Changing Pertussis Epidemiology: Everything Old is New Again

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Before vaccination, pertussis was a universal disease of early childhood. Although apparent control of the disease in the United States and other countries was achieved through vaccination, pertussis is resurgent. Though acellular vaccines have been in use for 20 years, new data are emerging on their effectiveness and durability of protection and the contribution of these characteristics to the resurgence of pertussis.

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In the earliest decades of the 20th century, infection with *Bordetella pertussis* was essentially universal by school entry. A high cumulative incidence and roughly 1 death per 10 cases meant that pertussis killed more children in the United States annually than polio and measles combined. With the development and widespread use of effective pertussis vaccines, dramatic changes were affected in the epidemiology of pertussis. However, the recent resurgence in many countries should prompt a closer look at the aspects of pertussis that cause it to persist.

Pertussis was made notifiable in the United States in 1922. For 2 decades, reported cases were never under 100,000 and in 1934 peaked at over 265,000 [1]. Results of a clinical trial documenting the effectiveness of a killed, whole-cell vaccine became available in 1940 and shortly after vaccine became available.

In 1943 the American Academy of Pediatrics suggested routine use of whole-cell pertussis vaccine, and in 1948 reported cases of pertussis in the United States dropped below 100,000 for the first time. An historic nadir of disease—1010 cases—was recorded in 1976 (Figure 1).

In the United States, whole-cell vaccines were replaced by acellular vaccines, first as the fourth and fifth doses beginning in 1992 and then for the entire childhood series beginning in 1997 [1]. Since that time, 2 important and unprecedented changes have occurred in the epidemiology of pertussis: the emergence of disease among vaccinated adolescents during the early 2000s and more recently the emergence of disease among school-aged children (Figure 2).

Throughout the prevaccination and whole-cell vaccine eras, several important observations were made about pertussis that would presage the difficulty in achieving control. Even in the early 1900s pertussis in adults was known, and although a milder disease it was observed that adults could transmit pertussis to naive children. This adult disease was presumably the result of subsequent rather than primary infection, indicating that immunity following natural disease was not life-long. We now know that naturally acquired immunity wanes substantially in 7–20 years, but second infections have been documented with intervals as short as 3.5 years after the confirmed first infection [2]. In the early days of vaccination, outbreaks of pertussis were observed among vaccinated children within just a few years of vaccination; however, disease was milder. This suggested that immunity from vaccination waned and that protection against infection was less complete than against the severest manifestations of disease. A final critical observation is that the cyclic nature of pertussis epidemics remained largely unchanged after the widespread use of vaccination. Interepidemic periods of 3–5 years persisted, suggesting that although vaccination prevented disease or at least its severest manifestations, transmission of infection continued.

Disease, severe morbidity, and death are most common in infants. The highest reported incidence rate (160/100,000) occurs in infants under age 2 months, but rates decline substantially with increasing age and vaccination [3]. More than 80% of pertussis cases in infants under 2 months are hospitalized, and this group accounts for 57% of all infant pertussis cases.
hospitalizations (CDC unpublished data). From 2001 through 2010, 189 deaths occurred among 27,995 reported infant cases, a case-fatality ratio of 6.8/1000 infant cases [3]. Infant disease and death is greatly under-reported, with hospitalizations for pertussis 2- to 3-fold higher than reported cases [4]. Recognition of this window of highest risk has led to consideration or adoption of strategies to reduce the infant burden of disease, including a birth dose of pertussis-containing vaccine, post-partum vaccination with tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) of mothers and close contacts of infants, and more recently Tdap during pregnancy [3, 5].

Despite the gradual increase in incidence of pertussis in the 1990s, incidence was generally lower with increasing age. This observation changed during the late 1990s and early 2000s as the incidence in adolescents began to increase disproportionately [6]. By the year 2000, the reported rate in persons aged 11–19 years (7.0/100,000) exceeded that in children aged 1–6 years and 7–10 years. In the epidemic years of 2004 and 2005, each comprising over 25,000 cases, adolescents comprised 36% and 30% of cases, respectively.

The rising burden of pertussis in adolescents led to the recommendation in 2005 for Tdap at age 11 or 12 years. Coverage among 13–17 year-olds gradually increased from the first assessment in 2006 (10.8%) to 55.6% by 2009, and the long trend of disproportionate increases in adolescent incidence reversed [6]. The incidence in infants remained largely unchanged, suggesting limited or absent herd benefit from adolescent and adult Tdap [3, 6].

The epidemics in 2010 and 2012 had a dramatically different epidemiology. Of the 27,550 cases reported in 2010, over 9000 occurred in in California [7, 8]. The overall incidence in the state was 23.4/100,000, but county-level incidence was as high as 138.4. The highest incidence was observed in infants under 1 year of age, but an unusually large burden of disease occurred among children aged 7–10 years. The large majority of the children in this age group with pertussis were fully vaccinated with 5 doses of diphtheria and tetanus toxoid, acellular pertussis (DTaP), indicating a problem of vaccine failure rather than failure to vaccinate. The risk of pertussis increased substantially with increasing age between 6 and 10 years, and children aged 10 years had a higher incidence than any other age group other than infants. During the first 6 months of the 2012 epidemic in Washington the rate of disease statewide was 37.5/100,000, exceeding that in the California epidemic of 2010. County-level incidence was as high 414.9/100,000. Following infants, the highest age-specific rate of disease in Washington was observed in 10 year-olds; however, a peak in incidence was also observed among 13 and 14 year-olds, a group that was highly and recently vaccinated with Tdap [9].

The epidemiology in the United States between 2010 and 2012 largely mirrored the California and Washington experiences. Case counts in 2012 reached 48,277—more than were reported in any year since 1959. Rates in children aged 7–10 and 13 and 14 were similarly elevated, and the
great majority of cases reported occurred among fully vaccinated persons. Collectively, these observations led to the hypothesis that the epidemics were being driven largely by waning of immunity and redevelopment of susceptibility within the birth cohorts of children vaccinated with acellular vaccines, even in the face of recent booster doses.

Results from acellular vaccine trials conducted before licensure and from observational studies during the early implementation of acellular vaccines suggested that effectiveness was high and durability of protection relatively sustained. In a trial conducted in Italy of 2 doses of 3-component DTaP vaccines, efficacy of 3 doses given at 2, 4, and 6 months of age, efficacy from age 3 to 6 years was 78%–81%, leading authors to conclude that protection was sufficient to delay a fourth dose until school entry [10]. Among children who received 4 doses of a 4-component DTaP vaccine in a clinical trial conducted in Germany, with the 4th dose at age 15 months, efficacy was 89% over 6 years of follow-up with no evidence of waning over time [11]. In an observational study conducted in the United States during 1998–2001 among children aged 6 to 59 months, the effectiveness of 3 or more doses was 95% or better for both whole-cell and acellular vaccines [12].

In light of the reemergence of pertussis among highly vaccinated children and adolescents, recent evaluations have looked again at the durability of protection afforded by acellular vaccines. In a large case-control study conducted during the California epidemic, receipt of 5 doses of DTaP was 98% protective among children aged 4–10 years within the first year of receipt, but protection waned to <90% after 3 years and was 71% by ≥5 years [13]. Another study from California among children aged 4–12 years, found that after the fifth dose of DTaP, the odds of acquiring pertussis increased by approximately 42% per year [14]. Largely based on evidence from acellular vaccine trials suggesting durability of protection was sufficient to delay a booster dose until school entry, in 2003 Australia dropped its recommended fourth dose in the second year of life. During the large epidemic experienced during 2008–2009, a dramatic increase in incidence occurred among children aged 1–4 years [15]. This large epidemic was preceded by an increase in the proportion of the population with very low antipertussis antibody levels, though whether this reflects changes in vaccine-induced immunity or natural circulation of disease, or some other factor, remains unknown [16]. However, data are emerging that children vaccinated with acellular vaccines are at greater lifelong risk of pertussis than those who received whole-cell vaccines, and that the order of priming doses is important—whole-cell doses earlier in the series resulted in lower risk [17, 18].

In addition to waning of vaccine-induced immunity, changes in the antigenic and genotypic characteristics of circulating B. pertussis strains are being described. In many countries, alleles of vaccine antigens expressed by circulating organisms largely differ from those expressed by the strains from which vaccines were originally derived [19, 20]. However, pertussis epidemics are not clonal [9]. In settings of increased disease, a diversity of strains is present even when single allelic variants of vaccine antigens predominate. It remains unclear whether the appearance and rapid emergence of these predominant strains reflect selective pressure from vaccination. In some countries the emergence of allelic variants coincides with disease resurgence, but in others it does not. Recently, strains have emerged which do not express the vaccine antigens pertactin and pertussis toxin but which still cause disease [21–23]. One explanation for this occurrence is that redundant mechanisms likely exist by which B. pertussis establishes infection and causes disease. Although the as-yet unidentified effectors of these redundancies could be explored as potential candidate antigens for new vaccines, whether the effectiveness of current vaccines is diminished against strains that fail to express vaccine antigens or that express allelic variants are urgent questions for investigation.

The epidemiology of pertussis largely reflects the cumulative immune responses to disease and vaccination in the population. Inasmuch as the epidemiology is changing dramatically, the underlying population immunity may be changing, resulting from changes in the organisms circulating and causing disease or changes in vaccine-induced immunity, or a combination of both. Despite high and increasing vaccination coverage among children and adolescents, pertussis incidence is increasing. Moreover, the age-specific changes suggest that increases in susceptibility observed by time since vaccination are playing a large role. Waning immunity leaves large numbers of children and adolescents susceptible, and even modest attack rates are sufficient to result in large epidemics when a substantial proportion of the population is susceptible. Immune responses that are insufficient to provide long-lasting protection or that do not interrupt the transmission of pertussis will limit the impact that can be achieved in reducing the burden of disease.

Globally, many countries are reporting increases in pertussis cases, including countries that use only whole-cell vaccines. However, the differences from country to country in surveillance systems and vaccination programs ultimately make the factors that contribute to these increases difficult to disentangle. The sensitivity of reporting can differ dramatically based on clinician index of suspicion, capacity for laboratory confirmation, and overall level of functioning of the surveillance system. Use of whole-cell versus acellular vaccines differs, as does the timing and nature of transition in those countries that adopted acellular vaccines, as well as the number and timing of doses and the coverage achieved. Strengthening surveillance and laboratory confirmation and developing a coordinated research agenda in coming years will be critical components in further
defining the problem. Public health should focus first and foremost on demonstrating the most effective strategy to limit death and severe pertussis in infants and fully implementing it. The extent to which the incidence will continue to increase across all age groups is unknown; however, defining the “true” burden of pertussis is less critical than understanding the transmission and evolution of B. pertussis over time and the underlying immunologic basis for vaccine failure.

Notes
See also Supplement to the Journal (April 1, 2014. Volume 209, Supplement 1) Prevention and Control of Pertussis. To earn journal-based continuing medical education (CME) credit for this article, visit http://nifd.org/pertussis-cme (available after 4/15/14).

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References