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Perspective

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Epidemic Pertussis in 2012 — The Resurgence of a Vaccine-Preventable Disease

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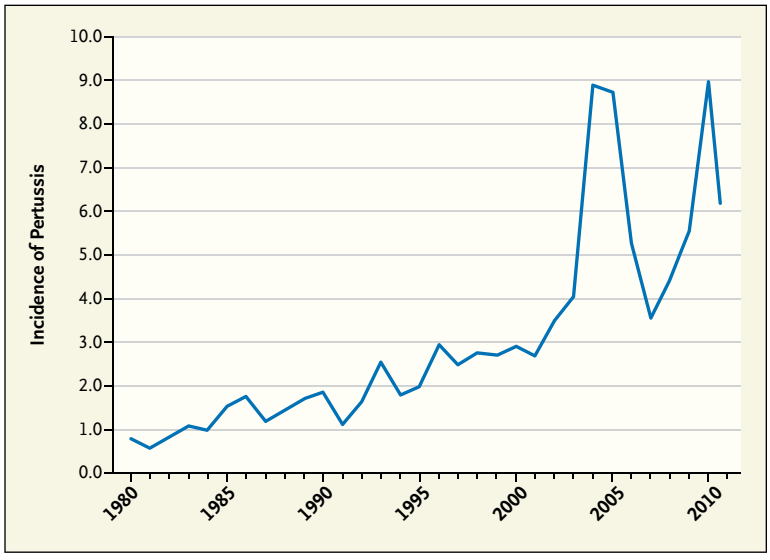
According to the Centers for Disease Control and Prevention, the United States is currently experiencing what may turn out to be the largest outbreak of reported pertussis (whooping cough) in 50 years. Why has this theoretically vaccine-preventable disease been on the upswing?

The past 45 years have seen concern about the safety of the diphtheria–tetanus–pertussis (DTP) vaccine, epidemics stemming from the vaccine's decreased use, and the development of new vaccines using acellular pertussis components (DTaP). In the prevaccine era, the number of reported cases of pertussis reached epidemic proportions every 2 to 5 years.[1,2] Pertussis immunization in the United States reduced the average incidence from 157 per 100,000 population in the early 1940s to less than 1 per 100,000 in 1973. Nevertheless, the cycles of outbreaks continued to occur, because neither infection nor immunization produces lifelong immunity to pertussis, as they do for diseases such as measles; as measles was being brought under control, the period between epidemics lengthened, and there was less clinical disease and less circulation of the virus. Since cycles of pertussis continue to occur today, we know that *Bordetella pertussis* is continuing to circulate in a manner similar to that of the prevaccine era. Around 1982, the incidence of pertussis started to gradually increase; in 2005 and 2010, substantial epidemics occurred, and another epidemic is now under way (see graph).[1-5]

There are actually two relevant epidemiologies to consider: the epidemiology of reported pertussis cases and the epidemiology of *B. pertussis* infection.[2] The former depends on the surveillance program we have in place: the more complete it is, the higher the reported incidence will be. As for the latter, over the past 25 years, three types of studies have been performed to gain insight into *B. pertussis* infection.[1,2] The first type examined the cause of prolonged illnesses involving cough in adolescents and adults; the findings suggested that 13 to 20% of these cough illnesses were attributable to *B. pertussis* infection. In the second type of study, a par-



Incidence of Pertussis per 100,000 Population in the United States, 1980–2011.
Data are from the Centers for Disease Control and Prevention.

ticipant's titer of antibody against the pertussis toxin was examined over time. The studies showed infection rates between 1 and 6%.

To date, only two prospective studies have been conducted to determine the incidence of cough illnesses associated with *B. pertussis* infection.[1,2] Both studies were hampered by substantial observer bias, and they involved only adolescents and adults. The incidence was 500 per 100,000 population in the first study and 370 per 100,000 population in the second. Although the studies were not conducted during known epidemic periods, they found 800,000 to 1 million cases per year.

So what are the causes of today's high prevalence of pertussis? First, the timing of the initial resurgence of reported cases (see graph) suggests that the main reason for it was actually increased awareness. What with the media attention on vaccine safety in the 1970s and 1980s, the studies of DTaP vaccine in the 1980s, and the efficacy trials of the 1990s comparing DTP vaccines with DTaP vaccines, literally hundreds of articles about pertussis were published. Although this information largely escaped physicians who care for adults, some pediatricians, public health officials, and the public became more aware of pertussis, and reporting therefore improved.

Moreover, during the past decade, polymerase-chain-reaction (PCR) assays have begun to be used for diagnosis, and a major contributor to the difference in the reported sizes of the 2005 and 2010 epidemics in California may well have been the more widespread use of PCR in 2010. Indeed, when serologic tests that require only a single serum sample and use methods with good specificity become more routinely available, we will see a substantial increase in the diagnosis of cases in adults.

In addition, of particular concern at present is the fact that DTaP vaccines are less potent than DTP vaccines.[4] Five studies done in the 1990s showed that DTP vaccines have greater efficacy than DTaP vaccines. Recent data from California also suggest waning of vaccine-induced immunity after the fifth dose of DTaP vaccine.[5] Certainly the major epidemics in 2005, in 2010, and now in 2012 suggest that failure of the DTaP vaccine is a matter of serious concern.

Finally, we should consider the potential contribution of genetic changes in circulating strains of *B. pertussis*.[4] It is clear that genetic changes have occurred over time in three *B. pertussis* antigens — pertussis toxin, pertactin, and fimbriae. In fact, changes in fimbrial agglutinogens related to vaccine use were noted about 50 years ago. Studies in the Netherlands and Australia have suggested that genetic changes have led to vaccine failures, but many people question these findings. If genetic changes had increased the rates of vaccine failure, one would expect to see those effects first in Denmark, which has for the past 15 years used a vaccine with a single pertussis antigen (pertussis toxin toxoid). To date, however, there is no evidence of increased vaccine failure in Denmark.

We should maintain some historical perspective on the renewed occurrences of epidemic pertussis and the fact that our current DTaP vaccines are not as good as the previous DTP vaccines: although some U.S. states have noted an incidence similar to that in the 1940s and 1950s, today's national incidence is about one twenty-third of what it was during an epidemic year in the 1930s. Nevertheless, I believe that better vaccines are something that industry, the Center for Biologics Evaluation and Research of the

Food and Drug Administration, and pertussis experts should begin working on immediately.

In the interim, we need to use the vaccines we have (DTaP and Tdap [tetanus–diphtheria–acellular pertussis]) in the best ways possible. Of particular concern are the frightening rates of complications and death associated with pertussis in unimmunized young infants. The "cocooning" strategy — vaccinating people who have contact with infants — has been implemented but is often impeded by logistics. Immunizing pregnant women is fundamentally sound because it reduces the risk that the mother will acquire pertussis around the time of delivery, and it gives the infant some protection for perhaps 1 to 2 months. But women who have multiple pregnancies within a few years present a problem, since immunization with a vaccine containing tetanus toxoid (i.e., Tdap) could result in increased local reactions.

Although some U.S. states have noted an incidence similar to that in the 1940s and 1950s, today's national incidence is about one twenty-third of what it was during an epidemic year in the 1930s. Nevertheless, better vaccines are something that industry, the FDA, and pertussis experts should begin working on immediately.

Another approach would be to start DTaP immunization at a younger age, with shorter intervals between doses. This schedule could be started at birth, and the first three doses could be completed by 3 months of age. Notably, during the period of greatest reduction in pertussis incidence in the United States (1954–1974), the three-dose primary series was completed between 3 and 5 months of age.

In 2012, it is time to recognize the successes of the past and to implement new studies and direction for the control of pertussis in the future.

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1. Mattoo S, Cherry JD. Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to Bordetella pertussis and other Bordetella subspecies. Clin Microbiol Rev 2005;18:326-82.
2. Cherry JD. The present and future control of pertussis. Clin Infect Dis 2010;51:663-7.
3. Pertussis epidemic — Washington, 2012. MMWR Morb Mortal Wkly Rep 2012;61:517-22.
4. Cherry JD. Why do pertussis vaccines fail? Pediatrics 2012;129:968-70.
5. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. J Pediatr 2012 July 20 (Epub ahead of print).

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Getting the Methods Right — The Foundation of Patient-Centered Outcomes Research

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Health care in the United States has changed dramatically over the past several decades. Today, patients have more options than ever. Making the right choices, whether for prevention, diagnosis, or treatment, requires a critical appraisal of the potential benefits and harms of the options, within the context of the patient's characteristics, conditions, and preferences.

Many of these choices are available thanks to advances in medical research. Yet most patients and many clinicians find research somewhat mysterious. They have difficulty sorting through the mountains of medical evidence to identify information that is reliable and actionable for their unique circumstances. Patient-centered outcomes research and comparative-effectiveness research promise to enhance decision makers' ability to fully understand and weigh alternatives. But just as health care interventions and delivery strategies have advanced markedly in recent decades, so have research methods (see table). Without systematic guidance for the appropriate and efficient use of these methods, their rapid growth and complexity will only add to the confusion.