Challenges to Pertussis Control

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In this issue of *Pediatrics*, the vaccine research group at Kaiser Permanente Northern California (KPNC) contributed another important article outlining the challenges of pertussis control in a highly vaccinated population.[1] Nearly one-half million children born between 1999 and 2016 and managed at KPNC from 2006 to 2017 were evaluated. Of those immunized children, all had received only diphtheria-tetanus-acellular pertussis (DTaP) vaccine. In total, 738 polymerase chain reaction–confirmed pertussis cases were diagnosed. Pertussis risk was 13 times higher among unvaccinated and nearly 2 times higher among undervaccinated children when compared with those who were fully vaccinated. However, >80% of the total pertussis cases were seen in children who had received all their recommended DTaP vaccine doses. Pertussis risk increased with increasing time since vaccination, clearly demonstrating waning immunity, which the KPNC group and others had previously reported.[2,3]

Those individuals who began their medical career after 1997, when DTaP totally replaced the conventional diphtheria, tetanus toxoids, and whole-cell pertussis (DTwP) vaccines, may question why DTaP replaced DTwP in the first place. When I began my academic career at Vanderbilt University School of Medicine in 1980, pertussis disease appeared to be well controlled.[4] Rarely would cases present to the medical center, and generally when they did, they were in unimmunized infants who were ill. However, the reactogenicity of DTwP, produced by formalin inactivation of whole-cell pertussis organisms, was remarkable, with many children developing fever and a fair number having febrile seizures. More parents were questioning DTwP vaccination for their children, and an increasingly litigious climate forced several of the manufacturers of DTwP to cease production.

Concern for the reactogenicity of whole-cell vaccines was addressed by the development of less reactive acellular vaccines. These vaccines, initially developed in Japan, contained 1 or more highly purified pertussis antigens selected from the myriad of antigens produced by the organism.[5] When we conducted 1 of the first randomized clinical trials in infants in the United States comparing DTaP to DTwP vaccines, the nurses who were blinded to vaccine assignment made home visits the day after vaccination. They predicted who had received DTaP and DTwP vaccines with 100% accuracy.[6] Supported by National Institutes of Health funding, 13 different DTaP vaccines were then studied head to head for their safety and immunogenicity and compared to DTwP vaccines produced by manufacturers in the United States. After the conclusion of this large trial, it was clear that the reaction profiles of all the DTaP vaccines were significantly improved over those seen with DTwP.[7,8]

The National Institutes of Health and industry then funded several large vaccine efficacy studies in Europe and Africa to compare selected DTaP to DTwP vaccines. By using a pertussis definition of ≥21 days of cough plus positive results of culture, the DTaP vaccines were shown to be more effective than 1 US-produced DTwP

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vaccine and comparable in efficacy to several other DTwP vaccines.[9] Given the improved safety profile, in 1997, DTaP vaccines were recommended to replace DTwP vaccines for both primary and booster immunization in children in the United States. DTwP vaccine is no longer available in the United States and many other high-income countries.

For about a decade, all seemed to be going well with pertussis control. Serological methods were employed to diagnose pertussis infections in adolescents and adults, and polymerase chain reaction methods were devised to more accurately detect pertussis organisms. Thus, the burden of pertussis disease was increasingly appreciated as the diagnostic methods improved. Then outbreaks occurred, including large ones in California, revealing that immunity after DTaP vaccination waned more quickly than after DTwP vaccination.[3] In the current study, Zerbo et al[1] add to the body of evidence documenting the increase in pertussis risk with time after DTaP vaccination.

What are the practical implications of this work? First, given the markedly increased risk of pertussis in unvaccinated and undervaccinated children, universal DTaP vaccination should be strongly recommended. Second, the addition of maternal Tdap vaccination administered during pregnancy has been shown to significantly reduce infant disease before primary immunization and should remain the standard.[10] How to address the waning immunity of DTaP vaccination is more problematic. Earlier this year, *Bordetella pertussis* experts from across the world met to discuss options to address this problem. One option presented was a live attenuated pertussis vaccine administered intranasally that would stimulate local immune responses and prevent colonization with pertussis organisms.[11] This vaccine is currently being studied in adults and might provide a solution for waning immunity seen with DTaP vaccine. Others suggest that the live vaccine might be given in combination with DTaP in infants to stimulate more long-lasting immunity. However, extensive safety studies in younger children would be needed before such an approach could be proposed. Another option is the addition of other antigens to the current acellular pertussis vaccines. Because whole-cell pertussis vaccines contain many more antigens than the those of the acellular vaccines, the addition of ≥1 antigens to the current acellular vaccines has been proposed. Such vaccines with additional antigens are being studied.[12] Finally, basic immunologic studies in both animals and humans have revealed that acellular vaccines generate functionally different T-cell responses than those seen after whole-cell vaccines, with the whole-cell vaccines generating more protective T-cell responses.[13] Studies are ongoing to determine if adjuvants can be added to acellular vaccines to modify their T-cell responses to a more protective immune response or whether the T-cell response remains fixed once primed with DTaP vaccine. In the interim, investigators at KPNC, other large health delivery organizations, and the Centers for Disease Control and Prevention need to continue to monitor the pertussis burden in the United States and work with scientists to improve the existing pertussis vaccines.

ABBREVIATIONS

DTaP: diphtheria-tetanus-acellular pertussis
DTwP: diphtheria, tetanus toxoids, and whole-cell pertussis
KPNC: Kaiser Permanente Northern California

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