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EMERGING Infections

Pertussis on the Rise

A troubling picture of waning immunity, with unvaccinated children especially vulnerable.

In July 2004, six infants were admitted to a children's hospital in Texas with a diagnosis of pertussis (also known as whooping cough).[1] Hospital staff members, noticing that all of the infants had been born at the same general hospital, reported this to the county health department. An investigation revealed that one staff member, a 24-year-old woman identified as "health care worker A," had cared for all six infants. A few weeks earlier, while working in the newborn nursery, she'd become ill with symptoms that included cough, dyspnea, and posttussive emesis. (Her husband had recently traveled to California and had returned with similar symptoms.) She tested positive for pertussis. Further investigation revealed that she'd directly cared for 113 infants while symptomatic; 11 were eventually diagnosed with pertussis. Of these 11 infants, five required admission to the pediatric ICU, four required care on the pediatric medical floor, one was cared for as an outpatient, and one was treated in the ED. Health care worker A had been fully vaccinated for pertussis as a child.

The 2004 Texas pertussis outbreak wasn't the last, but it serves to represent a pattern; similar localized or statewide outbreaks have continued to occur nationwide.[2] In 2010, nearly 9,500 "confirmed, probable, and suspect" cases were reported in California, the state's largest outbreak in 65 years.[3] Ten infants died; no deaths were reported in other age groups. Although all of the causative factors in the California outbreak have yet to be determined, a look at past pertussis outbreaks reveals a troubling picture of waning immunity, with under- or unvaccinated children especially vulnerable.

California residents lined up to get booster shots for whooping cough during 2010, when the state was in the midst of its largest outbreak in 65 years. Photo by Justin Sullivan / Getty Images.

EPIDEMIOLOGY

Pertussis, long considered a childhood illness, has been on the rise since at least the mid-1990s, with a sharp increase in incidence evident since the early 2000s (see Figure 1).[4] Because infants under the age of one year haven't yet completed the vaccination series required for immunization, they remain the population at highest risk for pertussis; Hispanic infants appear to be especially vulnerable. But since the 1990s, epidemiologists have noted a new trend: there have been increasing reports of cases among adolescents and adults (see Figure 2[5]), although in part this increase is likely due to better disease recognition and surveillance.[4,6] That said, the World Health Organization (WHO) reports that adolescents and adults "are significant sources of transmission" to unvaccinated infants.[6]

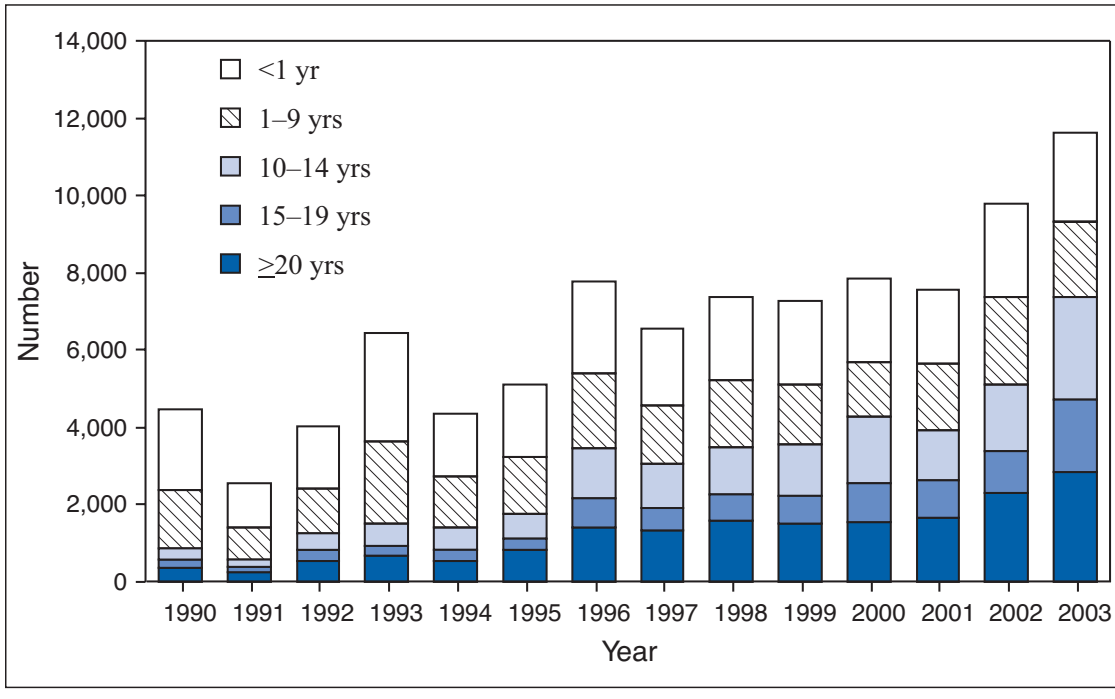
Although industrialized countries with high vaccination rates generally report lower incidences of pertussis, the disease still produces severe consequences in the developing world. In a recent

position paper, the WHO estimated that, in 2008, there were 16 million cases of pertussis worldwide; 95% of these cases occurred in developing countries, and 195,000 children died.[6] The WHO also reported that vaccination programs had prevented about 687,000 additional deaths, and that since the start of its Expanded Program on Immunization in 1974, about 82% of infants worldwide have received the pertussis vaccine in some form. In the United States, the Centers for Disease Control and Prevention (CDC) reports that, of those diseases for which universal childhood vaccination is recommended, "only pertussis has had an overall increase in reported cases since 1980."[7] This increase is common to many developed countries; in the prevaccine era, the disease tended to peak in cycles of every two to five years, and similar peaks continue to occur, perhaps even more frequently in some nations.[8-10]

One contributing factor for pertussis outbreaks may be lack of adherence to the recommended vaccination schedule. For example, one large U.S. study found that 48% of children under the age of 36 months were delayed in receiving one or more of the recommended doses of the childhood diphtheria, tetanus, and pertussis (DTaP) vaccine series, with 10% to 20% of children being undervaccinated for more than six months.[11] Only 26% of American children receive all vaccines in a timely fashion, and results vary widely by state.[11, 12] For pertussis, both delayed and early administration can be detrimental to protective immunity. A case–control study of a pertussis outbreak among school-aged children revealed that both missing doses of vaccine and receiving the fifth dose at age four rather than age five were significant predictors of illness.[13] Another factor believed partially responsible for increasing pertussis rates in adolescents and adults is waning immunity. A 2005 review found that natural immunity wanes after seven to 20 years and vaccine-induced immunity wanes after four to 12 years.[14]

It should be noted that there are questions about how surveillance methodology might affect reported pertussis rates.[4, 15] A European study revealed highly variable rates in countries that had similar populations and climate and were in close proximity.[8] For example, from 1998 through 2002, Switzerland's pertussis rate per 100,000 population was 123.9, while Austria's was only 1.8. The two countries border each other and rail travel

Figure 1. Number of reported pertussis cases,[a] by year and age group—National Notifiable Diseases Surveillance System, United States, 1990–2003



[a] Confirmed and probable. Reprinted from the Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep* 2005;54(50):1283-6.[4]

makes intercountry transportation simple and efficient. Reasonable inquiry would lead to questions about case finding. Intriguingly, overall incidence in people older than 14 years of age doubled during the study period.[8] Despite the knowledge that vigilant case finding increases reported rates, some experts believe the overall incidence of pertussis is likely underreported, with many cases in adolescents and adults misidentified as bronchitis or upper respiratory infection.[9, 16] Asymptomatic or atypical cases can further confound efforts to determine the pertussis rate. Adults and adolescents might not present with typical clinical features due to partial immunity from either previous infection or disease exposure.[17] And many cases of pertussis in adolescents and adults may be asymptomatic. One prospective, randomized trial estimated that in Americans ages 15 to 65 years, there are five asymptomatic infections for each symptomatic case.[16] The same trial also produced a projected incidence density of 370 to 450 cases of pertussis per 100,000 person-years for this population in the United States.[18] The fact that many pertussis cases are asymptomatic makes control much more difficult, and accurate estimates of incidence rates and infection risk remain elusive.

The organism. Pertussis is caused by *Bordetella pertussis*, an aerobic gram-negative rod. (Another organism, *Bordetella parapertussis*, causes a milder version.) Although pertussis is highly contagious, the organism is very fragile, which can complicate identification through laboratory testing.[15, 19] Features of the organism that help it to cause disease include the attachment structures fimbriae and filamentous hemagglutinin, and several toxins, including pertussis toxin.[15]

Epidemiologists use attack rates to gauge the virulence of a pathogen during an outbreak.[20] An attack rate, an alternative form of incidence rate, is used "when the nature of the disease or condition is such that a population is observed for a short time period, often as a result of specific exposure."[21] The higher the attack rate, the more likely an illness is to pass from one person to another. Even a disease with a relatively low mortality rate can have significant effects on a community when the attack rate is high (for example, if it results in a significant amount of lost work time). The only known reservoir of pertussis is human beings, which means that eradication is theoretically possible. Secondary attack rates—an indicator of the frequency of new cases among the contacts of known cases, and a measure of contagiousness—may be as high as 90%.[6, 20]

SYMPTOMS AND COMPLICATIONS

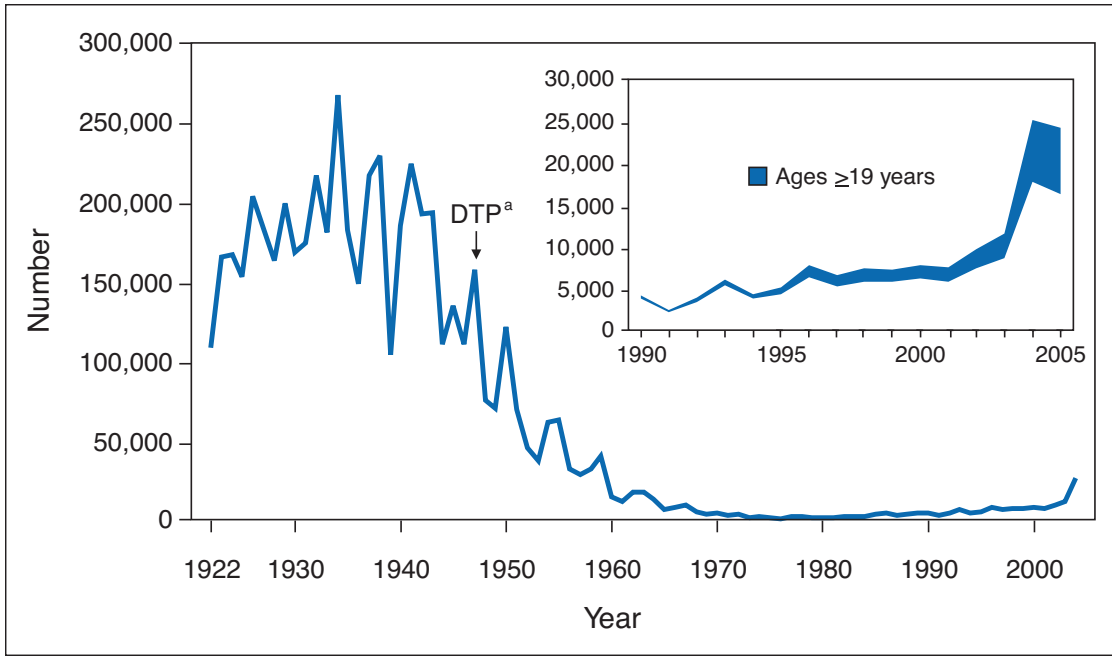
Pertussis is transmitted from infected individuals to those susceptible through respiratory droplets. According to the WHO's latest position paper on pertussis, the usual incubation period is nine to 10 days, with a range of six to 20 days,[6] although incubation periods of as long as 42 days have been noted.[17] Thus, in the first days after infection, people often still feel well enough to interact with, and potentially transmit infection to, many others. The clinical course of pertussis is generally described as having three distinct phases: catarrhal, paroxysmal, and convalescent.

The patient is most contagious during the catarrhal phase, which usually lasts one to two weeks. This is both because of the high bacterial load and because the symptoms—sneezing, runny nose, low-grade fever, and "a mild, occasional cough"—are similar to those of a common cold or upper respiratory infection.[15, 17] At this stage many people don't seek medical care, for either themselves or their children, because the symptoms seem unremarkable. Even if they do seek care, many clinicians may not suspect pertussis for the same reason.

After one to two weeks of cold-like symptoms, patients progress to the paroxysmal phase.[17] During this phase, children develop the characteristic cough, which involves a series of rapid coughs followed by a high-pitched whoop during intake of breath. (To hear an example, go to www.pkids.org/dis_pert_stsop.php.) It's worth noting that infants younger than six months might have paroxysmal coughing without the whoop. Coughing tends to be more severe at night and is often followed by vomiting. The paroxysmal phase typically lasts from one to six weeks, and possibly as long as 10 weeks.[17] Adults and adolescents might not present with typical symptoms; symptoms are like those seen with a cold or upper respiratory illness, and although the cough may be persistent, paroxysmal cough is uncommon. Further, people with partial vaccination protection (receipt of only some of the vaccination doses) are likely to develop milder cases.[17] The convalescent phase entails slow recovery over weeks to months, with gradual reduction in the frequency and severity of paroxysms.[17]

Complications. The WHO reports that in industrialized nations, the incidence of complications in children is estimated to be about 6%, and "may be" as high as 24% in infants younger than six months.[6] (Although the report doesn't cite comparable percentages in developing nations, they would presumably be much higher.) Pertussis complications tend to be most severe in infants.

Figure 2. Number of reported pertussis cases, by year—United States, 1922–2005



[a]Introduction of universal pediatric diphtheria and tetanus toxoids and whole-cell pertussis vaccine. Data sources: 1950–2005, Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System, and 1922–1949, passive reports to the Public Health Service. Reprinted from the Centers for Disease Control and Prevention, *MMWR Recomm Rep* 2006;55 (RR-17):1-33.[5]

For example, a CDC report on pertussis in the United States from 2001 through 2003 found that pneumonia was a complication in 2% of adolescents and 13% of infants younger than six months.[4] In infants with pertussis, a lack of respiratory competence to recover from paroxysms leads to periods of apnea; this in turn can cause neurologic complications such as seizures and encephalopathy, which are also most common among infants.[4, 17] Complications in patients of any age often stem from the severe pressure exerted during coughing. Examples include pneumothorax, subdural hematoma, epistaxis, and rectal prolapse.[17, 22]

Infants are the most likely of any age group to die as a result of contracting pertussis. CDC data from 2001 through 2003 showed that 91% of pertussis-related deaths occurred in infants younger than six months.[4] For all age groups, secondary bacterial pneumonia is the most common complication and a leading cause of pertussis-related death.[17, 23] One recent study, investigating the mechanism of fatal pertussis infections in infants, found evidence that secondary pneumonia may trigger a cascade of events that result in intractable pulmonary hypertension.[24]

VACCINATION

Pertussis is largely preventable through proper vaccination. Pertussis vaccine is always given in combination with vaccines against diphtheria, tetanus, or both. Two types of pertussis vaccine are available: an inactivated whole-cell type (abbreviated wP) based on the pertussis organism and an acellular version (abbreviated aP) based on selected components of the organism. The older, whole-cell type, still commonly used in developing countries, tends to have high rates (one in every two to 10 injections) of minor adverse reactions such as erythema, edema, fever, and agitation.[6] The newer, acellular type is associated with fewer adverse effects and better vaccine acceptance, and has become the more common form used in industrialized nations. But the higher costs associated with manufacturing the acellular type make its use in developing countries untenable.[6]

In industrialized countries, DTaP is the combination given to children younger than age seven. Since 2005, a reduced-dose acellular pertussis vaccine in combination with diphtheria and typhoid vaccines (Tdap) has been recommended for use in adolescents and adults to provide continued protection.[5] The

DTaP combination contains larger doses of the diphtheria and pertussis components than does the Tdap combination, because children require higher doses to achieve immunity than do adolescents and adults. (The uppercase letters D, T, and P indicate full-strength doses; the lowercase letters d and p indicated reduced doses. The lowercase letter a stands for acellular type.)

For children, the recommended DTaP vaccination series begins with the first dose given at two months of age.[25] Repeat doses are given at four months, six months, between 15 and 18 months, and again when the child enters school, usually between the ages of four and six years. (Not all states require a fifth dose for school entry, and the timing can vary; for specific requirements by state, visit www.immunizationinfo.org/vaccines/state-requirements.) For adolescents and adults, the CDC now recommends that Tdap dosing replace tetanus and diphtheria (Td) dosing.[26] Adolescents should receive a booster dose of Tdap vaccine at age 11 or 12, when immunity produced by the original series has waned.[26] Adults ages 20 and older should receive a booster dose of Tdap vaccine every 10 years and possibly more often.[27] For instance, new mothers who have never received Tdap vaccine are encouraged to receive it as soon as possible after delivery; and health care workers who have direct patient contact are encouraged to receive a dose as soon as possible, and within two years or sooner after a Td booster.[27]

Recent outbreak reports indicate that there's a need to reexamine vaccination practices for adults and adolescents. For example, a survey of college students following a campus outbreak of pertussis revealed that during the fall semester, 13% had had an illness consistent with the CDC definition of pertussis.[28] Another study found that initial pertussis transmission between adolescents using a high school weight room contributed to a community-wide outbreak of the disease.[29] And a study of household outbreaks in Brazil determined that adults were the primary case in 26% of the households, causing 43% of the secondary cases.[30] The potential for adult transmission is one reason the CDC now recommends that any adult caring for infants receive at least one dose of Tdap vaccine.[26]

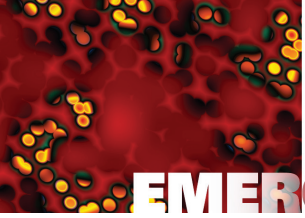
Any discussion about vaccine-preventable disease must also consider the consequences of failing to vaccinate, whether intentionally or accidentally. People of any age who are incompletely immunized or unimmunized can be expected to be at higher risk for contracting vaccine-preventable illnesses. According to the 2008 National Immunization Survey, the proportion of children ages 19 through 35 months whose parents refused or delayed vaccination for any of several diseases, including pertussis, rose from 22% in 2003 to 39% in 2008.[31] Incomplete vaccination has been linked to pertussis outbreaks.[32] The same survey also found that fewer than 1% of the children had never received *any* vaccine.[33] One large retrospective study found that being unvaccinated for pertussis left children about six times more likely to contract it.[34] Among unvaccinated adolescents and adults, the annual risk for contacting pertussis has been estimated at about 1%.[16]

PERTUSSIS IN THE HEALTH CARE ENVIRONMENT

Beyond their detrimental impact on staff and patients, pertussis outbreaks in health care environments can be both disruptive and costly.[35] Health care workers are generally at higher risk for communicable diseases; one Canadian study found that they were 1.7 times more likely to contract pertussis than were people in the general adult population.[23] In the 2004 Texas outbreak, significant resources were devoted to tracking potentially exposed individuals, prophylaxis, and hospitalization and health care expenditures for those infected.[1]

Other outbreaks have been similarly disruptive. For example, during a 1999 outbreak on a surgical unit, 23% of exposed health care workers contracted clinical pertussis.[36] (Interestingly, no exposed patients became infected, probably because of "mask use, cough etiquette, and limited face-to-face contact" by staff.) A 2003 outbreak at another facility resulted in a total measured cost of more than $80,000.[37] This outbreak also produced substantial work disruption, with 17 workers developing clinical symptoms and requiring time away from work; the investigators posited that vaccination of health care workers would be a cost-effective intervention. The CDC currently recommends that all health care workers with direct patient contact receive a booster of Tdap.[26]

Waning immunity and circulation of pathogens make pertussis an epidemiologically significant disease and a growing problem in our society. If you are often around infants at work or at home, speak with your primary care provider about getting a pertussis vaccination. If you directly provide patient care to patients of any age, please talk with your own provider and your employer's health or human resources department regarding your risk factors and the benefits of pertussis vaccination. Health care institutions should examine their



policies regarding employee vaccinations, and adjust these according to CDC recommendations. Robust vaccination practice remains the best defense against this potentially lethal illness. ▼

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