Pertussis is resurgent. After being largely controlled in children after the advent of routine pertussis immunization with whole-cell vaccine in the 1940s, and continuing control when a switch was made to acellular vaccines in the 1990s, recent reports from around the world suggest that more cases of pertussis are occurring than can be explained by better observation and better diagnostic methods [1]. Although the epidemiologic situation is unclear in some geographical areas, there is little doubt that pertussis incidence has risen in North America, Europe, and Australia, both in school children and adolescents [2, 3]. Pertussis has increased in practically every state in the United States and in some to epidemic proportions [4, 5]. The situation in adults is uncertain, as pertussis has always been common in that age group owing to the impermanence of immunity to *Bordetella pertussis* [6].

Five factors appear to be playing a role, although experts differ as to what weight to give each one: strain change in the presence of vaccine immunity; local collections of unvaccinated and therefore susceptible children; lower efficacy of acellular vaccines relative to whole-cell vaccines; waning immunity after acellular vaccines; and the predilection of those vaccines to induce Th2 rather than Th1 responses. A sixth possible factor is suggested by the recent finding that acellular vaccine does not protect against pertussis infection in a baboon model, although symptoms are prevented [7]. If this is true in humans, circulation of the organism would be intensified in countries using acellular vaccine.

Acellular pertussis vaccines contain 1–5 antigens: pertussis toxin (PT), filamentous hemagglutinin, pertactin (PRN), and 2 fimbrial agglutinogens. Strain change has been expressed in several ways: change in circulating organisms over the years in the alleles for each of the antigens [8]; replacement of older promoters of the PT allele with the so-called P3 promotor, which generates more toxin [9, 10]; and the appearance of pertactin-deficient strains [11, 12]. The latter makes vaccines containing PRN less useful.

Although most reported cases have occurred in vaccinated children, the presence of substantial numbers of unvaccinated children in a particular area increases the pertussis risk by a factor of 2.5 [13, 14].

Multiple studies, both epidemiologic and serologic, have confirmed that immunity wanes rapidly after the acellular vaccine booster at age 4–6 years and thepreadolescent dose at age 10–12 years [15–18]. Vaccine effectiveness is high for only about 2 years postdose. Moreover, in the many clinical trials conducted in the 1990s, one of the whole-cell pertussis vaccines that was compared with acellular vaccines was poorly immunogenic. In every trial where other whole-cell pertussis vaccines were used, their efficacy was greater than that of the acellular vaccine in the same trial [19]. Although opinions differ as to the correlation of protection with antibody levels, many authorities consider that high levels of PT and PRN antibodies are associated with protection [20, 21]. In addition, studies in mice and in baboons have demonstrated that whereas whole-cell
vaccines induce both Th1 and Th2 responses (and possibly Th17 responses as well), acellular vaccines induce only Th2 cells [22–26]. Retrospective data, though uncontrolled, suggest that the receipt of even 1 dose of whole-cell vaccine in infancy before exposure confers better protection against later exposure than receipt of all acellular pertussis vaccine doses [4,27–30].

### Possible Solutions to Increased Pertussis

What can be done to respond to this situation? Table 1 lists the possibilities. Although it may be possible to make a less reactogenic whole-cell vaccine, it is unlikely that the public in developed countries would accept a return to the whole-cell vaccine formerly used. Maternal vaccination to protect newborns is now recommended and should become widespread, but that will not stop pertussis in older age groups [31]. Although it is tempting to change the alleles in acellular pertussis vaccine to those from circulating strains, that step in itself is unlikely to be the complete answer to the problem. Increasing the dose of PT to generate more and longer-lasting antibodies to the PT could be helpful. Interestingly, Denmark claims to have a low incidence of pertussis and uses a vaccine containing PT only, but in a quantity at least 2-fold higher than formulations used in other countries [32].

More relevant may be the impact of formalin inactivation of PT. Some reports show that PT so inactivated induces antibody that binds PT but is not bactericidal [33]. A PT that had been inactivated genetically but not chemically was tested in the 1990s and produced antibody levels that were much higher than the formalin-inactivated products [34, 35]. This is an important point, inasmuch as the high antibody levels are likely to give a longer duration of protection even if they wane.

Another possible improvement of acellular pertussis vaccine would be the inclusion of additional virulence factors of *B. pertussis*. The most prominent candidate is adenylate cyclase toxin, an important toxic factor [36]. However, there are numerous other candidate antigens [37–39].

Perhaps the most obvious way of improving the immunogenicity of acellular vaccine is the incorporation of a stronger adjuvant than aluminum salts into the vaccine to drive a Th1 response, assuming that such a response is necessary. Many new types of adjuvants are available, including multiple Toll-like receptor agonists. In fact, an extensive literature exists reporting experiments in animals with adjuvants to improve antibody responses to pertussis antigens [40–44]. A recent report shows that oligosaccharides derived from *B. pertussis* lipopolysaccharide and conjugated with a protein could induce bactericidal antibody [45].

Last, an attenuated strain of *B. pertussis* that is administered intranasally has been developed [45]. Whereas that type of administration raises safety concerns in infants, a live vaccine conceivably would be a useful booster after primary acellular pertussis vaccination.

In the interim, the main strategy to prevent the worst disease is acellular vaccination of pregnant women in the last trimester to provide the newborn with passive protection [46]. Cocooning (vaccination of family contacts) may provide some additional advantage but is difficult in practice [47]. Boosters with acellular vaccine could be given more often, but that is a costly public health strategy, and at the moment all acellular pertussis vaccine is given in combination with diphtheria and tetanus toxoids. In addition, until the situation is clarified, the gradual switch from whole-cell to acellular vaccines that has been occurring in less affluent countries will probably stop.

### Difficulties of Vaccine Reformulation

To change the vaccine given to infants in the first 2 years of life is a daunting proposition, both because the requirements for safety data would be large and because the pertussis is often part of combinations with many other valences, thus requiring recertification of many products currently on the market. At a time when pertussis vaccination is recommended throughout the world, it is ethically impermissible to do an efficacy study in infants with an unvaccinated control group. Moreover, the data from outbreaks show reasonable levels of protection through age 6, with the problem coming later in life [15, 16, 18, 28]. Therefore, the focus should be on the booster vaccines given to pre–school age children and in adolescents.

However, even for a new booster vaccine, the regulatory pathway is unclear. A classical efficacy study would have to

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**Table 1. Possible Vaccination Strategies to Control the Resurgence of Pertussis**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to the use of wcP</td>
<td>Probably unacceptable</td>
</tr>
<tr>
<td>Develop less-reactogenic wcP</td>
<td>Not yet done</td>
</tr>
<tr>
<td>Maternal vaccination to provide transplacental antibody to protect newborn</td>
<td>Now generally recommended</td>
</tr>
<tr>
<td>Vaccination of newborn contacts (cocoon strategy)</td>
<td>Difficult to obtain complete coverage</td>
</tr>
<tr>
<td>More frequent boosters with acP</td>
<td>Costly and difficult to put in place</td>
</tr>
<tr>
<td>Change antigens in acP to those from currently circulating strains</td>
<td>Uncertain effect</td>
</tr>
<tr>
<td>Increase quantities of current antigens</td>
<td>Would require large trials</td>
</tr>
<tr>
<td>Inactivate PT by genetic mutation or milder chemical</td>
<td>Probably advisable to increase immunogenicity</td>
</tr>
<tr>
<td>Add new virulence factors</td>
<td>Would require large trials</td>
</tr>
<tr>
<td>Use stronger adjuvants</td>
<td>May require large trials</td>
</tr>
<tr>
<td>Administer live attenuated <em>Bordetella pertussis</em> intranasally</td>
<td>Early development</td>
</tr>
<tr>
<td></td>
<td>Probably best as a boost strategy</td>
</tr>
</tbody>
</table>

Abbreviations: acP, acellular pertussis vaccine; PT, pertussis toxin; wcP, whole-cell pertussis vaccine.
compare a new vaccine with a currently accepted one to show noninferiority or superiority. Such studies will be expensive and long, considering that the current vaccines are effective for the first couple of years after administration. Therefore, ideally the licensing authorities should consider other ways of demonstrating vaccine efficacy. Those ways might include protection data in animals such as baboons, human challenge with circulating strains of B. pertussis, or simply serologic data showing higher and more persistent antibody titers. Safety will have to be demonstrated in large numbers, although fewer subjects would be needed if current components are simply updated with analogous alleles or newer inactivation methods, rather than addition of new components. It should be kept in mind that because immunity is not permanent even after natural infection [48], boosters will be necessary even with new vaccines.

Last, perhaps the most difficult obstacle is to convince manufacturers to launch development programs for new pertussis vaccines. Large effort and investment was devoted in the 1990s to bring current acellular vaccines to market. Priorities for other new vaccines are pressing and even major manufacturers cannot afford to support multiple simultaneous clinical development programs, so demand from physicians and governments will be crucial to their decisions. In addition, academia and the National Institutes of Health should assist vaccine development by conducting research on the pathogenesis and immunology of pertussis. All of this implies an enormous effort, but I believe that we cannot allow a vaccine-preventable disease to be incompletely controlled, and that a new pertussis vaccine is needed.

Note

Potential conflicts of interest. The author is a consultant to vaccine manufacturers, including those who manufacture pertussis vaccines, but declares no financial conflict 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.

References


