Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality

Eleanor Burnett [a,*], Ben A. Lopman [b,c], Umesh D. Parashar [c]

[a] CDC Foundation, United States
[b] Department of Epidemiology, Emory University, United States
[c] Division of Viral Diseases, US Centers for Disease Control and Prevention, United States

ARTICLE INFO

Article history:
Received 21 June 2017
Received in revised form 22 August 2017
Accepted 12 October 2017
Available online xxxx

Keywords:
Rotavirus
Rotavirus vaccine
Diarrhea
Booster dose

ABSTRACT

Concern has grown that children vaccinated against rotavirus in developing countries may be vulnerable to rotavirus diarrhea in the second year of life due to waning immunity. Adding a booster dose of rotavirus vaccine at 9 or 12 months of age with measles vaccine has been suggested as a strategy to address this. We evaluated the hypothetical potential benefits of a booster dose on reduction of rotavirus mortality. The projected number of deaths averted were calculated using national level full series vaccination coverage, estimated national rotavirus deaths by week of age, and VE at <12 months of age and ≥12 months of age derived from the published literature. We assumed three functional forms of waning based on the VE estimates: stepwise, linear, and logarithmic. We modeled three potential boosting scenarios: (a) reduced VE waning in the second year of life by 50%, (b) reestablished second year of life VE to the levels in the first year of life, and (c) boosted first year VE by 50% of the difference between VE in the first and second years. To express uncertainty resulting from the parameters, each of the nine models were run 1000 times using a random sample of input values. Across all WHO regions, with the stepwise models we estimated a median of 9800 (95%CI: 9400, 10,200), 19,600 (95%CI: 18,800, 20,400), and 29,400 (95%CI: 28,200, 30,700) additional rotavirus deaths averted in the reduced VE waning, reestablished VE, and boosted VE scenarios. These estimates were highly sensitive to the assumed functional form of waning with approximately 65–80% fewer deaths averted if immunity waned in a linear or logarithmic fashion compared to the stepwise model. While these projections will benefit from improved input data points, our results inform consideration of booster doses of rotavirus vaccine.

Published by Elsevier Ltd.

1. Introduction

Since licensure in 2006, two rotavirus vaccines have been increasingly used worldwide to prevent rotavirus diarrhea morbidity and mortality in children less than 5 years of age. RotaTeq (Merck and Co) is a three-dose pentavalent bovine-human reassortant rotavirus vaccine and Rotarix (GSK Biologics) is a two-dose monovalent human rotavirus vaccine [1,2]. Two other three-dose vaccines, ROTAVAC (Bharat Biotech) and ROTASIIL (Serum Institute of India), were licensed recently and are under review for World Health Organization (WHO) prequalification [3,4].

Rotavirus vaccines are licensed for use as part of the infant immunization schedule concomitantly with diphtheria-tetanus-pertussis vaccine (DTP). Randomized control trials (RCT) for Rotarix and RotaTeq assessed vaccine efficacy beyond the first year of life; in low income countries, waning immunity after 1 year of age was observed in clinical trials [5,6] while protection was found to persist in the RCTs in high income countries [7]. Some post-licensure, "real world" effectiveness evaluations in several low and middle-income settings also indicate there may be waning protection after the first year of life, though they were not sufficiently powered to detect differential vaccine performance by age group [8–18]. Rotarix VE after 12 months of age was found to be a median of 31% lower in middle income countries, compared to 5% higher in high income countries in a recent systematic literature review [19]. These observations raise concern that waning immunity may leave vaccinated children vulnerable to rotavirus diarrhea morbidity and mortality in the second year of life and beyond. In the absence of vaccine, approximately 30% of rotavirus

* Corresponding author at: CDC Foundation for Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-34, Atlanta, GA 30329, United States.
E-mail address: wwg7@cdc.gov (E. Burnett).

https://doi.org/10.1016/j.vaccine.2017.10.027
0264-410X/Published by Elsevier Ltd.

deaths occur during the second year of life, though this varies substantially from region to region [20]. A booster dose of rotavirus vaccine later in infancy has been proposed as an approach to address waning rotavirus vaccine immunity [21].

Measles-containing vaccines (MCV) are generally recommended by national immunization programs for administration at 9 or 12 months of age. Delivering a booster dose of rotavirus vaccine at the same healthcare visit as MCV could be a logistically feasible way to integrate a booster dose of rotavirus vaccine into the Expanded Programme on Immunization (EPI) and extend protection into the second year of life. A RTC in Bangladesh recently demonstrated non-interference of a rotavirus vaccine dose delivered concomitantly with the injected, live measles-rubella vaccine, a necessary first step in determining feasibility of such a strategy [21]. As a secondary objective, the RTC assessed immunogenicity of the booster rotavirus vaccine dose; all children in the study received 2 infant doses of rotavirus vaccine. Among children in Bangladesh who were sero-negative at 9 months, 44% seroconverted after receiving a third dose of rotavirus vaccine with MCV, compared with 6% of placebo recipients. While seroconversion is not directly correlated with clinical outcomes [22], these results are encouraging.

Before any policy recommendation for a 9- or 12-month dose of RV can be considered, the potential benefits of booster dose will need to be weighed against the additional cost and vaccine supply requirements. Additionally, a clinical efficacy or large-scale immunogenicity trials will need to be conducted, which will be resource intensive. As a critical first step in deciding whether to pursue this strategy, we aimed to evaluate the potential impact of a booster dose of rotavirus vaccine on rotavirus mortality.

2. Methods

Using UNICEF 2014 <5 child mortality rates, we divided countries into three strata. Low mortality countries were defined as those with rates in the lowest quartile (1.9–7 deaths per 1000 live births), medium mortality countries as those in the second lowest quartile (8–17 deaths per 1000 live births), and high mortality countries as those in the highest two quartiles (18–157 deaths per 1000 live births) [23]. Countries categorized in the medium and high mortality strata are included in this exercise; countries with low child mortality were not, as waning protection of rotavirus vaccine has not been observed in these settings.

2.1. Model construction

We calculated national reductions in rotavirus deaths as follows:

$$Deaths\ Prevented_i = \sum_{j=1}^{j=103} VE_j \times Coverage_i \times Rotavirus\ Deaths_{i,j}$$

where *i* refers to country and *j* to the week of life. In this formula, *VE* refers to vaccine effectiveness and *Coverage* refers to full series rotavirus vaccine coverage.

We followed the PRISMA guidelines in a systematic literature review of full-series rotavirus vaccine VE estimates from medium- and high-mortality countries published between 1 January 2006 and 2 December 2016 using the PubMed, MEDLINE, Embase, and Global Health databases. The methods are described in detail elsewhere [19]. Briefly, we included post-licensure, observational evaluations that reported Rotarix VE estimates for children <12 months of age and children ≥12 months of age in low and middle income countries against hospitalization for rotavirus disease. Additionally, we included two pre-licensure evaluations that address waning in low and middle income countries [5,6,8–18]. We calculated summary VE estimates with a random effects model (Table 1); this portion of analysis was performed using R v3.2.4. We considered three functional forms for VE waning. In the stepwise model, we assumed full VE is achieved at 6 weeks of age and remains constant until waning at 9 months of age; in this model, VE is constant from 9 to 24 month of age (Fig. 1a and b). This model reflects the results of the meta-analysis, which summarize VE estimates from children in these broad age categories. We used the same <9 month and ≥9 month point estimates and 95%CIs to generate logarithmic and linear waning patterns by assigning the VE point estimates to 6 months of age and 18 months of age (Fig. 1c and d). VE estimates by week of age generated by the three waning forms were included as model inputs.

Full series vaccination coverage by country was obtained from the WHO/Unicef annual Joint Reporting Form (JRF), which provides a "best estimate" of national vaccine-specific coverage for children <12 months of age using administrative data, surveys, and other national estimates [24]. The JRF reports full series rotavirus vaccine coverage for countries that have introduced rotavirus vaccine in their national immunization programs. However in this exercise, we assumed full series rotavirus vaccine coverage to be equal to DTP coverage for all countries from 6 weeks of age, regardless of rotavirus vaccine introduction status or recommended schedule. As rotavirus vaccine is usually recommended for co-administration with DTP, coverage is expected to be similar for both vaccines. In countries that have introduced rotavirus vaccine, some countries have experienced an initial lag in coverage compared to DTP. We assumed coverage with a booster dose of rotavirus vaccine would be equal to first-dose measles or full-series DTP coverage, whichever was least [25].

The estimated national rotavirus deaths and distribution of deaths by week of age used in this exercise were previously published and were most recently updated in 2013 [20,26,27].

2.2. Booster scenarios

We calculated the baseline number of rotavirus deaths for each functional waning form. For countries that had not introduced rotavirus vaccine before 2013 we calculated the baseline number of deaths due to rotavirus, assuming that the primary series was introduced, by subtracting the number of deaths prevented under each of the three waning scenarios from the estimated number of rotavirus deaths in 2013. Among countries that introduced rotavirus vaccine before 2013, we used the number of rotavirus deaths in 2013 as baseline under all three waning scenarios.

Given that the true effect of a booster does is unknown, we simulated three scenarios with each waning model: (a) reduced VE waning in the second year of life by 50%, (b) reestablished second year of life VE to levels from the first year of life, and (c) boosted VE by 50% of the difference between VE in the first and second years of life. In all boosting scenarios, the slope and functional form of waning is assumed to be the same before and after the booster rotavirus vaccine dose. Regardless of vaccine introduction status, the number of deaths prevented under the nine boosting scenarios were calculated the same way for all countries. Summary results are presented globally and by WHO region. Booster doses were assumed to be administered concomitantly with MCV at either 9 or 12 months, based on the current recommended age of administration by country.

2.3. Simulations

To quantify uncertainty in averted death estimates, we performed a sensitivity analysis by generating 1000 simulations of each model. We independently sampled <12 month and ≥12

Please cite this article in press as: Burnett E et al. Potential for a booster dose of rotavirus vaccine to further reduce diarrhea mortality. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.10.027