

# Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?

Paul A. Offit, MD\*; Jessica Quarles‡; Michael A. Gerber, MD§; Charles J. Hackett, PhD||; Edgar K. Marcuse, MD¶; Tobias R. Kollman, MD#; Bruce G. Gellin, MD\*\*; and Sarah Landry‡

**ABSTRACT.** Recent surveys found that an increasing number of parents are concerned that infants receive too many vaccines. Implicit in this concern is that the infant's immune system is inadequately developed to handle vaccines safely or that multiple vaccines may overwhelm the immune system. In this review, we will examine the following: 1) the ontogeny of the active immune response and the ability of neonates and young infants to respond to vaccines; 2) the theoretic capacity of an infant's immune system; 3) data that demonstrate that mild or moderate illness does not interfere with an infant's ability to generate protective immune responses to vaccines; 4) how infants respond to vaccines given in combination compared with the same vaccines given separately; 5) data showing that vaccinated children are not more likely to develop infections with other pathogens than unvaccinated children; and 6) the fact that infants actually encounter fewer antigens in vaccines today than they did 40 or 100 years ago. *Pediatrics* 2002;109:124–129; *multiple vaccines, immunity, parental concerns.*

ABBREVIATIONS. Ig, immunoglobulins; Th, helper T-cell; Hib, *Haemophilus influenzae* type b; OPV, oral polio vaccine; HIV, human immunodeficiency virus; MMR, measles-mumps-rubella; DTP, diphtheria-tetanus-pertussis.

One hundred years ago, children received 1 vaccine (the smallpox vaccine). Forty years ago, children received 5 vaccines routinely (diphtheria, pertussis, tetanus, polio, and smallpox vaccines) and as many as 8 shots by 2 years of age. Today, children receive 11 vaccines routinely and as

From the \*Section of Infectious Diseases, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, and Wistar Institute of Anatomy and Biology, Philadelphia, Pennsylvania; ‡Division of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; §National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ||Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; ¶Section of Infectious Diseases, Children's Hospital and Regional Medical Center, University of Washington School of Medicine, Seattle, Washington; #Department of Pediatrics, University of Washington School of Medicine, Department of Epidemiology, University of Washington School of Public Health and Community Medicine, and Children's Hospital and Regional Medical Center, Seattle, Washington; and \*\*Department of Preventive Medicine, Vanderbilt Medical College, Nashville, Tennessee.

Received for publication Aug 7, 2001; accepted Oct 4, 2001.

Reprint requests to (P.A.O.) Children's Hospital of Philadelphia, Abramson Research Building, Room 1202C, 3516 Civic Center Blvd, Philadelphia, PA 19104. E-mail: offit@email.chop.edu

PEDIATRICS (ISSN 0031 4005). Copyright © 2002 by the American Academy of Pediatrics.

many as 20 shots by 2 years of age (Table 1). The increased number of vaccines given to children and the increased percentage of children receiving vaccines have resulted in a dramatic decrease in the number of vaccine-preventable diseases. Most young parents today have never seen many of the diseases that vaccines prevent. As a possible consequence of these trends, recent national surveys found that 23% of parents questioned the number of shots recommended for their children,<sup>1</sup> and 25% were concerned that vaccines might weaken the immune system.<sup>1</sup>

Because most parents receive information and recommendations about vaccines from their doctors,<sup>2</sup> and because these recommendations carry substantial weight with parents,<sup>3,4</sup> providers must be knowledgeable when addressing parents' concerns. This article will provide health care professionals with information about the effect of vaccines on the infant's immune system and the capacity of the immune system to respond safely to multiple vaccines.

## A BRIEF SUMMARY OF NEONATAL AND INFANT IMMUNE RESPONSES

### The Neonatal Immune System

Neonates develop the capacity to respond to foreign antigens before they are born. B and T cells are present by 14 weeks' gestation and express an enormous array of antigen-specific receptors.<sup>5</sup> Although the fetal immune system has the potential to respond to large numbers of foreign antigens, few foreign antigens are present in utero, and cells of the immune system are, therefore, primarily "naïve" at birth.

### Passively Acquired Immunity

The neonate is, in part, protected against disease by maternal immunoglobulins (Ig). Maternal IgG is transported across the placenta before birth and maternal secretory IgA is present in breast milk and colostrum. These passively acquired antibodies provide protection against pathogens to which the mother was immune. However, protection provided by passively transferred antibodies is short-lived. Passively acquired maternal IgG declines during the first few months of life,<sup>6</sup> and most infants are not breastfed beyond several months of age.<sup>7</sup> More importantly, maternal antibodies offer limited immunologic protection when compared with protection afforded by an infant's active immune response.

**TABLE 1.** Number of Vaccines and Possible Number of Injections Over the Past 100 Years

| Year  | Number of Vaccines | Possible Number of Injections by 2 Years of Age | Possible Number of Injections at a Single Visit |
|-------|--------------------|-------------------------------------------------|-------------------------------------------------|
| 1900* | 1                  | 1                                               | 1                                               |
| 1960† | 5                  | 8                                               | 2                                               |
| 1980‡ | 7                  | 5                                               | 2                                               |
| 2000§ | 11                 | 20                                              | 5                                               |

\* In 1900, children received the smallpox vaccine.

† In 1960, children received the smallpox, diphtheria, tetanus, whole-cell pertussis, and polio vaccines. The diphtheria, tetanus, and whole-cell pertussis vaccines were given in combination (DTP), and the polio vaccine (inactivated) was given as a series of 3 injections.

‡ In 1980, children received the DTP, polio, and MMR vaccines. The DTP and MMR vaccines were given in combination and the polio vaccine (live, attenuated) was given by mouth.

§ In 2000 children received the diphtheria-tetanus-acellular-pertussis, MMR, inactivated polio, Hib, varicella, conjugate pneumococcal, and hepatitis B vaccines.

### Active Immunity

Neonates are capable of generating both humoral and cellular immune responses to pathogens at the time of birth.<sup>8,9</sup> Active immunity in the newborn includes the full range of B-cell responses including the production of IgM, IgG, and secretory and monomeric IgA, as well as the development of helper T-cell (Th) and cytotoxic T-cell responses.<sup>8,9</sup> In addition, neonates can produce specific Th-cell subsets, including Th1-type cells that participate in cell-mediated immune responses and Th2-type cells that are primarily involved in promoting B-cell responses.<sup>8,9</sup>

The development of active humoral and cellular immune responses in the newborn is necessary to meet the tremendous number of environmental challenges encountered from the moment of birth. When children are born, they emerge from the relatively sterile environment of the uterus into a world teeming with bacteria and other microorganisms. Beginning with the birth process, the newborn is exposed to microbes from the mother's cervix and birth canal, then the surrounding environment. Within a matter of hours, the gastrointestinal tract of the newborn, initially relatively free of microbes, is heavily colonized with bacteria.<sup>10</sup> The most common of these colonizing bacteria include facultative anaerobic bacteria, such as *Escherichia coli* and streptococci, and strict anaerobic bacteria, such as *Bacteroides* and *Clostridium*.<sup>10</sup> Specific secretory IgA responses directed against these potentially harmful bacteria are produced by the neonate's intestinal lymphocytes within the first week of life.<sup>11</sup>

### Functional Differences Between Infant and Adult Immune Responses

Although infants can generate all functional T-cells (ie, Th1, Th2, and cytotoxic T-cells),<sup>8,9</sup> infant B-cell responses are deficient when compared with older children and adults. Infants respond well to antigens (such as proteins) that require T-cell help for development. However, until about 2 years of age, the B-cell response to T-cell-independent antigens (such as polysaccharides) is considerably less than that found in adults.<sup>12</sup> For this reason, infants are uniquely susceptible to bacteria that are coated with polysaccharides (such as *Haemophilus influenzae* type b [Hib] and *Streptococcus pneumoniae*).

### IMMUNE RESPONSE TO VACCINES BY NEONATES

The neonate is capable of mounting a protective immune response to vaccines within hours of birth.<sup>9</sup> For example, neonates born to mothers with hepatitis B virus infection mount an excellent protective immune response to hepatitis B vaccine given at birth, even without additional use of hepatitis B virus-specific immunoglobulin.<sup>13-15</sup> In addition, BCG vaccine given at birth induces circulating T-cells that protect against bacteremia and subsequent development of military tuberculosis and tuberculous meningitis.<sup>16-18</sup>

### IMMUNE RESPONSE TO VACCINES BY INFANTS

The young infant is fully capable of generating protective humoral and cellular immune responses to multiple vaccines simultaneously. Approximately 90% of infants develop active protective immune responses to the primary series of diphtheria-tetanus-acellular-pertussis, hepatitis B, pneumococcus, Hib, and inactivated polio vaccines given between 2 months and 6 months of age.<sup>19</sup>

To circumvent the infant's inability to mount T-cell-independent B-cell responses, polysaccharide vaccines (Hib and *S pneumoniae*) are linked to proteins (ie, diphtheria toxoid, diphtheria toxin mutant protein, tetanus toxoid, or meningococcal group B outer-membrane protein) that engage the infant's Th-cells. By converting a T-cell-independent immune response to a T-cell-dependent response, conjugate vaccines can be recognized by the infant's B-cells. Conjugate vaccines, therefore, induce protective immune responses in infants that are often greater than those found after natural infection.<sup>20</sup>

### IMMUNE RESPONSE TO VACCINES BY CHILDREN WITH IMMUNODEFICIENCIES

Severely immunocompromised children (specifically, those with T-cell defects) who receive live viral vaccines (eg, measles or varicella vaccines)<sup>21,22</sup> or live bacterial vaccines (eg, BCG vaccine)<sup>23,24</sup> may develop disseminated infections with these attenuated pathogens. However, the only live vaccine that was routinely given in the United States in the first year of life, the oral polio vaccine (OPV), has now been replaced with inactivated polio vaccine. Therefore, children do not receive their first live viral vaccines

until about 12 to 15 months of age. Most children with severe T-cell deficiencies (eg, severe combined immunodeficiency syndrome) will have been identified by 6 to 8 months of age.<sup>24,25</sup>

However, many children with immunodeficiencies respond well to live viral vaccines. Because the risk of severe infection is greater after natural infection with wild-type viruses than immunization with highly attenuated viruses, the Advisory Committee on Immunization Practices and American Academy of Pediatrics recommend that certain immunocompromised children should receive live viral vaccines. For example, children with human immunodeficiency virus (HIV) infection without severe T-cell deficiencies (Centers for Disease Control and Prevention class N1 or A1 and age-specific percentage of CD4<sup>+</sup> lymphocytes greater than 25%) should receive the measles-mumps-rubella (MMR), and varicella vaccines.<sup>26–28</sup> Immunizations are well-tolerated by this subset of HIV-infected children and confer protective immunity.<sup>29,30</sup> Immunization with live viral vaccines has also been demonstrated to be safe and effective in certain children with malignancies and in children following bone marrow transplantation.<sup>31,32</sup>

#### IMMUNE RESPONSE TO VACCINES BY CHILDREN WITH MILD, MODERATE, OR SEVERE ILLNESSES

Some parents may be concerned that children with acute illnesses are, in a sense, immunocompromised, and that they are less likely to respond to vaccines or more likely to develop adverse reactions to vaccines than healthy children. Alternatively, parents may believe that children who are ill should not further burden an immune system already committed to fighting an infection. However, vaccine-specific antibody responses and rates of vaccine-associated adverse reactions of children with mild or moderate illnesses are comparable to those of healthy children. For example, the presence of upper respiratory tract infections, otitis media, fever, skin infections, or diarrhea do not affect the level of protective antibodies induced by immunization.<sup>33–37</sup>

Data on the capacity of vaccines to induce protective immune responses in children with severe infections (such as those with bacterial pneumonia or meningitis) are lacking. Although a delay in vaccines is recommended for children with severe illnesses until the symptoms of illness resolve,<sup>26</sup> this recommendation is not based on the likelihood that the child will have an inadequate immune response to the vaccine. Rather, the reason for deferring immunization is to avoid superimposing a reaction to the vaccine on the underlying illness or to mistakenly attribute a manifestation of the underlying illness to the vaccine.<sup>26</sup>

#### DO VACCINES “OVERWHELM” THE IMMUNE SYSTEM?

##### Infants Have the Capacity to Respond to an Enormous Number of Antigens

Studies on the diversity of antigen receptors indicate that the immune system has the capacity to respond to extremely large numbers of antigens.

Current data suggest that the theoretical capacity determined by diversity of antibody variable gene regions would allow for as many as 10<sup>9</sup> to 10<sup>11</sup> different antibody specificities.<sup>38</sup> But this prediction is limited by the number of circulating B cells and the likely redundancy of antibodies generated by an individual.

A more practical way to determine the diversity of the immune response would be to estimate the number of vaccines to which a child could respond at one time. If we assume that 1) approximately 10 ng/mL of antibody is likely to be an effective concentration of antibody per epitope (an immunologically distinct region of a protein or polysaccharide),<sup>39</sup> 2) generation of 10 ng/mL requires approximately 10<sup>3</sup> B-cells per mL,<sup>39</sup> 3) a single B-cell clone takes about 1 week to reach the 10<sup>3</sup> progeny B-cells required to secrete 10 ng/mL of antibody<sup>39</sup> (therefore, vaccine-epitope-specific immune responses found about 1 week after immunization can be generated initially from a single B-cell clone per mL), 4) each vaccine contains approximately 100 antigens and 10 epitopes per antigen (ie, 10<sup>3</sup> epitopes), and 5) approximately 10<sup>7</sup> B cells are present per mL of circulating blood,<sup>39</sup> then each infant would have the theoretical capacity to respond to about 10 000 vaccines at any one time (obtained by dividing 10<sup>7</sup> B cells per mL by 10<sup>3</sup> epitopes per vaccine).

Of course, most vaccines contain far fewer than 100 antigens (for example, the hepatitis B, diphtheria, and tetanus vaccines each contain 1 antigen), so the estimated number of vaccines to which a child could respond is conservative. But using this estimate, we would predict that if 11 vaccines were given to infants at one time, then about 0.1% of the immune system would be “used up.”

However, because naive B- and T-cells are constantly replenished, a vaccine never really “uses up” a fraction of the immune system. For example, studies of T-cell population dynamics in HIV-infected patients indicate that the human T-cell compartment is highly productive.<sup>40</sup> Specifically, the immune system has the ability to replenish about 2 billion CD4<sup>+</sup> T lymphocytes each day. Although this replacement activity is most likely much higher than needed for the normal (and as yet unknown) CD4<sup>+</sup> T-cell turnover rate, it illustrates the enormous capacity of the immune system to generate lymphocytes as needed.

#### Children are Exposed to Fewer Antigens in Vaccines Today Than in the Past

Parents who are worried about the increasing number of recommended vaccines may take comfort in knowing that children are exposed to fewer antigens (proteins and polysaccharides) in vaccines today than in the past.

Table 2 summarizes the number of proteins and polysaccharides contained in routinely recommended vaccines administered over the past 100 years. Although we now give children more vaccines, the actual number of antigens they receive has declined. Whereas previously 1 vaccine, smallpox, contained about 200 proteins, now the 11 routinely recommended vaccines contain fewer than 130 pro-



**TABLE 2.** Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines Over the Past 100 Years

| 1900         |             | 1960          |              | 1980         |              | 2000           |                              |
|--------------|-------------|---------------|--------------|--------------|--------------|----------------|------------------------------|
| Vaccine      | Proteins    | Vaccine       | Proteins     | Vaccine      | Proteins     | Vaccine        | Proteins/<br>Polysaccharides |
| Smallpox*    | ~200        | Smallpox      | ~200         | Diphtheria   | 1            | Diphtheria     | 1                            |
| <b>Total</b> | <b>~200</b> | Diphtheria†   | 1            | Tetanus      | 1            | Tetanus        | 1                            |
|              |             | Tetanus‡      | 1            | WC-Pertussis | ~3000        | AC-Pertussis¶¶ | 2-5                          |
|              |             | WC-Pertussis§ | ~3000        | Polio        | 15           | Polio          | 15                           |
|              |             | Polio         | 15           | Measles¶¶    | 10           | Measles        | 10                           |
|              |             | <b>Total</b>  | <b>~3217</b> | Mumps#       | 9            | Mumps          | 9                            |
|              |             |               |              | Rubella**    | 5            | Rubella        | 5                            |
|              |             |               |              | <b>Total</b> | <b>~3041</b> | Hib††          | 2                            |
|              |             |               |              |              |              | Varicella‡‡    | 69                           |
|              |             |               |              |              |              | Pneumococcus§§ | 8                            |
|              |             |               |              |              |              | Hepatitis B    | 1                            |
|              |             |               |              |              |              | <b>Total</b>   | <b>123-126</b>               |

\* *Vaccinia* vaccine: Goebel SJ, Johnson GP, Perkus ME, et al. *Virology*. 1990;179:247-266.

† *Diphtheria* toxoid: *MMWR Morb Mortal Wkly Rep*. 1991 (August);40:1-28.

‡ *Tetanus* toxoid: *MMWR Morb Mortal Wkly Rep*. 1991 (August);40:1-28.

§ *Whole cell pertussis* vaccine: Number estimated from genome size. The sequence of *Bordetella pertussis* Tohama I strain will soon be completed at the Sanger Center in Great Britain.

¶ *Polio* vaccine: Wimmer E, Nomoto A. *Biologicals*. 1993;21:349-356; Kitamura N, Semler BL, Rothberg PG, et al. *Nature*. 1981;291:547-553; Five proteins per poliovirus virion and 3 poliovirus strains in the inactivated poliovirus vaccine (IPV).

¶¶ *Measles* vaccine: Griffen D, Bellini WL. *Measles virus*. In: Fields BN, ed. *Knipe DM, Howley PM, et al, eds. Philadelphia, PA: Lipincott-Raven Publishers; 1996.*

# *Mumps* vaccine: Elango N, Varsanyi TM, Kovamees J, Norrby E. *J Gen Virol*. 1988;69:2893-2900.

\*\* *Rubella* vaccine: Hofmann J, Gerstenberger S, Lachmann I, et al. *Virus Res*. 2000;68:155-160.

†† *Conjugate Haemophilus influenzae type b* vaccine: *MMWR Morb Mortal Wkly Rep*. 1991 (January);40:1-7.

‡‡ *Varicella* vaccine: Cohen JL. *Infect Dis Clin North Am*. 1996;10:457-468.

§§ *Streptococcus pneumoniae* vaccine: *MMWR Morb Mortal Wkly Rep*. 2000;49:1-29.

||| *Hepatitis B* vaccine: *MMWR Morb Mortal Wkly Rep*. 1991 (November);40:1-25.

¶¶¶ *Acellular pertussis* vaccine: *MMWR Morb Mortal Wkly Rep*. 1997 (March);46:1-25.

teins in total. Two factors account for this decline: first, the worldwide eradication of smallpox obviated the need for that vaccine, and second, advances in protein chemistry have resulted in vaccines containing fewer antigens (eg, replacement of whole-cell with acellular pertussis vaccine).

### Children Respond to Multiple Vaccines Given at the Same Time in a Manner Similar to Individual Vaccines

If vaccines overwhelmed or weakened the immune system, then one would expect lesser immune responses when vaccines are given at the same time as compared with when they are given at different times.<sup>41,42</sup> However, the following vaccines induce similar humoral immune responses when given at the same or different times: 1) MMR and varicella,<sup>43,44</sup> 2) MMR, diphtheria-tetanus-pertussis (DTP), and OPV,<sup>45</sup> 3) hepatitis B, diphtheria-tetanus, and OPV,<sup>46</sup> 4) influenza and pneumococcus,<sup>47</sup> 5) MMR, DTP-Hib, and varicella,<sup>48</sup> 6) MMR and Hib,<sup>49</sup> and 7) DTP and Hib.<sup>49</sup>

Achieving similar immune responses by giving vaccines at the same time at different sites may be more easily accomplished than by combining vaccines in the same syringe. Challenges to giving many vaccines in a single injection are based partly on incompatibilities of agents used to buffer or stabilize individual vaccines.<sup>50</sup>

### DO VACCINES "WEAKEN" THE IMMUNE SYSTEM?

#### Do Vaccines Increase the Risk of Other Infections?

Vaccines may cause temporary suppression of delayed-type hypersensitivity skin reactions or alter certain lymphocyte function tests in vitro.<sup>51-57</sup> How-

ever, the short-lived immunosuppression caused by certain vaccines does not result in an increased risk of infections with other pathogens soon after vaccination. Vaccinated children are not at greater risk of subsequent infections with other pathogens than unvaccinated children.<sup>58-60</sup> On the contrary, in Germany, a study of 496 vaccinated and unvaccinated children found that children who received immunizations against diphtheria, pertussis, tetanus, Hib, and polio within the first 3 months of life had fewer infections with vaccine-related and -unrelated pathogens than the nonvaccinated group.<sup>61</sup>

Bacterial and viral infections, on the other hand, often predispose children and adults to severe, invasive infections with other pathogens. For example, patients with pneumococcal pneumonia are more likely to have had a recent influenza infection than matched controls.<sup>62</sup> Similarly, varicella infection increases susceptibility to group A  $\beta$ -hemolytic streptococcal infections such as necrotizing fasciitis, toxic shock syndrome, and bacteremia.<sup>63</sup>

### SUMMARY

Current studies do not support the hypothesis that multiple vaccines overwhelm, weaken, or "use up" the immune system. On the contrary, young infants have an enormous capacity to respond to multiple vaccines, as well as to the many other challenges present in the environment. By providing protection against a number of bacterial and viral pathogens, vaccines prevent the "weakening" of the immune system and consequent secondary bacterial infections occasionally caused by natural infection.

## REFERENCES

- Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. 2000;106:1097–1102
- Davis TC, Fredrickson DD, Arnold CL, et al. Childhood vaccine risk/benefit communication in private practice office settings: a national survey. *Pediatrics*. 2001;107(2). Available at: <http://www.pediatrics.org/cgi/content/full/107/2/e17>
- Dias M, Marcuse E. When parents resist immunizations. *Contemp Pediatr*. 2000;7:1–4
- Taylor JA, Darden PM, Slora E, et al. The influence of provider behavior, parental characteristics, and a public policy initiative on the immunization status of children followed by private pediatricians: a study from pediatric research in office settings. *Pediatrics*. 1997;99:209–215
- Goldblatt D. Immunisation and the maturation of infant immune responses. *Dev Biol Stand*. 1998;95:125–132
- Siegrist CA, Cordova M, Brandt C, et al. Determinants of infants responses to vaccines in the presence of maternal antibodies. *Vaccine*. 1998;16:1409–1414
- Ryan AS. The resurgence of breastfeeding in the United States. *Pediatrics*. 1997;99(4). Available at: <http://www.pediatrics.org/cgi/content/full/99/4/e12>
- Fadel S, Sarazotti M. Cellular immune responses in neonates. *Int Rev Immunol*. 2000;19:173–193
- Siegrist C-A. Neonatal and early life vaccinology. *Vaccine*. 2001;19:3331–3346
- Mackie RI, Sghir A, Gaskins H. Developmental microbial ecology of the neonatal gastrointestinal tract. *Am J Clin Nutr*. 1999;69(suppl):1035S–1045S
- Mellander L, Carlsson B, Jalil E, et al. Secretory IgA antibody response against *Escherichia coli* antigens in infants in relation to exposure. *J Pediatr*. 1985;107:430–433
- Rijkers GT, Dollekamp EG, Zegers BJM. The in vitro B-cell response to pneumococcal polysaccharides in adults and neonates. *Scand J Immunol*. 1987;25:447–452
- Wheely SM, Jackson PT, Boxhall EH, et al. Prevention of perinatal transmission of hepatitis B virus (HBV): a comparison of two prophylactic schedules. *J Med Virol*. 1991;35:212–215
- Wong VC, Ip HM, Reesink HW, et al. Prevention of the HBsAg carrier state in newborns of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin: double-blind randomized placebo-controlled study. *Lancet*. 1984;28:921–926
- Prozesky OW, Stevens CE, Szmunes W, et al. Immune response to hepatitis B vaccine in newborns. *J Infect*. 1983;7(suppl 1):53–55
- Clark A, Rudd P. Neonatal BCG immunization. *Arch Dis Child*. 1992;67:473–474
- Marchant A, Gretghebuer T, Ota MO, et al. Newborns develop a TH1-type immune response to *Mycobacterium bovis* Bacillus Calmette-Guerin vaccination. *J Immunol*. 1999;163:2249–2255
- Colditz GA, Brewster TF, Berkey CS, et al. Efficacy of BCG vaccine in the prevention of tuberculosis: meta-analysis of the published literature. *JAMA*. 1994;271:698–702
- Plotkin SA, Orenstein WA. *Vaccines*. 3rd ed. Philadelphia, PA: WB Saunders Co; 1999
- Anderson P, Ingram DL, Pichichero M, Peter G. A high degree of natural immunologic priming to the capsular polysaccharide may not prevent *Haemophilus influenzae* type b meningitis. *Pediatr Infect Dis J*. 2000;19:589–591
- Monafu WJ, Haslam DB, Roberts RL, et al. Disseminated measles infection after vaccination in a child with a congenital immunodeficiency. *J Pediatr*. 1994;124:273–276
- Ghaffar F, Carrick K, Rogers BB, et al. Disseminated infection with varicella-zoster virus vaccine strain presenting as hepatitis in a child with adenosine deaminase deficiency. *Pediatr Infect Dis J*. 2000;19:764–766
- Casanova JL, Jounanguy E, Lamhamedi S, et al. Immunological conditions of children with disseminated BCG infections. *Lancet*. 1995;346:581
- Stephan JL, Vlekova V, Deist FL, et al. Severe combined immunodeficiency: a retrospective single-center study of clinical presentation and outcome in 117 patients. *J Pediatr*. 1993;123:564–572
- Buckley R, Schiff R, Schiff S, et al. Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. *J Pediatr*. 1997;130:378–387
- Update. Vaccine side effects, adverse reactions, contraindications, and precautions. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 1996;45:1–35
- American Academy of Pediatrics, Committee on Infectious Diseases. Varicella vaccine update. *Pediatrics*. 2000;105:136–141
- Prevention of varicella. Update recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 1999;48:1–5
- McLaughlin M, Thomas P, Onorato I, et al. Live virus vaccines in human immunodeficiency virus-infected children: a retrospective survey. *Pediatrics*. 1988;82:229–233
- Sprauer MA, Markowitz LE, Nicholson KA, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1993;6:1013–1016
- Meral A, Sevinir B, Gunay U. Efficacy of immunization against hepatitis B virus infection in children with cancer. *Med Pediatr Oncol*. 2000;35:47–51
- Gruber WC. Immunizations in the immunocompromised host. In: Patrick CC, ed. *Immunocompromised Infants and Children*. Baltimore, MD: Lippincott; 2001:511–536
- King GE, Markowitz LE, Heath J, et al. Antibody response to measles-mumps-rubella vaccine of children with mild illness at the time of vaccination. *JAMA*. 1996;275:704–707
- Dennehy PH, Saracen CL, Peter G. Seroconversion rates to combined measles-mumps-rubella-varicella vaccine of children with upper respiratory tract infection. *Pediatrics*. 1994;94:514–516
- Ratnam S, West R, Gadag V. Measles and rubella antibody response after measles-mumps-rubella vaccination in children with afebrile upper respiratory tract infection. *J Pediatr*. 1995;127:432–434
- Ndikuyezze A, Munoz A, Stewart J, et al. Immunogenicity and safety of measles vaccine in ill African children. *Int J Epidemiol*. 1988;17:448–455
- Halsey NA, Boulos R, Mode F, et al. Response to measles vaccine in Haitian infants 6 to 12 months old: influence of maternal antibodies, malnutrition, and concurrent illness. *N Engl J Med*. 1985;313:544–549
- Abbas AK, Lichtman AH, Pober JS. *Cellular and Molecular Immunology*. 2nd ed. Philadelphia, PA: WB Saunders Co; 1994
- Cohn M, Langman RE. The protecton: the unit of humoral immunity selected by evolution. *Immunol Rev*. 1990;115:9–147
- Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature*. 1995;373:123–126
- King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. *Pediatr Infect Dis J*. 1994;13:394–407
- American Academy of Pediatrics. Combination vaccines for childhood immunization: recommendations of the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, and the American Academy of Family Physicians. *Pediatrics*. 1999;103:1064–1077
- Englund JA, Suarez C, Kelly J, et al. Placebo-controlled trial of varicella vaccine given with or after measles-mumps-rubella vaccine. *J Pediatr*. 1989;114:37–44
- Brunell PA, Novelli VM, Lipton SV, Pollock B. Combined vaccine against measles, mumps, rubella, and varicella. *Pediatrics*. 1988;81:779–784
- DeForest A, Long SS, Lischner HW, et al. Simultaneous administration of measles-mumps-rubella vaccine with booster doses of diphtheria-tetanus-pertussis and poliovirus vaccines. *Pediatrics*. 1988;81:237–246
- Giammanco G, Volti S, Mauro L, et al. Immune response to simultaneous administration of a recombinant DNA hepatitis B vaccine and multiple compulsory vaccines in infancy. *Vaccine*. 1991;9:747–750
- DeStefano F, Goodman RA, Noble GR, et al. Simultaneous administration of influenza and pneumococcal vaccines. *JAMA*. 1982;247:2551–2554
- Shinefield HR, Black SB, Staehle BO, et al. Safety, tolerability, and immunogenicity of concomitant infections in separate locations of MMR<sub>II</sub>, Varivax and Tetramune in healthy children vs concomitant infection of MMR<sub>II</sub> and Tetramune followed six weeks later by Varivax. *Pediatr Infect Dis J*. 1998;17:980–985
- Dashefsky B, Wald E, Guerra N, Byers C. Safety, tolerability, and immunogenicity of concurrent administration of *Haemophilus influenzae* type b conjugate vaccine (meningococcal conjugate) with either measles-mumps-rubella vaccine or diphtheria-tetanus-pertussis and oral poliovirus vaccines in 14- to 23-month-old infants. *Pediatrics*. 1990;85:682–689
- Katkocin DM, Hsieh C-L. Pharmaceutical aspects of combination vaccines. In: Ellis R, ed. *Combination Vaccines: Development, Clinical Research, and Approval*. Totowa, NJ: Humana Press Inc; 1999:51–93
- Brody JA, McAlister R. Depression of tuberculin sensitivity following measles vaccination. *Am Rev Resp Dis*. 1964;90:607–611
- Ganguly R, Cusumano CL, Waldman RH. Suppression of cell-mediated

- immunity after infection with attenuated rubella virus. *Infect Immun.* 1976;13:464–469
53. Starr S, Berkovich S. Effects of measles, gamma-globulin-modified measles and vaccine measles on the tuberculin test. *N Engl J Med.* 1964;270:386–391
  54. Brody JA, Overfield T, Hammes LM. Depression of the tuberculin reaction by viral vaccines. *N Engl J Med.* 1964;271:1294–1296
  55. Kupers T, Petrich JM, Holloway AW, St Geme JW. Depression of tuberculin delayed hypersensitivity by live attenuated mumps virus. *J Pediatr.* 1970;76:716–721
  56. Zweiman B, Pappagianis D, Maibach H, Hildreth EA. Effect of measles immunization on tuberculin hypersensitivity and in vitro lymphocyte reactivity. *Int Arch Allergy.* 1971;40:834–841
  57. Hirsch RL, Mokhtarian F, Griffin DE, et al. Measles virus vaccination of measles seropositive individuals suppresses lymphocyte proliferation and chemotactic factor production. *Clin Immunol Immunopathol.* 1981;21:341–350
  58. Black SB, Cherry JD, Shinefield HR, et al. Apparent decreased risk of invasive bacterial disease after heterologous childhood immunization. *Am J Dis Child.* 1991;145:746–749
  59. Davidson M, Letson W, Ward JI, et al. DTP immunization and susceptibility to infectious diseases. Is there a relationship? *Am J Dis Child.* 1991;145:750–754
  60. Storsaeter J, Olin P, Renemar B, et al. Mortality and morbidity from invasive bacterial infections during a clinical trial of acellular pertussis vaccines in Sweden. *Pediatr Infect Dis J.* 1988;7:637–645
  61. Otto S, Mahner B, Kadow I, et al. General non-specific morbidity is reduced after vaccination within the third month of life—the Greifswald study. *J Infect.* 2000;41:172–175
  62. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. *Clin Infect Dis.* 2000;30:784–789
  63. Laupland KB, Davies HD, Low DE, et al. Invasive group A streptococcal disease in children and association with varicella-zoster virus infection. *Pediatrics* 2000;105(5). Available at: <http://www.pediatrics.org/cgi/content/full/105/5/e60>

## POSTDOC TRAIL LONG AND FILLED WITH PITFALLS

“The annual number of doctorates awarded in science nationwide has greatly outpaced the growth in the number of faculty jobs over the last 20 years . . . What used to be 2 or 3 years of career development often becomes 5 or more years in one post after another. Many of the postdocs are almost 40 before they start their first permanent positions and begin saving for retirement . . . The bottleneck means that the number of university postdocs in science and engineering has grown to an unprecedented size, doubling from 1981 to 1998, to 39,000, with most of that growth in the life sciences . . . In November 2000, the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine issued a report that said it was in the long-term interests of American science for postdocs to get better treatment . . . ‘It’s really unfortunate that people spend all these times in all these temporary positions and that they are 35 or 40,’ said Dr Walter T. Schaffer, a research training officer at the National Institutes of Health. ‘To some extent it discourages very bright people from entering science.’”

Lee J. *New York Times.* August 21, 2001

Noted by JFL, MD

## Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?

Paul A. Offit, Jessica Quarles, Michael A. Gerber, Charles J. Hackett, Edgar K. Marcuse, Tobias R. Kollman, Bruce G. Gellin and Sarah Landry

*Pediatrics* 2002;109;124

DOI: 10.1542/peds.109.1.124

|                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Updated Information &amp; Services</b> | including high resolution figures, can be found at:<br><a href="http://pediatrics.aappublications.org/content/109/1/124">http://pediatrics.aappublications.org/content/109/1/124</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>References</b>                         | This article cites 56 articles, 12 of which you can access for free at:<br><a href="http://pediatrics.aappublications.org/content/109/1/124.full#ref-list-1">http://pediatrics.aappublications.org/content/109/1/124.full#ref-list-1</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Subspecialty Collections</b>           | This article, along with others on similar topics, appears in the following collection(s):<br><b>Fetus/Newborn Infant</b><br><a href="http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub">http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub</a><br><b>Infectious Disease</b><br><a href="http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub">http://classic.pediatrics.aappublications.org/cgi/collection/infectious_diseases_sub</a><br><b>Vaccine/Immunization</b><br><a href="http://classic.pediatrics.aappublications.org/cgi/collection/vaccine:immunization_sub">http://classic.pediatrics.aappublications.org/cgi/collection/vaccine:immunization_sub</a> |
| <b>Permissions &amp; Licensing</b>        | Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:<br><a href="https://shop.aap.org/licensing-permissions/">https://shop.aap.org/licensing-permissions/</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Reprints</b>                           | Information about ordering reprints can be found online:<br><a href="http://classic.pediatrics.aappublications.org/content/reprints">http://classic.pediatrics.aappublications.org/content/reprints</a>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2002 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## **Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?**

Paul A. Offit, Jessica Quarles, Michael A. Gerber, Charles J. Hackett, Edgar K. Marcuse, Tobias R. Kollman, Bruce G. Gellin and Sarah Landry

*Pediatrics* 2002;109:124

DOI: 10.1542/peds.109.1.124

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/109/1/124>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2002 by the American Academy of Pediatrics. All rights reserved. Print ISSN:

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

