shortly after the prevaccination period.

The ARIMA model for deaths in South Dakota did not converge due to an extreme observation of 120 deaths in 1934, compared with an average of 6 deaths in other years. Instead of ARIMA predictions, we used the mean prevaccination measles mortality rate and its 95% confidence interval as the counterfactual estimate for South Dakota.

#### Costs of Measles Disease

We used nationwide cost data for 2 types of measles-specific hospitalization: (1) nonencephalitis measles (NEM), that is, uncomplicated measles or measles with diarrhea; and (2) measles encephalitis (EM). We used national cost data available for 1995 to compute the proportion of all-cause hospitalization costs that was spent on each type of measles. We then multiplied these proportions by the all-cause hospitalization costs for each state and year to estimate annual state-level hospitalization costs for each type of measles (Supplementary Figure 6).

We computed the cost related to NEM hospitalizations for each state by multiplying the annual number of measles cases by the probability and cost of NEM. We did the same for EM hospitalizations. We added the costs of NEM and EM hospitalizations to obtain the total direct costs related to measles hospitalization.

We estimated indirect costs related to measles using the human capital approach [25]. We assumed that 1 caregiver would be unable to work for the duration of the average hospitalization period for NEM and EM [2]. We computed the average hourly and daily income per state from annual income information (Supplementary Figure 7) [26], assuming 8-hour work days and 40-hour work weeks. We then multiplied each measles case by the average number of days hospitalized and by the average daily income (Supplementary Text).

We estimated the average direct and indirect cost of a measles case per state and year based on 1000 Monte Carlo simulations of the annual direct and indirect costs of measles, per state, using a gamma distribution. We then multiplied the Monte Carlo cost averages with ARIMA counterfactual case projections to obtain the total direct and indirect cost per state and year. We multiplied the Monte Carlo cost average with the ARIMA counterfactual 80% uncertainty bounds to represent uncertainty bounds of cost estimates. We defined total societal costs related to measles as the sum of direct and indirect costs. We estimated the costs of measles for both the observed and counterfactual scenarios.

#### Costs of the Measles Vaccination Program

The US immunization program included 2 doses of the measles-containing vaccine from 1989 onwards. We assumed that vaccination coverage represented a 1-dose vaccination schedule between 1964 and 1989 and a 2-dose vaccination schedule after 1989. We estimated the costs of the vaccination program per state and year by multiplying the number of births by the vaccination coverage and the vaccine price per dose (Supplementary Text).

#### Health and Economic and Impact of Measles Vaccination

We estimated the epidemiological impact of measles vaccination by subtracting the estimated number of counterfactual cases or deaths from the observed number. We calculated the costs prevented by subtracting the total societal costs of observed measles during the vaccination period and the costs of the vaccination program from the total societal costs of counterfactual cases. We reported all costs in this study in 2014 dollars. We stratified our impact estimates by phase of the vaccination period: (1) the vaccine introduction phase, (2) the 1-dose phase (starting when coverage reached 60% in 1971), and (3) the 2-dose phase (starting with introduction of the second dose in 1990).

We computed the nationwide health and economic impact of vaccination as the sum of all state-level cases, deaths, and costs prevented.

We used the Wilcoxon rank-sum test to estimate the association between the number of cases and costs prevented and state-level income, and between vaccination coverage and state-level income.

#### Sensitivity Analysis

We estimated the impact of measles vaccination for 8 additional scenarios, each using a different imputation method for missing data (substitution with 0s, substitution with a random count of the same week in a different year), and a different model for estimating counterfactual measles cases or measles-related deaths (linear model, prevaccination mean rates) (Supplementary Figure 8).

**Table 1. Observed and Prevented Measles Cases, Deaths, and Related Costs in the United States, With 80% Uncertainty Range**

| | Prevaccination | Vaccination | | | |
|---|---|---|---|---|---|
| | (1931–1963) | Introduction (1964–1970) | 1-dose Vaccine (1971–1989) | 2-dose Vaccine (1990–2014) | Entire Period (1964–2014) |
| Cases, millions | | | | | |
| Observed[a] | 16.81 | 1.14 | 0.39 | 0.05 | 1.57 |
| Prevented | — | 2.49 (0.30 to 8.35) | 10.12 (3.19 to 31.89) | 17.17 (5.59 to 57.60) | 29.78 (9.08 to 97.84) |
| Deaths, thousands | | | | | |
| Observed | 45.52 | 1.19 | 0.28 | 0.11 | 1.59 |
| Prevented | — | 1.46 (–1.18 to 10.50) | 10.51 (–0.28 to 76.48) | 19.61 (–0.11 to 334.61) | 31.57 (–1.57 to 421.59) |
| Health care costs, USD, billions[b] | | | | | |
| Estimated | 4.27 (4.26–4.28) | 0.28 (0.28 to 0.28) | 0.16 (0.16 to 0.16) | 0.03 (0.03 to 0.03) | 0.47 (0.47 to 0.48) |
| Prevented | — | 0.65 (0.09 to 2.14) | 4.86 (1.55 to 15.29) | 16.71 (5.44 to 56.07) | 22.22 (7.08 to 73.50) |
| Lost income, USD, billions[b] | | | | | |
| Estimated | 3.43 (3.42–3.44) | 0.34 (0.34 to 0.34) | 0.16 (0.16 to 0.16) | 0.02 (0.02 to 0.02) | 0.53 (0.52 to 0.53) |
| Prevented | — | 0.90 (0.15 to 2.90) | 4.59 (1.47 to 14.23) | 10.20 (3.36 to 33.60) | 15.69 (4.99 to 50.72) |
| Vaccination costs, USD, billions | | | | | |
| Estimated | — | 0.56 (0.45 to 0.68) | 2.05 (1.64 to 2.46) | 9.54 (7.63 to 11.45) | 12.15 (9.72 to 14.58) |
| Societal cost, USD, billions | | | | | |
| Prevented | — | 0.99 (–0.32 to 4.48) | 7.40 (0.97 to 27.47) | 17.36 (–0.74 to 80.13) | 25.75 (–0.08 to 112.07) |

[a]Observed cases, as reported by the US Centers for Disease Control and Prevention (CDC; data from Project Tycho and the CDC).

[b]Estimated costs due to hospitalization or lost income associated with reported measles cases based on state-level cost estimates.

## RESULTS

Since 1964, 149.4 million (M) children have been vaccinated against measles in the United States at a cost of $12.2 billion, preventing 29.8M cases and 32 000 deaths and saving $25.8 billion in societal costs (Table 1).

### Nationwide Impact

The national average prevaccination measles incidence rate (IR) was 344 cases/100 000 (Table 1, Figure 1). During the vaccine introduction phase, the annual IR dropped by 76% to 83/100 000, and by a further 99% to 0.6/100 000 during the 2-dose phase.

Before vaccination, the national measles-related mortality rate (mMR) was 0.93 deaths/100 000, representing an average of 1379 deaths per year (Table 1). In the 6 years following vaccine introduction, the mMR dropped by 91% to 0.09 deaths/100 000. In the 25 years between 1989 and 2014 (2-dose vaccination phase), only 4 measles-related deaths were reported, on average, per year for the entire United States.

We estimated that $0.6 billion was invested in measles vaccination during the vaccine introduction phase, when 12.7M children were vaccinated; $2.1 billion was invested during the 1-dose phase (45.1M children vaccinated), and $9.5 billion during the 2-dose phase (91.5M vaccinated) (Table 1).

Measles vaccination saved $0.72 per person in the entire population of the United States during the vaccine introduction period. As vaccination coverage improved, cost savings more than doubled during the 1-dose period to $1.71 per person, and tripled to $2.44 per person during the 2-dose period (Table 1). On average, these cost savings represent a return of $2.12 dollars per $1 invested by the United States in vaccination between 1964 and 2014.

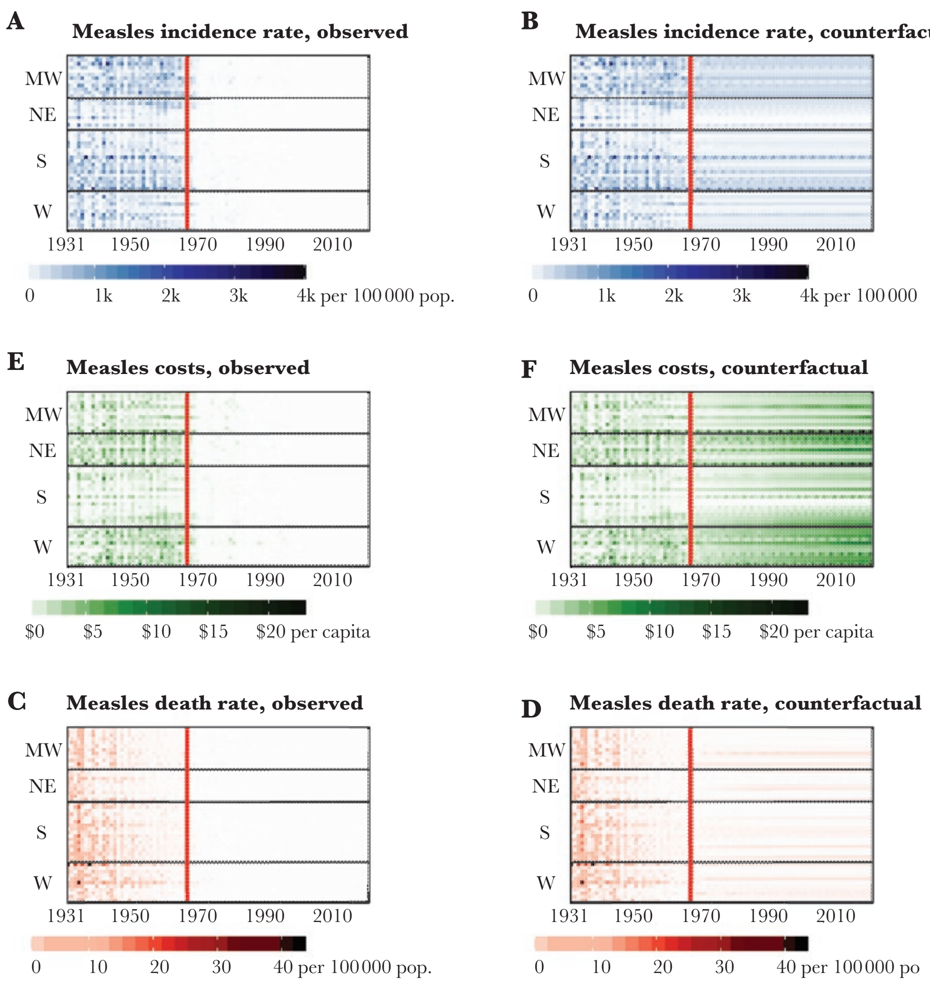


**Figure 1.** Annual state-level observed and counterfactual measles cases, deaths, and societal costs between 1931 and 2014 for each state, ordered by region: Midwest (IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI), Northeast (CT, MA, ME, NH, NJ, NY, PA, RI, and VT), South (AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV), and West (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, and WY). A, the annual observed measles incidence rate (IR). B, The annual observed and counterfactual measles IR, C, The annual observed measles death rate. D, The annual observed and counterfactual measles death rate. The red line indicates the year of vaccine introduction (1964).

**Table 2. Absolute Number of Measles Cases and Deaths Observed and Prevented in the United States Between 1964 and 2014, by Region and State**

| | Cases, 1000s | | Deaths | |
|---|---|---|---|---|
| | Observed | Prevented (80% Uncertainty Range) | Observed | Prevented (80% Uncertainty Range) |
| **Midwest** | 499 | 7350 (2040 to 24 417) | 332 | 4855 (–331 to 68 557) |
| Iowa | 52 | 199 (11 to 943) | 10 | 635 (–10 to 1962) |
| Illinois | 66 | 1135 (292 to 3936) | 97 | 672 (–97 to 8740) |
| Indiana | 52 | 396 (69 to 1590) | 37 | 196 (–37 to 6501) |
| Kansas | 11 | 184 (23 to 1065) | 19 | 160 (–19 to 1736) |
| Michigan | 113 | 1701 (511 to 5182) | 34 | 317 (–34 to 13 296) |
| Minnesota | 10 | 262 (63 to 986) | 18 | 531 (–18 to 3162) |
| Missouri | 12 | 202 (44 to 794) | 35 | 490 (–35 to 9700) |
| North Dakota | 15 | 80 (10 to 353) | 2 | 306 (–1 to 1036) |
| Nebraska | 5 | 77 (12 to 381) | 3 | 347 (–3 to 1203) |
| Ohio | 63 | 1204 (327 to 4027) | 44 | 321 (–44 to 15 378) |
| South Dakota | 3 | 12 (–1 to 139) | 11 | 271 (–11 to 1885) |
| Wisconsin | 97 | 1898 (680 to 5022) | 22 | 607 (–22 to 3958) |
| **Northeast** | 277 | 6750 (2279 to 20 682) | 208 | 9364 (–207 to 39 863) |
| Connecticut | 27 | 613 (224 to 1608) | 12 | 856 (–12 to 2548) |
| Massachusetts | 39 | 1287 (521 to 3108) | 14 | 111 (–14 to 2574) |
| Maine | 11 | 215 (49 to 846) | 15 | 65 (–15 to 1097) |
| New Hampshire | 5 | 66 (15 to 255) | 1 | 7 (–1 to 982) |
| New Jersey | 39 | 1814 (590 to 5429) | 25 | 1718 (–25 to 5531) |
| New York | 98 | 1987 (730 to 5218) | 77 | 6422 (–76 to 20 003) |
| Pennsylvania | 45 | 487 (69 to 3207) | 62 | –50 (–62 to 4078) |
| Rhode Island | 8 | 94 (11 to 529) | 1 | 28 (–1 to 2285) |
| Vermont | 5 | 187 (71 to 482) | 1 | 207 (–1 to 764) |
| **South** | 502 | 7096 (1596 to 29 657) | 783 | 10 551 (–777 to 237 461) |
| Alabama | 29 | 244 (45 to 964) | 44 | 65 (–44 to 4549) |
| Arkansas | 6 | 110 (9 to 978) | 26 | –16 (–26 to 286) |
| District of Columbia | 2 | 42 (9 to 181) | 2 | 28 (–2 to 549) |
| Delaware | 3 | 60 (11 to 276) | 1 | –1 (–1 to 2959) |
| Florida | 31 | 704 (195 to 2332) | 40 | 2983 (–40 to 22 400) |
| Georgia | 6 | 233 (42 to 1126) | 51 | 54 (–51 to 6544) |
| Kentucky | 34 | 600 (105 to 2975) | 48 | 344 (–48 to 5217) |
| Louisiana | 6 | 67 (11 to 297) | 41 | 883 (–41 to 8709) |
| Maryland | 11 | 507 (135 to 1821) | 16 | 1118 (–16 to 4452) |
| Mississippi | 15 | –3 (–14 to 127) | 63 | 446 (–63 to 3396) |
| North Carolina | 9 | 96 (–2 to 1676) | 50 | 220 (–45 to 10 910) |
| Oklahoma | 8 | 159 (41 to 560) | 31 | –15 (–31 to 4123) |
| South Carolina | 10 | 254 (73 to 819) | 47 | 1464 (–47 to 10 887) |
| Tennessee | 55 | 512 (166 to 1397) | 47 | 344 (–47 to 7675) |
| Texas | 204 | 2131 (375 to 9257) | 223 | –102 (–223 to 130 708) |
| Virginia | 37 | 926 (319 to 2560) | 35 | 2435 (–35 to 8418) |
| West Virginia | 34 | 452 (76 to 2310) | 18 | 298 (–18 to 5681) |
| **West** | 291 | 8589 (3160 to 23 086) | 264 | 6823 (–257 to 75 043) |
| Arizona | 22 | 818 (267 to 2419) | 37 | 1523 (–37 to 28 291) |
| California | 125 | 4590 (1884 to 10 922) | 148 | 2077 (–148 to 29 211) |
| Colorado | 19 | 680 (205 to 2160) | 12 | 206 (–12 to 3864) |
| Idaho | 12 | 120 (37 to 347) | 5 | 128 (–5 to 1077) |
| Montana | 17 | 193 (64 to 534) | 6 | 366 (–6 to 1167) |
| New Mexico | 7 | 214 (62 to 696) | 28 | –15 (–28 to 123) |
| Nevada | 3 | 150 (65 to 338) | 3 | 208 (–3 to 3348) |
| Oregon | 21 | 469 (162 to 1288) | 11 | 655 (–11 to 1931) |
| Utah | 13 | 376 (73 to 1732) | 6 | 580 (0 to 2317) |
| Washington | 48 | 894 (312 to 2422) | 7 | 1057 (–7 to 3221) |
| Wyoming | 3 | 84 (30 to 227) | 1 | 38 (–1 to 492) |

### State-Level Impact

Between 1964 and 2014, Western states prevented 8.6M measles cases with vaccination (80% uncertainty interval [UI], 3.2M–23.1M), compared with 7.4M in the Midwest (80% UI, 2.0M–24.4M), 7.1M in the South (80% UI, 1.6M–29.7M), and 6.8M in the Northeast (80% UI, 2.3M–20.7M) (Table 2; Supplementary Table 4). California prevented the most cases of all states (4.6M), followed by Texas (2.1M) and New York (2.0M). After adjustment for population size, states in the West and Northeast prevented 329 and 257 cases/100 000, respectively, compared with lower rates in the Midwest and the South, with 236 and 159 cases prevented per 100 000, respectively (Figure 2). Wisconsin prevented the most cases per 100 000 (745), followed by Vermont (670.4/100 000) (Figure 2). Mississippi was the only state where our models indicated an increase in cases (2/100 000), but only during the introduction phase of the vaccination period (Figure 3). This estimated increase was likely due to underreporting of cases before vaccination (45/100 000 vs 344/100 000 nationally). Underreported prevaccination case counts led to a low number of counterfactual cases and an underestimated impact during the vaccine introduction phase. During the 1- and 2-dose phases, vaccination prevented cases in all states, including 2 and 8 cases/100 000, respectively, in Mississippi (Figure 3).

We estimated that vaccination prevented 10 551 measles-related deaths in the South, 9364 in the Northeast, 6823 in the West, and 4855 in the Northeast (Table 2; Supplementary Table 5). Uncertainty bounds for the number of deaths prevented are wide due to variability in prevaccine count values and uncertainty in ARIMA counterfactual predictions. After adjusting for population size, Northeastern states prevented the most deaths (0.36/100 000), followed by the West (0.26/100 000), the South (0.24/100 000), and the Midwest (0.16/100 000). Interestingly, a Midwestern state (North Dakota) prevented the most deaths per capita with 0.92/100 000, followed by Montana with 0.86/100 000 (Figure 2). Our models predicted a minor increase in measles-related mortality for Arkansas (0.013/100 000), Delaware (0.002/100 000), New Mexico (0.019/100 000), Oklahoma (0.009/100 000), Pennsylvania (0.008/100 000), and Texas (0.011/100 000). For these states, our ARIMA model predicted close to 0 counterfactual deaths after vaccine introduction based on already low mortality in the prevaccine period. Outbreaks continued to occur in the early years of the vaccination period, and deaths that occurred in these years exceeded the very low counterfactual mortality.

Between 1964 and 2014, Southern states invested the most in measles vaccination, $4.4 billion, followed by the West ($2.8 billion), the Midwest ($2.8 billion), and the Northeast ($2.2 billion) (Table 3; Supplementary Table 6). The largest cost savings due to vaccination occurred in Western states, with a total of $8.5 billion saved in total societal cost. After adjusting for population size, Western states invested the most in vaccination with $1.06 per person, followed by Southern states with $0.99 per person. Utah invested the

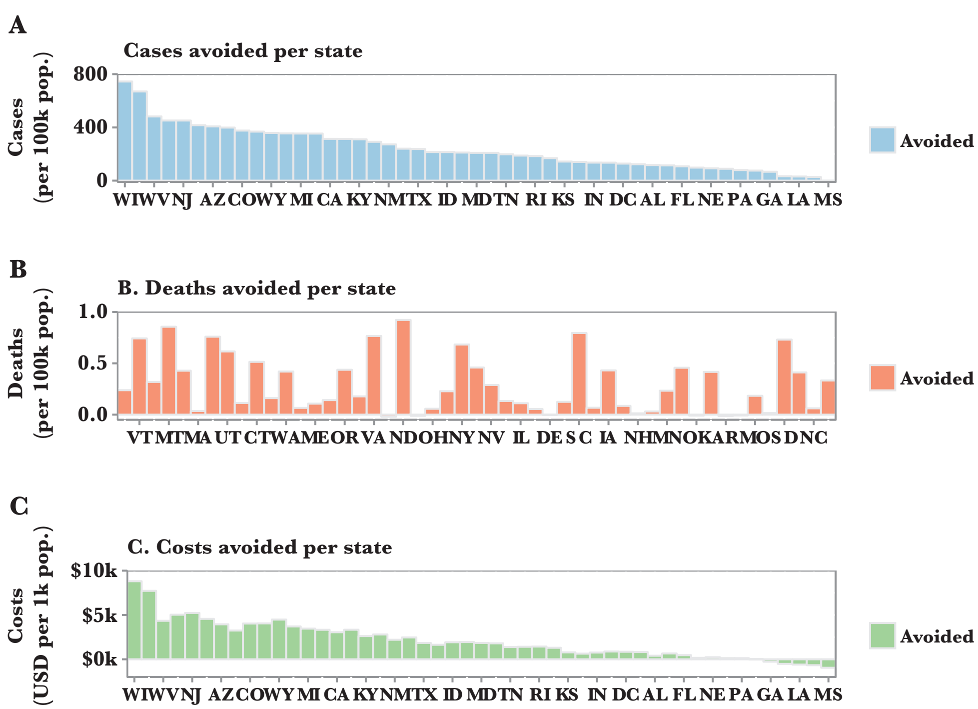


**Figure 2.** Measles cases, deaths, and costs avoided by vaccination in the United States between 1964 and 2014, by state. A, Ranking of states by the number of avoided cases/100 000 (WI, VT, WV, MT, NJ, MA, AZ, UT, CO, CT, WY, WA, MI, ME, CA, OR, KY, VA, NM, ND, TX, US, OH, ID, NY, MD, NV, TN, IL, RI, DE, KS, SC, IN, IA, DC, NH, AL, MN, FL, OK, NE, AR, PA, MO, GA, SD, LA, NC, and MS). B, Avoided deaths/100 000 for states ranked by number of avoided cases/100 000. C, Avoided measles-related.

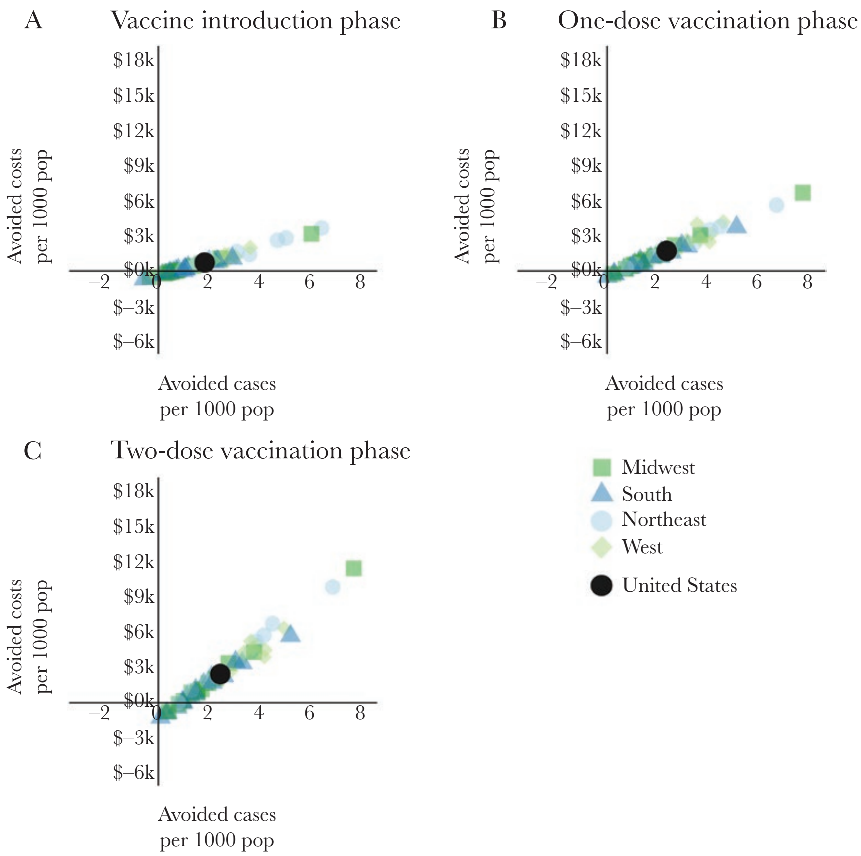


**Figure 3.** Relationship between measles cases and costs avoided by vaccination during different phases of the vaccination period, by region. The right top quadrant of each plot represents cases prevented and cost savings, the right bottom quadrant represents cases prevented at a cost, and the left bottom quadrant represents no cases prevented at a cost. A, Cost savings (/1000 people) by the number of cases avoided by measles vaccination in the United States during the vaccine introduction phase (1964–1970). B, As in (A), but during the 1-dose vaccination phase (1971–1989). C, As in (A), but during the 2-dose vaccination phase (1990–2014).

most in vaccination with $1.42 per person, and West Virginia invested the least with $0.74 per person (Figure 2). The largest cost savings occurred in states that prevented the most cases, that is, Wisconsin ($8.81 per person) and Vermont ($7.72 per person). Four states prevented measles cases but not costs (Georgia, Louisiana, North Carolina, and South Dakota). We estimated that these states prevented between 8.1 (North Carolina) and 1.7 (Georgia) cases/100 000 at a cost ranging from $0.27 (Arkansas) to $0.96 per person (North Carolina) (Figure 2).

We found substantial differences in the health and economic impact of measles vaccination among states. The difference in impact was associated with income. During the 2-dose phase, states with a per-capita income above the national level prevented 12% more cases (95% confidence interval [CI], 11%–12%), 43% more deaths (95% CI, 40%–43%), and 28% more costs (95% CI, 28%–28%) vs low-income states. A higher impact in high-income states is likely due to stronger vaccination programs: High-income states had 0.5% higher vaccine coverage vs low-income states (95% CI, 0.1%–1.7%).

### Sensitivity Analyses

We conducted a sensitivity analysis to compare estimates for cases and costs prevented using different counterfactual models and different imputation methods for missing data (Figure 4; Supplementary Figure 8). The lowest number of cases prevented (21.7M) and the lowest cost savings ($15.5 billion) resulted from imputing missing data with 0s and using the mean prevaccine IR as counterfactual. The highest number of cases prevented (43.9M) and largest cost savings ($43.9 billion) resulted from imputing missing data with linear interpolation and using the mean prevaccine IR as counterfactual.

## DISCUSSION

We found substantial heterogeneity in vaccine impact between states. We found that high-income states prevented more measles cases and deaths and more measles-related costs compared with states with lower income. States with higher incomes would also have higher cost savings, all else being equal, as high-income households would lose more income when a parent stayed home with a sick child. We found substantial variation in the average cost of all-cause hospitalization between states,

**Table 3. Costs From Measles, Investments in Measles Vaccination, and Cost Savings by Vaccine in the United States Between 1964 and 2014, by Region and State**

| | Total Societal Costs From Measles (80% Uncertainty Range), USD, Millions | Vaccine Investment (80% Uncertainty Range), USD, Millions | Total Societal Cost Savings (80% Uncertainty Range), USD, Millions |
|---|---|---|---|
| **Midwest** | 327 (326 to 327) | 2761 (2209 to 3313) | 6363 (–50 to 27 108) |
| Iowa | 31 (31 to 31) | 122 (98 to 147) | 1299 (–84 to 987) |
| Illinois | 47 (47 to 47) | 556 (445 to 668) | 8510 (–172 to 4264) |
| Indiana | 31 (31 to 31) | 261 (209 to 314) | 2230 (–155 to 1611) |
| Kansas | 9 (9 to 9) | 120 (96 to 144) | 1007 (–88 to 1144) |
| Michigan | 76 (76 to 76) | 406 (325 to 487) | 16 620 (244 to 5856) |
| Minnesota | 9 (9 to 9) | 211 (169 to 253) | 1508 (–122 to 1161) |
| Missouri | 8 (8 to 8) | 237 (190 to 285) | 19 (–183 to 703) |
| North Dakota | 9 (9 to 9) | 28 (23 to 34) | 820 (–8 to 439) |
| Nebraska | 3 (3 to 3) | 78 (62 to 94) | 195 (–61 to 396) |
| Ohio | 40 (40 to 40) | 484 (387 to 581) | 9184 (–82 to 4153) |
| South Dakota | 3 (3 to 3) | 36 (28 to 43) | –192 (–36 to 165) |
| Wisconsin | 61 (61 to 61) | 221 (176 to 265) | 22 433 (696 to 6229) |
| **Northeast** | 202 (201 to 202) | 2213 (1770 to 2655) | 6623 (781 to 25 425) |
| Connecticut | 18 (18 to 18) | 138 (110 to 165) | 6745 (165 to 1988) |
| Massachusetts | 26 (26 to 26) | 259 (207 to 311) | 14 099 (418 to 3803) |
| Maine | 6 (6 to 6) | 47 (37 to 56) | 2019 (13 to 929) |
| New Hampshire | 4 (4 to 4) | 47 (37 to 56) | 440 (–26 to 309) |
| New Jersey | 28 (28 to 28) | 352 (281 to 422) | 20 986 (445 to 7062) |
| New York | 80 (80 to 80) | 824 (659 to 989) | 18 269 (135 to 6342) |
| Pennsylvania | 30 (30 to 30) | 483 (387 to 580) | 789 (–414 to 3810) |
| Rhode Island | 5 (5 to 5) | 41 (33 to 49) | 731 (–24 to 592) |
| Vermont | 3 (3 to 3) | 22 (18 to 27) | 2151 (68 to 590) |
| **South** | 273 (272 to 273) | 4399 (3519 to 5279) | 4299 (–2262 to 32 289) |
| Alabama | 14 (14 to 14) | 192 (153 to 230) | 840 (–127 to 852) |
| Arkansas | 3 (3 to 3) | 113 (91 to 136) | 163 (–102 to 1167) |
| District of Columbia | 2 (2 to 2) | 30 (24 to 36) | 278 (–18 to 221) |
| Delaware | 2 (2 to 2) | 34 (27 to 41) | 460 (–18 to 343) |
| Florida | 20 (20 to 20) | 600 (480 to 720) | 3051 (–339 to 2385) |
| Georgia | 4 (4 to 4) | 376 (301 to 451) | –937 (–323 to 989) |
| Kentucky | 18 (18 to 18) | 170 (136 to 204) | 5053 (–48 to 3361) |
| Louisiana | 4 (4 to 4) | 205 (164 to 246) | –1281 (–191 to 127) |
| Maryland | 8 (8 to 8) | 231 (185 to 277) | 4490 (–50 to 2249) |
| Mississippi | 8 (8 to 8) | 133 (106 to 160) | –1283 (–140 to 24) |
| North Carolina | 5 (5 to 5) | 356 (285 to 427) | –2376 (–356 to 1991) |
| Oklahoma | 5 (5 to 5) | 152 (122 to 182) | 261 (–105 to 481) |
| South Carolina | 5 (5 to 5) | 172 (137 to 206) | 1156 (–86 to 751) |
| Tennessee | 26 (26 to 27) | 238 (190 to 286) | 3564 (–25 to 1340) |
| Texas | 107 (107 to 108) | 1032 (826 to 1239) | 16 582 (–470 to 10 514) |
| Virginia | 23 (23 to 23) | 296 (237 to 356) | 8906 (124 to 2974) |
| West Virginia | 18 (18 to 18) | 69 (55 to 83) | 4064 (13 to 2521) |
| **West** | 199 (199 to 200) | 2780 (2224 to 3336) | 8467 (1448 to 27 254) |
| Arizona | 13 (13 to 13) | 229 (183 to 275) | 7918 (110 to 2789) |
| California | 97 (97 to 98) | 1586 (1269 to 1903) | 44 747 (928 to 12 808) |
| Colorado | 12 (12 to 12) | 182 (145 to 218) | 7293 (97 to 2731) |
| Idaho | 8 (8 to 8) | 60 (48 to 72) | 1082 (–4 to 418) |
| Montana | 12 (12 to 13) | 36 (29 to 43) | 2152 (51 to 652) |
| New Mexico | 4 (4 to 4) | 81 (65 to 98) | 1731 (–5 to 739) |
| Nevada | 3 (3 to 3) | 79 (63 to 95) | 1299 (13 to 390) |
| Oregon | 12 (12 to 12) | 131 (105 to 157) | 4996 (95 to 1583) |
| Utah | 8 (8 to 8) | 134 (107 to 161) | 3060 (–43 to 1885) |
| Washington | 28 (28 to 28) | 240 (192 to 288) | 9339 (183 to 2932) |
| Wyoming | 2 (2 to 2) | 22 (18 to 26) | 1056 (24 to 326) |

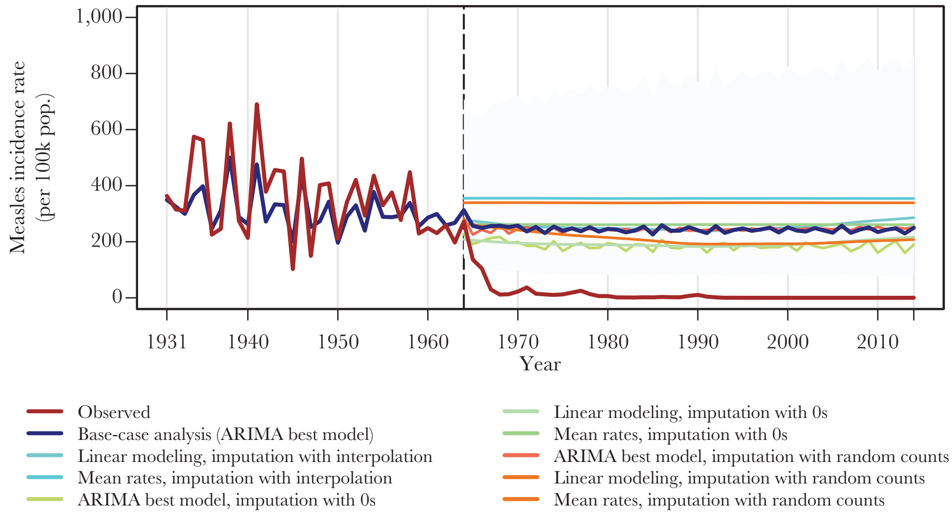


**Figure 4.** Observed measles incidence rate and counterfactual incidence rates resulting from our default and alternative imputation and counterfactual models. All incidence rates (IRs) resulted from combining state-level rates into a national-level overview. Observed measles IRs (/100 000) and fitted values from the best autoregressive integrated moving average (ARIMA) models are shown for the prevaccination period (pre-1964). For the vaccination period, observed values and counterfactual IRs are shown resulting from our default model and various combinations of alternative imputation and counterfactual models. The 80% confidence interval of counterfactual IRs from our default ARIMA models are shown in shaded blue.

from $3104 per hospitalization in the District of Columbia to $4891 per hospitalization in Wyoming for the 1964–2014 vaccination period. We did not, however, find a statistically significant association between hospitalization cost and income for states between 1964 and 2014, meaning that differences in hospitalization cost would not explain the heterogeneity of vaccine impact between states. Higher income may explain a higher economic impact of vaccination in high-income states but would not explain the higher number of cases and deaths prevented. We found that high-income states also had higher vaccination coverage compared with low-income states (in the 2-dose phase for which state-level vaccination data were available), suggesting a more effective vaccination program in such states. Other factors could also explain heterogeneity in impact between states, such as population density, level of urbanization, and improved clinical treatment. Indeed, the number of cases prevented did not follow the same pattern as the number of deaths prevented among states due to differences in the prevaccination measles case fatality rate (CFR) among states. The prevaccine CFR ranged from an average low of 0.06% in Wisconsin to a high of 3.66% in Mississippi (Supplementary Figure 9). Differences in CFRs can be caused by a variety of factors, including heterogeneity in access to health care between states and heterogeneity in the decline of measles mortality before vaccination due to improvements in nutrition, housing, sanitation, and other factors [23, 27].

Previous studies at the national level have estimated that measles vaccination in the United States has saved $8–$11 billion and has prevented 0.5–3.8 million cases per year [2–4, 28–31]. Many studies have estimated counterfactual cases based on the average IR during the prevaccination period, and some have used an expansion factor to account for underreporting. Limited historical data about underreporting at the state level have prevented us from using an expansion factor, leading to more conservative estimates by our study.

Our study had several limitations. A lack of impact was most likely due to underreporting of measles IRs before vaccine introduction and to uncertainty in the ARIMA model fit. For example, the reported prevaccination IR in Mississippi was 87% lower (44/100 000) compared with the national average of 344/100 000. When we substituted prevaccine measles IRs for states with IRs below the fifth percentile of the national distribution, with the national average IR, the nationwide impact increased to 30.8 million cases and $26.2 billion prevented. As done in previous vaccine impact studies [1, 22, 23], we based our impact model on comparing measles incidence rates before and after vaccine introduction, assuming that all other factors remained unchanged before and after vaccine introduction. Other factors, such as better health care or reducing birth rates, have likely contributed to the decline of infectious diseases, but a lack of detailed information about such factors has limited the possibility of disentangling the impact of vaccination from other factors. Recent studies using mathematical modeling of national-level data have started to disentangle the effect of demographic changes and vaccination on the decline of measles, showing that almost half of the decline in measles incidence in high-income countries could be explained by the reduction in fertility rates [32, 33]. Future studies should be able to disentangle vaccination from demographic and other effects at the state and local levels as well, when detailed historical information about demographic changes and social determinants of health become available for research. Although extrapolations are difficult to make without sufficient information, even if half of the decline in measles in the United States could be attributed to demographic changes, the prevention of 15 million cases, 15 thousand deaths, and $13 billion in cost could be attributed to vaccination.

The US measles vaccination program was cost saving. Other medical interventions, such as screening programs, can avoid disease, but often at a cost. For example, the breast cancer screening program is estimated to cost a net of $17 050 per life-year saved [34], and combination antiretroviral therapy for HIV-infected patients costs $29 000 per quality-adjusted life-year gained [35]. Measles vaccination saved $821 per case prevented instead of costing money.

In conclusion, the substantial human impact and cost savings of measles vaccination in the United States should motivate parents and policy makers around the world to participate in, sustain, and expand vaccination programs toward measles elimination. The differences in vaccination impact across states should encourage all of us to strive for equal vaccination coverage and equal access to vaccination services throughout the United States and worldwide.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Acknowledgments

We would like to thank Anne L. Cross and Michael Sharbaugh at the University of Pittsburgh Graduate School of Public Health for their support with data preparation and analysis. We would like to thank Dr. Elizabeth Van Nostrand for her editorial suggestions to improve the manuscript.

***Financial support.*** This work was supported by research awards from the Bill and Melinda Gates Foundation (Grant 49276, "Evalation of Candidate Vaccine Technologies Using Computational Models") and from the US National Institute of General Medical Sciences (Grant U54 GM088491, "Computational Models of Infectious Disease Threats"). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

***Potential conflicts of interest.*** We declare no conflict of interest for any author. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. van Panhuis WG, Grefenstette J, Jung SY, et al. Contagious diseases in the United States from 1888 to the present. N Engl J Med **2013**; 369:2152–8.
2. Zhou F, Reef S, Massoudi M, et al. An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. J Infect Dis **2004**; 189(Suppl 1):S131–45.
3. Bloch AB, Orenstein WA, Stetler HC, et al. Health impact of measles vaccination in the United States. Pediatrics **1985**; 76:524–32.
4. Roush SW, Murphy TV; Vaccine-Preventable Disease Table Working Group. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA **2007**; 298:2155–63.
5. Kennedy A, Lavail K, Nowak G, et al. Confidence about vaccines in the United States: understanding parents' perceptions. Health Aff (Millwood) **2011**; 30:1151–9.
6. Godlee F, Smith J, Marcovitch H. Wakefield's article linking MMR vaccine and autism was fraudulent. BMJ **2011**; 342:c7452.
7. Phadke VK, Bednarczyk RA, Salmon DA, Omer SB. Association between vaccine refusal and vaccine-preventable diseases in the United States: a review of measles and pertussis. JAMA **2016**; 315:1149–58.
8. Minnesota Department of Health. Measles (Rubeola). St Paul, MN: Minnesota Department of Health. Available at: http://www.health.state.mn.us/divs/idepc/diseases/measles/stats.html. Accessed 1 June 2017.
9. Mello MM, Studdert DM, Parmet WE. Shifting vaccination politics–the end of personal-belief exemptions in California. N Engl J Med **2015**; 373:785–7.
10. PA Department of Health. School immunizations. **2017**. Available at: https://www.pabulletin.com/secure/data/vol47/47–9/377.html. Accessed 16 February 2018.
11. Centers for Disease Control and Prevention. Summary of Notifiable Infectious Diseases. Atlanta, GA: US Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/mmwr/mmwr_nd/index.html. Accessed 1 September 2016.
12. Centers for Disease Control and Prevention. Publications and Information Products from the National Center for Health Statistics. Vital Statistics of the United States. Atlanta, GA: US Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/nchs/products/vsus.htm. Accessed 1 September 2016.
13. US Census Bureau. Statistical abstracts series. Available at: https://www.census.gov/library/publications/time-series/statistical_abstracts.html. Accessed 8 November 2016.
14. Kaiser Family Foundation. Hospital adjusted expenses per inpatient day. Available at: http://kff.org/other/state-indicator/expenses-per-inpatient-day/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort%22:%22asc%22%7D. Accessed 1 June 2016.
15. Centers for Disease Control and Prevention. Public-sector vaccination efforts in response to the resurgence of measles among preschool-aged children—United States, 1989–1991. MMWR Morb Mortal Wkly Rep **1992**; 41:522–5.
16. US Department of Commerce Bureau of Economic Analysis. Bureau of Economic Analysis. Available at: https://bea.gov/. Accessed 8 November 2016.
17. Hamborsky J, Andrew Kroger M, Charles Wolfe M. Immunology and Vaccine-Preventable Diseases—Pink Book—2015. Washington, DC: Public Health Foundation; **2015**.
18. Centers for Diseases Control and Prevention. Vaccination Coverage | NIS Child. CDC; **2016**.
19. De la Hoz-Restrepo F, Castañeda-Orjuela C, Paternina A, Alvis-Guzman N. Systematic review of incremental non-vaccine cost estimates used in cost-effectiveness analysis on the introduction of rotavirus and pneumococcal vaccines. Vaccine **2013**; 31:C80–7.
20. Jit M, Brisson M, Laprise JF, Choi YH. Comparison of two dose and three dose human papillomavirus vaccine schedules: cost effectiveness analysis based on transmission model. BMJ **2015**; 350:g7584.
21. Zhou F, Reef S, Massoudi M, et al. An economic analysis of the current universal 2-dose measles-mumps-rubella vaccination program in the United States. J Infect Dis **2004**; 189:S131–45.
22. Pezzotti P, Bellino S, Prestinaci F, et al. The impact of immunization programs on 10 vaccine preventable diseases in Italy: 1900–2015. Vaccine **2018**; 36:1435–43.
23. van Wijhe M, McDonald SA, de Melker HE, et al. Effect of vaccination programmes on mortality burden among children and young adults in the Netherlands during the 20th century: a historical analysis. Lancet Infect Dis **2016**; 16:592–8.
24. Halloran ME, Struchiner CJ. Study designs for dependent happenings. Epidemiology **1991**; 2:331–8.
25. Drummond M. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; **2015**.
26. US Department of Commerce Bureau of Economic Analysis. Bureau of Labor Statistics Data. Washington, DC: US Department of Commerce. Available at: https://www.bea.gov. Accessed 1 August 2016.
27. Merler S, Ajelli M. Deciphering the relative weights of demographic transition and vaccination in the decrease of measles incidence in Italy. Proc Biol Sci **2014**; 281:20132676.
28. Whitney CG, Zhou F, Singleton J, Schuchat A; Centers for Disease Control and Prevention. Benefits from immunization during the vaccines for children program era—United States, 1994–2013. MMWR Morb Mortal Wkly Rep **2014**; 63:352–5.
29. Zhou F, Shefer A, Wenger J, et al. Economic evaluation of the routine childhood immunization program in the United States, 2009. Pediatrics **2014**; 133:577–85.
30. Fontanesi J, De Guire M, Kopald D, Holcomb K. The price of prevention. cost of recommended activities to improve immunizations. Am J Prev Med **2004**; 26:41–5.
31. Zhou F, Santoli J, Messonnier ML, et al. Economic evaluation of the 7-vaccine routine childhood immunization schedule in the United States, 2001. Arch Pediatr Adolesc Med **2005**; 159:1136–44.
32. Merler S, Ajelli M. Deciphering the relative weights of demographic transition and vaccination in the decrease of measles incidence in Italy. Proc Biol Sci **2014**; 281:20132676.
33. Trentini F, Poletti P, Merler S, Melegaro A. Measles immunity gaps and the progress towards elimination: a multi-country modelling analysis. Lancet Infect Dis **2017**; 17:1089–97.
34. Melnikow J, Tancredi DJ, Yang Z, et al. Program-specific cost-effectiveness analysis: breast cancer screening policies for a safety-net program. Value Health **2013**; 16:932–41.
35. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness–the curious resilience of the $50 000-per-QALY threshold. N Engl J Med **2014**; 371:796–7.