Pneumococcal Vaccines in Preterm Infants: Are More Doses Better? Implications for Other Vaccines

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Pneumococcal conjugate vaccines (PCVs) have significantly decreased invasive pneumococcal disease (IPD) in whole populations, and they are among the many ongoing stories of vaccine successes around the world. However, IPDs remain far too common, especially in certain populations. When it comes to the timing of PCV administration, most physicians follow their nationally recommended vaccine schedules, which have been well studied in specific and well-defined populations. In the United States the recommended immunization schedule for children is the one approved by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and endorsed by the major professional societies including the American Academy of Pediatrics.[1] The timing of vaccine doses in the schedule recommended by the Centers for Disease Control and Prevention is based on a thorough evaluation of available science, age-dependent variation in the immune system, vaccine interactions, and practical considerations related to vaccine delivery, but we have more to learn to truly optimize vaccine delivery.[2]

It turns out for PCV that the levels of antibody achieved, the rate of decline of those antibodies, and probably the degree and duration of protection from disease vary a great deal between the different serotypes and the timing of vaccine doses. The study in this issue by Kent et al[3] has provided insight into this phenomenon for a unique and vulnerable population: preterm infants. In this study, 3 different primary PCV schedules were used: 1 used in the United Kingdom (a "reduced schedule" with doses at 2 and 4 months of age), 1 used in many other countries (an "accelerated schedule" with doses at 2, 3, and 4 months of age), and 1 used in the United States (an "extended schedule" with doses at 2, 4, and 6 months of age). All infants received a 12-month booster dose. All of the schedules were safe and achieved "acceptable" levels of antibody, but significant variation was noted. But what is an "acceptable" level of antibody? Kent et al[3] observed that antibody levels achieved for each pneumococcal serotype contained in the vaccine vary significantly by schedule. In addition to the timing of doses, other predictors of immune response were gestational age and receipt of antenatal steroids. Studies with various PCV vaccines conducted in the United States and in countries using these different schedules confirm that each schedule generally leads to protection from IPD, but the optimization of protection and the evaluation of protection against other types of pneumococcal disease such as pneumonia remains challenging.[4–9]

The results from the current study illustrate some of the challenges in making vaccine policy and why there are differences in pneumococcal vaccine policies around the world, because there was no clearly superior schedule. Although there was variation between serotypes, in

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general the "reduced schedule," only 2 vaccine doses in primary series at 2 and 4 months, produced lower antibody titers in the first year of life compared with the "extended schedule" of 3 doses at 2, 4, and 6 months but higher titers after the 12-month booster. The "accelerated schedule" of 3 doses at 2, 3, and 5 months produced antibody titers in between the other 2. Although it is difficult to translate specific antibody levels to protection, to some extent you can have optimal protection in the first year of life or in the second but not both. Which do you choose?

This conundrum is not unique to pneumococcal vaccines. Immune responses to many vaccines vary by age, dosing interval, and the population to whom they are given. For example, human papilloma virus vaccine induces higher antibody titers in young adolescents compared with older populations, and a 2-dose regimen may work if the spacing of doses is optimized.[10] Some conjugated *Haemophilus influenzae* type b vaccines induce high antibody titers faster than others[11] and are therefore recommended for certain high-risk populations. Waning antibody levels after conjugated meningococcal vaccine may make the timing of that vaccine important.[12] Undoubtedly we will eventually learn that genetic factors underlie individual variation in vaccine response and duration of protection and be able to better individualize vaccine administration. Vaccine schedules vary between countries, in part based on when disease risk is highest, the available vaccines, the population for which the recommendation is intended, programmatic considerations such as the timing of health visits, and in some cases, but not always, a detailed understanding of the immune response. As illustrated in the current study of conjugated pneumococcal vaccine in preterm infants,[3] there is room to learn more about the immune response to vaccines to refine our vaccine policies, and we will not all come up with the same answers.

ABBREVIATIONS

IPD: invasive pneumococcal disease
PCV: pneumococcal conjugate vaccine

REFERENCES

1. Centers for Disease Control. Recommended immunization schedules for persons aged 0 through 18 years. 2016. Available at: www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html. Accessed March 16, 2016
2. Edwards KM, Maldonado Y, Byington CL, Jefferson T, Demicheli V. Is the timing of recommended childhood vaccines evidence based? *BMJ*. 2016;352:i867
3. Kent A, Ladhani SN, Andrews NJ, et al Schedules for pneumococcal vaccination of preterm infants: an RCT. *Pediatrics*. 2016;138(3):e20153945
4. Palmu AA, Kilpi TM, Rinta-Kokko H, et al. Pneumococcal conjugate vaccine and clinically suspected invasive pneumococcal disease. *Pediatrics*. 2015;136(1). Available at: www.pediatrics.org/cgi/content/full/136/1/e22
5. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003;349(14):1341–1348
6. Cutts FT, Zaman SM, Enwere G, et al; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet*. 2005;365(9465):1139–1146
7. Deceuninck G, De Wals P, Boulianne N, De Serres G. Effectiveness of pneumococcal conjugate vaccine using a 2+1 infant schedule in Quebec, Canada. *Pediatr Infect Dis J*. 2010;29(6):546–549
8. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case–control study. *Lancet*. 2006;368(9546):1495–1502
9. Rückinger S, van der Linden M, Reinert RR, von Kries R. Efficacy of 7-valent pneumococcal conjugate vaccination in Germany: an analysis using the indirect cohort method. *Vaccine*. 2010;28(31):5012–5016
10. Markowitz LE, Dunne EF, Saraiya M, et al; Centers for Disease Control and Prevention (CDC). Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1–30
11. Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC. Prevention and control of *Haemophilus influenzae* type b disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-01):1–14
12. Cohn AC, MacNeil JR, Clark TA, et al; Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2013;62(RR-2 RR02):1–28

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