

## Role of Maternal Pertussis Antibodies in Infants

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**Abstract:** Pertussis remains a serious infection in young infants. Most deaths occur in the first 3 months of life, before administration of the first dose of pertussis vaccine. Pertussis antibodies are transferred from mother to infant; but because of the lack of serologic correlates of protection, it is difficult to determine the proportion of infants born with a protective concentration of maternal antibodies. Indirect evidence suggests that maternal antibodies provide short lived protection against fatal pertussis. It is hoped that the protection of young infants could be enhanced by maternal or neonatal vaccination. The possibility of protecting young infants against pertussis by immunizing their mothers during pregnancy was investigated in the 1930s and 1940s; no further studies have been published since. Recent animal and human studies have provided evidence that neonatal immunization with acellular pertussis vaccine can efficiently prime T and B cells and act as a basis for future immune response. The limited data on neonatal and maternal pertussis immunization are promising and call for further research to reduce the vulnerability of young infants to pertussis disease.

**Key Words:** pertussis, disease, maternal antibodies, infants, immunity

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In the early 20th century, pertussis disease was responsible for more deaths during the first year of life than were measles, diphtheria or scarlet fever.<sup>1</sup> Since the introduction of diphtheria-tetanus-whole cell pertussis immunization in the late 1940s, the incidence of pertussis has dropped dramatically. However, pertussis has remained a serious infection in young infants, and the reported incidence in infants has always been high compared with other age groups.<sup>2</sup> In the

1990s, pertussis in young infants was responsible for >60% of pertussis-related complications, 86% of hospitalizations and 92% of pertussis deaths in the United States.<sup>2</sup> Even today, pertussis deaths occur most often in the first 3 months of life, before administration of the first dose of pertussis vaccine.<sup>3</sup>

This article reviews the role of maternal antibodies in protecting against pertussis infection and the potential interference of maternal antibodies with active immunization [with whole cell (wP) or acellular (aP) pertussis vaccines] in the first months of life.

### PLACENTAL TRANSPORT OF MATERNAL ANTIBODIES

All subclasses of IgG are transported from mother to infant across the placenta, predominantly during the third trimester. IgG1 is the most efficiently transferred immunoglobulin subclass.<sup>4,5</sup> Placental transfer of IgG is initiated by the binding of maternal IgG to Fc receptors in the placenta, although the exact mechanism of IgG transport across the endothelium of fetal capillaries is not yet well-understood.<sup>4</sup> The active placental transfer of IgG is specific and has variable efficacy; this means that cord blood levels can be as low as 20% of maternal levels or can exceed maternal levels by 200%.<sup>6</sup> Most data on placental transfer of antipertussis IgG date from the 1940s. These data demonstrated transplacental transfer of pertussis IgG at a relatively low efficiency, as measured by the opsonophagocytic index, agglutination or complement fixation.<sup>1,7–12</sup> In only 2–12% of mother-infant pairs did the infants' titers exceed maternal levels. These historic data also showed a direct correlation between antibody concentrations in mother-infant pairs, with the highest titers found in infants born to mothers with a history of pertussis disease or maternal pertussis immunization.<sup>1,9,13,14</sup> More recent studies have shown conflicting results on the relative efficiency of the transplacental transfer of specific maternal pertussis IgG. Although one study demonstrated that pertussis toxin (PT) IgG might be more efficiently transferred than IgG against other pertussis antigens,<sup>15</sup> other studies found no difference among the different pertussis antigens.<sup>16,17</sup>

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## PROTECTION OF INFANTS BY MATERNAL ANTIBODIES

As early as the 1930s, it was observed that mothers transfer antibodies to their infants, thus providing infants with some degree of protection against diseases such as measles, diphtheria and poliomyelitis.<sup>1,9,18</sup> Maternal antibodies can protect infants from infections and modify the severity of infectious diseases in infants for a varying period of time, depending on the level of placental transmission and the rate of decay of passively acquired antibodies. Although there is a highly significant correlation between the level of vaccine-induced anti-PT IgG antibody in the serum and protection against pertussis,<sup>19–23</sup> there is no definitive serologic correlate of protection for pertussis. It is therefore difficult to determine the proportion of infants born with a protective level of maternal antibodies.

Pertussis notification data from the prevaccine era provide indirect evidence that maternal antibodies provide short lived protection against fatal pertussis by demonstrating that the rate of pertussis deaths in the first month of life was approximately one-third of that in the second and third months of life.<sup>24</sup> In contrast, pertussis surveillance data in the vaccine era no longer demonstrate a substantial difference in pertussis-related mortality between the first and second months of life (Table 1).<sup>25</sup> This could be the consequence of reduced levels of circulation of *Bordetella pertussis* in young women of childbearing age after the introduction of mass immunization. Although it is difficult to draw direct comparisons because of the different laboratory methods, this hypothesis is supported indirectly by serologic data. In the prevaccine era, 30–50% of pregnant women had circulating antibodies against pertussis<sup>8,11</sup>; whereas more recent studies found low anti-PT IgG levels (geometric mean titer, <10 enzyme-linked immunosorbent assay units/mL) in the majority of women.<sup>17,26</sup> A recent study of maternal IgG antiper-

tussis antibody in U.S. women showed very low levels of antibody in women and their infants to pertussis toxoid, filamentous hemagglutinin and fimbrial proteins and demonstrated that most of this antibody was absent by 2 months of age in infants born to these mothers.<sup>27</sup>

There is also some evidence from animal studies that maternal anti-PT IgA and IgG transferred via colostrum or breast milk could be protective.<sup>9,28</sup>

## ENHANCED PASSIVE PROTECTION THROUGH MATERNAL IMMUNIZATION

The possibility of protecting young infants against pertussis by immunizing their mothers during the third trimester of pregnancy has been investigated since the 1930s.<sup>13</sup> After maternal immunization, concentrations of pertussis antibodies in infants ranged from 50% of maternal titers to approximately equal titers in mother-infant pairs.<sup>1,9,13,14</sup> Babies born to immunized mothers had ~2.9 times greater levels of antibodies to pertussis than did control babies.<sup>14</sup> Unfortunately no efficacy studies of maternal immunization on infant protection have been performed to assess whether infant titers resulting from maternal immunization were protective, given that no clear serologic correlates of protection exist. Animal studies were able to demonstrate protection in mice that received serum from infants born to mothers immunized during pregnancy and were challenged with virulent *B. pertussis*.<sup>1</sup>

Maternal PT and filamentous hemagglutinin IgG antibodies have a half-life of ~5 weeks (36.3 and 40.3 days, respectively) and drop to undetectable levels by 4 months of life in infants whose mothers were not immunized or by 6 months of life in infants whose mothers were immunized.<sup>9,15,29</sup>

## INTERFERENCE OF MATERNAL ANTIBODIES WITH ACTIVE INFANT IMMUNIZATION AND THE POTENTIAL OF NEONATAL VACCINATION

*Humoral Immunity.* In the 1930s, infant immunization was recommended during the second half-year of life because young infants did not appear to respond as well as older infants to the pertussis vaccine.<sup>13</sup> Studies conducted during the 1940s demonstrated that adequate immunity against pertussis could be achieved in infants by 6 months of age if the first dose was given at 2 months of age.<sup>7,9</sup> Immunizations given within 24 hours of birth resulted in a decreased humoral immune response or “temporary immune paralysis.”<sup>30,31</sup> Observations in a recent murine model confirm the findings of transient unresponsiveness after neonatal immunization with wP vaccine and further indicate that this phenomenon is antigen-specific and does not imply the induction of long-lasting immune tolerance or the absence of protective efficacy.<sup>32</sup>

**TABLE 1.** Pertussis Deaths in Infants Younger Than 1 Year of Age in 1938–1940 and 1990–1999 in the United States

Age (mo)	1938–1940 <sup>24</sup>		1990–1999 <sup>25*</sup>	
	n	%	n	%
0	396	5.6	35	38.0
1	1166	16.4	33	34.8
2	1061	14.9	12	13.0
3	791	11.1	4	4.4
4	646	9.1	3	3.3
5	515	7.2	2	2.2
6	502	7.0	1	1.1
7	458	6.4	3	3.3
8	447	6.3	0	0.0
9	417	5.9	0	0.0
10	361	5.1	0	0.0
11	363	5.1	0	0.0

\*Also personal communication with Dr Tanaka.

The reason for the poor immune response in infants vaccinated at birth (or shortly thereafter) is believed to be the immaturity of the neonatal immune response as well as the impact of competing maternal antibodies. Historic studies demonstrated that the immune response to immunization with wP vaccine was lower in infants with high cord blood anti-PT antibody levels than in infants with a low level of circulating maternal antibodies.<sup>7,11,14,29,31,33,34</sup> In contrast with maternal antibodies inhibiting infants' immune responses to wP vaccine, immunization with aP vaccine is not inhibited by circulating maternal antibodies.<sup>15,26,32,35</sup>

Both animal and human studies have recently provided further evidence of the potential of neonatal immunization with aP vaccine. Immunization with aP vaccine in neonatal (1-week-old) mice mounted as strong a response as in infant (3-week-old) mice.<sup>32</sup> A human study suggests that it might currently be possible to induce early protection against pertussis as 10% of infants vaccinated at birth reached a 4-fold increase in anti-PT IgG levels, and a rapid induction of antibodies after the second dose was observed in those infants vaccinated at birth.<sup>17</sup>

**T Cell-Mediated Immunity.** The inhibitory influence of maternal antibodies on infants' immune responses to wP vaccines is B cell determinant-specific and leaves the infant T cell responses largely unaffected.<sup>36</sup> The weak neonatal T cell-mediated cytotoxicity and T cell help for B cell differentiation results in an immature immune response. Although neonatal immunization does not generally lead to rapid antibody responses, strong induction of pertussis-specific antibody-secreting cells and memory cells can be achieved, and subsequent vaccine doses will induce infant antibody responses as soon as circulating maternal antibody titers decline below the infant's response threshold, as demonstrated by experiments in which neonatal mice were vaccinated with aP vaccine. Neonatal immunization may thus efficiently prime B and T cells and act as a basis for future immune response.<sup>32</sup>

## CONCLUSION

Despite immense progress in reducing the morbidity and mortality of pertussis through universal infant and childhood immunization, pertussis disease in infants too young to be fully vaccinated remains a public health problem worldwide. New vaccination strategies are being considered to improve pertussis control during the first months of life. Considerable logistic issues, high costs and the unknown impact challenge these vaccination strategies. Alternative options in addition to adolescent or adult immunization include maternal and neonatal immunization. Vaccine liability issues and the potential impact of this approach on subsequent infant immune responses remain the greatest barriers to development and implementation of maternal pertussis vaccination. Data on neonatal immunization with aP are limited but promising. Research should focus on the question of

whether maternal or neonatal vaccination can reduce the vulnerability of young infants to pertussis.

## REFERENCES

- Cohen P, Scandron SJ. Placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother. *JAMA*. 1943;121:656–662.
- Centers for Disease Control and Prevention. Pertussis: United States, 1997–2000. *MMWR*. 2002;51:73–76.
- Centers for Disease Control and Prevention. Pertussis deaths: United States, 2000. *MMWR*. 2002;51:616–618.
- Simister NE. Placental transport of immunoglobulin G. *Vaccine*. 2003; 21:3365–3369.
- Einhorn MS, Granof DM, Nahm MH, Quinn A, Schakelford PG. Concentrations on antibodies in paired maternal and infant sera: relationship to IgG subclasses. *J Pediatr*. 1987;111:738–788.
- Siegrist CA, Lambert PH. Maternal immunity and infant responses to immunization: factors influencing infant responses. *Dev Biol Stand*. 1998;95:133–139.
- Rambar AC, Howell K, Cenenzholz EJ, Glodman M, Stanrad R. Studies in immunity to pertussis. *JAMA*. 1941;117:79–85.
- Mishulow L, Leifer L, Sherwood C, Schlesinger AL, Berkey SR. Pertussis antibodies in pregnant women: protective, agglutinating, and complement-fixing antibodies before and after vaccination. *Am J Dis Child*. 1942;64:608–617.
- Adams JM, Kimball AC, Adams FH. Early immunization against pertussis. *Am J Dis Child*. 1947;74:10–18.
- Bradford WL, Slavin B. Opsono-cytophagic reaction of the blood in pertussis. *Pediatrics*. 1949;4:711–717.
- Miller JJ, Harold KF, Ryan ML, Silverberg RJ, Lew E. Immunization against pertussis during the first four months of life. *Pediatrics*. 1949; 4:468–478.
- Goerke LS, Roberts P, Chapman JM. Neonatal response to DTP vaccines. *Public Health Rep*. 1958;73:511–519.
- Lichty JR, Slavin B, Bradford WL. Attempt to increase resistance to pertussis in newborn infants by immunizing their mothers during pregnancy. *J Clin Invest*. 1938;17:613–621.
- Kendrick P, Thompson M, Elderling G. Immunity response of mothers and babies to injections of pertussis vaccine during pregnancy. *Am J Dis Child*. 1945;70:25–28.
- 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;161:487–492.
- Novotny P, Macaulay ME, Hart TC, Skavril F. Analysis of antibody profiles in children with whooping cough. *Dev Biol Stand*. 1990;73:267–273.
- Belloni C, De Silvestri A, Tinelli C, et al. Immunogenicity of a three-component acellular pertussis vaccine administered at birth. *Pediatrics*. 2003;111:1042–1045.
- McKahn CF, Chu FT. Antibodies in placental extracts. *J Infect Dis*. 1933;52:268.
- Cherry JD, Gornbein J, Heininger U, Stehr K. Search for serologic correlates of immunity to *Bordetella pertussis* cough illnesses. *Vaccine*. 1998;16:1901–1906.
- Storsaeter J, Hallander HO, Gustafsson L, Olin P. Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. *Vaccine*. 1998;16:1907–1916.
- Taranger J, Trollfors B, Lagergard T, et al. Correlation between pertussis toxin IgG antibodies in postvaccination sera and subsequent protection against pertussis. *J Infect Dis*. 2000;181:1010–1013.
- Hellwig SM, Rodriguez ME, Berbers GA, van de Winkel JG, Mooi FR. Crucial role of antibodies to pertactin in *Bordetella pertussis* immunity. *J Infect Dis*. 2003;188:738–742.
- Storsaeter J, Hallander HO, Gustafsson L, Olin P. Low levels of anti-pertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to *Bordetella pertussis*. *Vaccine*. 2003;21:3542–3549.
- Sako W, Treuting WL, Witt DB, Nichamin SJ. Early immunization against pertussis with alum precipitated vaccine. *JAMA*. 1945;127:379–

- 384.
25. Tanaka M, Vitek CR, Pascual FB, Bisgard KM, Tate JE, Murphy TV. Trends in pertussis among infants in the United States, 1980–1999. *JAMA*. 2003;290:2968–2975.
  26. Englund JA, Anderson EL, Reed GF, et al. 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;96:580–584.
  27. Healy CM, Munoz FM, Rench MA, Halasa N, Edwards KM, Baker CJ. Prevalence of pertussis antibodies in maternal delivery, cord, and infant serum. *J Infect Dis*. 2004;190:335–340.
  28. Oda M, Cowell JL, Burstyn DG, Thaib S, Manclark CR. Antibodies to *Bordetella pertussis* in human colostrum and their protective activity against aerosol infection in mice. *Infect Immun*. 1985;47:441–445.
  29. Baraff LJ, Leake RD, Burstyn DG, et al. Immunologic response to early and routine DTP immunization in infants. *Pediatrics*. 1984;73:37–42.
  30. Du Plan RM. Vaccination of the newborn infant against pertussis. *J Pediatr*. 1958;53:180–186.
  31. Provenzano RW, Wetterlow LH, Sullivan CL. Immunization and antibody response in the newborn infant. *N Engl J Med*. 1965;273:959–965.
  32. Roduit C, Bozzotti P, Mielcarek N, et al. Immunogenicity and protective efficacy of neonatal vaccination against *Bordetella pertussis* in a murine model: evidence for early control of pertussis. *Infect Immun*. 2002;70:3521–3528.
  33. Burstyn DG, Baraff LJ, Peppler MS, Leake RD, St Geme J, Manclark CR. Serological response to filamentous hemagglutinin and lymphocytosis-promoting toxin of *Bordetella pertussis*. *Infect Immun*. 1983;41:1150–1156.
  34. Osborn JJ, Dancis J, Julia JF. Studies of the immunology of the newborn infant, II: interference with active immunization by passive transplacental circulating antibody. *Pediatrics*. 1952;10:328–334.
  35. Heining U, Cherry JD, Christenson PD, et al. Comparative study of Lederle/Takeda acellular and Lederle whole-cell pertussis-component diphtheria-tetanus-pertussis vaccines in infants in Germany. *Vaccine*. 1994;12:81–86.
  36. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. *Vaccine*. 2003;21:3406–3412.