Impact of Routine Childhood Immunization in Reducing Vaccine-Preventable Diseases in the United States

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abstract

BACKGROUND AND OBJECTIVES: Current routine immunizations for children aged ≤10 years in the United States in 2019 cover 14 vaccine-preventable diseases. We characterize the public-health impact of vaccination by providing updated estimates of disease incidence with and without universally recommended pediatric vaccines.

METHODS: Prevaccine disease incidence was obtained from published data or calculated using annual case estimates from the prevaccine period and United States population estimates during the same period. Vaccine-era incidence was calculated as the average incidence over the most recent 5 years of available surveillance data or obtained from published estimates (if surveillance data were not available). We adjusted for underreporting and calculated the percent reduction in overall and age-specific incidence for each disease. We multiplied prevaccine and vaccine-era incidence rates by 2019 United States population estimates to calculate annual number of cases averted by vaccination.

RESULTS: Routine immunization reduced the incidence of all targeted diseases, leading to reductions in incidence ranging from 17% (influenza) to 100% (diphtheria, *Haemophilus influenzae* type b, measles, mumps, polio, and rubella). For the 2019 United States population of 328 million people, these reductions equate to >24 million cases of vaccine-preventable disease averted. Vaccine-era disease incidence estimates remained highest for influenza (13 412 per 100 000) and *Streptococcus pneumoniae*-related acute otitis media (2756 per 100 000).

CONCLUSIONS: Routine childhood immunization in the United States continues to yield considerable sustained reductions in incidence across all targeted diseases. Efforts to maintain and improve vaccination coverage are necessary to continue experiencing low incidence levels of vaccine-preventable diseases.

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WHAT'S KNOWN ON THIS SUBJECT: The United States childhood vaccination program has dramatically reduced morbidity, mortality, and disability for targeted diseases. Updated estimates of disease incidence and cases averted, reflecting changes in disease epidemiology, vaccine utilization, and vaccine recommendations (based on the 2017 to 2021 schedule), are needed.

WHAT THIS STUDY ADDS: The childhood vaccination program reduced the incidence of all targeted diseases—with reductions ranging from 17% (influenza) to 100% (diphtheria, *Haemophilus influenzae* type b, measles, mumps, polio, and rubella)—and averted >24 million disease cases for the 2019 United States population.

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Childhood vaccination has dramatically reduced morbidity, mortality, and disability caused by vaccine-preventable diseases, with ~21 million hospitalizations, 732 000 deaths, and 322 million cases of disease averted in the United States between 1994 and 2013.[1] Among diseases targeted by vaccines recommended before 1980, 3—polio, measles, and rubella—have achieved elimination status as defined by the World Health Organization[2] and 1—smallpox—has been eradicated.[3] Diphtheria and tetanus have declined markedly in incidence with routine immunization and are well controlled,[2] whereas the incidence of pertussis and mumps has declined when compared with prevaccine levels but still fluctuates given periodic outbreaks since vaccination was introduced.[3] The public health burden of diseases targeted in the childhood immunization program between 1980 and 2005, including hepatitis A, hepatitis B, invasive *Haemophilus influenzae* type b (Hib), varicella, and invasive pneumococcal disease (IPD), has decreased by more than 80%[3]; reductions in related nontargeted diseases (eg, acute otitis media caused by *Streptococcus pneumoniae*) have also been observed.[4] After 2005, the routine immunization schedule[5] for United States children ≤10 years of age targeted additional pathogens, such as rotavirus and further pneumococcal serotypes.[5]

This study updates estimates of the reduction in overall and age-specific disease incidence associated with the routine childhood immunization program in the United States (based on the 2017 to 2021 vaccination schedule). This update incorporates changes in vaccine utilization rates and observed incidence of the targeted vaccine-preventable diseases since previous evaluations.[3,6] The present analysis will be of interest to policy makers, public health decision makers, and modelers concerned with public health interventions to minimize the burden of vaccine-preventable diseases. A companion study evaluated the value of the childhood immunization program for the 2017 United States birth cohort.[7]

METHODS

We estimated the epidemiologic impact of the United States routine childhood immunization program (ages ≤10 years) by calculating the percent reduction in overall and age-specific disease incidence rates for each disease targeted by the program. We multiplied the prevaccine and vaccine-era incidence rates (using age-specific data, where available) by 2019 United States population estimates,[8] accounting for underreporting where necessary, to calculate the 2019 clinical disease burden with and without childhood immunization and to estimate the cases averted by vaccination. As in previous studies, we assumed that the difference between incidence rates during these periods was entirely attributable to the childhood immunization program.[3,6]

For the prevaccine period, we estimated disease incidence using published incidence estimates or calculated incidence using published annual case estimates and United States population data from the same period. For the vaccine era, we calculated incidence as the average incidence over the most recent 5 years of available surveillance data; we used published incidence estimates if surveillance data were not available. For both periods, we accounted for underreporting where necessary.

Prevaccine and Vaccine-Era Disease Estimates

Table 1 summarizes the prevaccine and vaccine-era disease incidence sources. Age-specific incidence data were used for all diseases except diphtheria, polio, tetanus, and rotavirus. Incidence of Hib and rotavirus was limited to ages <5 years and diphtheria to ages ≤10 years, given lack of data in older age groups in the prevaccine period and the fact that clinical burden was largely limited to those age groups in both periods. Incidence of measles, mumps, and rubella was included only up to age 40 years, as prevaccine incidence data in ages ≥40 years was unavailable. For pneumococcal pneumonia, pneumococcal acute otitis media (AOM), and rotavirus, resource use estimates (ie, hospitalizations, emergency department [ED] visits, and outpatient visits) are reported instead of incidence and disease cases because of limitations in the source data.

Diphtheria

We obtained prevaccine diphtheria disease incidence for children aged ≤10 years from an economic evaluation by Zhou et al,[9] which estimated incidence from a 1916 to 1919 survey of childhood vaccine-preventable diseases in 31 353 United States children and physician-reported data.[10] We assumed the incidence reported by Zhou et al[9] for ages 5 to 9 years uniformly applied to all children ≤10 years. We calculated vaccine-era incidence among children aged ≤10 years as the average value over the most recent 5 years (2014 to 2018) of available data from the Centers for Disease Control and Prevention (CDC) National Notifiable Disease Surveillance System (NNDSS) reports.[11–15]

TABLE 1 Summary of Prevaccine and Vaccine-Era Disease Incidence Sources

Disease	Dates of Vaccination Program Initiation[a]	Prevaccine Source	Vaccine-Era Source
Diphtheria	1928–1943	Zhou et al[9] citing Ekwueme et al[48]	2014–2018 NNDSS[11–15]
Hepatitis A	1995	1990–1994 NNDSS[16–20]	2014–2018 NNDSS[11–15]
Hepatitis B	1981, 1986	1976–1980 NNDSS[24–28]	2014–2018 NNDSS[11–15]
Haemophilus influenzae type b	1985, 1987, 1990	Zhou et al[29] based on incidence data from 1976–1984	2013–2017 ABC surveillance reports[30–34]
Influenza	1945	Calculated based on CDC estimated cases and cases averted for seasons 2014–2015 through 2018–2019[35–42] and US population size for ages <5 and 5–10 y[8]	Calculated based on CDC estimated cases for seasons 2014–2015 through 2018–2019[35–42] and US population size for ages <5 and 5–10 y[8]
Measles	1963, 1967, 1968	Zhou et al[43]	2014–2018 NNDSS[11–15]
Mumps	1940s, 1967	Zhou et al[43]	2014–2018 NNDSS[11–15]
Pertussis	1914–1941	Age <11 y: Zhou et al[9] citing Ekwueme et al[48]; Age ≥11 y: Roush and Murphy[3] and Cherry[95,b,c]	2014–2018 NNDSS[11–15c]
Streptococcus pneumoniae	2000		
IPD		1997–1999 ABC surveillance reports[57–59]	2013–2017 ABC surveillance reports[60–64]
All-cause pneumonia hospitalizations		Griffin et al[65] based on data from 1997–1999	Tong et al[68] based on data from 2014
All-cause pneumonia outpatient visits		Age <18 y: Kronman et al[66] based on data from 1998–1999; Age ≥18 y: Nelson et al[67] based on data from 1998–2000	Tong et al[68] based on data from 2014
Pneumococcal pneumonia (inpatient and outpatient)		Percent caused by pneumococcus: Age <18 y: 34% from Wahl et al[69]; Age ≥18 y: 27% from Said et al[70]	Percent caused by pneumococcus: Age <18 y: 4% from Jain et al[71]; Age ≥18 y: 7% from Isturiz et al[72]
All-cause AOM outpatient visits		Kawai et al[4] based on data from 1997–1999	Kawai et al[4] based on data from 2012–2014
Pneumococcal AOM outpatient visits		Percent caused by pneumococcus (44%) from Kaur et al[73] based on data from 1995–2001	Percent caused by pneumococcus (21%) from Kaur et al[73] based on data from 2010–2016
Polio	1955, 1961–1963, 1987	Calculated based on 1951–1954 cases from Roush and Murphy[3,d]	2014–2018 NNDSS[11–15]
Rotavirus	1998 (first licensed but withdrawn); 2006	Calculated based on 1993–2002 cumulative risk of event (hospitalization, ED visit, outpatient visit) by age 59 mo without vaccine from Widdowson et al[76]	Calculated based on prevaccine incidence from Widdowson et al[76] and % reduction in events with vaccine from Getachew et al[77] and Krishnarajah et al[78]
Rubella	1969	Zhou et al[43]	2014–2018 NNDSS[11–15]
Tetanus	1933–1949	Calculated based on 1947–1949 cases from Roush and Murphy[3]	2014–2018 NNDSS[11–15]
Varicella	1995	1990–1994 NNDSS[16–20,e]	2014–2018 NNDSS[11-15f]

ABC, Active Bacterial Core; AOM, acute otitis media; CDC, Centers for Disease Control and Prevention; ED, emergency department; IPD, invasive pneumococcal disease; NNDSS, National Notifiable Diseases Surveillance System.

[a] Dates of immunization program initiation correspond to dates of vaccine licensure and/or routine recommended use.[3,96] For additional details on vaccines with multiple dates listed, please see Roush and Murphy[3] and Widdowson et al.[76]

[b] Prevaccine pertussis incidence estimates for ages >10 y were estimated from all cases reported by Roush and Murphy,[3] adjusted to account for the estimate from Cherry[95] that approximately 93% of pertussis infections in the first half of the 20th century were among ages <10 y.

[c] An underreporting factor of 10 was taken from economic evaluations and burden-of-illness studies[53–55] and was multiplied by prevaccine pertussis incidence in ages >10 y and vaccine-era pertussis incidence for all ages; prevaccine incidence from birth to age 10 y (taken from Zhou et al) already accounted for underreporting.[9] This underreporting factor is conservative compared with previous studies that have tested underreporting of pertussis up to 100 to 200 times reported cases among adolescents and adults.[53,55,56]

[d] A prevaccine underreporting factor was calculated based on an estimated 48% of notifiable polio cases being paralytic in 1954.[74] This implied underreporting factor (1 of 0.48 = 2.1 cases per reported case) was used to calculate the estimated total number of notifiable polio cases (both paralytic and nonparalytic) based on the incidence of paralytic polio reported by Baicus.[75]

[e] The prevaccine underreporting factor (22.2) was calculated from the 1994 NNDSS report,[20] which reported that approximately 3.7 million cases of varicella occurred annually prevaccine, with 4% to 5% of cases reported.[11–15]

[f] Because cases of varicella were not reported by age in 2014 and 2015, the total cases were distributed by age using the same age distribution of cases from 2016 when calculating the age-specific 5-year incidence rate. The vaccine-era underreporting factor (10.4) was calculated based on the underreporting factor used by Roush and Murphy[3] (12.7 = 612 768 cases estimated of 48 445 cases reported by 33 states in 2006), adjusted for 40 states reporting varicella cases in 2015 versus 33 states in 2006 ($12.7 \times 33/40 = 10.4$).

Hepatitis A

We calculated prevaccine hepatitis A incidence using the average number of reported cases between 1990 and 1994 from the NNDSS[16–20] divided by the 1994 United States population for each respective age group.[21] We calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15] A systematic review and meta-analysis of underreporting of hepatitis A in nonendemic countries found that reported hepatitis A cases ranged from 4% to 97% of total estimated cases across 8 included studies, with a pooled proportion of 59%.[22] As a result, an underreporting factor of 1.7 (1/59% = 1.7) was applied for prevaccine and vaccine-era estimates,[22] which is similar to underreporting factors found in other studies.[23]

Hepatitis B

We estimated prevaccine hepatitis B incidence as the average number of reported cases between 1976 and 1980 from the NNDSS[24–28] and calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15] The underreporting factor for hepatitis B (6.5) was obtained from a probabilistic model estimating underreporting of hepatitis A, B, and C.[23]

Haemophilus Influenzae Type b

We obtained prevaccine disease incidence for Hib for children aged <5 years for 1976 to 1984 from an economic analysis by Zhou et al.[29] We calculated overall incidence by summing the incidence values reported separately for Hib-related meningitis, epiglottitis, bacteremia, pneumonia, cellulitis, arthritis, and other invasive diseases reported in Zhou et al.[29] We calculated vaccine-era incidence among children aged <5 years as the average value over the most recent 5 years (2013–2017) of available data from CDC Active Bacterial Core (ABC) surveillance reports.[30–34]

Influenza

For influenza, instead of using data from the period before influenza vaccines were routinely recommended, we estimated prevaccine incidence among children aged ≤10 years by using the number of cases and averted cases estimated by the CDC, assuming all averted cases would have occurred without vaccination.[35–42] Specifically, we summed the number of reported cases to the cases averted by vaccination among children <5 years and children aged 5 to 10 years for 5 recent influenza seasons (2014–2015 to 2018–2019) and then divided the total number of cases by the number of children in the United States in each respective age group for the same period.[8] An average incidence across the 5 years was then calculated for both age groups. For vaccine-era incidence, we used the same source and calculated the average incidence over the same 5 recent seasons (2014–2015 to 2018–2019). Our analyses did not account for the impact of adolescent and adult influenza vaccination or herd immunity in older age groups; therefore, incidence of influenza was restricted to ages ≤10 years, and we attributed all changes in incidence to vaccination in this age cohort.

Measles, Mumps, and Rubella

For measles, mumps, and rubella, we obtained prevaccine disease incidence from Zhou et al.[43–47] For the vaccine era, we calculated incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15]

Pertussis

We estimated prevaccine pertussis incidence for birth to 10 years from 2 economic evaluations of diphtheria, tetanus, and acellular pertussis vaccine, which derived age-specific risk of pertussis from United States data in the 1920s and from Sweden in the 1980s.[9,48] Prevaccine incidence for ages >10 years was calculated using the number of reported pertussis cases estimated by Roush and Murphy[3] for ages >10 years during 1934 to 1943 (before the start of routine pertussis vaccination in the late 1940s) divided by the size of the United States population >10 years old over the same period.[49,50] We calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15] An underreporting factor of 10 was applied in the prevaccine and vaccine eras (Table 1).[51–56]

Streptococcus Pneumoniae

For IPD, we calculated prevaccine disease incidence as the average value from the 1997 to 1999 ABC surveillance reports[57–59] and calculated vaccine-era incidence as the average value from the 2013 to 2017 ABC surveillance reports.[60–64]

For pneumococcal pneumonia, we obtained prevaccine, age-specific, all-cause pneumonia hospitalization rates per 100 000 for the period 1997 to 1999[65] and all-cause outpatient visit rates per 100 000 for the period 1998 to 2000[66,67] (Table 1). For the vaccine era, we used the incidence of all-cause pneumonia from 2014 based on an analysis of a large convenience insurance claims dataset (MarketScan) multiplied by the percentage hospitalized or treated in an outpatient or ED setting taken from the same study.[68] We multiplied the all-cause rates by the prevaccine[69,70] and postvaccine[71,72]

percentage of all-cause pneumonia caused by pneumococcus (Table 1).

For pneumococcal AOM, we used prevaccine, age-specific incidence from 1997 to 1999 and vaccine-era incidence from 2012 to 2014 from a retrospective analysis of the National Ambulatory Medical Care Survey comparing ambulatory visit rates before the introduction of 7-valent and following 13-valent pneumococcal conjugate vaccine.[4] We summed annual rates of physician office, hospital outpatient, and hospital ED visits to calculate a total annual ambulatory visit rate per 1000 children. To calculate pneumococcal AOM burden for each period, we multiplied all-cause rates by the percentage of AOM caused by pneumococcus in the prevaccine period (1995 to 2001) (44%) and vaccine era (2010 to 2016) (21%).[73]

Polio

For polio, we obtained the average number of paralytic poliomyelitis cases for the period 1951 to 1954 (before the introduction of the first polio vaccine in 1955) from Roush and Murphy[3]. We divided the total number of cases by the average United States population size from 1951 to 1954 to estimate an overall incidence rate.[49] Age-specific data were not available in the prevaccine period; therefore, the same incidence rate was used for all ages. A prevaccine underreporting factor of 2.1 was applied (Table 1).[74,75] We calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15]

Rotavirus

We calculated prevaccine estimates of rotavirus-related burden among children aged <5 years using 1993 to 2002 data on the cumulative individual risk of event by age 59 months for events including hospitalizations, ED visits, and hospital or ambulatory outpatient visits.[76] The median values were used to calculate annual probabilities of each type of rotavirus-related resource use. We further assumed rotavirus events were uniformly distributed from birth to age 5 years (Supplemental Table 3). In the vaccine era, we calculated rotavirus-related burden by multiplying prevaccine event rates by the estimated reduction in hospitalizations[77] and reduction in ED and outpatient visits.[78]

Tetanus

We calculated prevaccine tetanus incidence based on the number of cases reported during 1947 to 1949 (before routine vaccination began in the late 1940s[3]) divided by the average size of the United States population during that same period.[49] Data were not available by age in the prevaccine period; therefore, the same incidence rate was used across all ages in the model. We calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15]

Varicella

We calculated prevaccine varicella incidence using the average number of reported varicella cases between 1990 and 1994 (before vaccine introduction in 1995) from the NNDSS[16–20] divided by the 1994 United States population for each respective age group.[20,21] We calculated vaccine-era incidence as the average value over the most recent 5 years (2014 to 2018) of available data from the NNDSS.[11–15] Underreporting factors of 22.2 and 10.4 were applied to prevaccine and vaccine-era incidence, respectively (Table 1).[3,20]

Analyses

We report calculated incidence overall and by age for both the prevaccine and 2019 vaccine-era periods. We calculated the percent reduction in incidence overall and by age group for each disease by comparing the 2 periods. Using 2019 United States population estimates from the United States Census Bureau, we calculated the number of cases of each disease that would be expected in 2019 without and with the routine childhood immunization program and the number of cases of disease averted.

RESULTS

For infants (<1 year), prevaccine annual incidence per 100 000 was highest for pneumococcal AOM (49 324), influenza (18 903), measles (9200), and pertussis (4720) (Supplemental Tables 3–5). For young children (ages 1 to 4 years), as for infants, incidence in the prevaccine period was highest for pneumococcal AOM (15 004–49 324), influenza (18 903), measles (10 641–11 503), and pertussis (4720), as well as for varicella (4519). For school-aged children (ages 5–18 years), prevaccine incidence varied by age group but was highest for influenza (14 066), varicella (389–6480), pneumococcal AOM (4840), and pertussis (131–4720). For adults, prevaccine incidence was highest for pneumococcal pneumonia (29–1553), rubella (300), mumps (99–256), and pertussis (131).

After vaccines were introduced, incidence decreased for all diseases evaluated (Fig 1; Table 2). Incidence was reduced to less than 1 per 100 000 for 6 of the diseases: diphtheria, Hib, measles, polio, rubella, and tetanus. The incidence of mumps was reduced by >99% and varicella by 98%. The incidence of rotavirus-related hospitalizations among children aged <5 years was reduced by 91%; a lower reduction was observed for rotavirus-related ED visits (61%) and outpatient

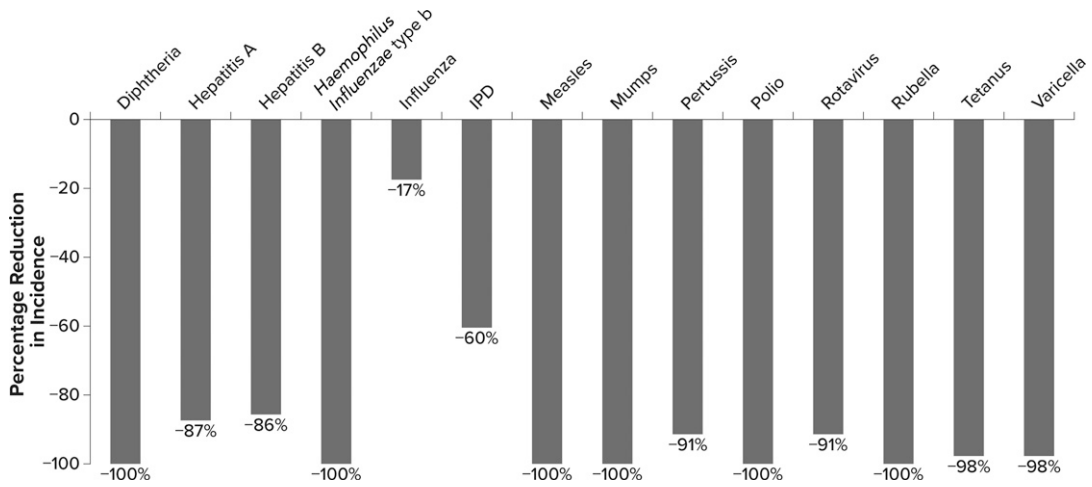

FIGURE 1

Percentage reduction in disease incidence in the vaccine era by disease. Percentage reduction for rotavirus is hospitalizations. IPD does not include pneumococcal pneumonia or acute otitis media. Percentage reductions in disease incidence round up to 100% for several diseases, although there are still some cases in the vaccine era (Table 2). IPD, invasive pneumococcal disease.

visits (45%). The incidence of pertussis was reduced by 91%, hepatitis A by 87%, hepatitis B by 86%, and IPD by 60%. Pneumococcal pneumonia hospitalization rates and outpatient visit rates decreased by 84% and 69%, respectively, and incidence of pneumococcal AOM decreased by 75%. The incidence of influenza among people aged <11 years was reduced by 17%.

For the 2019 United States population of 328 million people, the number of cases of each disease without and with the childhood immunization program and the estimated number of cases averted are shown in Table 2. In the vaccine era with routine immunization, the annual number of cases of disease was 0 for polio, <10 cases per year for diphtheria and rubella, and <100 cases per year for Hib and tetanus. Pneumococcal AOM and influenza represented the largest clinical burden annually (>1 000 000 cases per year), followed by pertussis, pneumococcal pneumonia, outpatient rotavirus gastroenteritis, and outpatient varicella (between 100 000 and 1 million cases per year).

Routine immunization was estimated to avert over 24 million cases of vaccine-preventable disease in 2019 across all age groups, ranging from approximately 1000 cases of tetanus averted to more than 4.2 million varicella cases averted (Table 2). Cases averted were greatest (>1 000 000) for influenza, measles, mumps, rubella, pertussis, varicella, and outpatient visits for pneumococcal AOM.

DISCUSSION

This analysis found that routine childhood immunization in the United States has continued to reduce the incidence of all targeted diseases. Landmark achievements have been the reduction in incidence of diphtheria, Hib, measles, polio, rubella, and tetanus to negligible levels (<1 case per 100 000 population annually); and >90% reduction in incidence for 10 diseases targeted by the routine childhood immunization program for children ≤10 years of age. These reductions equate to the prevention of over 24 million cases of disease for the 2019 US population.

Roush and Murphy[3] evaluated the impact of routine childhood immunization on vaccine-preventable diseases for which recommendations were in place before 2005, using 2006 disease data. Our estimates were generally consistent with the previous results and other published studies,[79] although we estimated a greater reduction in incidence of IPD (60% versus 34%) and of varicella (98% versus 85%). A potential explanation for these differences may be that our analysis used vaccine-era incidence from 2013 to 2017 for pneumococcal disease and from 2014 to 2018 for varicella, capturing the greater impact of the 13-valent pneumococcal conjugate vaccine (recommended in 2010 for infants) compared with the 7-valent pneumococcal conjugate vaccine and capturing the greater impact of 2-dose varicella vaccine compared with 1 dose (second dose added to recommendations in 2007).[80]

With sustained vaccine coverage at levels greater than 80% for most pediatric vaccines (with the

TABLE 2 Prevaccine and Vaccine-Era Disease Incidence Estimates, Annual Cases, and 2019 Cases Averted in the United States by Disease

	Without Immunization		With Immunization		
Disease	Prevaccine Disease Incidence per 100 000[a]	Annual Cases (2019)[b]	Vaccine-Era Disease Incidence per 100 000[a]	Annual Cases (2019)[b]	Cases Averted (2019)
Diphtheria	600	263 000	<1	<1	263 000
Hepatitis A	17	56 000	2	7000	49 000
Hepatitis B	46	150 000	7	22 000	128 000
Haemophilus influenzae type b	92	18 000	<1	<100	18 000
Influenza	1 232	7 115 000	13 412	5 879 000	1 236 000
Measles	2129	3 639 000	<1	<1000	3 639 000
Mumps	1312	2 243 000	2	3000	2 240 000
Pertussis	744	2 442 000	66	217 000	2 225 000
Streptococcus pneumoniae					
IPD	24	79 000	10	31 000	48 000
Pneumonia hospitalizations[c]	152	500 000	24	78 000	422 000
Pneumonia outpatient visits[c]	282	927 000	88	289 000	638 000
AOM[c]	11 141	8 138 000	2756	2 013 000	6 124 000[d]
Polio	21	70 000	0	0	70 000
Rotavirus[c]					
Hospitalizations	340	67 000	29	6000	61 000
ED visits	1072	210 000	420	82 000	128 000
Outpatient visits	2228	436 000	1222	239 000	197 000
Rubella	1124	1 921 000	<1	<10	1 921 000
Tetanus	<1	1000	<1	<100	1000
Varicella	1328	4 359 000	30	97 000	4 262 000

Annual cases are rounded to the nearest thousand. AOM, acute otitis media; ED, emergency department; IPD, invasive pneumococcal disease.

[a] Incidence estimates are adjusted by underreporting factors of 1.7 for hepatitis A, 6.5 for hepatitis B, 10.0 for pertussis (in ages 11 y and older prevaccine and all ages in the vaccine era), 2.1 for polio prevaccine (to capture paralytic and nonparalytic cases), 22.2 for varicella prevaccine, and 10.4 for varicella in the vaccine era (with all other diseases assumed fully reported and/or already adjusted to account for underreporting from the source data).

[b] Prevaccine and vaccine-era case estimates are calculated using 2019 United States population estimates and are rounded to the nearest thousand. For *Haemophilus influenzae* type b and rotavirus, the population size for ages <5 y (n = 19 576 683) was used to calculate annual cases. Annual cases for diphtheria and influenza were calculated using the population size for ages ≤10 y (n = 43 833 518). The population size for ages <40 y (n = 170 936 198) was used to calculate annual cases for measles, mumps, and rubella. For all other diseases, the total United States population size (n = 328 239 523) was used to calculate annual prevaccine and vaccine-era cases.

[c] Rotavirus and pneumococcal disease results are shown separately by healthcare resource use because of a lack of incidence data.

[d] The calculated value for cases averted may not precisely equal the difference between the number of cases in the "with immunization" and "without immunization" period because of rounding.

exception of hepatitis A, rotavirus, and annual influenza vaccine), many vaccine-preventable diseases are now controlled as a public health problem or eliminated in the United States. However, despite significant impact of vaccines, continued risk from these vaccine-preventable diseases remains. When whole-cell pertussis vaccine was withdrawn in Sweden in 1979 because of concerns about safety and efficacy, incidence rates of pertussis similar to those observed in the prevaccine era returned in Sweden within a few years; after introduction of the diphtheria, tetanus, and acellular pertussis vaccine in 1996, incidence rates decreased markedly compared with the 1986 to 1995 10-year period.[81,82] Similarly, despite elimination status being declared for measles in 2000, under-vaccination has led to continued measles outbreaks in the United States, jeopardizing elimination status for the disease.[83–85] Diphtheria outbreaks continue to occur where vaccination rates are low, particularly in areas of social disruption, and are often associated with high rates of mortality.[86,87] The most recent large outbreak occurred in Russia from 1990 to 1997, resulting in ∼115 000 cases and 3000 deaths across the population.[88] These experiences underscore the importance of continued immunization in sustaining reductions in incidence of infectious diseases.

This analysis includes some limitations. First, consistent with previous studies,[3,6] the analysis does not directly account for other public health measures (eg, better sanitation, healthcare access, and improved standards of care) that have been introduced over the past 70 years and likely contributed to the reduction in vaccine-preventable diseases. Furthermore, this analysis did not account for random error in the parameter estimates or account for the proportion of disease incidence reduction that may be attributed to adolescent and adult vaccines or to booster doses. As a result, the analysis may overestimate reductions in burden directly attributable to childhood immunization. Future analyses could address these methodological limitations using time-series analysis to identify and adjust for trends to explore the extent to which adolescent and adult vaccination programs, which have

expanded since 2005,[80,89,90] contribute to reduction in disease incidence.

Second, owing to limited data on differences among racial and ethnic groups, this analysis did not account for racial or ethnic disparities in vaccine coverage and incidence of vaccine-preventable diseases. Evaluating the public health impact of routine immunization among racial and ethnic groups is an important direction for future research. Moreover, this analysis was limited in scope to vaccine-preventable disease for vaccines included in the United States routine childhood immunization program for children ages ≤10 years. Expansion of this analysis to include vaccine-preventable diseases, such as meningococcus and human papillomavirus targeted by routine adolescent vaccines, is another potential area of future research.

Third, because annual incidence varies substantially from year to year for many vaccine-preventable diseases, we have calculated prevaccine and vaccine-era incidence as averages across multiple years, where data allowed. Despite our efforts to estimate average incidence values in both periods, significant epidemics or outbreaks occurred for some diseases that may not be reflected in the annual averages used in this analysis.[91] For the vaccine era, data used to derive disease incidence were for years preceding the coronavirus disease 2019 (COVID-19) pandemic. There are multiple factors that may influence the impact of COVID-19 on the incidence of vaccine-preventable diseases. For example, behavior changes caused by nonpharmaceutical interventions, including lockdowns, face-covering use, and other social distancing measures may reduce the transmission of some diseases, while simultaneously causing disruptions to vaccine uptake and coverage for the pediatric population that may adversely impact the prevention of vaccine-preventable diseases.[92–94] Future surveillance and survey data will help to understand the impact of the COVID-19 pandemic and other potential "shocks" to the immunization program on the transmission of other vaccine-preventable diseases.

CONCLUSIONS

Routine childhood immunization in the United States has continued to reduce the incidence of all targeted vaccine-preventable diseases. In the vaccine era, the incidence of diphtheria, Hib, measles, polio, rubella, and tetanus has been reduced to <1 per 100 000; across all targeted diseases, ~24 million cases have been averted because of vaccination for the 2019 United States population. Routine immunization remains an effective public health intervention to avert disease; maintenance of high rates of vaccination coverage is necessary for sustained impact.

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ABBREVIATIONS

ABC: active bacterial core
AOM: acute otitis media
CDC: Centers for Disease Control and Prevention
COVID-19: coronavirus disease 2019
ED: emergency department
Hib: *Haemophilus influenzae* type b
IPD: invasive pneumococcal disease
NNDSS: National Notifiable Disease Surveillance System

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