Pertussis Is Less Severe in Vaccinated Than in Unvaccinated Patients

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(Keywords. pertussis; pertussis vaccine; waning immunity.

After the introduction of vaccines against pertussis, there was a dramatic decrease of the disease, and the problem was considered to have been solved. But it was not. Recently, large outbreaks have occurred in the United States, in several European countries, and in Australia [1, 2]. It is evident that there are still many unresolved questions in pertussis, the first of which is that we do not know enough about the exact pathogenesis of this infection and the real appearance of Bordetella pertussis organisms in vivo. We also do not know much about the intracellular living of the bacteria and possible transition between the virulent and non-virulent phenotypes in the mucosal environment in the lungs. Perhaps we should again pay more attention to the old questions of molecular mimicry [3]. The infection cascade is very complex, and immunity is multifactorial. During and after the development of the acellular vaccine, the main focus has been on the extracellular living of B. pertussis and humoral immunity. In pertussis, the function of Th1 and Th17 cells seems to be very important [4]. Surprisingly, even some 100 years after the discovery of B. pertussis, we do not even understand the exact mechanism behind the typical paroxysmal cough in whooping cough.

Young infants are most vulnerable if they get B. pertussis infection. Historically, pertussis has been a serious killer, and recent outbreaks show that infants have a real risk of death and complications even today [1, 2]. One of the main problems is how to induce immunity against pertussis in young infants. The situation was so alarming in California in 2012 and in the United Kingdom that vaccinations against tetanus, diphtheria, and pertussis (Tdap) during pregnancy were introduced [5, 6]. How did we arrive at this situation? In the 1980s, there was much pressure to replace the reactogenic diphtheria, tetanus, and whole-cell pertussis (DTP) vaccine with a more safe endotoxin-free vaccine. Now, many of the increased problems are considered to be caused by the acellular pertussis vaccines.

Serological studies indicated that even before the switch to the acellular vaccines, pertussis was already common in adolescent and adult populations, which formed a reservoir of B. pertussis. More than 20 years ago, 2 serological studies indicated a high infectivity rate (83% in both) of pertussis in families [7, 8]. Serology also indicated that many infected individuals (earlier vaccinated) were totally asymptomatic. Thus, the whole-cell vaccine prevented more disease than infection. In early 1990s, before the era of acellular vaccines and preschool boosters, it was found that during a local outbreak in a day-care center, among vaccinated children, pertussis polymerase chain reaction (PCR) positivity was less common in recently vaccinated children 1–3 years of age than in those 4–6 years of age [9]. Asymptomatic pertussis infection was more common in exposed preschool children than in schoolchildren during outbreaks. The older children more often had typical pertussis than the preschool children. This indicates that during a short period after the immunization, DTwP might have prevented infection; then, some years after immunization, there was a risk of asymptomatic PCR-positive infection and, later, when the major part of the immunity had waned, the symptomatic disease appeared.

Now, in the era of the acellular pertussis vaccine, the study by Barlow et al in this issue of Clinical Infectious Diseases focuses on the question if vaccination status is associated with disease severity [10]. This surveillance study was based on 624 patients (aged 6 weeks–18 years) with pertussis in Oregon. Special attention was paid to obtain the vaccination status of the patients from Oregon’s...
“ALERT” immunizations information system. About half of the study population was found to be up-to-date on vaccinations as recommended by the Advisory Committee on Immunization Practices (ACIP). The main message is that ever-vaccinated cases were significantly less likely to be hospitalized or develop severe pertussis. Stratified analysis of the different age groups indicated the largest magnitude of protection against severe disease among infants. Confounding factors, such as therapy, were analyzed; antibiotic therapy was naturally common in these patients, and 75% had received therapy during the first 3 weeks. Vaccinated children initiated the antibiotic later than the unvaccinated ones, and one would therefore expect that earlier therapy was more beneficial, if anything, for the unvaccinated group.

Altogether, complications in the entire study group were rather rare; hospitalization was needed in 2%, and 3% had radiography-positive pneumonia. Two children had acute encephalopathy and 3 developed seizures. It is of note that the youngest infants (under vaccination age) were excluded from the study. All observational studies have these limitations, such as the rate of loss to follow-up, which was 19% in this study; a higher proportion of patients lost to follow-up were in the unvaccinated group. Even with some limitations, the authors’ results are encouraging and are in line with the experience in Sweden. There, even 1 or 2 doses of diphtheria, tetanus, and acellular pertussis (DTPA) vaccine in infancy reduced the incidence of pertussis and the risk of hospitalization [11].

The results from Barlow et al suggest that the current ACIP recommendations are effective at limiting individual-level pertussis severity and morbidity, and the authors stress the importance of high vaccine coverage. The important question is, are we able to obtain with the current vaccines high enough herd immunity to effectively protect vulnerable young infants under the vaccination age? The cumulating data indicate that the answer is negative. A study in a non-human primate pertussis challenge model indicated that acellular pertussis vaccines protect against disease but are ineffective in preventing infection and transmission to other animals [12]. In fact, a similar type of phenomenon was already noticed during the DTwP era. But now the reduction of antigens and endotoxin in acellular vaccines has resulted even less protection against colonization.

There are several reasons for the “reappearance” of pertussis. It is well known that not even pertussis disease will induce lifelong immunity, and the same is true with the whole-cell vaccines. The waning of immunity in the population might be, however, faster after the introduction of the acellular vaccines [13, 14]. As pointed out by Barlow et al, differentially waning immunity to some antigens could have different consequences in protection and in severity of the disease in the waning phase of immunity. In addition, genetic polymorphisms, especially in Toll-like receptors, could be of importance both in protection and in the development of the immunity and its waning [15].

One could argue that giving more boosters to all age groups would resolve the problem. This might not be realistic. Also, the risk of having more local reactions is increased with repeated use of the tetanus and diphtheria antigens in Tdap. We are now in a new situation because the B. pertussis population has changed, and these changes have been very fast during the era of the acellular vaccines [16]. This is not surprising, because the immunity after these vaccines is much more narrow than it was after the whole-cell vaccines or after natural infection. Resurgence of pertussis might be a compound effect of pathogen adaptation and waning immunity [16]. Genetic changes in B. pertussis have occurred in genes controlling the production of the protein virulence factors against which the acellular vaccines are aimed to give immunity. Changes in the pertactin genes have been noticed in several countries, and pertactin-negative strains have appeared. A large analysis of 1300 B. pertussis isolates indicates that there has been a recent dramatic increase in pertactin-deficient B. pertussis isolates throughout the United States [17].

It is highly likely that more active use of PCR has increased the number of diagnosed cases in seriously ill infants and also in other age groups. With PCR and modern serology, the true epidemiology is easier to understand. On the other hand, the exact diagnosis of pertussis has new problems. The current PCR technology is often based on targeting the insertion sequence (IS) 481 of B. pertussis. Several copies of this IS element are present in the genome of B. pertussis, and this increases the assay sensitivity. The problem is that also Bordetella holmesii has IS elements. Earlier it was not a problem because B. holmesii was considered to be very rare. Now, a recent report from Ohio describes a mixed outbreak of 48 B. holmesii and 112 B. pertussis cases [18]. Bordetella holmesii particularly affected the adolescent population, and the symptoms were pertussis-like. This would stress the need for bacterial cultures. There is another problem, because, unlike B. pertussis, B. holmesii is sensitive to cephalaxin, an antibiotic that is often used in growth media on plates for diagnosis of B. pertussis. So with B. holmesii, one would have a pertussis-positive PCR result but a negative culture. This means that a more specific, but still sensitive, PCR technology should be developed. Currently, some of the PCR-based data might be misleading.

As recently concluded by Stanley Plotkin, we cannot allow a vaccine-preventable disease to be incompletely controlled, and new pertussis vaccines are needed [2]. There are several important targets in the design of the new vaccines: to block the transmission (prevent adhesion); to introduce immunity in both the humoral and cell-mediated sides; and to have a long-lasting memory. It is highly likely that boosters will be needed because
not even the disease will cause lifelong immunity. There are several possibilities, from attenuated whole-cell vaccines to new booster vaccines with alternative adjuvants or new antigens [1, 2, 4]. New types of booster vaccines to adolescents and adults could be an achievable first step [4]. Introduction of a new vaccine is not going to be easy, but the manufacturers should take an active role in the development. Before new formulations are available, we should keep the vaccine coverage high. The current vaccines, even with their limitations, are protective and reduce the severity of pertussis.

Note

Potential conflicts of interest. The author has conducted several published studies with the acellular vaccines, but declares no financial conflicts of interest related to this article.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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