Reining in the "100-day cough": unfinished business

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Although rare today, a shocking 1374 deaths due to pertussis occurred in Canada in 1923.[1] Vaccination played a pivotal role in decreasing cases of pertussis. The adverse-event profile of the whole-cell vaccine prompted a switch to the acellular vaccine in the late 1990s. Although still cyclical, the incidence of pertussis in children declined overall within a few years.[2] In the early 2000s, an increase in cases among teenagers prompted the recommendation for a booster dose in adolescents and, subsequently, in adults. However, the findings of a linked research paper show that there has been an increase in both outbreaks and sporadic disease, despite good vaccine coverage in Canada and globally.[3,4]

In their study, Schwartz and colleagues[4] used linked databases from the public health laboratory and population-based health administrative data in Ontario to determine vaccine effectiveness over time. The adjusted vaccine effectiveness was 80% (95% confidence interval [CI] 71%–86%) at 15–364 days, 84% (95% CI 77%–89%) at one to three years, 62% (95% CI 42%–75%) at four to seven years and 41% (95% CI 0%–66%) at eight or more years since last vaccination.[4] Their results yielded good news (the acellular vaccine works) and bad (the effectiveness does not last forever).

The group then exploited the presence of the two cohorts (pertussis positive and pertussis negative) to create a case–control study and compared those who had been "primed" or not with whole-cell vaccine. People who received only the acellular vaccine had a 2.2 times higher odds of pertussis than those primed with three doses of whole-cell pertussis vaccine, and a 1.82 times higher odds than those who had at least one priming dose of a whole-cell vaccine. This suggests that even one prior dose of whole-cell vaccine conferred added protection.

After seeing success in decreasing disease, why are we witnessing a resurgence of pertussis that has apparently accelerated in a cohort that received only the acellular vaccine? This phenomenon is not completely understood, but these epidemiologic studies are critical in understanding the biology of prevention. Other factors, such as increased reporting and the discovery of pertactin-negative pertussis strains (or other genetic variants), could also be operating, but they appear to be of less importance currently.

At the heart of the issue is the current pertussis vaccine. Both the acellular and whole-cell vaccines in human and animal models induce high, protective antibody titers to pertussis toxins and therefore confer protection against disease, at least in the short term.[5] However, the antibody decay may be faster with the acellular vaccine than was seen with the whole-cell vaccine. Using epidemiologic modelling of disease incidence in the United States, investigators were able to show that even a small decrease in efficacy and duration of protection with the acellular vaccine compared with the whole-cell vaccine could account for the increased incidence of pertussis and the curious shifts in high incidence from adolescents to preadolescents in the last decade.[6] If waning immunity is the only issue, why does the current study find incremental increases in incidence, even after adolescent doses were added? Why does having at least one dose of whole-cell vaccine add a protective effect to a series of acellular vaccine?[7]

New research into the cellular arm of the immune response has provided insights into the biology of pertussis that may help to explain the findings of Schwartz and colleagues. Detailed immunologic studies using an animal model have provided contemporary information concerning the cellular immune responses to vaccines and natural pertussis disease. The data from a baboon pertussis model indicate that,

Key points

- After seeing a decrease in pertussis, we are now witnessing a resurgence of the disease despite good vaccine coverage in Canada and globally; this may be due to effectiveness of the acellular vaccine waning over time.
- Even a small decrease in efficacy and duration of protection with the acellular vaccine compared with the whole-cell vaccine could account for the increased incidence of pertussis in particular age groups in the last decade.
- The pertussis vaccination schedule needs careful reconsideration given emerging evidence.

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although acellular vaccines induce primarily a T helper cell (T_h) 2 or mixed T_h2/T_h1 response, whole-cell vaccination induced a strong, more persistent T_h1 response.[8] Smits and colleagues[9] showed that a higher proportion of children (88%) aged nine to twelve years who had received priming with the whole-cell vaccine had a broader cytokine and T-cell proliferative response than children primed with the acellular vaccine, suggesting that the difference in later immune response was qualitative rather than quantitative. Thus, these and other data support the premise that infant priming with whole-cell vaccination may produce longer-lasting immunity, and may explain the higher odds of clinical pertussis in people who did not receive the whole-cell vaccine in this study.

Why is there continued transmission despite more booster doses? One of the truisms of infectious diseases epidemiology is that, for infection to persist in populations, transmission to susceptible individuals must occur at sufficiently high numbers. Substantial herd immunity, however, is impossible to achieve if colonization persists despite vaccination. Using this premise, the animal model noted that neither vaccine completely prevented the *Bordetella pertussis* from colonizing the upper airway (though carriage was shorter with whole-cell vaccination).[8] Despite having antibodies, these colonized animals were able to transmit *B. pertussis* and cause disease to naive, susceptible animals. Why was this? Studies of the cellular immune response showed that natural pertussis disease produced a newly described T_h17 response, felt to be critical to the induction of mucosal immunity and elimination of bacterial colonization. Neither the acellular nor whole-cell vaccines, however, was able to elicit a T_h17 response.[8,10] These early findings may provide us with tantalizing information about why current vaccines are effective at preventing disease in people who are vaccinated but in whom bacteria are still allowed to persist and, potentially, transmit to others who are susceptible owing to age or low antibody levels. Thus, although prior focus has been mainly on humoral immune responses, characterizing the more complex cellular immune responses to vaccines and natural disease may pave the way to the development of newer pertussis vaccines.[11]

What can public health do currently to tame the stubborn cough and to protect infants from exposure? Given that we know that the current vaccine works, the first step assuredly lies in timely, complete vaccine coverage in all age groups. However, until newer vaccines with a longer duration of protection and the ability to create mucosal immunity are available, a rethinking of the optimal use of the current pertussis vaccine is needed. Perhaps a booster at ten years of age should be recommended to reduce the incidence among preadolescents, or perhaps regular boosting throughout life is needed. We don't yet have a clear answer.

The new business plan will require engagement of immunologists and epidemiologists with the practical, steady hand of public health to succeed. This study is a great start.

References

1. Varughese P. Incidence of pertussis in Canada. *CMAJ* 1985;132:1041-2.
2. Bettinger JA, Halperin SA, De Serres G, et al. The effect of changing from whole-cell to acellular pertussis vaccine on the epidemiology of hospitalized children with pertussis in Canada. *Pediatr Infect Dis J* 2007;26:31-5.
3. Tan T, Dalby T, Forsyth K, et al. Pertussis across the globe: recent epidemiologic trends from 2000 to 2013. *Pediatr Infect Dis J* 2015;34:e222-32.
4. Schwartz K, Kwong J, Deeks SL, et al. Effectiveness of pertussis vaccination and duration of immunity. *CMAJ* 2016 Sept. 26 [Epub ahead of print].
5. Edwards KM, Meade BD, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. *Pediatrics* 1995;96:548-57.
6. Gambhir M, Clark TA, Cauchemez S, et al. A change in vaccine efficacy and duration of protection explains recent rises in pertussis incidence in the United States. *PLoS Comput Biol* 2015;11:e1004138.
7. Klein NP, Bartlett J, Fireman B, et al. Comparative effectiveness of acellular versus whole-cell pertussis vaccines in teenagers. *Pediatrics* 2013;131:e1716-22.
8. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A* 2014;111:787-92.
9. Smits K, Pottier G, Smet J, et al. Different T cell memory in preadolescents after whole-cell or acellular pertussis vaccination. *Vaccine* 2013;32:111-8.
10. Kolls JK, Khader SA. The role of Th17 cytokines in primary mucosal immunity. *Cytokine Growth Factor Rev* 2010;21:443–8.
11. Locht C, Mielcarek N. Live attenuated vaccines against pertussis. *Expert Rev Vaccines* 2014;13:1147-58.

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