Number and Order of Whole Cell Pertussis Vaccines in Infancy and Disease Protection

To the Editor: Due to their lower rate of adverse events, acellular pertussis vaccines (diphtheria-tetanus-acellular pertussis; DTaP) replaced whole cell vaccines (diphtheria-tetanus-whole cell pertussis; DTwP) in many developed countries during the 1990s. DTaP became available in Queensland, Australia, in 1996 and replaced DTwP for publicly funded primary course immunizations delivered at ages 2 months, 4 months, and 6 months in March 1999. This meant children born in 1998 could receive a primary course consisting of only DTwP, only DTaP, or a mixed schedule.

Similar to North America,[1] Australia is experiencing a sustained pertussis epidemic,[2] with the highest incidence rates in Queensland during 2011 in children aged 6 to 11 years. The recent changes in pertussis epidemiology may be related to the shift from DTwP to DTaP. To test this hypothesis, we compared pertussis reporting rates by primary course vaccination in the 1998 birth cohort.

Methods. Reporting pertussis cases to the health department is mandatory in Queensland. For children born in 1998, we calculated pertussis reporting rates in both the preepidemic (1998-2008) and outbreak periods (2009-2011), by number and order of DTwP doses given before their first birthday. We linked data from the Queensland vaccination register (QVR) with case reports of pertussis. The QVR is not a population-based register so we could not construct a group of wholly unvaccinated children for comparison. Children were censored following initial reporting. We calculated average annual incidence rates, incidence rate differences, incidence rate ratios, and 95% confidence intervals using Stata version 12 (StataCorp). The Queensland Children's Health Services ethics committee approved the study.

Results. Of 58 233 children born in 1998 identified in the QVR, 40 494 (69.5%) received at least 3 doses of any per-

tussis-containing vaccine during the first year from a Queensland vaccine service provider and were included in the analysis. Overall, 267 first pertussis cases were reported from this cohort between 1999 and 2011; 2 second reports were excluded.

Children who received a 3-dose DTaP primary course had higher rates of pertussis than those who received a 3-dose DTwP primary course in the preepidemic and outbreak periods (TABLE and FIGURE). Among those who received mixed courses, rates in the current epidemic were highest for children receiving DTaP as their first dose. This pattern remained when looking at subgroups with 1 or 2 DTwP doses in the first year of life, although it did not reach statistical significance (Table). Children who received a mixed course with DTwP as the initial dose had incidence rates that were between rates for the pure course DTwP and DTaP cohorts (Table).

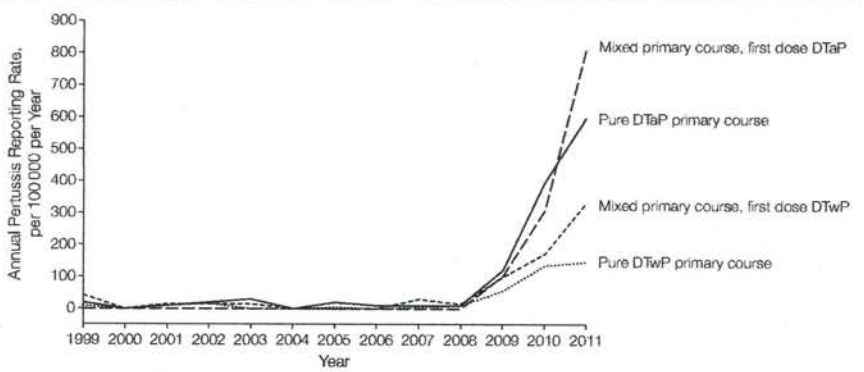
Comment. Infant priming with DTwP was associated with a lower risk of subsequent pertussis than DTaP only primed children in this cohort. This difference persisted for more than a decade, being evident in preepidemic and outbreak periods. A primary course using even a moderately effective DTwP vaccine may be more protective than DTaP.[3] In the preacellular era, Australia used a locally produced DTwP

Table. Pertussis Reports Between 1999 and 2011 for Children Born in 1998 (N = 40 694)[a]

	No. of Reports	Incidence (95% CI)			
		Average Annual Rate[b]	Rate Difference[b]	Rate Ratio	Rate Ratio[c]
Preepidemic (1999-2008)					
Pure course[d]					
DTaP primary course (n = 9827)	13	13.2 (7.0 to 22.6)	8.0 (0 to 15.8)	2.53 (1.06 to 6.07)	
DTwP primary course (n = 22 956)	12	5.2 (2.7 to 9.1)	1 [Reference]	1 [Reference]	
Outbreak (2009-2011)					
Pure course					
DTaP primary course (n = 9827)	110	373.1 (306.7 to 449.7)	259.9 (185.7 to 334.0)	3.29 (2.44 to 4.46)	
DTwP primary course (n = 22 956)	78	113.3 (89.5 to 141.3)	1 [Reference]	1 [Reference]	
Mixed course					
First dose of DTaP (n = 978)	12	409.0 (211.3 to 714.4)	295.7 (63.0 to 528.5)	3.61 (1.79 to 6.67)	
First dose of DTwP (n = 6933)	42	201.9 (145.5 to 273.0)	88.7 (22.6 to 154.7)	1.78 (1.20 to 2.63)	
Mixed course by No. of DTwP doses					
1 dose of DTwP only					
First dose of DTaP (n = 549)	6	364.3 (133.7 to 792.9)	251.0 (–41.5 to 543.6)	3.22 (1.15 to 7.32)	1.37 (0.45 to 3.53)
First dose of DTwP (n = 2501)	20	266.6 (162.8 to 411.7)	153.3 (33.8 to 272.8)	2.35 (1.36 to 3.89)	1 [Reference]
≥2 doses of DTwP					
First dose of DTaP (n = 429)[e]	6	466.2 (171.1 to 1014.7)	352.9 (–20.9 to 726.8)	4.12 (1.47 to 9.37)	2.82 (0.93 to 7.17)
First dose of DTwP (n = 4432)[f]	22	165.5 (103.7 to 250.5)	52.2 (–21.4 to 125.8)	1.46 (0.87 to 2.37)	1 [Reference]

Abbreviations: DTaP, diphtheria-tetanus-acellular pertussis; DTwP, diphtheria-tetanus-whole cell pertussis.
[a] A primary vaccination course is defined as 3 or more doses of a pertussis-containing vaccine for infants younger than 12 months of age. Analysis excludes records for infants with no vaccination history recorded before 12 months of age (n=6806), those with vaccination history provided by outside source (not a Queensland vaccine service provider; n=4129), those with irregularity of the vaccine dose by number or description (n=191), and those with less than 3 vaccination doses recorded (n=6412).
[b] Rate per 100 000 per year.
[c] Comparing dose order in mixed course cohorts.
[d] Defined as 3 or more doses of a single vaccine only.
[e] Only 2 children had 3 doses of DTwP before the age of 12 months.
[f] Only 40 children had 3 doses of DTwP before the age of 12 months.

Figure. Pertussis Reporting Rates Between 1999 and 2011 by Primary Course of Pertussis Vaccination for Children Born in 1998



DTaP indicates diphtheria-tetanus-acellular pertussis; DTwP, diphtheria-tetanus-whole cell pertussis.

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vaccine with very good to excellent effectiveness.[4] Our findings suggest the most important factor, in this cohort, may be the initial vaccine received.

It is unlikely our findings during the current outbreak are the result of detection bias because this would require health care–seeking behavior, or the likelihood of laboratory testing or reporting, to be associated with the primary course received by children over a decade previously.

Possible explanations for our findings could include antigenic shifts in circulating *Bordetella pertussis* strains[2] or the different immune responses from acellular and whole-cell priming.[5] The lesser protection provided by DTaP, both as the initial vaccine or full primary course, may be due to linked epitope suppression, when the initial exposure locks in the immune response to certain epitopes and inhibits response to other linked epitopes on subsequent exposures.[6]

The challenge for future pertussis vaccine development is to address the benefit-risk trade-off highlighted by our study, and to develop vaccines that induce long-lasting protection from the first dose, without the adverse events associated with DTwP use.

previously called "original antigenic sin"

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Author Contributions: Dr Sheridan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sheridan, Ware, Grimwood, Lambert.
Analysis and interpretation of data: Sheridan, Ware, Lambert.
Drafting of the manuscript: Sheridan, Lambert.
Critical revision of the manuscript for important intellectual content: Sheridan, Ware, Grimwood, Lambert.
Statistical analysis: Sheridan.
Administrative, technical, or material support: Sheridan, Ware.
Study supervision: Grimwood, Lambert.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Drs Grimwood and Lambert reported receiving honoraria for serving on the GlaxoSmithKline advisory boards for pneumonia and pneumonia conjugate vaccine, serving as an investigator on clinical studies sponsored by GlaxoSmithKline and sanofi-pasteur (both manufacturers of pertussis-containing vaccines), and serving on GlaxoSmithKline and sanofi-pasteur advisory boards for pneumococcal and influenza vaccines, respectively. Drs Sheridan and Ware did not report any disclosures.

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CORRECTION

Clarification of Conflict of Interest Disclosure: In a Viewpoint entitled "Studying Complementary and Alternative Therapies" published in the May 2, 2012, issue of *JAMA* (2012;307[17]:1803-1804), the conflict of interest disclosure for Dr Offit should have read as follows: "Dr Offit reports having held the patent and received royalties from the sale of Rotateq vaccine within the last 3 years, although his interest in the vaccine was sold 2 years ago." A letter regarding the correction appears in this issue. The article has been corrected online.