Review

Association Between Vaccine Refusal and Vaccine-Preventable Diseases in the United States
A Review of Measles and Pertussis

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IMPORTANCE Parents hesitant to vaccinate their children may delay routine immunizations or seek exemptions from state vaccine mandates. Recent outbreaks of vaccine-preventable diseases in the United States have drawn attention to this phenomenon. Improved understanding of the association between vaccine refusal and the epidemiology of these diseases is needed.

OBJECTIVE To review the published literature to evaluate the association between vaccine delay, refusal, or exemption and the epidemiology of measles and pertussis, 2 vaccine-preventable diseases with recent US outbreaks.

EVIDENCE REVIEW Search of PubMed through November 30, 2015, for reports of US measles outbreaks that have occurred since measles was declared eliminated in the United States (after January 1, 2000), endemic and epidemic pertussis since the lowest point in US pertussis incidence (after January 1, 1977), and for studies that assessed disease risk in the context of vaccine delay or exemption.

FINDINGS We identified 18 published measles studies (9 annual summaries and 9 outbreak reports), which described 1416 measles cases (individual age range, 2 weeks-84 years; 178 cases younger than 12 months) and more than half (56.8%) had no history of measles vaccination. Of the 970 measles cases with detailed vaccination data, 574 cases were unvaccinated despite being vaccine eligible and 405 (70.6%) of these had nonmedical exemptions (eg, exemptions for religious or philosophical reasons, as opposed to medical contraindications; 41.8% of total). Among 32 reports of pertussis outbreaks, which included 10 609 individuals for whom vaccination status was reported (age range, 10 days-87 years), the 5 largest statewide epidemics had substantial proportions (range, 24%-45%) of unvaccinated or undervaccinated individuals. However, several pertussis outbreaks also occurred in highly vaccinated populations, indicating waning immunity. Nine reports (describing 12 outbreaks) provided detailed vaccination data on unimmunized cases; among 8 of these outbreaks from 59% through 93% of unvaccinated individuals were intentionally unvaccinated.

CONCLUSIONS AND RELEVANCE A substantial proportion of the US measles cases in the era after elimination were intentionally unvaccinated. The phenomenon of vaccine refusal was associated with an increased risk for measles among people who refuse vaccines and among fully vaccinated individuals. Although pertussis resurgence has been attributed to waning immunity and other factors, vaccine refusal was still associated with an increased risk for pertussis in some populations.

JAMA. 2016;315(11):1149-1158. doi:10.1001/jama.2016.1353

Editorial page 1115

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Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Vaccine coverage, estimates of the number of people who have received vaccines, remains high among young children for most routine vaccines. For example, in 2013 national coverage was 91.9% for 1 dose or more of measles, mumps, and rubella vaccine, and 83.1% for 4 doses or more of diphtheria, tetanus, and acellular pertussis (DTaP) vaccine.[1] Many childhood vaccine-preventable diseases have been effectively controlled.[2] However, recent outbreaks of vaccine-preventable diseases in the United States have prompted clinicians, public health officials, politicians, the media, and the public to pay greater attention to the growing phenomenon of vaccine refusal and hesitancy.[3-5]

In individual studies, vaccine refusal has been associated with outbreaks of invasive *Haemophilus influenzae* type b disease,[6] varicella,[7] pneumococcal disease,[8] measles,[9] and pertussis.[10] The most direct measure of vaccine refusal is the rate of parents claiming nonmedical exemptions to school immunization requirements. Nonmedical exemptions can include religious exemptions, if a parent feels that immunizations conflict with their religious or spiritual beliefs (eg, objection to the use of fetal tissue in the production of some vaccines), or personal belief exemptions, if a parent objects to immunizations for moral or philosophical reasons (eg, objection to the use of nonnatural products or the total number of vaccines to be administered). Sometimes it is difficult to distinguish between purely religious or philosophical objections to immunization and safety concerns about vaccines that manifest as nonmedical exemptions.[3-5] Over the past 20 years, rates of nonmedical exemptions have steadily increased.[10,11] Initially this increase in exemptions was seen only among states that more readily offered personal belief exemptions (ie, those with easier procedures for obtaining such exemptions).[10] However, more recently, states with moderately difficult exemption procedures and religious exemptions have experienced increases in rates.[12]

An outbreak of measles in late 2014 that originated at Disneyland in Anaheim, California, highlighted vaccine refusal and related disease outbreaks.[13] This outbreak was associated with 111 cases (accounting for two-thirds of the total measles cases reported by April 2, 2015) in 7 US states, Canada, and Mexico.[14,15] Approximately half the cases were among unvaccinated persons, most of whom were eligible for vaccination yet intentionally remained unvaccinated.[14,16] Although previous studies demonstrated associations between rates of nonmedical exemption and the risk of acquiring vaccine-preventable diseases, they have been of varying design (eg, modeling studies) and quality, and did not systematically examine measles (or other vaccine-preventable diseases) and the contribution of refusals to disease outbreaks. This review evaluates the available evidence to characterize the relationship between vaccine refusal and the epidemiology of measles and pertussis, 2 vaccine-preventable diseases with recent outbreaks in the United States.

Methods

Measles

We first searched for US-based measles outbreaks using PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) for studies published through November 30, 2015, using the following search terms: *measles vaccinated "United States," measles unvaccinated "United States," measles outbreak "United States," measles import* "United States," measles case* "United States,"* and *measles MMWR*. We restricted our search to after the measles elimination era (reports published on or after January 1, 2000[17]) to provide the most relevant review of recent measles epidemiology. To evaluate the risk of measles associated with exemptions to vaccine mandates, we also searched using the terms: *measles risk exemption*. For this latter search we used no date restriction because we wanted to capture studies that directly assessed risk related to vaccine exemption, regardless of whether the outbreak occurred before or after elimination.

Pertussis

Unlike measles, pertussis remains endemic in the United States, and its incidence has been steadily rising since it reached a nadir in 1976.[18] To account for this important difference between measles and pertussis, we adapted the search strategy for pertussis as follows: we first searched for US-based pertussis outbreaks, this time restricting our search to reports of nonoverlapping community or state pertussis outbreaks that have occurred since the lowest point in US pertussis incidence (those published after January 1, 1977). We again searched PubMed for studies published through November 30, 2015, using the following search terms: *pertussis epidemic*, *pertussis endemic*, *pertussis outbreak*, and *pertussis MMWR*. To evaluate the risk of pertussis associated with vaccine exemption, we also searched using the terms: *pertussis vaccine refusal*, *pertussis vaccine exemption*, *pertussis vaccine delay*, *pertussis vaccine hesitan**, *pertussis undervaccination*, and *pertussis cluster*. For this latter search we again used no date restrictions to capture studies that may have been published earlier than the start of the pertussis resurgence, because we expected any association between vaccine refusal and disease risk to be similar.

Results

Measles

Recent Epidemiology of Measles in the United States

Measles-containing vaccines were first licensed in the United States in 1963. Following their widespread introduction and 2 intensive elimination efforts over the following 2 decades, the incidence of measles fell dramatically, from more than 300 cases per 100 000 population in the prevaccine era to a median 1.3 cases per 100 000 from 1982 through 1988.[19] From 1989 through 1992 there was a resurgence of measles in multiple countries, including the United States, thought to be primarily due to suboptimal vaccine coverage among preschool-aged children, as well as a small number of vaccine failures after a single dose of measles-containing vaccine. This motivated an intense public health effort to improve vaccine coverage in this age group.[20] A third elimination effort, which started in the 1990s and included formal introduction of a second dose of measles-containing vaccine, further reduced the incidence of measles to less than 1 case per 1 million population by 1997-1999, culminating in successful elimination of endemic measles in the United States by 2000.[17] Since then, there have been a number of measles outbreaks in the United States, without reemergence of indigenous transmission. These importation-related outbreaks (eg, linked to individuals who acquired measles outside the United States and introduced it into their community upon return) totaled fewer than 250 measles cases annually until 2014, when the United States experienced 23 measles outbreaks and the Centers for Disease Control and Prevention (CDC) reported 668 measles cases, the highest number recorded since elimination (Box 1).[15]

Vaccine Refusal and Measles Outbreaks

Using the search strategy for measles outbreaks, a total of 687 articles were identified (eFigure 1A in the Supplement), of which 65 were reports of measles outbreaks between 2000 and 2015. Of these 65 reports, we excluded 34 that were either duplicate reports (eg, a *JAMA* republication of an *Morbidity and Mortality Weekly Report* [*MMWR*] article) or that contained data that were updated or summarized in later reports. Of the remaining 31 reports, we selected 18 to generate a summary of measles outbreaks in the United States from 2000 through 2015 (Table 1).[14,21-37] Nine of these reports are surveillance summary reports from the CDC, summarizing multiple outbreaks during the reporting period.[14,21-24,27,33,34,36] The remaining 9 reports are investigations related to a specific measles outbreak or importation.[25,26,28-32,35,37] The 13 reports not used in the summary of measles outbreaks described individual outbreaks whose case data were captured and/or updated in the other 18 summary reports.

Since January 1, 2000, there were 1416 reported measles cases (individual age range, 2 weeks-84 years; 178 cases younger than 12 months) in the United States associated with outbreaks or periodic summary reports published through November 30, 2015.[14,21-37] A total of 199 cases (14.1%) involved individuals with a history of receiving a measles-containing vaccine, whereas 804 cases (56.8%) involved individuals with no history of receiving a measles-containing vaccine. Additionally, there were 231 cases (16.3%) that involved individuals with unknown history of measles-containing vaccine receipt and 174 cases (16.3%) that involved individuals for whom the reported measles vaccination status did not distinguish between unknown or unvaccinated (eg, reported as "unknown or unvaccinated"). In 7 of these outbreak reports and annual summaries,[14,29,33,34,36-38] there was sufficient information to determine the number of unvaccinated individuals with nonmedical exemptions. In these 7 reports, there were 970 cases, of which 574 cases occurred in unvaccinated individuals who were age-eligible for measles vaccination, and 405 of the unvaccinated individuals (70.6%) were unvaccinated due to nonmedical exemptions (comprising 41.8% of the total cases reported).

There were 18 outbreaks that had sufficient data (ie, day of symptom onset and vaccination status for measles cases) to construct a cumulative epidemic curve (Figure 1).[23,26,29,31,35,37-49] These outbreaks consisted of 145 cases (median cases per outbreak, 6.5 [range, 1-22]); of these cases, 111 individuals were unvaccinated, 11 individuals had unknown vaccination status, and 23 individuals had received at least 1 dose of vaccine. These 145 cases included index cases (ie, the first case to be identified in an outbreak) as well as additional cases that were identified in the course of each individual outbreak investigation. Each outbreak investigation classified individual cases within a specific "generation of spread" based on an established chain of transmission, or by inferring the sequence of transmission based on the date of symptom onset. For example, individuals that developed measles following exposure to the index case were considered to be in the first generation of outbreak spread, those who developed measles following exposure to those in the first generation were considered to be in the second generation of spread, and so on. The outbreaks evaluated in the cumulative epidemic curve included cases that occurred up to 5 generations of spread after the index case, with the latest related case occurring 12 weeks after identification of the index case. When viewed by week of outbreak, unvaccinated individuals constituted a larger fraction of the total measles cases per week in the earliest weeks of an outbreak (eg, earlier generations).

Box 1. Recent Epidemiology of Measles and Pertussis in the United States

Measles

- 1963: Measles-containing vaccines are first licensed in the United States
- 1988: Following the introduction of measles-containing vaccines and 2 measles elimination efforts, measles incidence falls to 1.3 cases per million population
- 1989-1992: Measles resurgence in multiple countries, including the United States, attributed to suboptimal vaccine coverage in preschool-aged children
- 1989: Introduction of a routine second dose of measles-containing vaccines for preschool-aged children and beginning of third elimination effort
- 2000: Measles is declared eliminated from the United States
- 2014: 23 measles outbreaks—including 1 that originated in Disneyland in Anaheim, California—and 668 measles cases are reported in the United States, the largest annual total in the era after elimination

Pertussis

- 1940s: Whole-cell pertussis vaccines come into widespread use in the United States
- 1976: Pertussis incidence reaches a nadir, with only 1010 cases reported in the United States
- 1990s: Acellular pertussis vaccines replace whole-cell vaccines in the immunization schedule
- 2004: 25 827 cases of pertussis are reported in the United States, the largest number since 1959
- 2005: Acellular pertussis vaccines are licensed for use in adults and adolescents (tetanus, reduced diphtheria, and acellular pertussis [Tdap] vaccine)
- 2010: Epidemic of pertussis in California that included 9154 reported cases, with the highest incidence of disease in infants younger than 6 months, followed by children aged 7-10 years; in the latter age group, disease risk was associated with an increasing interval since the last dose of pertussis-containing vaccine
- 2012: Tdap vaccine administration is recommended during every pregnancy
- 2014: Epidemic of pertussis in California that included 9935 reported cases

Vaccine Refusal and Measles Risk

We identified 12 articles using the search for studies evaluating measles risk in the context of vaccine exemption (eFigure 1B in

Table 1. Characteristics of Measles Outbreak and Summary Reports Used to Evaluate Vaccine Refusals Among Measles Cases in the Era After Elimination

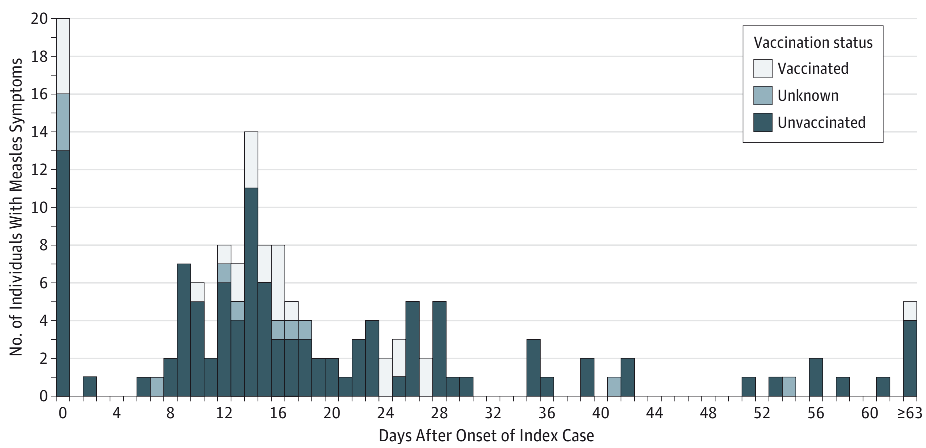
Type of Report	Location	Year(s)	Measles Cases, No.	Vaccination Status Reported	Vaccine Status of Individuals, No.			
					Vaccinated	Unvaccinated	Unvaccinated With NME[a]	Unknown
Summary[21]	Nationwide	2000	86	86	23	40	NA	23
Summary[22]	Nationwide	2001-2003	216	216	42	174[b]	NA	0
Summary[23]	Nationwide	2004	37	35	4	26	NA	7
Summary[24]	Nationwide	2005	66	66	8	50	NA	8
Outbreak[25]	Missouri, California, Washington	2006	3	3	3	0	NA	0
Outbreak[26]	Pennsylvania, Michigan, Texas	2007	7	7	2	3	NA	2
Summary[27]	Nationwide	2008	131	123	11	112	63	0
Outbreak[28]	Arizona	2008	15	15	0	8	NA	6
Outbreak[29]	Pennsylvania	2009	6	6	2	3	2	1
Outbreak[30]	Kentucky	2010	1	1	0	0	NA	1
Outbreak[31]	California, Maryland, North Carolina, Wisconsin	2011	8	8	0	6	NA	2
Outbreak[32]	California	2011	4	4	1	3	NA	0
Summary[33]	Nationwide	2011	222	222	31	144	50	47
Summary[34]	16 US states	2013	159	159	13	131	92	15
Outbreak[35]	Missouri, Minnesota, Washington	2013	4	4	1	3	NA	0
Summary[36]	Nationwide	2014	288	288	30	200	165	58
Outbreak[37]	Florida	2014	5	5	0	4	4	1
Outbreak[14]	Nationwide	2014-2015	159	99	28	71	29	60
Total	**United States**	**2000-2015**	**1416**	**1408**	**199**	**804**	**405**	**231**

Abbreviations: NA, not available; NME, nonmedical exemption.

[a] This column is a subset of the unvaccinated column.

[b] The 2001-2003 report[22] did not distinguish between unvaccinated and unknown vaccination status, therefore the total at the bottom of the column does not include these 174 individuals.

Figure 1. Cumulative Epidemic Curve of 18 Measles Outbreaks From 2000 Through 2015[a]



Day 0 indicates index cases. Median cases per outbreak, 6.5 (range, 1-22).

[a] The cumulative epidemic curve presents data of measles outbreaks for which individual-level day of symptom onset and vaccination status was available (N = 145).

the Supplement). Of these, 10 were excluded: 1 was not published in English, 1 was an outbreak investigation, 5 were vaccine coverage analyses, 1 was a surveillance summary, and 2 were review articles related to the topic. Two studies directly examined the individual and community risks of measles associated with intentionally unvaccinated children (Table 2).[9,50] Both were retrospective cohort studies conducted using measles case data from the era before measles elimination (before 2000), and were therefore not included in our analysis of recent measles epidemiology. The first study used national measles surveillance data reported

Table 2. Characteristics of Studies Used to Evaluate Measles Risk Associated With Vaccine Refusal

Source	Study Design	Period	Location	Data Sources
Salmon et al,[9] 1999	Population-based retrospective cohort study to determine the individual risk for measles among exempt and fully vaccinated individuals; mathematical modeling study to determine the community risk of measles associated with clustering of exempt individuals	1985-1992	Nationwide	CDC Measles Surveillance System and annual state immunization program reports
Feikin et al,[50] 2000	Population-based retrospective cohort study to determine the individual risk for measles (and pertussis) among exempt and fully vaccinated individuals, as well as the association between county-level measles incidence and school-based outbreaks with the rate of vaccine exemptions	1987-1998	Colorado	Colorado Department of Public Health and Environment and annual state immunization program reports

Abbreviation: CDC, Centers for Disease Control and Prevention.

to the CDC from 1985 through 1992, inclusive of the 1989-1992 measles resurgence.[9] In this study, unvaccinated children who had a vaccine exemption were 35 times more likely to contract measles compared with vaccinated children. The epidemic curve of measles determined that the resurgence started a year earlier among children with exemptions compared with vaccinated children.[9] The investigators also used mathematical modeling to determine that the prevalence of exemptions in a geographic region was also associated with disease risk in the nonexempt population in that region, with high local aggregation of individuals with exemptions (ie, clustering) being associated with greater measles incidence. A second study used Colorado measles cases from 1987 through 1998 and found that children with exemptions were 22 times more likely to contract measles than vaccinated children.[50] The absolute and relative risk of disease was highest among individuals with exemptions aged 3 to 10 years. This study also found that the frequency of exemptions at the county level was associated with county measles incidence, though there was no association between schools with higher rates of exemptions and school-based measles outbreaks. Exemptions were more likely to be in the index case and first generation (eg, individuals that acquired measles following exposure to the index case) (14.5%) compared with later generations (eg, those who acquired measles from individuals in the first generation or later rather than the index case) (7.1%). Among vaccinated children who contracted measles, 11% contracted it from an individual with an exemption (Box 2).[50]

Pertussis

Recent Epidemiology of Pertussis in the United States

Unlike measles, pertussis remains endemic in the United States. Following the widespread introduction of whole-cell pertussis vaccines into the routine childhood immunization schedule in the mid-1940s, there was a marked reduction in pertussis incidence, from 150 000 to 260 000 cases annually to a nadir of 1010 cases in 1976.[18] Since then, there has been a steady increase in the incidence of pertussis in the United States,[51-53] with an interepidemic interval similar to the prevaccine era.[54] For the past 10 years, more than 10 000 cases have been reported annually (>25 000 in the last 3 years), matching figures that have not been observed in more than 5 decades (Box 1).[18]

This resurgence in pertussis has been attributed to multiple potential factors. Increased physician awareness and improvements in diagnostic techniques likely contributed to enhanced disease reporting early in the resurgence. Then, beginning in the mid-1990s, acellular pertussis vaccines replaced whole-cell vaccines in the childhood immunization schedule[55]—although these acellular vaccines cause fewer local (eg, pain, swelling, and redness) and systemic (eg, fever and irritability) reactions,[56] they are less effective than whole-cell vaccines for preventing pertussis.[57] More recently, waning immunity to pertussis has been increasingly recognized as an important factor in disease resurgence.[58] Multiple observational studies, spanning epidemic and interepidemic periods, from a variety of geographic regions within the United States, found that a longer interval since receipt of the last pertussis-containing vaccine—including both the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) booster for adolescents or DTaP—was associated with an increased risk of pertussis.[59-64] A recent meta-analysis, which included studies within and outside the United States, estimated that the odds of acquiring pertussis increased 1.33 times for each additional year since the last dose of childhood DTaP.[65]

Vaccine Refusal and Pertussis Outbreaks

In the context of the now well-established association between waning immunity to pertussis and increased disease risk, we sought to identify the contribution of vaccine exemptions to outbreak-related pertussis. Because multiple doses of pertussis-containing vaccine are needed to develop and maintain protective immunity to pertussis, pertussis vaccination status can be classified as completely unvaccinated (ie, having received no doses of pertussis-containing vaccine) or undervaccinated (ie, having received fewer than the recommended number of age-appropriate doses of pertussis-containing vaccine). The Advisory Committee on Immunization Practices currently recommends 5 DTaP doses at age 2, 4, and 6 months, at 15 to 18 months, and again at 4 to 6 years, as well as a Tdap booster in adolescence (between age 11 and 18 years) and adulthood (19 years or older).[66]

We identified 1384 articles pertaining to pertussis outbreaks that have been described since the start of the pertussis resurgence (from January 1, 1977, through November 30, 2015). Of these, we screened 1123 unique titles and abstracts, and excluded

Box 2. Vaccine Refusal and the Epidemiology of Measles and Pertussis in the United States

Measles

- Since measles was declared eliminated from the United States (eg, 2000), 1416 measles cases have been reported in published summaries or outbreak reports, and more than half (56.8%) of these cases had no history of measles vaccination
- Among the unvaccinated, age-eligible measles cases for whom the reason for nonvaccination was available, 405 (70.6%) had a nonmedical exemption to vaccination
- Unvaccinated individuals made up a greater proportion of measles cases in the index or first generation of a cumulative epidemic curve of 18 measles outbreaks
- Children with vaccine exemptions have a substantially greater risk for acquiring measles than fully vaccinated children—in 1 study the risk was 35 times that of the vaccinated population
- Higher rates of vaccine exemption in a community are associated with greater measles incidence in that community, among both the exempt and nonexempt population

Pertussis

- In at least 7 statewide pertussis epidemics and multiple more geographically restricted outbreaks a substantial proportion of pertussis cases in certain age groups were unvaccinated or undervaccinated
- At least 7 pertussis outbreaks have been described in highly vaccinated populations, illustrative of waning vaccine-induced immunity
- Reasons for nonvaccination are infrequently reported in pertussis outbreaks, however in 8 outbreaks, between 59%-93% of the cases were intentionally unvaccinated or undervaccinated
- Individuals with vaccine exemptions have a greater risk for pertussis than those who are fully vaccinated
- Undervaccinated individuals—those who have received fewer than the recommended number of age-appropriate doses of pertussis-containing vaccine—also have an elevated risk for pertussis compared with fully vaccinated individuals
- Schools, communities, and states with higher exemption rates have higher rates of pertussis, including among the fully vaccinated population
- States with allowances for personal belief exemptions or with easier exemption policies have higher incidence rates of pertussis

1028 from further review: these were studies conducted outside the United States, articles focusing on nonpertussis diseases, or papers deemed not relevant to the search query (eg, review articles, editorials, guideline or position statements, studies of vaccine coverage, immunogenicity, or safety, articles on general epidemiology that were not specific to pertussis, basic science studies, and studies on diagnosis, treatment, and prophylaxis of pertussis). After full-text review of the remaining 95 articles, 63 were excluded because they were duplicate reports of the same outbreak or they did not provide data relevant to this review, yielding 32 reports of nonoverlapping community or statewide pertussis outbreaks that we used for this summary (eFigure 2A in the Supplement).[67-98] These reports included 10 609 pertussis cases among individuals for whom a vaccination status was reported (age range, 10 days-87 years).

In the 5 largest statewide epidemics, unvaccinated (or undervaccinated) individuals comprised a substantial proportion of cases in various age groups. For example, investigation of 781 cases during the Arizona pertussis epidemic of 1988 revealed that 33% of the 598 cases involving individuals who were age-eligible to have received at least 3 doses of pertussis-containing vaccine (ie, >6 months) were not appropriately immunized.[73] More recently, during the 2010 California pertussis epidemic, among the 4415 pertussis cases in children aged 6 months to 18 years for whom a vaccination history was available, 2001 children (45%) had not received age-appropriate pertussis-containing vaccines (380 unvaccinated children and 1621 undervaccinated children).[88] Similarly, in Washington in 2012, among 1829 cases in children aged 3 months to 19 years with available vaccination histories, 508 children (28%) were not up-to-date with their pertussis immunizations.[87] Oregon also experienced a pertussis epidemic in 2012, and among the pertussis cases aged 2 months to 6 years, 31% were unvaccinated and 24% were undervaccinated.[92] Finally, during the most recent 2014 California pertussis epidemic, of the 222 cases among neonates and infants under the age of 12 months with detailed vaccine histories only 53 neonates and infants (24%) had received any doses of DTaP, even though more than half (51%) of all the infants in this age group were age-eligible (older than 2 months) for pertussis vaccination.[93]

Similar to the 5 statewide epidemics described above, there were 2 previous statewide outbreaks[68,71] as well as multiple more geographically restricted outbreaks[73,74,83,84,90,92,94] that also had substantial numbers of unvaccinated case patients; however, we also found reports of epidemics within populations with high rates of vaccination coverage,[72,75,80,81,86,89,98] illustrating the important contribution of waning immunity to pertussis to disease epidemiology.[86,98] Importantly, there was substantial heterogeneity among these reports in the criteria used to identify pertussis cases, the types of vaccine available for use at the time (ie, whole-cell, acellular, and adult boosters), the proportion of cases in which an immunization history was available, the methods used to ascertain immunization histories, and how immunization status was described (eg, number of previous doses, above or below a threshold number of doses). In addition, owing to the inherent challenges of accurately identifying and diagnosing pertussis, chains of transmission could not be established in the vast majority of pertussis outbreaks. However, in 2 studies, secondary cases among fully vaccinated individuals, whose immunity had presumably waned and who likely acquired disease from intentionally unvaccinated individuals, were clearly identified.[73,94]

Only 9 reports (describing 12 pertussis outbreaks) characterized the reason(s) that case patients were intentionally unvaccinated or undervaccinated—these reasons included personal belief (or philosophical) exemptions (70% of unvaccinated cases in Oregon in 2012[92]), religious beliefs[68] or exemptions (84% of unvaccinated cases in Florida in 2013[94]; 59%-93% of unvaccinated cases in 4 separate outbreaks in Massachusetts from 1986-1988[74]), cultural norms (72% unvaccinated in an Amish community in Delaware in 2004-2005[84]; 79% unvaccinated in an Amish community in Illinois in 2009-2010[90]), illness at the time a vaccine dose was due,[68,71] inability to appear for the vaccination appointment,[71] or hesitance on the part of the vaccine provider.[68,73]

Vaccine Refusal and Pertussis Risk

We identified 383 articles in the search for studies evaluating the association between nonmedical exemptions to routine vaccination and the individual or community risk for pertussis. Of these, 359 nonduplicate titles and abstracts were reviewed and 350 were excluded, yielding 9 studies that were included in this summary (eFigure 2B in the Supplement).[10,12,50,99-104] The excluded papers included studies not specific to pertussis or to its epidemiology in the United States, review articles, opinion pieces, studies of vaccine effectiveness, immunogenicity, or safety, and articles on the basic science or clinical aspects of pertussis disease.

Three studies evaluated the individual risk of pertussis associated with vaccine refusal—1 retrospective cohort study used Colorado pertussis surveillance and immunization data from 1987-1998 and determined that those with exemptions were 5.9 times more likely to acquire pertussis compared with fully vaccinated individuals.[50] A different case-control study analyzed pertussis cases from 1996-2007 within a large managed care organization and computed a nearly 20-fold increased risk of pertussis among individuals with exemptions[100]—11% of the pertussis cases in that cohort were attributed to vaccine refusal. Another case-control study used pooled longitudinal data (2004-2010) from 8 Vaccine Safety Datalink sites and determined that even undervaccinated individuals had an increased risk of pertussis, with the risk being proportional to the number of missed doses of DTaP.[102]

We also found 6 observational studies that showed that high rates of vaccine exemption in a community or state are associated with an increased risk of pertussis in that community or state compared with communities or states without high rates of vaccine exemptions. For example, 4 different state-specific studies—in Colorado,[50] Michigan,[99] New York,[101] and California (during the 2010 epidemic)[12]—all demonstrated that schools and communities with high vaccine exemption rates also had higher rates of pertussis. The risk for acquiring pertussis was higher even for those who were appropriately vaccinated. More generally, 3 different ecological studies found that states with allowances for personal belief exemptions[10] or those with easier exemption processes[10,104] have an elevated incidence of pertussis (approximately 1.5 times higher in 1 study[10]) compared with states with difficult exemption processes, an association that was confirmed using vaccine-specific uptake data.[103] This geospatial association between clusters of vaccine refusers and pertussis cases cannot be adequately explained by waning immunity because there should not be geographic heterogeneity in the duration of protection afforded by pertussis-containing vaccines. Together these data therefore suggest an association between high rates of vaccine exemption and the sustained transmission of vaccine-preventable diseases in the community (Box 2).

Discussion

In this review, unvaccinated or undervaccinated individuals comprised substantial proportions of cases in measles and some pertussis outbreaks, and vaccine refusal—as measured by population-level vaccine exemption rates—was associated with an elevated risk for measles and pertussis, including among fully vaccinated individuals. However, the available literature also suggests that vaccine refusal is not the only factor associated with outbreaks of vaccine-preventable diseases, and the relative importance of vaccine refusal varies by disease (eg, measles more than pertussis) and epidemiological context (eg, prevalence and density of individuals with exemptions in a community).

There are several limitations to our review. A formal assessment of study quality was not performed. Most, if not all, of the data on measles and pertussis outbreaks can be accessed using publicly available resources. We included several studies that analyzed measles and pertussis disease risk in the context of vaccine exemption rates, and such studies are subject to multiple important biases common to ecological, case-control, or cohort studies, including ascertainment and misclassification bias. However, these limitations would tend to bias estimates of disease risk toward the null (eg, classifying fully vaccinated individuals as exempted would only underestimate disease risk among those with exemptions). Thus the association between high rates of vaccine exemption and measles or pertussis risk is likely to be even greater than that reported in previous studies. In addition, given that the evidence for waning immunity to pertussis has been previously evaluated,[65] and its association with disease resurgence has been established,[59-64] in this review we focused on the additional factor of vaccine refusal.

This review has broad implications for vaccine practice and policy. For instance, fundamental to the strength and legitimacy of justifications to override parental decisions to refuse a vaccine for their child is a clear demonstration that the risks and harms to the child of remaining unimmunized are substantial. Similarly, central to any justification to restrict individual freedom by mandating vaccines to prevent harm to others is an understanding of the nature and magnitude of these risks and harms. However, the risks of vaccine refusal remain imperfectly defined, and the association between vaccine refusal and vaccine-preventable diseases may be both population- and disease-specific. Vaccine refusal–specific strategies to optimize vaccine uptake could include state or school-level enforcement of vaccine mandates, or increasing the difficulty with which vaccine exemptions can be obtained. At the same time, immunization policy makers must also address the reasons for vaccine hesitancy, which may include parental perceptions regarding the risk and severity of vaccine-preventable diseases, the safety and effectiveness of routine immunizations, and confidence in medical professionals, corporations, and the health care system.[105] Recognizing the limitations of the existing evidence should not stifle practitioners' and policy makers' ability to counsel families and craft effective policy, but should serve as motivation to develop, refine, and improve disease surveillance, detection, and outcomes-based research.

Conclusions

A substantial proportion of the US measles cases in the era after elimination were intentionally unvaccinated. The phenomenon of vaccine refusal was associated with an increased risk for measles among people who refuse vaccines and among fully vaccinated individuals. Although pertussis resurgence has been attributed to waning immunity and other factors, vaccine refusal was still associated with an increased risk for pertussis in some populations.

ARTICLE INFORMATION

Author Contributions: Dr Phadke had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Salmon, Omer.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Salmon reports receiving grant funding from Crucell, Pfizer, and Merck and personal fees from Parents of Kids with Infectious Diseases. No other disclosures are reported.

Funding/Support: This work is supported by award T32AI074492 from the Emory Vaccinology Training Program of the National Institute of Allergy and Infectious Diseases (Dr Phadke).

Role of the Funder/Sponsor: The sponsor had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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