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Review

Estimating the herd immunity effect of rotavirus vaccine

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ABSTRACT

Introduction: Diarrhea is one of the leading causes of death in children under 5, and an estimated 39% of these deaths are attributable to rotavirus. Currently two live, oral rotavirus vaccines have been introduced on the market; however, the herd immunity effect associated with rotavirus vaccine has not yet been quantified. The purpose of this meta-analysis was to estimate the herd immunity effects associated with rotavirus vaccines.

Methods: We performed a systematic literature review of articles published between 2008 and 2014 that measured the impact of rotavirus vaccine on severe gastroenteritis (GE) morbidity or mortality. We assessed the quality of published studies using a standard protocol and conducted meta-analyses to estimate the herd immunity effect in children less than one year of age across all years presented in the studies. We conducted these analyses separately for studies reporting a rotavirus-specific GE outcome and those reporting an all-cause GE outcome.

Results: In studies reporting a rotavirus-specific GE outcome, four of five of which were conducted in the United States, the median herd effect across all study years was 22% [19–25%]. In studies reporting an all-cause GE outcome, all of which were conducted in Latin America, the median herd effect was 24.9% [11–30%].

Conclusions: There is evidence that rotavirus vaccination confers a herd immunity effect in children under one year of age in the United States and Latin American countries. Given the high variability in vaccine efficacy across regions, more studies are needed to better examine herd immunity effects in high mortality regions.

1. Introduction

Diarrhea is one of the leading causes of death among children under 5 years of age globally [1–3]. It has been estimated that 39% of these diarrhea deaths in children under 5 years of age are due to rotavirus [4]. Vaccination has played an important role in the reduction of rotavirus morbidity in high-income countries, but introduction has been slow in many low- and middle-income countries. WHO recommends rotavirus vaccine to be included in all national immunization programs, particularly in countries with high rates of rotavirus gastroenteritis (GE)-associated child deaths [5].

Currently two live, oral rotavirus vaccines have been introduced: RotaTeq (Merck), a pentavalent human-bovine reassortant vaccine, and Rotarix (GlaxoSmithKline), a monovalent attenuated human rotavirus vaccine. A systematic review conducted in 2010 demonstrated that currently licensed vaccines prevent up to 74% of severe rotavirus episodes, which is a proxy for rotavirus mortality [6]. Regional variation in efficacy has been observed, ranging from >90% in high-income countries to 50% in low-income countries, though the reasons for this variation remain unclear [7–9].

Review papers thus far have focused on the direct effect of vaccination (i.e. the benefit to the vaccinated individual). Many countries have achieved scale-up, enabling measures of the indirect benefit of vaccination in a population, i.e. herd immunity. Herd immunity is usually achieved by interrupting the transmission of the organism by preventing infections in immunized individuals. Thus, there is less opportunity for the unimmunized individual to be exposed to the organism. This has been demonstrated for a number of vaccines including pneumococcal and Hib vaccines. The herd effect is formally defined as "the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of

Abbreviations: GE, Gastroenteritis; LiST, Lives Saved Tool.

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the population" [10]. Thus, when the protective effect of a vaccine surpasses the expected level of the vaccine efficacy and vaccine coverage, this is known as herd protection [11]. It is important to quantify the effect of herd immunity to fully capture the potential benefits of vaccine introduction to the population. Assessing the herd effect of vaccines is critical for rotavirus control programs and can provide evidence for the guidance and planning of child health programs and policy advocacy. Furthermore, herd immunity has important implications for the cost-effectiveness of vaccines. For example, in high mortality countries where uptake may be lower or slower to reach saturation, the direct effect of the rotavirus vaccine would be lower than in countries with high coverage [6]. Calculating the added benefit via herd immunity is important for determining the cost effectiveness of vaccine introduction and scale up.

The *Lives Saved Tool (LiST)* is a computer-based tool that models and estimates the impact of scaling up proven interventions on maternal, neonatal and child mortality (http://www.livessavedtool.org). This tool has been used to guide decision-making and advocacy for the implementation of programs based on disease burden and proven efficacy of interventions [12,13]. *LiST* has also been used to estimate the current and projected impact of rotavirus as well as other vaccines for GAVI as part of their review and planning process [14]. In that work we have only included the direct impact of vaccination using estimates of vaccine efficacy, as there has been no robust estimate of herd effects for rotavirus vaccination. To date, research on rotavirus has primarily focused on estimating the efficacy and impact of rotavirus vaccination, while there have been few efforts to estimate the herd effects of rotavirus vaccination. Thus, in this paper we present a systematic review and meta-analysis to estimate the herd effects of rotavirus vaccines and present a herd immunity effect size that can be used in *LiST* and other models to more accurately estimate the impact of rotavirus vaccine scale-up.

2. Methods

2.1. Systematic literature search

We conducted a systematic search of published literature to identify studies presenting data on rotavirus vaccination coverage and impact in children. Specifically, we searched for observational studies conducted pre- and post-introduction of rotavirus vaccine in a particular population. We first searched papers published between 2008 and August 5, 2011. Then, we updated our search, including articles published from 2011 to 2014. We searched PubMed/Medline, Embase, the Global Health Library, the Cochrane Library, the Literature on the Health Sciences in Latin America and the Caribbean (LILACS), and World Health Organization Regional Databases, in addition to regional databases (AIM, PAHO, and IndMED) and used the following terms for the search:

Rotavirus Vaccines[mesh] OR "rotavirus vaccine"[all fields] OR "rotavirus vaccines"[all fields] OR "rix 4414" OR "rix4414" OR "rotamune" OR "rotarix" OR "rotashield" OR "rotateq" OR ((rotavirus OR rotaviruses OR "rota virus" OR "rota viruses") AND ("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR vaccinations[tiab] OR "immunization"[tiab] OR immunizations[tiab] OR "immunisation"[tiab] OR immunisations[tiab] OR "immunized"[tiab] OR "immunised"[tiab]))

Immunity, Herd[mesh] OR "herd immunity" OR "population effects" OR "population effect" OR "indirect effects" OR "herd effects" OR "transmission interruption" OR "indirect effect" OR "herd effect" OR "herd benefit" OR "herd benefits" OR "herd protection" OR "indirect immunity" OR "herd protective" OR herd OR Effectiveness OR "community immunity" OR efficacy OR impact OR "post marketing surveillance" OR population surveillance[mesh] OR "population surveillance" OR "vaccine coverage" OR ((decline[tiab]) AND (rotavirus[tiab] OR rotaviruses[tiab] OR "rota virus"[tiab] OR "rota viruses"[tiab]) AND ("vaccine"[tiab] OR "vaccines"[tiab] OR "vaccination"[tiab] OR "vaccinated"[tiab] OR "immunization"[tiab] OR "immunisation"[tiab] OR "immunized"[tiab] OR "immunised"[tiab])) NOT animal filter: animals[mesh] NOT (humans[mesh] AND animals[mesh]).

2.2. Inclusion/exclusion criteria

We included studies that met the following inclusion criteria: (1) the publication was of original work using original data; (2) coverage of rotavirus vaccination (monovalent and/or pentavalent) was reported in the original target population (children younger than five years of age); (3) outcome data related to rotavirus disease (morbidity, mortality, hospitalizations, or consultations due to acute GE or rotavirus-specific GE) during both the pre-vaccine and post-vaccine period was included. We excluded studies that were conducted in special populations (i.e. HIV patients, travelers, military personnel, etc.).

2.3. Study quality

Study quality was assessed based on a modification of the methods for systematic reviews as described by the Child Health Epidemiology Reference Group [15]. Studies were evaluated for study design (prospective versus retrospective data collection, time between vaccine initiation and disease outcome data collection, etc.), population representativeness (broad target population, generalizable to entire population of interest), quality of coverage measurement (administrative records versus active data acquisition) and quality of outcome measurement (e.g. administrative versus study-collected coverage data, quality of outcome surveillance, number years of pre-vaccine outcome data reported).

Our initial search yielded 4678 articles. Two reviewers then screened all titles and abstracts and dropped studies that did not meet inclusion criteria. In the second phase, the reviewers screened the full text of the remaining studies for adequate information on coverage and rotavirus outcomes. During the last phase, the reviewers read the studies in full, extracted data from the 53 selected articles, and re-evaluated them for inclusion and exclusion criteria, as well as study quality, to determine final eligibility for inclusion (see Fig. 1).

2.4. Data abstraction, synthesis, and analysis

The following information was recorded from the 53 articles: study location, type and length of disease surveillance, vaccine type (pentavalent or monovalent), coverage data and dosing information, data for all reported outcomes, and number of pre-vaccine years of outcome data reported. Of the 53 studies evaluated and extracted, an additional 35 had insufficient coverage, outcome data, or study quality and were excluded (see Fig. 1).

The final complete dataset for children 0–1 years of age included 15 studies [16–30] from six countries (United States, Brazil, Nicaragua, El Salvador, Panama, Mexico). While our initial search and coding included data for children under 5, data points for children older than 1 year of age were excluded due to inconsistencies between mortality and coverage data, and in order to include the largest number of studies possible given the variability across studies in how age groups were divided. Of these 15 studies, five had data for rotavirus-specific outcomes and four were from high-income countries. The final dataset included

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