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LETTERS

Letter to the editor in response to: Rotavirus vaccine administration patterns in Italy: potential impact on vaccine coverage, compliance and adherence

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Letter to the editor

We read with interest the publication by Martinelli et al. on rotavirus vaccines.[1] Rotavirus gastroenteritis is a diarrheal disease that, prior to universal vaccination, would infect virtually all children before the age of 5, causing high morbidity and infant mortality in low-resource settings.[2] Currently, there are two rotavirus vaccines licensed for use in Europe: Rotarix (RV1, that contains one human rotavirus strain), produced by GlaxoSmithKline and RotaTeq (also known as RV5, a live, oral vaccine that contains five reassortant rotavirus strains developed from human and bovine parent rotavirus strains, produced by Merck & Co., Inc., Kenilworth, NJ, USA). Vaccine efficacy and safety for RV1 and RV5 have been established in large clinical trials; post-licensure studies continue to confirm high vaccine effectiveness and vaccine impact worldwide with significant reductions in disease burden.[3–5] We would like to thank the authors for drawing attention to a topic of public health relevance and provide the following comments on their review.

Our first comment relates to age at administration of the first dose. The authors note that "In accordance with the SmPC of HRV [RV1] the administration of the first dose of HRV [RV1] is possible up to 20 weeks of age in order to complete the vaccination course by Week 24 as prescribed, thus extending the administration interval of the first dose by an additional 8 weeks compared to the 12 weeks authorized for HBRV [RV5]".[1] We would like to note that the timing of vaccination suggested by the authors is not consistent with guidelines issued by the European Society for Pediatric Infectious Diseases and the European Center for Disease Prevention and Control, which recommend early rotavirus vaccination.[6,7] In a recent publication, several Italian public health experts also emphasized the need to start rotavirus vaccination from the sixth week of life: "The early start of administration of the rotavirus vaccine improves not only the efficacy, but also the safety. For this reason, we recommend to start the vaccination schedule from the sixth week of life".[8]

The authors also discuss the impact of the maximum age for series completion on averted cases: "If we consider the maximum vaccination periods, i.e., 24 weeks (HRV) [RV1] or 32 weeks (HBRV) [RV5], a delay of 8 weeks may lead to an estimate of approximately 120 unprevented hospitalizations due to RVGE per year".[1] Such calculations do not reflect the established epidemiology of the disease, and vaccine efficacy and effectiveness estimates from clinical trials and observational studies that show high vaccination effectiveness after the first dose. RV5 has been demonstrated to confer protection between the first and second doses, and between the second and third doses in post-hoc clinical trial analyses.[9] Dennehy et al. estimated that between the first and second dose, RV5 decreased the combined rates of hospitalization and ED visits by 100% for G1-G4 serotypes and by 82% regardless of serotype.[9] Similarly, between the second and third dose, RV5 decreased the combined rates of hospitalization and ED visits by 91% for G1-G4 serotypes and by 84% regardless of serotypes.[9]

Martinelli et al. emphasize differences in schedule compliance and series completion between the two vaccines, stating that "During the first 6 months after RV vaccination implementation, 770 (19.7%) of the 3,912 children vaccinated with HBRV [RV5] received their first dose outside the prescribed time limits."[1] The authors refer to a study involving the administration of 5,566 RV5 doses during the first 6 months of the RV5 vaccine availability (August 1, 2006, to January 31, 2007; the number of doses refer to those registered in the immunization system) in Philadelphia, PA, USA.[10] In this study, Daskalaki et al. provided estimates from a single city in the immediate months following program implementation.[10] These estimates are neither generalizable nor reflective of current compliance rates in the United States. More robust and representative estimates have been provided by the US Centers for Disease Control and Prevention (CDC) using data from Immunization Information System (IIS) sentinel sites and the Vaccine Safety Datalink (VSD).[11] In the first year following universal RV recommendation, 107,128 and 90,151 RV5 doses were reported by IIS sentinel sites and the VSD, respectively; >85% of IIS and >92% of VSD first doses of RV5 were administered within the recommended time interval. More than 98% of IIS and VSD doses were administered within the recommended 6–32 weeks schedule. Vaccination coverage in the United States (where RV5 is the most widely used vaccine[12]) has increased since 2007, with the highest

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vaccination coverage for the complete series achieved by any state increasing from 72% in 2009 to 80% in 2011 and 85% in 2017.[13]

Martinelli et al. further note that: "Another study conducted within the Medicaid system evaluated compliance rates and adherence to the vaccination schedule in a cohort of 673,956 children under the age of one year, comparing the two approved RV vaccines, HRV [RV1] and HBRV [RV5]". While different estimates for series completion have been obtained using Medicaid data (a federal health insurance program for which some Americans without private insurance may be eligible) these estimates may not reflect actual vaccination coverage. Medicaid providers use various codes for rotavirus vaccines, some of which do not differentiate between rotavirus vaccines. Thus, estimating RV vaccination coverage for Medicaid enrollees using this data-source may not be reliable.[14] Data from other European countries, where both vaccines are present, may be more relevant and illustrative for Italy. For instance, in Germany, overall series completion for RV vaccination in a post-licensure study has been estimated to be >90% in regions using both RV1 and RV5; Marlow et al., in Portugal, found no statistical difference in series completion for both vaccines in a case–control effectiveness study.[15,16]

Durability of protection is also an important consideration. RV5 is the only rotavirus vaccine for which long-term protection of at least seven years has been demonstrated after the complete series in a study involving 2961 infants.[17–19] Household studies from different countries including the United States, Netherlands, and Ecuador show that rotavirus is highly transmissible within households.[20–22] In particular, a household study from Ecuador showed that when a younger child has rotavirus, older siblings are at risk for rotavirus infection.[22] Thus, long-term protection acquired as infants may prove beneficial for families as infants suffer multiple exposures to rotavirus infection.

In summary, we thank the authors for their attention to this topic and appreciate the opportunity to add relevant information to their discussion. Efficacy and safety of both RV1 and RV5 have been demonstrated in large clinical trials; there is no evidence to support differences in public health outcomes by posology.

Disclosure of potential conflicts of interest

CC, SS, RD, TP and NK are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who own stock and/or hold stock options in Merck & Co., Inc., Kenilworth, NJ, USA.

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