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INFECTIOUS DISEASE (MS PASTERNACK, SECTION EDITOR)

The Complexity of the Resurgence of Childhood Vaccine-Preventable Diseases in the United States

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Abstract Vaccines have saved the lives of innumerable children from infectious diseases. In the United States, state mandates for school immunization requirements and federal funding have enabled high immunization coverage and have resulted in historic low levels of many infectious diseases. However, in recent years, there have been widespread outbreaks of a number of vaccine-preventable infectious diseases, including measles, mumps, and pertussis. Reasons for these resurgences vary and are complex. They include decreases in vaccination rates, waning immunity, changes in the vaccine, and changes in the pathogen.

Keywords Vaccine immunizations · Vaccine hesitancy · Vaccine safety · Vaccine-preventable disease · Outbreaks · Measles · Mumps · Pertussis · Pneumococcus

Introduction

In recent years, there have been outbreaks and a rising incidence of certain vaccine-preventable diseases (VPDs). In this review, we will discuss the development of vaccine programs in the US which enabled high vaccine coverage and reductions in VPDs, vaccine hesitancy which has impacted vaccine coverage, and changes in the epidemiology of measles, mumps, pertussis, and invasive infections due to *Streptococcus pneumoniae*.

Infectious diseases were the leading causes of death among US children at the beginning of the twentieth century. Vaccines are credited with preventing an estimated 103 million cases of childhood diseases since 1924 [1••]. The decrease in morbidity from specific VPDs between the "prevaccine era" and 2010 is provided in Table 1. A recent analysis found that by vaccinating a US birth cohort with the currently recommended schedule (excluding influenza, meningococcal, and human papillomavirus vaccines), 20 million cases of disease and 42,000 deaths are prevented; this translates into approximately $13.5 billion of direct cost savings and $68.8 billion in societal cost savings [2]. The 2014 recommended childhood vaccine schedule includes 13 vaccines which aim to prevent 16 infectious diseases, including tetanus, diphtheria, pertussis, poliomyelitis, measles, mumps, rubella, varicella, influenza, and infections from hepatitis A virus, hepatitis B virus, *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, *Neisseria meningitidis*, rotavirus, and human papillomavirus [3].

Several legislative initiatives enabled establishment of high rates of vaccination in children, which have facilitated development of herd immunity. In 1963, Section 317 of the Public Health Service Act provided a mechanism to support health department immunization activities. In 1977, a federal Childhood Immunization Initiative enabled a system to provide comprehensive immunization services. By 1980, all states had school-entry immunization laws which promoted high coverage of certain vaccines at school entry. In 1993, a second Childhood Immunization Initiative was aimed at increasing vaccination rates in preschool-aged children. Also in 1993, the Vaccines for Children (VFC) program provided

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Table 1 Comparison of annual morbidity from vaccine-preventable diseases during the twentieth century and 2010

Disease	Twentieth century[a]	2010[b]	% Reduction
Diphtheria	21,053	0	100
Hepatitis A	117,333	8,493[c]	93
Hepatitis B, acute	66,232	9,419[c]	86
Haemophilus influenzae type b in children aged <5 years	20,000	240[d]	99
Measles	530,217	63	>99
Mumps	162,344	2,612	98
Pertussis	200,752	27,538	86
Pneumococcus invasive			
All ages	63,607	44,000[e]	30
<5 years	16,069	4,700[e]	72
Poliomyelitis, paralytic	16,316	0	100
Rotavirus, hospitalizations	62,500[f]	28,125[c]	55
Rubella	47,745	5	>99
Congenital rubella syndrome	152	0	100
Smallpox	29,005	0	100
Tetanus	580	26	96
Varicella	4,085,120	408,572[c]	90

[a] Estimated annual average number of cases in the prevaccine era for each disease. *Source* Roush et al. [61]

[b] *Source* See reference [62]

[c] 2009 estimate

[d] 23 type b and 223 unknown serotype (among children <5 years of age)

[e] http:/www.cdc.gov/abcs/reports-findings/survreports/spneu09.html

[f] *Source* Cortese et al. [63]

Source Hinman et al. [4, p. 51]

funding for recommended vaccines for Medicaid eligible children, uninsured children, underinsured children if they received vaccines at a Federally Qualified Health Center, and American Indians/Alaskan Natives [4•].

Although these programs have resulted in high coverage at school entry (CDC estimates 95 % for recommended vaccines [4•]), many children do not receive vaccinations on time. A study in Chicago, which examined vaccination records of more than 66,500 children completing kindergarten in 2001–2002, found that only 31 % at 7 months of age and 59 % at 36 months of age had received all recommended immunizations on time. In addition, there were significant racial disparities with 25 % of black children receiving vaccinations more than a year after the recommended age [5]. On-time vaccination is important to protect children from VPDs.

Widespread use of vaccines has resulted in substantial decreases in certain infectious diseases. Notably, smallpox has been eradicated from the world; measles, rubella, and congenital rubella syndrome have been eliminated (this can include imported cases with limited local transmission, but no sustained endemic transmission) from the US; and poliomyelitis has been eliminated from most of the world. Hib, once the primary cause of meningitis and other invasive infections, is now rare in young children. However, there have been resurgences in certain VPDs. Vaccine refusal has contributed to VPD resurgence because of the vulnerability of unvaccinated children to VPDs and decreased herd immunity in a community where there are clusters of vaccine refusers. In addition, there are other factors involved in the resurgence of VPDs. We will discuss vaccine hesitancy and then examine specific examples of resurgences in VPDs.

Vaccine Hesitancy and Vaccine Refusal

There have been individuals reluctant to use vaccines since vaccines became available. The reluctance may stem from philosophic, religious, or vaccine safety concerns.

Philosophic Concerns

A philosophic concern refers to a personal belief opposing vaccination. Philosophic concerns can include alternative approaches to vaccines in preventing and controlling infectious diseases, or not wanting government interference in a child's care. Some parents cite philosophic concerns, but actually have concerns about vaccine safety, often related to a particular vaccine. A notable example of early organized philosophic opposition is the establishment of the Anti-Vaccination League, in response to the Vaccination Act of 1853 which made smallpox vaccine compulsory in London [6]. Anti-smallpox vaccination groups became popular in many countries during periods of low disease incidence, when people did not personally encounter smallpox and its resulting morbidity and mortality. Similarly, many who are vaccine hesitant today have generally not encountered VPDs and do not consider them to be a significant threat to their children [7]. Notably, increases in measles vaccine receipt and increases in "on time" receipt occurred during 1989 and 1990, when Chicago was experiencing a measles outbreak, although there was not a concurrent increase in DPT and polio vaccines [8]. States that have easy exemption policies have higher rates of vaccine exemption [9]. This suggests that some individuals may be swayed away from a philosophic exemption, if the process is arduous.

Religious Concerns

Religious concerns have been cited frequently as a reason to refuse vaccination. Notably, opposition is more often

philosophic or related to vaccine safety concerns among members of a community that is organized around faith than conflict with specific theological principles of the faith [10••]. There are some exceptions, such as members of the Church of Christ, Scientist, who believe that disease is cured or prevented by prayer, and therefore, vaccines are not needed. Interestingly, the founder, Mary Baker Eddy, said "Rather than quarrel over vaccination, I recommend, if the law demand, that an individual submit to this process, that he obey the law, and then appeal to the gospel to save him from bad physical results [11]." Other churches, such as the Dutch Reformed Church, have members who are concerned that vaccines will make a person less dependent on God, although others view vaccines as a gift from God that should be used [12]. Many Amish and Mennonite communities view vaccines as components of the modern world, and therefore, do not readily accept them. However, during outbreaks of VPDs, district leaders have often accepted vaccination [10••]. Although in the first half of the twentieth century, Jehovah's Witnesses opposed immunizations, in the 1990s, they acknowledged the benefit of vaccination. There are several Christian groups that relay on "faith healing" for wellness, rather than medical forms of prevention and treatment. To support vaccination, doctrines from many religions call for preserving life, caring for others, and responsibility to the community [10••].

Religious concerns have included issues related to vaccine manufacture, specifically vaccines made in cell lines derived from aborted fetuses. The Roman Catholic Church determined that being immunized does not involve taking moral responsibility for the abortions which produced the cell lines; further, those abortions were not done with the objective of producing the cell lines. However, the Roman Catholic Church asked parents and clinicians to raise the concern of using fetal cell lines in vaccines to governments and vaccine manufacturers [13]. Similarly, the Roman Catholic Church has said it is permissible to use a vaccine with Rubella virus strain RA 27/3, which was derived from an infected fetus [13]. Porcine constituents (such as hydrolyzed trypsin or gelatin) in vaccines have been of concern to Jews and Muslims. Religious leaders have typically permitted these vaccines to be administered because the components have been transformed from the original swine origins, the minute qualities have been extensively diluted, and the vaccine is intended for a medicinal purpose, and thus is not subject to dietary restrictions. Further, the purpose is to save a life and there is not an alternative product [10••].

Safety Concerns

Safety concerns raised in the past 40 years have impacted specific vaccination programs, particularly in association with whole cell pertussis vaccine, measles, mumps and rubella vaccine (MMR), and the use of thimerosal. In 1974, a study suggested that there were neurologic complications associated with whole cell pertussis vaccine, and diphtheria, pertussis, tetanus (DPT) vaccine rates plummeted in the UK as a result of intensive media reporting [14]. Pertussis, which had previously been controlled due to widespread vaccination, returned in the form of large outbreaks in the UK. In 1982, a television documentary "DPT: Vaccine Roulette" resulted in extensive negative publicity for DPT in the US and consequently there was a rise in litigation from parents blaming DPT for a variety of neurologic syndromes. These lawsuits threatened the continued manufacture of vaccines. In response, Congress passed the National Childhood Vaccine Injury Act in 1986, which established a no-fault compensation program for individuals injured following receipt of a recommended vaccine. Whole cell pertussis vaccines were associated with fever, local tenderness, and occasionally febrile seizures. As a result of public concern, acellular pertussis vaccines, which have a much lower rate of fever and local reactions, were developed and replaced whole cell vaccine in the US in the 1990s [15]. Safety concerns have remained an issue for some parents. Notably, a recent case–control study encompassing more than 2 million children, found no evidence of an association between whole cell pertussis vaccine and the occurrence of encephalopathy [16].

In the late 1990s, Andrew Wakefield, a British gastroenterologist, proposed an association between measles vaccine and autism [17]. MMR coverage rates in the UK decreased from >90 % in 1995 to 80 % in 2003 (with pockets of lower vaccine coverage). Large outbreaks of measles occurred in the UK as well as in multiple countries in Europe. The US Institute of Medicine (IOM) reviewed available published and unpublished epidemiologic studies and found no evidence of a causal relationship between MMR and autism [18]. In 2010, after findings from an inquiry done by the British Medical Council, the *Lancet* retracted Wakefield's article [19].

Thimerosal, an ethyl mercury-containing preservative, was thought to be a potential cause of mercury toxicity and autism in the late 1990s because of increased use of vaccines containing thimerosal (Hib and hepatitis B vaccines, in addition to DPT). The level of ethyl mercury during the first 6 months of life exceeded the US. Environmental protection agency's safety level for methyl mercury (a more toxic mercury salt) [4•]. As a precaution, in 1999, the Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) recommended that manufacturers decrease thimerosal in vaccines [20]. Manufacturers responded by removing thimerosal or decreasing it to trace amounts in vaccines for young children, with the exception of some multi-dose vial formulations of

inactivated influenza vaccine which contains small amounts (0.01 %) [21]. Subsequent studies have found no association between use of thimerosal in vaccines and autism [18, 22].

Some parents have concerns about the number of vaccines an infant receives, resulting in vaccines being given at different ages than those recommended by the Advisory Committee on Immunization Practices (ACIP). By using an alternate vaccination schedule, children may not be protected from a VPD during a high risk age period. For example, a 20-month-old child in Minnesota, whose parents used a schedule that began vaccinations at age 5 years, developed invasive Hib disease (epiglottitis) at age 20 months (R. Lynfield, unpublished data). The IOM recently reviewed the childhood vaccination schedule and found no evidence of safety concerns specifically associated with the currently recommended childhood vaccine schedule [23].

There are resources to inform and persuade vaccine hesitant parents. It can be challenging to change the intent of a parent, as found in a recent study on providing information about MMR and measles using a variety of messages including textual information, images of diseases, and a narrative of a critical case of measles in an infant [24•]. Leask and colleagues have developed a framework and strategies to communicate with parents depending on the parental position [25••]. These authors promote building rapport, answering concerns, providing information, and facilitating valid consent. Resources for information on vaccine safety can be found on the websites of Children's Hospital of Philadelphia, AAP, and CDC [26–28]. Healthcare providers play a key role in dealing with vaccine hesitancy.

Resurgences of Specific Vaccine-Preventable Diseases

In this section, we discuss resurgences of measles, mumps, pertussis, and invasive pneumococcal disease that have occurred following periods of decreased incidence to illustrate the complexity of the problem.

Measles

Measles has been controlled by widespread vaccination. Measles vaccine was introduced in the US in 1963 and disease decreased dramatically from >500,000 reported cases and 500 deaths to 3,000 reported cases per year [4•, 29]. Measles virus is very transmissible and can be spread through the airborne route. The R_0 or reproduction number (the average number of secondary cases produced by a primary case in a susceptible population) of measles virus is high- 15–17 [30]. It is estimated that there is a >90 % chance of transmission to a susceptible individual after face-to-face contact [29]. In 1989–1991, the US experienced a resurgence of measles with 55,000 cases and 123 deaths [4•]. Cases occurred in high-school and college students who had a high level of coverage with a single dose of vaccine administered at 12–15 months of age. Because measles virus could cause infection and be transmitted in 2–5 % of individuals who received a dose of vaccine but do not mount a primary immune response, the ACIP in 1989, recommended a routine second dose of MMR at 4–6 years of age [4•]. In the late 1980s, it was noted that many inner-city children, particularly belonging to racial and ethnic minorities, were not receiving MMR. This resulted in state and local immunization action plans to achieve 90 % coverage of preschool children for vaccines recommended in the first 2 years of life. VFC provided the means to vaccinate many children, and by 1996, racial and ethnic disparities significantly narrowed [31, 32]. In 2000, elimination of endemic transmission of measles virus was achieved in the US [33].

According to CDC, an average of 60 cases of measles occurs each year in the US [34]. These cases are associated with importation of measles virus, although there may be limited local transmission if susceptible persons encounter the virus. Increased number of cases were observed in 2008 (140 cases), 2011 (220 cases), and 2013 (189 cases), and included outbreaks associated with unimmunized children who were old enough to receive vaccine, but whose parents declined vaccination [29]. For example, in 2011, 21 cases occurred in Hennepin County, Minnesota, linked to a 30-month-old unvaccinated child who acquired measles, while visiting Kenya [35]. Fourteen cases were hospitalized and over 3000 people were exposed. Sixteen cases were unvaccinated, seven of nine who were age eligible had parents with safety concerns. Six of these cases were of Somali descent (including the index case). Notably, MMR immunization rates had decreased to 54 % among Somali children in Hennepin County associated with concerns about autism promoted by Andrew Wakefield, who made several visits to Minneapolis. In 2013, a large measles outbreak (58 cases) occurred in New York City in an Orthodox Jewish community [36]. The index case was an unimmunized 17-year old that had traveled to London. Infection spread in two neighborhoods in Brooklyn, and approximately 3,500 people were exposed. All cases were unimmunized, with 12 cases being too young for vaccine. Ensuring high levels of vaccination among individuals in a community can help prevent spread of imported measles cases.

Mumps

Mumps has also been controlled by widespread immunization. However, in contrast to the resurgence of measles, cases

of mumps in the US appear to be due in large part to waning immunity, and periodic exposure to mumps virus. In 1967, live attenuated mumps vaccine was licensed. Prior to licensure, >150,000 reported cases occurred annually (incidence of 88/100,000), this decreased to 5,270 cases (incidence of 2.5/100,000) in 1982 [37]. Mumps virus is spread mainly via large droplets and the R_0 is 10–12 [30]. Beginning in late 1986, a resurgence of mumps occurred with close to 13,000 cases reported in 1987 [37]. The resurgence was rapid and focal, with eight of the highest incidence states occurring in central, rural US states. The peak age of cases shifted from 5–9-year olds to 10–19-year olds. In 1989, ACIP recommended a second dose of measles vaccine for measles control, but because of concern about the resurgence of mumps, it was recommended that the dose to be given as MMR. In 1992, the incidence of mumps decreased to 1.0/100,000 and decreased further to 0.1/100,000(an average of 268 cases annually) in 2001–2005 [37].

In 2006, there was another rapid resurgence of mumps with 6,584 cases reported, again mostly occurring in rural, midwestern states [37]. The peak age shifted from 5–9-year olds to 18–24-year olds, many of whom were college students and 89–99 % had received 2 doses of vaccine (though most >10 years prior). In 2009–2010, outbreaks of mumps occurred in colleges and religious schools in northeastern US. A recent report described 3,502 outbreak-related cases in New York and New Jersey in an Orthodox Jewish community [38]. Overrepresented were adolescent males, who had spent many hours in "intense face-to-face contact." Among 884 cases in children 13–17-years old, 89 % had received two doses of MMR and 8 % had one dose of MMR. In this outbreak, rates of orchitis were significantly higher in those who were not vaccinated versus those who received two doses of MMR (11 vs. 4 %, $p = 0.04$) [38]. Notably, there have not been outbreaks among military populations, many of whom received a third dose of MMR as recruits [37]. Studying immunogenicity and long-term effectiveness of a third dose of mumps vaccine would be helpful in approaching the issue of waning immunity.

Pertussis

The epidemiology of pertussis is complex. There was an excellent response to whole cell pertussis vaccines, but in recent years cases have increased, particularly in the era of acellular pertussis vaccines. Whole cell pertussis vaccines became available in the US in the 1940s and the annual incidence of disease declined with widespread use of vaccine, from an average of 150/100,000 population (150,000–260,000 cases with up to 9,000 deaths) prior to vaccine availability, to a nadir of 0.5/100,000 (1,010 cases) in 1976 [15, 39, 40]. *Bordetella pertussis* is thought to spread mainly via the droplet route, but is very transmissible to those who are non-immune, with an R_0 of 15–17, and able to spread to >80 % of susceptible household contacts [15, 30]. Interestingly, *B. pertussis* infection or immunization does not provide life-long immunity; recurrent infections (often not severe) occur, and immunity to whole cell vaccine is thought to wane after 5–10 years [15]. Due to concerns about reactions associated with whole cell vaccine (see "safety concerns" section), acellular pertussis vaccines were introduced in the US, replacing booster vaccine doses (age 15–18 months and age 4–6 years) in 1992 and primary series (ages 2, 4, 6 months) doses in 1997. There are three infant acellular pertussis vaccine formulations available in the US (containing 2, 3, or 5 pertussis antigens). In clinical trials, vaccine efficacy point estimates ranged from 80 to 85 % with overlapping confidence intervals, suggesting that these vaccines are comparable in effectiveness [15].

Because of school-entry requirements, coverage with at least three doses of pertussis-containing vaccines has been high. However, the number of reported cases has risen. In 2004, close to 26,000 cases of pertussis were reported. Notably, many of these cases occurred in adults (29 %) and adolescents (34 %) [41]. In 2006, ACIP recommended an additional dose of a pertussis-containing vaccine (Tdap –a different formulation than the infant diphtheria, pertussis, and tetanus vaccine) at age 11–12 years, and for adults including post-partum women [41, 42]. Infants are at the highest risk for severe pertussis including apnea, pneumonia, seizures, and encephalopathy. Approximately, 50 % of infant cases are hospitalized and 1.6 % of these infants die [43]. In 2011, in a further effort to protect infants, ACIP recommended Tdap for pregnant women and those in contact with young infants, and in 2012 ACIP updated guidance so that Tdap was recommended with each pregnancy [44, 45]. It will be important to assess the effectiveness of this recommendation.

Large outbreaks of pertussis occurred in the US in 2010 (9,000 cases, 809 hospitalizations, and ten deaths in California alone), and the number of reported cases peaked in 2012, with >48,000 cases [46, 47]. Notably, since 2010 a new peak was observed in 7–10-year olds, and approximately 75 % of these cases have been appropriately vaccinated. In 2012, a second peak was noted around age 13–14 years [47, 48•].

A number of factors have been suggested as contributing to the resurgence of pertussis, including waning vaccine-related immunity, a less protective immune response from acellular vaccines compared with whole cell pertussis vaccines, and negligible impact of acellular vaccines on halting transmission of the bacterium. A case–control study in California found that the vaccine effectiveness of five doses of DTaP was 98 % (95 % CI 96–99 %) within 12 months of

vaccine, but decreased to 71 % (95 % CI 46–85 %) by ≥60 months after vaccine receipt [49•]. A case–control study with adolescents in Washington state, found that vaccine effectiveness of Tdap within 12 months was 75 % (95 % CI 62–83 %), but waned to 41 % (95 % CI 7–63 %) ≥2 years post vaccination [50]. An Australian study found that children who received acellular vaccine (for at least the first dose of their primary series) were more likely to get pertussis than those who had received whole cell vaccine (either for first dose of their primary series or the entire series), suggesting that initial, priming antigens are important in eliciting an immune response, and that whole cell vaccines are more effective [51•]. A study from Oregon found that children primed with acellular vaccine had a higher rate of pertussis than those primed with whole cell vaccine [52•]. Animal model data indicate that whole cell vaccines elicit Th1 and Th17 responses, which may result in a more effective immune response to *B. pertussis* than the Th2 and Th17 responses elicited by acellular vaccines. Notably, addition of a Th1 promoting adjuvant to acellular vaccine alters the response to Th1 [53•]. Recent work has found that baboons immunized with acellular vaccine and exposed to *B. pertussis* can be colonized with *B. pertussis* and transmit infection, suggesting that acellular vaccine may not have a big impact on interrupting transmission [54•].

Another recent finding is that there has been a shift to predominately pertactin-negative strains among *B. pertussis* strains currently circulating in the US [55•]. Pertactin is a component in acellular vaccines, which is involved in attachment of the organism to epithelial cells. It is hypothesized that vaccine-induced antibody pressure has resulted in a predominance of pertactin-negative strains, although it is unknown if the vaccine effectiveness for these strains is different.

In addition to issues of changes in the immune response, waning of vaccine-induced immunity, lack of impact on transmission, and antigenic changes in the organism, some investigators have evaluated the role of vaccine refusal in pertussis resurgence. Omer and colleagues have found an association between geographic areas that had children with non-medical vaccine exemption and the occurrence of pertussis clusters, identifying a contribution of vaccine hesitancy in the complex picture of pertussis resurgence [56, 57]. In addition to maternal vaccination and ensuring high rates of vaccination, research resulting in more effective pertussis vaccines is an important step in addressing the resurgence of pertussis.

Invasive Disease Due to *Streptococcus pneumoniae* (Pneumococcus)

The epidemiology of invasive pneumococcal disease (IPD) reveals the enormous impact of widespread immunization of children with pneumococcal conjugate vaccine (PCV). However, a shift in the serotypes causing disease was observed a number of years after the introduction of the 7-valent PCV (PCV7). Prior to the licensure of PCV7 in 2000, an estimated 65,000 cases of IPD occurred each year in US children <5 years. The seven serotypes accounted for approximately 80 % of IPD in young children, and within six years PCV-7 serotypes accounted for 2 %; overall IPD rates in this group decreased from 87.4/100,000 in 1999 to 20.8/100,000 in 2004 [58, 59]. Decreased incidence was also observed in other age groups because colonized young children were a reservoir for pneumococcus, and PCV protected young children against colonization with the seven vaccine serotypes. However, within a few years, non-vaccine serotypes, particularly 19-A, began playing a bigger role in causing IPD. In 2010, a 13-valent PCV (PCV13) was licensed which included 19-A and five additional serotypes; these serotypes accounted for 63 % of IPD in 2006–2007 in young children [58]. The incidence of IPD has again decreased and was 9/100,000 in children <5 years in 2012 [59]. A recent study modeled potential changes in incidence of IPD by 2020, based on serotype changes occurring after widespread use of PCV13 [60•]. It found that 170,000 cases would be prevented in all age groups from 2011 to 2020 with no serotype replacement, and 167,000 cases would be prevented if there was a replacement similar to that seen with 19A after PCV7. Although the model is promising for continued effective control of IPD with PCV13, it is important to track the serotypes causing IPD to ascertain potential changes that could herald an increase in incidence.

Conclusions

Vaccines have proven to be effective, safe, and valuable for ensuring children's health. Legislation has enabled all US children to have access to vaccines and has enabled high levels of vaccine coverage. Resurgence of certain VPDs has been experienced in recent years and occurs for a number of reasons including decreases in vaccine coverage, waning immunity in an individual, changes in the vaccine, and changes in the organism. Herd immunity has been threatened in geographic locations where there are pockets of multiple families refusing vaccine. Clinicians should understand the reasons for vaccine hesitancy and work with families to address their concerns about vaccines. Careful surveillance is needed to identify cases of VPD in order to understand the evolving epidemiology of these diseases post-vaccine licensure. Additional research to comprehend better the components of the immune response to different vaccines and the infections they

prevent, and to develop more accurate correlates of protection is needed. We hope this additional research will enable a new generation of vaccines that can provide extended and effective protection against infectious diseases.

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