Safer Pertussis Vaccines for Children: Trading Efficacy for Safety

Flor M. Munoz, MD

The decision to replace effective whole-cell vaccines for pertussis with less reactogenic but potentially less efficacious acellular vaccines for the primary immunization of children in the United States in the 1990s was carefully considered.[1] The performance of the heat- or formalin-inactivated *Bordetella pertussis* whole-cell vaccine combined with diphtheria and tetanus toxoids (diphtheria, tetanus, whole-cell pertussis [DTwP]) licensed in the 1940s had resulted in a dramatic decrease in the number of cases of pertussis to a nadir in the mid-1970s.[2] However, parallel to this success, the occurrence of rare but potentially serious adverse events associated with DTwP administration became unacceptable. Particularly concerning was the occurrence of high fever, febrile seizures, prolonged crying, and acute encephalopathy that sometimes followed whole-cell pertussis vaccination in some young infants.

The development and licensure of diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in the United States in the 1990s was an anticipated event for pediatric providers and parents who feared the reactogenicity associated with the administration of DTwP vaccines in infants and toddlers. The composition, safety, and immunogenicity of various DTaP vaccines were extensively studied before and after their licensure in 1991, when DTaP was recommended for the fourth and fifth doses in toddlers, and through and after 1997, when the recommendation was extended to the primary infant vaccination series. Implementation of DTaP in the routine immunization schedule came with a call for active surveillance of the safety and efficacy of acellular vaccines relative to the whole-cell vaccine as a priority in programs that made the switch.[3]

In this issue of *Pediatrics*, Moro et al[4] report on the safety of the DTaP vaccine, evaluated through the review of data from the Vaccine Adverse Event Reporting System (VAERS) of the Centers for Disease Control and Prevention in the United States. The authors include in their review all reports submitted to VAERS in the 26 years since the introduction of DTaP, from 1991 to 2016. This important review of >50 000 reports revealed that a vast majority (nearly 90%) were not serious adverse events. Common reactogenicity events reported included injection site reactions (erythema, swelling, and warmth) and pyrexia, which were transient and occurred within 1 or 2 days of vaccination. Serious adverse events represented only 11% of the reports (and included death reports), most of which were reviewed in detail and for which causes were determined to be consistent with the following background rates: neurologic conditions (including seizures and febrile seizures), gastrointestinal conditions (such as intussusception), and allergic and anaphylactic reactions. Of note, the causality of these events cannot be ascertained via VAERS, particularly given that in most cases

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Opinions expressed in these commentaries are those of the author and not necessarily those of the American Academy of Pediatrics or its Committees.

DOI: https://doi.org/10.1542/peds.2018-1036

Accepted for publication Apr 3, 2018

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The author has indicated she has no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The author has indicated she has no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-4171.

To cite: Munoz FM. Safer Pertussis Vaccines for Children: Trading Efficacy for Safety. *Pediatrics*. 2018;142(1):e20181036

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(87.7%), DTaP was administered concurrently with other vaccines. Another observation is that the events reported occurred after the administration of different types of DTaP vaccines available in the United States and used during this 26-year period, including DTaP alone and DTaP as a component of combination vaccines. Unfortunately, VAERS was not in place before 1990 to allow a comparison of adverse event reporting of DTwP in which the same methodology is used. Nevertheless, VAERS provides confirmation that DTaP vaccines are safe and have a relatively low frequency of adverse events that are consistent with their known safety profiles. Importantly, no new or unexpected adverse events were identified.

Shortly after the introduction of acellular vaccines, the resurgence of pertussis in the United States raised concerns on the efficacy of DTaP, which has now been associated with a shorter duration of protection, leaving older children, adolescents, and adults unprotected. Therefore, pertussis control in the United States today requires the administration of booster doses of acellular vaccines in adolescents, adults, and pregnant women. Countries that never switched to acellular vaccines are encouraged to continue to use DTwP vaccines, despite their reactogenicity, because of their consistent higher efficacy.[5]

There is an imperative need to develop more immunogenic pertussis vaccines that are also safe. Fortunately, active research is ongoing for the development of novel vaccines, including live attenuated vaccines, whole-cell vaccines with reduced endotoxin content to be less reactogenic, outer membrane vesicles–based vaccines, and acellular vaccine formulations prepared with new adjuvants or additional and novel antigens.[6] As we go back to the drawing board in the fight against *B pertussis*, much work is needed to learn more about this fascinating pathogen and its interactions with humans, to improve our understanding of how immunity and long lasting protection can be achieved, to engineer and produce novel vaccines, and to design and perform the clinical studies that will eventually lead to the control of pertussis disease and its global impact, with safe and effective vaccines for all.[7]

ABBREVIATIONS

DTaP: diphtheria, tetanus, and acellular pertussis
DTwP: diphtheria, tetanus, whole-cell pertussis
VAERS: Vaccine Adverse Event Reporting System

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-1036 originally published online June 4, 2018;

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Pediatrics 2018;142;
DOI: 10.1542/peds.2018-1036 originally published online June 4, 2018;

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