Pertussis control: time for something new?

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Childhood acellular pertussis vaccines were licensed and implemented in the US in the 1990s following an effort to improve on the safety profile of whole-cell vaccines. However, waning of immunity from acellular vaccines may be driving the recent resurgence of pertussis, raising the need to consider new prevention strategies.

Before the introduction of effective vaccines in the 1940s, upwards of tens of thousands of children in the US died each year from pertussis. In 2010 there were 27 deaths, with most occurring in children too young to be fully vaccinated. When mortality is the metric, the US pertussis vaccination program is a remarkable success. However, pertussis continues to circulate and the incidence has increased steadily since the 1980s (Figure 1). Over 27,000 cases were reported in 2010. Infants are at highest risk for infection, complications and death, and the majority of the 4298 infants reported with pertussis in 2010 required hospitalization. Infants are most often exposed to pertussis in their own homes, underscoring the public health importance of continued transmission and disease among older children, adolescents, and adults. Seroprevalence surveys and studies including diagnostic testing in persons with cough suggest that up to 1 million pertussis infections occur in the US each year [1]. When disease burden is the metric, the US pertussis control program has not lived up to the promise of >99% reduction achieved for many other vaccine-preventable diseases.

Differences in vaccination programs and surveillance systems limit the direct comparison of pertussis burden among countries, but some patterns are evident. Many countries with fully implemented childhood acellular vaccination programs report sustained control, but a few are observing increasing incidence in school-aged children [2,3]. Owing to concerns over adverse events associated with whole-cell vaccines, a concerted effort among government, academia, and industry to develop improved vaccines led to licensure of acellular products in the 1990s. Since 1997, the US has recommended a childhood series of five acellular vaccine doses before school entry (Table 1). Among children receiving whole-cell vaccines before the 1990s, sustained effectiveness was suggested by a low risk of disease during childhood that gradually increased during adolescence. By contrast, since 2005, an increase in risk has emerged among children aged 7 to 10 years – the first birth cohorts to receive primarily acellular vaccines [3]. A similarly worrisome development has occurred in Australia, which until 2003 employed a similar schedule to the US – after discontinuing the fourth acellular dose recommended at 18 months of age, 3-year-olds are at greater risk of pertussis than infants, suggesting rapid waning of immunity from the primary series [2]. Increasing risk among school-aged children despite high vaccination coverage may represent the first public health impact of the change to acellular vaccines. Although vaccines currently in use remain the most effective tools to prevent pertussis, if both preventing deaths and reducing morbidity are our goals, new strategies or tools may be needed.

Expanding the current program to include universal, lifespan vaccination is the first strategy to consider in efforts to reverse the trend in pertussis. In 2005, the US recommended a single Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis) dose for all adolescents and adults, and by 2010 much of the increased incidence of disease in adolescents had been reduced [3]. Adolescent vaccination programs in other countries have resulted in similar reductions in incidence in that age group [4,5]. A ‘cocooning’ strategy of vaccinating people who have contact with infants is recommended to prevent transmission to this vulnerable group, and the US recently became the first country to recommend vaccination during pregnancy to provide immunity to both mother and baby [6]. Tdap vaccines are safe and immunogenic with subsequent doses [7,8]. Enhancing decennial tetanus–diphtheria booster vaccination by adding protection against pertussis is one important measure to consider, but the potential impact is unclear. Measures of Tdap effectiveness within a few years of receipt range from 66% to 78% – less than expected from prelicensure studies [9–11]. The excellent protection in the short term provided by the preschool DTaP (diphtheria and tetanus toxoids, acellular pertussis) booster dose wanes, resulting in appreciable increased risk by the time an adolescent booster dose is due [2,3,12]. The duration of Tdap protection is unclear but can be expected to wane similarly to DTaP. Moreover, adult vaccination coverage is suboptimal and our ability to improve it may be limited [1]. Even childhood vaccination plus boosting throughout the lifespan may be insufficient to realize substantial reductions in transmission and fully control pertussis.

Modified or novel vaccines may be needed to improve pertussis control. Although acellular and whole-cell vaccines were in many cases developed from the same Borde-tella pertussis strains, they have important differences. Acellular vaccines include pertussis toxin, an important pathogenic factor, and several surface-expressed adhesins that play a role in establishing infection. Other pathogenic factors, however, are absent from acellular vaccines.
Adenylate cyclase probably contributes to the organism’s evasion of immune defenses, and therefore has been advocated as a contributory antigen [13]. Other components such as lipopolysaccharide are immunogenic themselves, but can also act as adjuvants, augmenting the immune response to other vaccine antigens.

Important challenges to improving pertussis control lie in our incomplete understanding of the immune response to infection and to vaccination. Adaptive immunity generally comprises two complementary, interdependent arms. A humoral response is activated by type 2 helper T cells (Th2), which stimulate B cell production of antibodies that can protect against pertussis. Acellular and whole-cell vaccines induce robust humoral responses and have excellent initial effectiveness. However, no direct or absolute correlation has been identified between antibodies and protective immunity, and the effectors of long-term immunity are likely to differ from those associated with short-term protection [13]. A cell-mediated immune response resulting from type 1 helper T cell (Th1) activation of macrophage uptake and intracellular killing of B. pertussis also contributes to protection. Infection and whole-cell vaccines induce robust Th1 responses, but a relatively diminished Th1 response to acellular vaccines might lead to increasing susceptibility to infection as antibodies wane or delayed clearance of bacteria if infection occurs [13].

At least one novel vaccine for intranasal administration has been developed with favorable characteristics demonstrated in animal models – a live, attenuated vaccine with three toxins genetically eliminated or deactivated [14]. The immune response to live, attenuated vaccines might more closely mirror immunity resulting from natural infection, including development of IgA-mediated mucosal immunity. Even natural infection, however, does not confer life-long immunity. Durable immunity and the ability to interrupt transmission, not just to protect against severe or symptomatic disease, should be goals of new vaccine development and evaluation.

One important question is the effect of antigenic variability on vaccine effectiveness. Variability among circulating strains for vaccine–antigen alleles is common and vaccine–antigen mismatch occurs [13]. One allelic variant of the pertussis toxin promoter has been associated with increased toxin production in vitro, and its frequency in circulating isolates correlated with a striking increase in notified cases, hospitalizations, and deaths in the Netherlands beginning in 1996 [15]. Whether this is a result of genetic drift or vaccine pressure remains unclear, but the epidemiology of disease in the US and other countries differs. The notable changes in age-specific incidence despite excellent initial vaccine effectiveness suggest that the contribution of strain variability is less consequential than the accumulation of susceptible individuals due to waning immunity among cohorts of children receiving acellular vaccines [3,12]. Nonetheless, broad protection against genetically diverse disease-causing strains is a desirable attribute for pertussis vaccines.

Table 1. The current US pertussis vaccination schedule with vaccine type and year recommended

<table>
<thead>
<tr>
<th>Dose</th>
<th>Vaccine type</th>
<th>Schedule</th>
<th>Year recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary series</td>
<td>DTaP</td>
<td>2, 4, 6 months</td>
<td>1997</td>
</tr>
<tr>
<td>Toddler booster</td>
<td>DTaP</td>
<td>15–18 months</td>
<td>1992</td>
</tr>
<tr>
<td>Preschool booster</td>
<td>DTaP</td>
<td>4–6 years</td>
<td>1992</td>
</tr>
<tr>
<td>Adolescent booster</td>
<td>Tdap</td>
<td>11–12 years$^c$</td>
<td>2005</td>
</tr>
</tbody>
</table>

$^a$Diphtheria and tetanus toxoids, acellular pertussis vaccine.
$^b$Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine.
$^c$Age 11–12 years is preferred, but other adolescents and adults who have not received it are recommended a single dose.
The regulatory pathway to licensure of new or modified vaccines remains a significant hurdle. All countries vaccinate children against pertussis so there is no setting in which it is feasible to conduct a traditional efficacy trial. Absent a clinical outcome, antibody responses from new vaccines must be bridged to those observed in the original efficacy trials of acellular vaccines in children. BANKED serum from these trials is limited, and only antigens that are present in DTaP vaccines can be evaluated. Requiring antibody responses to adolescent or adult reduced-dose vaccines to equal those observed following three infant DTaP doses may not be a realistic surrogate for effectiveness. Furthermore, there is currently no method to demonstrate the benefit conferred by novel antigens or the role of cellular immunity. The barriers to regulatory approval of novel pertussis vaccines in the US are substantial, but pathways to licensure based on immunologic correlates of protection are used for other vaccines, and an accepted animal model of disease and immunity could facilitate determining their efficacy. The absence of these two crucial tools remains a challenge for pertussis vaccine candidate development.

Much has been achieved through our pertussis vaccination program, but we should not be satisfied. Absent a ‘game-changer’, the steady increases in pertussis observed since the 1980s will undoubtedly continue. Similar to previous efforts to improve pertussis vaccines, it is time for all disciplines of vaccinology – epidemiology, microbiology, and immunology – to take up the challenge of understanding this problem and try to solve it.

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