Pertussis on the Rise:

NEW VACCINE TARGETS ADOLESCENTS

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Pertussis (whooping cough) is a highly contagious respiratory tract infection caused by *Bordetella pertussis*. In contrast to most other infectious diseases for which a vaccine is available, the number of reported cases of pertussis in the United States is increasing. In 2003, there were 11,647 cases of pertussis reported to the Centers for Disease Control and Prevention (CDC), the highest number of cases since 1964.[1] The pattern of pertussis incidence over time can be seen in Figure 1.[2-5] Following the introduction of pertussis vaccine in the 1940s, the incidence of the disease decreased dramatically from an average of 175,000 cases per year to fewer than 5000 cases per year by 1968. However, despite high infant immunization rates, the annual incidence of pertussis began to rise in the early 1980s. More importantly, the occurrence of pertussis is not limited to infants and young children. Of growing concern is that pertussis among adolescents has emerged as a substantial and growing public health problem.[1]

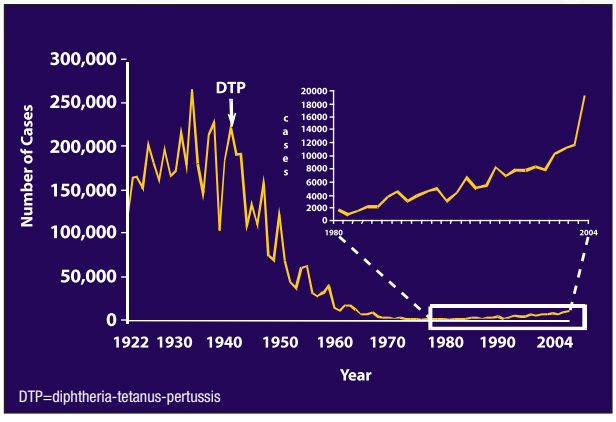

Figure 1. Incidence of pertussis over time.[2-5]

Clinical Presentation Not Always Typical

Following an incubation period typically lasting 7 to 10 days, the first (catarrhal) stage of pertussis begins with nonspecific symptoms that are similar to those of the common cold (eg, runny nose, sneezing, low-grade fever, mild occasional cough). The cough gradually becomes more severe. After 1 to 2 weeks,

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the second (paroxysmal) stage begins, and the characteristic coughing "fits," heavy inspiration (whoops), and posttussive vomiting occur.[1] The paroxysmal stage can last up to 10 weeks, after which patients finally enter a convalescent stage, in which the symptoms gradually resolve over weeks to months.[1]

Although infected infants usually display the classic symptoms described above, adolescents and older individuals have a much more atypical presentation that is often indistinguishable from other upper respiratory tract infections.[1] These older patients may present with a persistent cough (>7 days); however, the inspiratory whoop is less common. Many adolescents present with paroxysmal coughing and vomiting; approximately 30% experience whooping; and in some, apnea and cyanosis can occur (Table 1).[6]

Table 1. Clinical Symptoms in Adolescents With Pertussis[6]

Clinical Symptoms	Percent of Adolescents With Symptoms at Time of Diagnosis
Paroxysm	83
Whoop	30
Apnea	19
Cyanosis	6
Vomiting	45
Requiring hospitalization	1.4
Cough >4 weeks	41

In addition, pertussis morbidity in adolescents can be considerable. Rates of hospitalization, serious complications, and death among adolescents are low, but cough illness is prolonged and health impact (medical visits, antimicrobial treatment, and experience of illness) is significant.[7] In a survey of 314 adolescents with pertussis, 83% missed school (mean 5.5 days missed) and 38% were still coughing at the time of the interview, which occurred an average of 106 days after cough onset.[8] Furthermore, and perhaps more importantly, these individuals may serve as a reservoir for infecting other more susceptible persons (ie, not yet vaccinated or incompletely vaccinated infants).[1]

Diagnostic Challenges

The diagnosis of pertussis is usually based on history and physical examination, although in atypical cases and young infants, laboratory testing may be useful.[1] The isolation of *B pertussis* by culture is the standard and preferred method of diagnosis, with a positive culture confirming the disease. However, cultures are not sensitive, and the pathogen may be difficult to isolate and culture if the patient has previously taken antibiotics effective against pertussis (eg, erythromycin, trimethoprim/sulfamethoxazole) or if the specimen is collected more than 2 weeks after the onset of the illness (ie, beyond the catarrhal stage).[1,9] Other laboratory tests, such as polymerase chain reaction (PCR), direct fluorescent antibody (DFA), and serological testing, have demonstrated some value but are either not standardized (PCR, serology) or have a low specificity and sensitivity (DFA).[1] In addition, many of these tests may not be available at all laboratories and can be expensive.

Another difficulty with identifying emerging cases of pertussis is that physicians may not consider pertussis when evaluating a cough illness, resulting in a delay of diagnosis. One study found that among families with a confirmed case of pertussis, a mean of 1.6 office visits (range 0-7) was required before diagnosis was confirmed.[10] Further, disease surveillance methods are not optimal. It is estimated that the number of reported cases of pertussis represents only 1% to 36% of the true number of cases.[9] Therefore, widespread underrecognition, underreporting, and misdiagnosis of the disease—particularly in those individuals with less typical presentations (ie, adolescents)—represent more than 1 million new cases annually.[11]

Increased Prevalence in Adolescents

Although the occurrence of pertussis among infants remains a substantial clinical problem due to the increased risk of complications in this age group, the pattern of infection has been evolving in recent years, with an increased incidence among the adolescent population. CDC data indicate that the increased incidence of pertussis in the last decade has been due mainly to an increase in the number of reported cases in persons ≥10 years of age. During the period from 1994 to 1996, the incidence of pertussis was 106% higher among persons 10 to 19 years of age than it was for this same age group during the period from 1990 to 1993. In contrast, the incidence of pertussis remained stable among those <5 years of age, presumably because of protection by vaccination.[12]

An increased prevalence of pertussis among adolescents has also been observed in the most recently updated statistics from the CDC. In 2004, a total of 18,957 provisional cases of pertussis were reported. Of these, 7161 (38%) were reported among adolescents. This number translates into an incidence rate of 17.43/100,000, which is 1.4-fold higher than the rate

reported in 1- to 4-year-olds, nearly 2-fold higher than that reported in 5- to 9-year-olds, and 7-fold higher than the rate reported in persons 20 years of age and older (Figure 2).[5]

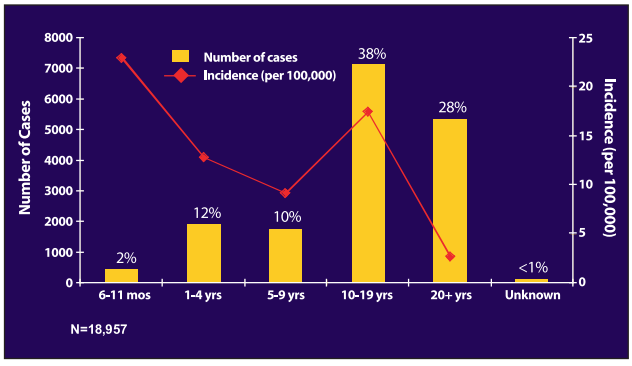

Figure 2. Incidence of pertussis in 2004 according to age.[5]

The exact reason for the trend of increasing incidence of pertussis is unknown, but there are several possible explanations, including improvements in diagnostic and surveillance practices and a decline in population immunity.[6,9] It appears that the key factor for the continuing endemicity of pertussis in countries where there are high rates of vaccination is that, without boosting, both vaccine-induced and naturally acquired immunity wane over time.[9] Although the exact duration of immunity is not known, data suggest that, in most cases, immunity wanes 5 to 10 years after the last diphtheria-tetanus-pertussis vaccine.[13]

Local/State Outbreaks

The number of reported cases of pertussis is highly dependent on both the availability of confirmatory diagnostic tests and awareness of health practitioners of the possibility of infection. States where there is an extensive and well-established surveillance program can provide a more complete picture of recent epidemiological trends. For example, between 1989 and 1998, the crude incidence of pertussis in Massachusetts increased from 3.2/100,000 to 12.8/100,000.[6] More importantly, while the incidence of pertussis remained relatively stable among infants and children ≤10 years of age, the incidence among adolescents increased more than 9-fold.[6] In addition, during the years from 2000 through 2003, there were 120 outbreaks of pertussis in Massachusetts, most of which (87%) were detected in schools.[14]

Another outbreak was reported in Pike County, Arkansas, in 2001 and was traced to members of a school football team. Thirty-two percent (77/242) of middle and high school students were infected, resulting in school closures and spreading of the disease to 109 households. Sixty-four percent of the total 140 reported cases of pertussis were reported in adolescents 12 to 18 years of age.[14]

A similar outbreak of pertussis occurred in Yavapai County, Arizona, from September 2002 through February 2003 that included 485 total cases.[15] Two hundred three (42%) cases were associated with schools, including 113 (56%) in students, 8 (4%) in school staff, and 82 (40%) in family members. The median age of infected persons was 13 years (range 0-83 years). The highest rate of attack was among eighth graders, with 10% (20/198) of students in this grade contracting pertussis.

A fourth example was an outbreak that occurred in Fond du Lac, Wisconsin. It was first detected in a high school weight room. Of the 313 total cases in the county, 220 (70%) occurred in 10- to 19-year-olds, corresponding to an incidence rate of 1505/100,000.[14] Aggressive notification of clinicians of this outbreak led to the identification of 5020 cases of pertussis in Wisconsin in 2004. Forty percent of these cases (2028/5020) involved adolescents 10 to 19 years of age. In addition, there was serious morbidity from pertussis among these adolescents, including 15 hospitalizations and 33 cases of pneumonia.

Strategies to Reduce Pertussis

As noted, the incidence of pertussis is increasing despite the availability of effective diphtheria-tetanus-acellular pertussis (DTaP) vaccines.[7] Of primary importance to preventing the occurrence of pertussis is continued vigilance to maintain high levels of vaccine coverage, including the timely completion of the pertussis vaccination schedule. The current recommendation for pertussis vaccination consists of a primary series of DTaP, which includes 3 doses given at 4- to 8-week intervals beginning at 6 to 8 weeks of age, with a fourth dose given 6 to 12 months after the third dose (typically at approximately 15 to 18 months of age).[16] A fifth dose is administered in children who received all 4 primary doses prior to their fourth birthday. Despite these guidelines, coverage rates with ≥4 doses of DTaP remain below that of other vaccines, with the exception of varicella and pneumococcal vaccines. According to the CDC, only 84.8% of children received at least 4 doses of DTaP in 2003.[17]

Another possible tool for controlling pertussis outbreaks is to vaccinate adolescents, since middle and high school students are often the source of outbreaks. Until recently, no approved pertussis vaccine was available for children older than 7 years. At present, booster vaccines are available in several countries, including Canada, Germany, France, Australia, and most recently, the United States. The high rate of outbreaks in this age group is presumably due to a waning of immunity and to high interpersonal contact rates. Thus, pertussis vaccination in adolescents could be a method for controlling pertussis incidence in this age group. It may also protect young infants who may be exposed to *B pertussis* through contact with older children.[6]

Rationale for Pertussis Boosting in Adolescents

Because adolescents represent a large proportion of infected persons in recent outbreaks and immunity has waned in the decade after vaccination,[6] many epidemiologists and infectious disease experts have advocated the addition of a booster vaccination against pertussis in adolescents as a rational way to combat the increased incidence of the disease. Indeed, adolescents and older individuals are an important reservoir for potentially serious infections in the very young who are either unvaccinated or whose vaccination schedule has not been completed. The risk that infected adolescents pose to infants is underscored by the observation that up to 90% of susceptible household contacts develop clinical disease following exposure to an index case.[18]

Since the direct and indirect costs of pertussis are substantial, a targeted vaccination program has the potential to be cost-effective. It has been estimated that among adolescents, the costs of pertussis could total $3.2 billion over a 10-year period. A recent pharmacoeconomic analysis has concluded that vaccination for all adolescents 10 to 19 years of age could prevent 0.4 to 1.8 million cases of adolescent pertussis, saving $0.3 billion to $1.6 billion over 10 years.[19]

Several countries have vaccination policies that include a diphtheria and tetanus toxoids booster during adolescence. Although recommendations regarding the immunization of adolescents in the United States have not yet been formulated, Melinda Wharton, MD, of the National Immunization Program, CDC, has recently stated, "A recommendation aimed at vaccination of young adolescents would likely be considered feasible. Such a recommendation would be compatible with existing childhood and adolescent recommendations, and could be implemented at the recommended early adolescent immunization visit." She added, "…a recommendation to vaccinate young adolescents for prevention of pertussis is most consistent with what we know about pertussis." [7]

US Food and Drug Administration Approves New Pertussis Booster for Adolescents

A new combination vaccine (Boostrix® [tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed]) has recently been approved by the US Food and Drug Administration for booster administration in adolescents. Boostrix® contains the same diphtheria toxoid, tetanus toxoid, and pertussis antigens as Infanrix® (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) and Pediarix® (diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B [recombinant] and inactivated poliovirus vaccine combined), but with reduced quantities of these antigens. Boostrix® can be used as a single dose for active booster immunization against diphtheria, tetanus, and pertussis in individuals 10 to 18 years of age. Replacing the routine tetanus-diphtheria booster (Advisory Committee on Immunization Practices-recommended at 11 to 12 years of age) with Boostrix® adds needed pertussis protection to the routine tetanus-diphtheria vaccine. Use of Boostrix® at the early adolescent visit, or prior to entry to middle school, may be an effective strategy to prevent this serious and highly contagious disease among adolescents in the United States[7,11] and may possibly reduce community outbreaks of pertussis.[6]

In clinical studies of Boostrix®, adverse events included pain, redness, and swelling at the injection site; headache, fatigue, and gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain). As with other vaccines, rare adverse events may occur. Hypersensitivity to any component of Boostrix®, Infanrix®, or Pediarix® is a contraindication. As with any vaccine, Boostrix® may not protect 100% of individuals receiving the vaccine. ◆

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