Rotavirus Vaccines—OK to Mix and Match

Carrie L. Byington, MD, FAAP[a] Yvonne Maldonado, MD, FAAP[b]

The US Food and Drug Administration regulates vaccines in the United States and requires vaccine manufacturers to conduct scientifically valid clinical trials to demonstrate the safety and efficacy of vaccines before they can be licensed. Despite the rigorous testing required for licensure, questions about vaccine administration in clinical settings may persist, particularly when there are multiple products licensed to prevent the same infection. These products can have different components, dosing schedules, and recommendations for administration. In practice, these differences may result in children receiving a mixture of vaccine products, as individuals change providers or providers change their vaccine stocks.

Physicians in practice and those who draft guidance for them, including the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices and the American Academy of Pediatrics' Committee on Infectious Diseases (COID), are faced with making decisions about the use of these products in "real-world" scenarios that may differ from the clinical trials environment in which these products were studied. The COID frequently evaluates the impact and use of vaccine product combinations to make recommendations, including recent guidelines regarding the use of rotavirus vaccines.[1] Expert opinion has led the COID to advise providers that timely completion of immunization with any available licensed product is better than delaying immunization for a specific product. The article by Libster et al[2] in this issue of *Pediatrics* supports this principle and reassures us that for rotavirus vaccines, immunization with a mixed series of vaccines is safe and results in an immune response that is noninferior to that generated by immunization with any single product.

The authors[2] conducted a randomized study in which children received either RotaTeq (RV5; Merck & Co, Inc, Whitehouse Station, New Jersey) or Rotarix (RV1; GlaxoSmithKline Biologicals, Rixensart, Belgium) for the first dose, followed by 5 distinct combinations of the 2 vaccines to complete the immunization series. RV5 is a live virus vaccine with a combination of 5 human/bovine reassortant rotaviruses, and RV1 is a live, attenuated human rotavirus vaccine prepared from a single human strain. The primary outcome was noninferiority of the vaccine combinations based on attainment of serum antirotavirus immunoglobulin A levels ≥20 U 1 month after the last dose of vaccine. Importantly, the study met the enrollment goals for statistical power. The proportion of children seropositive for at least 1 vaccine antigen was high and was similar for all vaccine combinations. All combinations of vaccine were well tolerated, and there were no statistical differences in adverse events postvaccination between the sequential schedule groups compared with the single-vaccine RV5; the RV5 group had higher proportions reporting fever and vomiting compared with the RV1 group, however. Serious adverse events were rare with any of the vaccine combinations and, in

[a]*University of Utah, Department of Pediatrics, Salt Lake City, Utah; and* [b]*Stanford University, Department of Pediatrics, Palo Alto, California*

Dr Byington is Chair of the American Academy of Pediatrics Committee on Infectious Diseases

Dr Maldonado is Vice Chair of the American Academy of Pediatrics Committee on Infectious Diseases

DOI: 10.1542/peds.2015-3618

Accepted for publication Nov 16, 2015

Address correspondence to Carrie L. Byington, MD, FAAP, University of Utah Health Sciences Center, 26 2000 East, HSEB Suite 5515, Salt Lake City, UT 84112. E-mail: carrie.byington@hsc.utah.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Dr Byington has intellectual property in and receives royalties from BioFire Diagnostics, Inc. Dr Maldonado is a member of a data safety monitoring board for Pfizer.

FUNDING: Dr Byington is supported by an H.A. and Edna Benning Presidential Endowment and the National Center for Advancing Translational Sciences of the National Institutes of Health (1ULTR001067). Dr Maldonado is supported by the Bill and Melinda Gates Foundation and the National Institutes of Health (AI100748 and AI06858106). Funded by the National Institutes of Health (NIH).

To cite: Byington CL and Maldonado Y. Rotavirus Vaccines—OK to Mix and Match. *Pediatrics.* 2016;137(2):e20153618

the majority of cases, unrelated to vaccine administration.

The findings of Libster et al,[2] in addition to demonstrating the efficacy of multiple vaccine combinations for rotavirus, also serve as a reminder of the importance of the infrastructures of the National Institutes of Health–supported Vaccine and Treatment Evaluation Units (VTEU) and the Clinical and Translational Science Awards (CTSA) in supporting the health of children. The VTEUs were established in 1962 with the purpose of conducting clinical trials of vaccines and treatments for infectious diseases. Currently, the VTEUs are located in 9 centers, 6 of which participated in the trial by Libster et al. The VTEUs have conducted hundreds of clinical trials over 4 decades, many of which include trials of vaccines that directly benefit children.[3] For example, the VTEUs conducted trials leading to the licensure of the *Haemophilus influenzae* type B and the pneumococcal conjugate vaccines; during the 2009 pandemic, the VTEUs were able to rapidly test candidate vaccines to prevent H1N1 in adults, including pregnant women, and in children. More recently, the CTSAs, established in 2006, have a goal of supporting translational science and research designed to improve health.[4] Many CTSA hubs include children's hospitals, and the national consortium has a goal to support research across the life span.[5] Both the VTEUs and the CTSA hubs played an important role in the study reported by Libster et al. Without these federally funded resources, it is unlikely that the evaluation of multiple rotavirus vaccine combinations would have been conducted. Individual vaccine manufacturers have little or no incentive to test their licensed products in combination with those of other manufacturers. As child health advocates, we regularly encourage the use of vaccines. We must remember that our advocacy should also include working to ensure that the research infrastructure of the nation is strong and that adequate resources are devoted to investigations that will benefit the health of children.

ABBREVIATIONS

COID: Committee on Infectious Diseases
CTSA: Clinical and Translational Science Award
RV1: Rotarix
RV5: RotaTeq
VTEU: Vaccine and Treatment Evaluation Units

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. American Academy of Pediatrics Committee on Infectious Diseases. *Red Book 2015 Report of the Committee on Infectious Diseases*. 30th ed. Chicago, IL: American Academy of Pediatrics; 2015
2. Libster R, McNeal M, Walter E, et al. Safety and immunogenicity of sequential rotavirus vaccine schedules. *Pediatrics*. 2015;137(2):e20152603
3. NIH–National Institute of Allergy and Infectious Diseases (NIAID). Vaccine and treatment evaluation units. Available at: www.niaid.nih.gov/about/organization/dmid/researchers/clinical/vteu/Pages/introduction.aspx. Accessed September 28, 2015
4. National Institutes of Health. CTSA, Clinical & Translational Science Awards. Available at: https://ctsacentral.org. Accessed September 28, 2015
5. Huskins WC, Sullivan CD, Wang J, et al. Tracking the impact of the National Institutes of Health Clinical and Translational Science Awards on child health research: developing and evaluating a measurement strategy. *Pediatr Res*. 2012;71(5):619–624

Rotavirus Vaccines—OK to Mix and Match

Carrie L. Byington and Yvonne Maldonado

Pediatrics 2016;137;
DOI: 10.1542/peds.2015-3618 originally published online January 28, 2016;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Rotavirus Vaccines—OK to Mix and Match

Carrie L. Byington and Yvonne Maldonado

Pediatrics 2016;137;
DOI: 10.1542/peds.2015-3618 originally published online January 28, 2016;