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Immune Responses to Pertussis Vaccines and Disease

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Target Audience
Physicians and other healthcare professionals interested in the causes, prevention, and treatment of serious infections due to pertussis.

Educational Objectives
Following the education activity, participants will be able to:

1. Describe the humoral immune responses to pertussis vaccines and natural infection.
2. Highlight the variable immune responses to different acellular and whole cell vaccines, with particular focus on the kinetics of antibody decline.
3. Review transplacental antibody transfer from mother to infant and what impact that has on infant immune responses.
4. Describe T Cell Immunity to pertussis induced by whole cell and acellular vaccines and natural infection and how it differs.
5. Discuss the Memory responses that are induced with pertussis vaccines and natural disease.

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SUPPLEMENT ARTICLE

Immune Responses to Pertussis Vaccines and Disease

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In this article we discuss the following: (1) acellular vaccines are immunogenic, but responses vary by vaccine; (2) pertussis antibody levels rapidly wane but promptly increase after vaccination; (3) whole-cell vaccines vary in immunogenicity and efficacy; (4) whole-cell vaccines and naturally occurring pertussis generate predominantly T-helper 1 (Th1) responses, whereas acellular vaccines generate mixed Th1/Th2 responses; (5) active transplacental transport of pertussis antibody is documented; (6) neonatal immunization with diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine has been associated with some suppression of pertussis antibody, but suppression has been seen less often with acellular vaccines; (7) memory B cells persist in both acellular vaccine– and whole cell vaccine–primed children; and (8) in acellular vaccine–primed children, T-cell responses remain elevated and do not increase with vaccine boosters, whereas in whole-cell vaccine–primed children, these responses can be increased by vaccine boosting and natural exposure. Despite these findings, challenges remain in understanding the immune response to pertussis vaccines.

Keywords. pertussis vaccines; acellular pertussis vaccines; whole cell pertussis vaccines; DTwP; DTaP.

With the development and testing of new acellular pertussis vaccines in the 1990s, assays to measure the humoral immune responses to the new vaccines were established [1, 2]. Scientists working at the Food and Drug Administration and in academia compared the performance of enzyme-linked immunosorbent assays (ELISAs) in the measurement of humoral responses to pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (PRN), and fimbrae (FIM) after administration of the acellular and whole-cell pertussis vaccine candidates in the National Institutes of Health (NIH)–funded Multicenter Acellular Pertussis Trial (MAPT). The ELISA results were reproducible and stable over time, and the assays could be performed in other laboratories with a high degree of reproducibility [3]. As shown in Figure 1, the reverse cumulative distribution curves for the PT antibody response after receipt of the 13 acellular and one of the whole-cell vaccines in MAPT are plotted, with the highest PT antibody response noted with the genetically detoxified PT [1]. Table 1 demonstrates the humoral responses to all of the pertussis vaccine antigens measured in the MAPT study and again shows the variability among the responses, with the whole-cell vaccines generally stimulating antibody levels somewhere in the middle of those seen with the acellular vaccines [4]. The acellular vaccines differed from the whole-cell vaccine with respect to antigen content and quantity, production methods, and adjuvant content, which contributed to differences in the immune responses noted.

After the MAPT trial, several vaccines were selected for inclusion in 2 NIH-funded vaccine-efficacy trials, one in Sweden and the other in Italy [5, 6], as summarized in a previous report [7]. Unfortunately, neither of the whole-cell vaccines studied in the MAPT trial was included in these efficacy trials. Instead, a whole-cell vaccine produced by Connaught Laboratories, DTwP, was included in both efficacy trials. Review of the serologic data obtained from the efficacy studies demonstrated that the immunoglobulin G (IgG) PT levels detected by ELISA and the PT-neutralizing antibody

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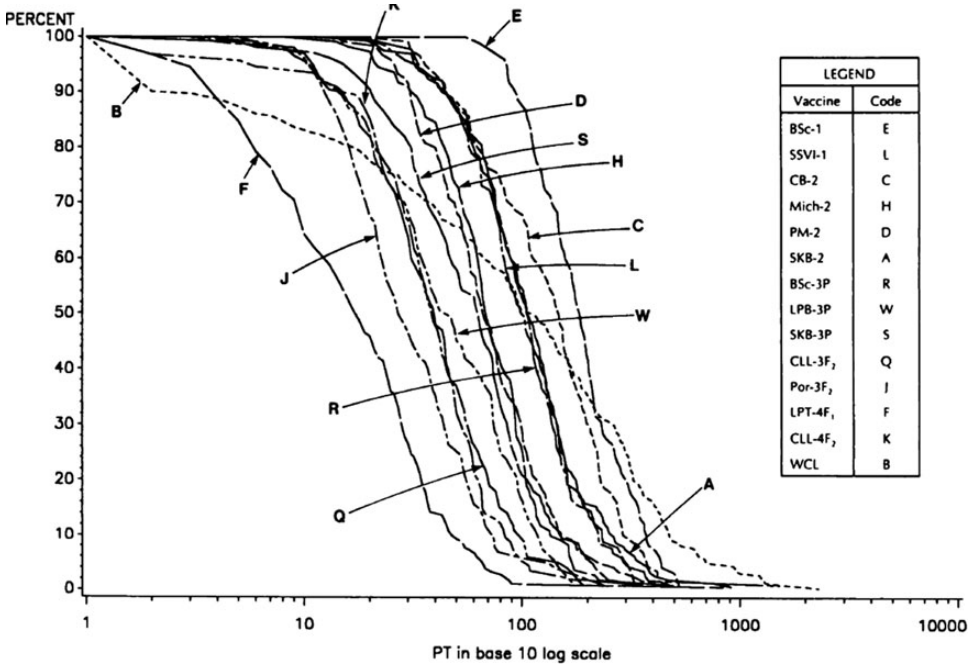

Figure 1. Reverse cumulative distribution curves, by vaccine, for antibody to pertussis toxin (PT). Each curve plots the proportion of vaccinees (ordinate) whose postimmunization concentration equals or exceeds the concentration shown on the abscissa. If a vaccine produced precisely the same results in each vaccinee, the curve would form a rectangle perpendicular to the ordinate at 100%, then straight down to the abscissa at the achieved antibody concentration. The key indicates that the whole-cell vaccine is denoted by B and the remainder of the vaccines are acellular vaccines [4].

responses to the Connaught DTwP vaccine were significantly less than the responses seen with the 2 DTaP (diphtheria toxoid, tetanus toxoid, and acellular pertussis) vaccines included in the efficacy trials [8] (Table 2).

As the children enrolled in the MAPT trial reached the age for their fourth and fifth doses of the DTaP or DTwP vaccines, they were enrolled in comparative studies of the whole-cell and acellular vaccines combined with diphtheria and tetanus toxoids [9, 10]. The DTaP vaccines were associated with fewer adverse events than the DTwP vaccine, and most DTaP vaccines stimulated comparable or higher serum antibody responses than the DTwP vaccine. Serum antibody concentrations before boosting were lower than those obtained 1 month after the primary and initial booster immunizations. After the fourth and fifth doses, significant increases in antibodies directed against the included antigens were observed for all vaccines.

Although humoral immune responses to pertussis vaccines were well characterized during that period, few studies of cell-mediated immunity were conducted. Italian investigators conducted cell-mediated immunity studies during the efficacy trials in infants, using lymphoproliferative assays. Both of the DTaP vaccines were better inducers of cell-mediated immune responses than the DTwP vaccine, particularly against PT, and the cell-mediated immune responses persisted, in contrast to the rapid decline in antibody levels [11]. Cytokine profiles were also examined. DTaP vaccines induced both a type 1 and type 2 cytokine profile, while the DTwP vaccine induced predominantly a type 1 pattern [12]. Both the acellular pertussis and whole-cell pertussis vaccines also induce a T-helper 17 (Th17) response [13]. Recently reported studies from the Netherlands also demonstrate that persistent T-cell responses to pertussis antigens are seen 3 years after booster DTaP vaccination at 11 months of age and that enhanced immunoglobulin E (IgE) and IgG4 responses to pertussis antigens are also noted after preschool booster vaccination at 4 years [14]. These IgE and IgG4 responses might be associated with the local side effects found after this booster. After naturally occurring *Bordetella pertussis* infection in children, T cells produced interferon γ but a low or undetectable level of interleukin 5, suggesting that Th1 cells were primarily seen after *B. pertussis* infection [15].

Between July 1997 and December 1998, a double-blind, randomized NIH-funded clinical trial in adolescents and adults 15–65 years of age was conducted at 8 study sites in the United States to evaluate the reactogenicity, immunogenicity, and protective efficacy of the acellular pertussis vaccine [16]. A total of 2781 individuals were enrolled in the study, with 200 each providing 5 serum samples over an 18-month period. On the basis of laboratory-confirmed pertussis with cough, vaccine efficacy was 92% (95% confidence interval, 32%–99%). The antibody titers to each of the pertussis antigens declined rapidly over this

Table 1. Antibody Levels 1 Month Following the Third Dose of Vaccine: Results From the Multicenter Acellular Pertussis Trial and a Follow-Up Trial

		Antibody Level,[a] Geometric Mean (95% CI), by Antigen			
Manufacturer or Distributor	Vaccine	PT	FHA	PRN	FIM
Sanofi Pasteur (Canada)	Tripacel	36 (32–41)	37 (32–42)	114 (93–139)	240 (204–282)
Sanofi Pasteur (Canada)	CLL-3F$_2$	38 (33–44)	36 (31–41)	3.4 (3.1–3.6)	230 (183–290)
Sanofi Pasteur (France)	Triavax	68 (60–76)	143 (126–161)	3.3 (3.1–3.6)	1.9 (1.6–2.1)
Sanofi Pasteur (US)	Tripedia	127 (111–144)	84 (73–95)	3.5 (3.2–3.9)	2.0 (1.7–2.3)
Baxter Laboratories	Certiva	54 (41–71)	1.1 (1.0–1.2)	NA	NA
Biocine Sclavo	BSc-1	180 (163–200)	1.2 (1.1–1.4)	3.4 (3.1–3.7)	1.8 (1.7–2.0)
Chiron Vaccines	Acelluvax	99 (87–113)	21 (18–25)	65 (53–79)	1.9 (1.7–2.1)
GlaxoSmithKline	Infanrix	54 (46–64)	103 (88–120)	185 (148–231)	1.9 (1.7–2.2)
Massachusetts Public Health Biologic Labs	SSVI-1	99 (87–111)	1.2 (1.1–1.3)	3.4 (3.1–3.6)	2.1 (1.8–2.4)
Michigan Department of Public Health	MIch-2	66 (59–75)	237 (213–265)	3.2 (3.0–3.4)	2.0 (1.8–2.3)
SmithKline Beecham Biologicals	SKB-2	104 (94–116)	110 (99–122)	3.3 (3.1–3.5)	1.9 (1.7–2.1)
Speywood (Porton) Pharmaceuticals	Por-3F$_2$	29 (25–33)	20 (17–23)	3.0 (3.0–3.1)	361 (303–430)
Wyeth Lederle Vaccines and Pediatrics	LPB-3P	39 (32–48)	144 (127–163)	128 (109–150)	19 (13–27)
Wyeth Pharmaceuticals	ACEL-IMUNE	14 (12–17)	49 (45–54)	54 (47–62)	51 (41–63)
Wyeth Lederle Vaccines and Pediatrics	Whole cell	67 (54–83)	3.0 (2.7–3.4)	63 (54–74)	191 (161–227)

Abbreviations: CI, confidence interval; FHA, filamentous hemagglutinin; FIM, fimbrial protein; MAPT, Multicenter Acellular Pertussis Trial; NA, not available; PRN, pertactin; PT, pertussis toxin.

[a] Following immunization at 2, 4, and 6 months.

period, with a remarkable decline in the PT antibody responses [17]. Others have reported similar marked declines in pertussis antibody titers in immunized adolescents and adults [18].

During a suspected pertussis outbreak at an academic medical center, adults received a single dose of Tdap (tetanus toxoid and reduced-dose diphtheria toxoid and acellular pertussis vaccine), and the kinetics of the IgG antibody responses to pertussis antigens were measured. By as early as 2 weeks after vaccination, 88%–94% of the adults demonstrated a booster response to each of the included antigens, supporting a role for Tdap in pertussis outbreak control [19].

Antibodies to PT and FHA readily cross the placenta and are found in infant sera in concentrations comparable to or higher than those in maternal sera, with a half-life of about 6 weeks [20, 21]. However, low maternal pertussis antibody levels in the absence of adolescent-adult pertussis booster vaccination, and the rapid decay of maternally derived antibodies in infant sera, leave infants with little humoral antibody protection against pertussis [22]. Active pertussis vaccination of pregnant women during the third trimester was studied in the early 20th century, with few adverse events and elevated antibody titers in both mother and infant [23, 24]. However, high preexisting pertussis antibody levels in infants suppressed the immune responses to DTwP vaccines and led to the rejection of maternal immunization. In contrast, ecological studies of antibody responses to acellular pertussis vaccines in infants with high versus those with low maternal antibody titers have not shown this suppression. However, the high maternal antibody levels in these studies were materially lower than would be expected after maternal Tdap during pregnancy [20, 25]. The Advisory Committee on Immunization Practices recently recommended the immunization of all pregnant women with each pregnancy [26].

Several studies have been conducted to assess the safety and immunogenicity of administering acellular pertussis vaccines to neonates at birth or within the first few weeks of life. Belloni et al administered a 3-component acellular pertussis vaccine to 45 infants at birth and at 3, 5, and 11 months of age (group 1) and compared their responses to those of 46 infants who were immunized at ages 3, 5, and 11 months (group 2) [27]. At ages 5 and 6 months, the geometric mean titers of anti-FHA and anti-PRN were significantly greater in group 1 (which had received 2 doses) than in group 2 (which had received 1 dose). At 12 month, the PT titers were significantly lower in group 1, suggesting that there was suppression of the immune response to PT with the birth dose. In another study of neonatal immunization, 50 infants 2–14 days of age were randomly assigned to receive either DTaP and hepatitis B vaccines (experimental group) or hepatitis B vaccine alone (control group) at birth [28]. At 2, 4, 6, and 17 months of age, DTaP and routine vaccines were administered to both groups. Infants in the experimental group demonstrated lower geometric mean antibody concentrations for diphtheria toxoid at 7 months of age and significantly lower geometric mean antibody concentrations for PT and PRN at 6, 7, and 18 months of age; for FIM at 6, 7, 17, and 18 months of

Table 2. Antibody Titers to Vaccines Containing Various Combinations of Diphtheria Toxoid, Tetanus Toxoid, and Acellular or Whole-Cell Pertussis

	1 Mo After Dose 3		15 Mo After Dose 3	
Antibody, Vaccine	Samples, No.	GMT (95% CI)	Samples, No.	GMT (95% CI)
IgG PT				
DTwP	449	1.2 (1.1–1.3)	332	1.1 (1.1–1.2)
DTaP produced by CB	486	94.3 (88.8–100.3)	403	4.5 (4.0–5.0)
DTaP produced by SB	476	51.3 (47.9–54.9)	389	2.7 (2.4–3.0)
DT	161	1.0 (1.0–1.1)	127	1.1 (1.0–1.2)
IgG FHA				
DTwP	449	5.03 (4.7–5.8)	332	1.6 (1.4–1.8)
DTaP produced by CB	486	52.6 (49.1–56.3)	403	4.7 (4.2–5.4)
DTaP produced by SB	476	146.9 (138.3–156.1)	389	11.4 (10.2–12.8)
DT	161	1.5 (1.3–1.6)	127	1.2 (1.0–1.3)
IgG PRN				
DTwP	449	9.8 (8.6–11.3)	332	2.3 (2.1–2.5)
DTaP produced by CB	486	136.6 (127.0–146.8)	403	9.9 (8.9–11.1)
DTaP produced by SB	476	274.2 (253.6–296.7)	389	17.9 (16.1–20.1)
DT	161	1.6 (1.6–1.7)	127	1.6 (1.5–1.7)
PT NAb				
DTwP	237	23.0 (21.4–24.6)	176	21.4 (20.2–22.7)
DTaP produced by CB	251	787.6 (718.2–863.5)	208	148.7 (124.7–177.4)
DTaP produced by SB	239	223.0 (203.7–259.7)	190	67.9 (56.0–82.3)
DT	81	22.0 (20.2–23.9)	60	21.2 (18.8–23.7)

Abbreviations: CB, Chiron Biocine; CI, confidence interval; DT, diphtheria toxoid and tetanus toxoid vaccine; DTaP, diphtheria toxoid, tetanus toxoid, and acellular pertussis vaccine; DTwP, diphtheria toxoid, tetanus toxoid, and whole-cell pertussis vaccine; FHA, filamentous hemagglutinin; GMT, geometric mean titer; IgG, immunoglobulin G; NAb, neutralizing antibody; PRN, pertactin; PT, pertussis toxin; SB, SmithKline Beecham.

age; and for FHA at 18 months of age. These data suggested that the administration of an additional dose of DTaP at birth was safe but was associated with a significantly lower response to diphtheria toxoid and to 3 of 4 pertussis antigens. A third study, using only acellular pertussis vaccine without diphtheria and tetanus toxoids, was conducted in Germany [29]. Neonates (n = 121) were randomly assigned (1:1) to receive either acellular pertussis vaccine or hepatitis B vaccine (controls) at birth, followed by receipt of DTaP, hepatitis B vaccine, inactivated polio vaccine, and *Haemophilus influenzae* type B vaccine at 2, 4, and 6 months of age. At 3 months of age, vaccination with acellular pertussis vaccine at birth had induced significantly higher antibody responses to the 3 pertussis antigens, but at 7 months, antibody titers were similar in both groups. However, antibody concentrations to *H. influenzae* type B and hepatitis B virus were significantly lower in the acellular pertussis vaccine group. Finally, Wood et al in Australia randomly assigned 76 newborns at birth to 3 groups: acellular pertussis vaccine at birth and 1 month, acellular pertussis vaccine at birth, and no additional vaccine (control) [30]. All infants received the other vaccines at the recommended times. By 2 months of age, 88% of 2-dose recipients had detectable IgG PT, compared with 43% who received a birth dose only and 15% of controls. Although neonatal vaccination elicited earlier IgG responses, T-cell memory responses displayed a strong Th2 bias, with high interleukin 5 and interleukin 13 production [31]. Additional studies are ongoing in Australia to assess the safety, immunogenicity, and effectiveness of neonatal acellular pertussis vaccination.

In the Netherlands, the coverage rate with the DTwP vaccine at 3, 4, 5, and 11 months of age was >96% for decades. But despite these vaccination rates, rises in the incidence of *B. pertussis* infection were seen every 2–3 years, starting in 1996. On the basis of IgG PT seroprevalence data among individuals >9 years of age, the incidence of pertussis was estimated to be 4.0% per year during 1995–1996 and increased to 9.3% in 2006–2007 [32]. After an attempt to improve the whole-cell vaccine and to accelerate the primary vaccination schedule to 2, 3, and 4 months of age, in 2001 a DTaP vaccine for preschool-aged children was recommended, and in 2005, the DTwP vaccine was replaced by the DTaP vaccine. Despite these changes, the incidence of pertussis continued to increase, stimulating research on humoral and cellular immune responses to pertussis vaccines. Before and after the preschool booster, significantly higher IgG levels to PT, FHA, and PRN were found in acellular

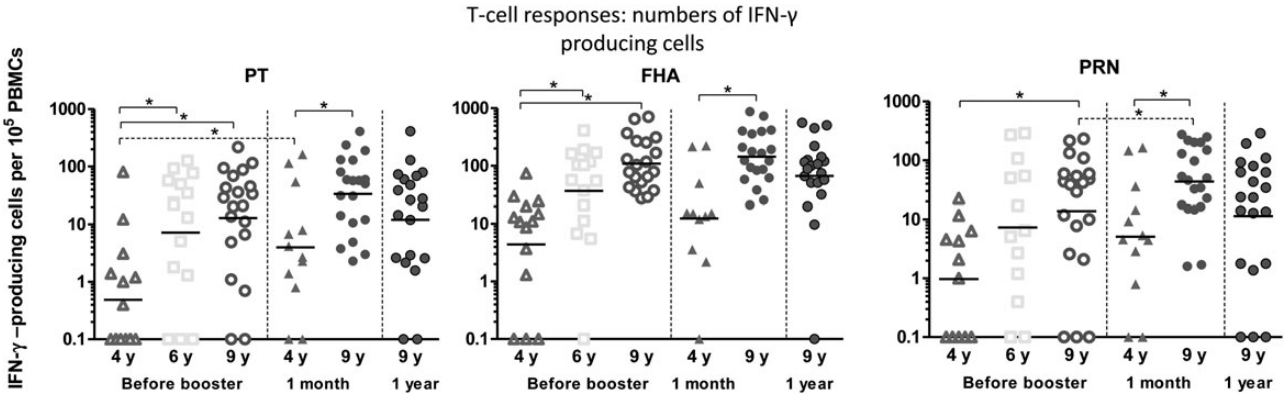

Figure 2. Peripheral blood mononuclear cells (PBMCs) obtained from children 4 years of age (open triangles; n = 14), 6 years of age (open squares; n = 15), and 9 years of age (open circles; n = 20) before booster receipt were stimulated with pertussis toxin (PT), filamentous hemagglutinin (FHA), or pertactin (PRN) for 5 days, and numbers of interferon γ (IFN-γ)–producing cells were subsequently determined. Children 9 years of age were studied longitudinally beginning 1 month (closed circles) and 1 year (dark filled circles in the 1 year column) after receipt a second acellular pertussis booster vaccine (n = 20), and children 4 years of age were studied cross-sectionally 1 month after receipt of the first acellular pertussis booster vaccine (filled triangles; n = 11). Horizontal lines represent geometric means of IFN-γ–producing cells per 100 000 stimulated PBMCs. The asterisk indicates a significant difference between groups [38].

vaccine–primed children, compared with whole-cell vaccine–primed children [33]. The effect of priming with either acellular or whole-cell vaccines on pertussis-specific memory B-cell responses before and after a booster vaccination at 4 years of age [34] was studied. After a DTaP booster, higher memory B-cell responses were demonstrated in acellular vaccine–primed children, compared with whole-cell vaccine–primed children. In addition, long-term pertussis-specific memory B-cell responses in children who were primed in infancy with whole-cell vaccine were also documented [35, 36]. The T-cell responses in children 4 years of age were found to be still elevated 3 years after acellular vaccine priming, and they did not increase after booster vaccination; in contrast, the T-cell responses in whole-cell vaccine–primed children increased after the acellular vaccine booster. Finally, after receipt of a second acellular vaccine booster in Dutch whole-cell vaccine–primed children at 9 years of age, 5 years after a preschool booster vaccination [37], increased pertussis-specific Th1 and Th2 cytokine responses were demonstrated. However, almost all T-cell responses had already increased with age, suggesting natural boosting due to pertussis outbreaks and the resulting high circulation of the bacterium (Figure 2) [38].

Although there are no agreed upon correlates of protection for pertussis, we have presented the antibody levels and cellular immunity data as a basis on which additional studies can build. In summary, (1) acellular vaccines are immunogenic, but responses vary by vaccine (2) pertussis antibody levels rapidly wane, but promptly increase after vaccination; (3) whole-cell vaccines vary in immunogenicity and efficacy, (4) whole-cell vaccines and naturally acquired pertussis generate predominantly Th1 responses, whereas acellular vaccines generate mixed Th1/Th2 responses; (5) active transplacental transport of pertussis antibody is documented; (6) neonatal immunization with DTaP has been associated with some suppression of pertussis antibody, but this has been seen less often with acellular vaccines; (7) memory B cells have been found to persist in both acellular vaccine– and Dutch whole-cell vaccine–primed children; (8) in acellular vaccine–primed children, T-cell responses remain elevated and do not increase with acellular vaccine boosters, whereas in whole-cell vaccine–primed children, these responses are increased by acellular vaccine boosters and exposure to natural infection. This suggests that priming in the first months of life is defining the nature and level of the immune response to an acellular booster vaccine later in life.

Despite these findings, a number of challenges remain in understanding the immune response to pertussis vaccines. (1) What are the factors that stimulate very different immune responses to whole-cell pertussis and acellular pertussis? (2) What immunologic studies could be used to compare responses to acellular vaccine and whole-cell vaccine with the goal of understanding protective responses? (3) What are the implications of the different immune responses to the acellular and whole-cell vaccines? (4) How can this information be used to design better vaccines? It is hoped that over the next several years advances in immunology and systems biology can be used to address these important questions.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Edwards KM, Meade BD, Decker MD, et al. Comparison of 13 acellular pertussis vaccines: overview and serologic response. Pediatrics **1995**; 96:548–57.
2. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. Pediatrics **1995**; 96:557–66.
3. Meade BD, Deforest A, Edwards KM, et al. Description and evaluation of serologic assays used in a multicenter trial of acellular pertussis vaccines. Pediatrics **1995**; 96:570–5.
4. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WAOffit PA, eds. Vaccines. 6th ed. Philadelphia: Elsevier, **2013**:447–92.
5. Gustafsson L, Hallander HO, Olin P, Reizenstein E, Storsaeter J. A controlled trial of two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. N Engl J Med **1996**; 334:349–55.
6. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progretto Pertosse Working Group. N Engl J Med **1996**; 334:341–8.
7. Lambert L. Pertussis vaccine trials in the 1990s. J Infect Dis **2014**: S12–7.
8. Giuliano M, Mastrantonio P, Giammanco A, Piscitelli A, Salmaso S, Wassilak SG. Antibody responses and persistence in the two years after immunization with two acellular vaccines and one whole-cell vaccine against pertussis. J Pediatr **1998**; 132:983–8.
9. Pichichero ME, Deloria MA, Rennels MB, et al. A safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fourth dose in 15- to 20-month-old children. Pediatrics **1997**; 100:772–88.
10. Pichichero ME, Edwards KM, Anderson EL, et al. Safety and immunogenicity of six acellular pertussis vaccines and one whole-cell pertussis vaccine given as a fifth dose in four- to six-year-old children. Pediatrics **2000**; 105:e11.
11. Cassone A, Ausiello CM, Urbani F, et al. Cell-mediated and antibody responses to Bordetella pertussis antigens in children vaccinated with acellular or whole-cell pertussis vaccines. The Progetto Pertosse-CMI Working Group. Arch Pediatr Adolesc Med **1997**; 151:283–9.
12. Ausiello CM, Urbani F, la Sala A, Lande R, Cassone A. Vaccine- and antigen-dependent type 1 and type 2 cytokine induction after primary vaccination of infants with whole-cell or acellular pertussis vaccines. Infect Immun **1997**; 65:2168–74.
13. Ross PJ, Sutton CE, Higgins S, et al. Relative contribution of Th1 and Th17 cells in adaptive immunity to Bordetella pertussis: towards the rational design of an improved acellular pertussis vaccine. PLoS Pathogens **2013**; 9:e1003264.
14. Schure RM, Hendrikx LH, de Rond LG, et al. T-cell responses before and after the fifth consecutive acellular pertussis vaccination in 4-year-old Dutch children. Clin Vaccine Immunol **2012**; 19:1879–86.
15. Ryan M, Murphy G, Gothefors L, Nilsson L, Storsaeter J, Mills KH. Bordetella pertussis respiratory infection in children is associated with preferential activation of type 1 T helper cells. J Infect Dis **1997**; 175:1246–50.
16. Ward JI, Cherry JD, Chang SJ, et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. N Engl J Med **2005**; 353:1555–63.
17. Le T, Cherry JD, Chang SJ, et al. Immune responses and antibody decay after immunization of adolescents and adults with an acellular pertussis vaccine: the APERT Study. J Infect Dis **2004**; 190:535–44.
18. McIntyre PB, Turnbull FM, Egan AM, Burgess MA, Wolter JM, Schuerman LM. High levels of antibody in adults three years after vaccination with a reduced antigen content diphtheria-tetanus-acellular pertussis vaccine. Vaccine **2004**; 23:380–5.
19. Kirkland KB, Talbot EA, Decker MD, Edwards KM. Kinetics of pertussis immune responses to tetanus-diphtheria-acellular pertussis vaccine in health care personnel: implications for outbreak control. Clin Infect Dis **2009**; 49:584–7.
20. Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. J Infect Dis **1990**; 161:487–92.
21. Shakib JH, Ralston S, Raissy HH, Stoddard GJ, Edwards KM, Byington CL. Pertussis antibodies in postpartum women and their newborns. J Perinatol **2010**; 30:93–7.
22. Healy CM, Munoz FM, Rench MA, Halasa NB, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. J Infect Dis **2004**; 190:335–40.
23. Lichty JA, Slavin B, Bradford WL. An attempt to increase resistance to pertussis in newborn infants by immunizing their mothers during pregnancy. J Clin Invest **1938**; 17:613–21.
24. Kendrick P, Eldering G, Thompson M. Reenforcing or booster injection of pertussis vaccine in previously immunized children of kindergarten age. Am J Dis Child **1946**; 72:382–8.
25. Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. Pediatrics **1995**; 96:580–4.
26. Centers for Disease Control and Prevention. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women–Advisory Committee on Immunization Practices (ACIP), 2012. MMWR **2013**; 62:131–5.
27. Belloni C, De Silvestri A, Tinelli C, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. Pediatrics **2003**; 111:1042–5.
28. Halasa NB, O'Shea A, Shi JR, LaFleur BJ, Edwards KM. Poor immune responses to a birth dose of diphtheria, tetanus, and acellular pertussis vaccine. J Pediatr **2008**; 153:327–32.
29. Knuf M, Schmitt HJ, Wolter J, et al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr **2008**; 152:655–60.
30. Wood N, McIntyre P, Marshall H, Roberton D. Acellular pertussis vaccine at birth and one month induces antibody responses by two months of age. Pediatr Infect Dis J **2010**; 29:209–15.
31. White OJ, Rowe J, Richmond P, et al. Th2-polarisation of cellular immune memory to neonatal pertussis vaccination. Vaccine **2010**; 28:2648–52.
32. de Greeff SC, de Melker HE, van Gageldonk PG, et al. Seroprevalence of pertussis in The Netherlands: evidence for increased circulation of Bordetella pertussis. PLoS One **2010**; 5:e14183.
33. De Melker HE, Versteegh FG, Schellekens JF, Teunis PF, Kretzschmar M. The incidence of Bordetella pertussis infections estimated in the population from a combination of serological surveys. J Infect **2006**; 53:106–13.
34. Hendrikx LH, Berbers GA, Veenhoven RH, Sanders EA, Buisman AM. IgG responses after booster vaccination with different pertussis vaccines in Dutch children 4 years of age: effect of vaccine antigen content. Vaccine **2009**; 27:6530–6.
35. Hendrikx LH, de Rond LG, Oztürk K, et al. Impact of infant and preschool pertussis vaccinations on memory B-cell responses in children at 4 years of age. Vaccine **2011**; 29:5725–30.
36. Hendrikx LH, Oztürk K, de Rond LG, et al. Identifying long-term memory B-cells in vaccinated children despite waning antibody levels specific for Bordetella pertussis proteins. Vaccine **2011**; 29:1431–7.
37. Schure RM, Hendrikx LH, de Rond LG, et al. Differential T- and B-Cell Responses to Pertussis in Acellular Vaccine-Primed versus Whole-Cell Vaccine-Primed Children 2 Years after Preschool Acellular Booster Vaccination. Clin Vaccine Immunol. **2013**; 20:1388–95.38.
38. Schure RM, de Rond L, Ozturk K, et al. Pertussis circulation has increased T-cell immunity during childhood more than a second acellular booster vaccination in Dutch children 9 years of age. PLoS One **2012**; 7:e41928.