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Rotavirus vaccine effectiveness in low-income settings: An evaluation of the test-negative design

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ABSTRACT

Background: The test-negative design (TND), an epidemiologic method currently used to measure rotavirus vaccine (RV) effectiveness, compares the vaccination status of rotavirus-positive cases and rotavirus-negative controls meeting a pre-defined case definition for acute gastroenteritis. Despite the use of this study design in low-income settings, the TND has not been evaluated to measure rotavirus vaccine effectiveness.

Methods: This study builds upon prior methods to evaluate the use of the TND for influenza vaccine using a randomized controlled clinical trial database. Test-negative vaccine effectiveness (VE-TND) estimates were derived from three large randomized placebo-controlled trials (RCTs) of monovalent (RV1) and pentavalent (RV5) rotavirus vaccines in sub-Saharan Africa and Asia. Derived VE-TND estimates were compared to the original RCT vaccine efficacy estimates (VE-RCTs). The core assumption of the TND (i.e., rotavirus vaccine has no effect on rotavirus-negative diarrhea) was also assessed.

Results: TND vaccine effectiveness estimates were nearly equivalent to original RCT vaccine efficacy estimates. Neither RV had a substantial effect on rotavirus-negative diarrhea.

Conclusions: This study supports the TND as an appropriate epidemiologic study design to measure rotavirus vaccine effectiveness in low-income settings.

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1. Introduction

Globally, an estimated 200,000 deaths due to rotavirus diarrhea occur annually in children <5 years old, with a majority of the burden in low-income settings [1]. Starting in 2006, two rotavirus vaccines have been introduced worldwide; GlaxoSmithKline's live-attenuated human monovalent vaccine (Rotarix [RV1]) and Merck's live-attenuated pentavalent human-bovine reassortant vaccine (RotaTeq [RV5]). Large multi-site randomized controlled trials (RCTs) of RV1 and RV5 in low-income settings have demonstrated moderate vaccine efficacy against severe rotavirus gastroenteritis in the first year of life (VE: 51–64%) [2–6]. As of May 1, 2016, rotavirus vaccines have been introduced nationally in 38 Gavi-eligible countries. However, many high-burden countries have not introduced the vaccine and approximately 70% of the world's infants still do not have access to rotavirus vaccine [7]. Accurate post-introduction monitoring of effectiveness measures is important as results can influence the adoption of rotavirus vaccines in new areas and sustain support in countries where vaccines have been introduced.

Case-control studies are an efficient means to monitor effectiveness and provide confidence in vaccine performance. In low-income settings, identifying community controls, either using a demographic surveillance system or sampling the community in-person, can be impractical and expensive. Hospital controls can be used to minimize bias due to healthcare seeking behavior. However, for rotavirus vaccine studies, careful consideration must be made to use hospital controls without diarrhea or any illness associated with vaccine-preventable diseases. The test-negative design (TND) can theoretically overcome the limitations of both

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traditionally-used control groups, while also limiting bias due to healthcare seeking behavior [8]. TND rotavirus vaccine studies enroll cases presenting to a medical facility for acute gastroenteritis and are rotavirus-positive using standard laboratory methods. Controls include those presenting to a medical facility with the same pre-defined case definition of acute gastroenteritis, but are rotavirus-negative. Both traditional case-control and test-negative study designs require rotavirus testing on infants presenting to the clinic with diarrhea to identify cases. The TND is efficient and cost-effective in that those testing-negative for rotavirus serve as the control group, instead of being excluded from the study.

The TND has been used extensively to measure annual influenza vaccine effectiveness [8,9]. Simulation experiments have validated the test-negative design for influenza vaccine under specific core assumptions: (1) vaccine has no effect on the incidence of non-influenza pathogens, (2) a highly sensitive and specific laboratory test is used for pathogen detection, and (3) other sources of bias present in observational studies are minimized [8–14]. De Serres et al. validated the TND for influenza vaccine utilizing RCT databases to verify the accuracy and precision of TND estimates and to test the assumption that the vaccines had no effect on non-influenza respiratory illness [15]. RCTs are appropriate to validate this design due to limited selection bias and confounding as a result of randomization and blinding, the use of standardized laboratory testing, and enhanced surveillance. Derived test-negative vaccine effectiveness estimates for influenza vaccines were almost identical to the original RCT vaccine efficacy estimates. Importantly, the vaccine coverage in the test-negative controls represented the vaccine coverage in the underlying study population, upholding the key assumption that the vaccine had no effect on non-influenza illness. Together, these results indicated the TND was a valid epidemiologic study design to measure influenza vaccine effectiveness [15].

The TND is being increasingly used to estimate rotavirus vaccine effectiveness in middle- and low-income settings due to its low cost and feasibility,[16–26] but little has been done to assess this epidemiologic study design in the context of rotavirus vaccine effectiveness in low-income settings. In the present analysis, RCT databases for RV1 and RV5 in sub-Saharan Africa and Asia were used to evaluate the TND.

2. Methods

2.1. Participants and study design

Databases from three multi-center, double-blind, individual-randomized, placebo-controlled, trials of rotavirus vaccines in sub-Saharan Africa and Asia were used [2–6]. Table 1 summarizes location, vaccine schedule, per-protocol population size, and surveillance type of the three RCTs.

2.1.1. RV1

This trial was conducted in South Africa and Malawi. Between 2005 and 2007, 4939 healthy infants aged 5–10 weeks were randomly assigned to one of three groups in a 1:1:1 ratio: two doses of RV1, three doses of RV1, or three doses of placebo. Gastroenteritis was defined as three or more loose or watery stools within 24 h. Clinical characteristics of each diarrheal episode were documented to define severity based on the Vesikari score [27]. Stool samples were tested for rotavirus using enzyme-linked immunosorbent assay (ELISA). The primary outcome was at least one episode of severe rotavirus gastroenteritis (Vesikari score $\geqslant$11). Vaccine efficacy was estimated during the period from two weeks after the last dose until the first year of age. Within each study site, a sub-cohort was followed into the second year of life. The mean age at the end of follow-up was 14 months and 19 months for South Africa and Malawi, respectively.

2.1.2. RV5

Two trials of RV5 were conducted in sub-Saharan Africa and Asia between 2007 and 2009. Both trials were conducted under similar protocols; however, the trials were powered and implemented separately. In sub-Saharan Africa, 5468 healthy infants were enrolled in Ghana, Kenya, and Mali. In Asia, 2036 healthy infants were enrolled in Bangladesh and Vietnam. Infants aged 4–12 weeks were randomly assigned to one of two groups in a 1:1 ratio: three doses of RV5 or three doses of placebo. As in the RV1 trial, severe rotavirus gastroenteritis was defined based on a positive ELISA laboratory result and Vesikari score $\geqslant$11. Vaccine efficacy was estimated during the period from two weeks after the last dose until the end of follow-up (March 31, 2009). The mean age at the end of follow-up was 20 months and 19 months for sub-Saharan Africa and Asia, respectively.

For the purposes of this analysis, participants with an episode of severe diarrhea meeting the pre-defined case definition and with an available ELISA test result were categorized as a case if the test was positive for rotavirus or a control if the test was negative for rotavirus. Continuous diarrheal surveillance during the study period allowed for the identification of multiple diarrheal episodes for each participant. A participant was defined as a case if at least one severe rotavirus-positive diarrheal episode occurred during follow-up. A participant was defined as a control if at least one severe rotavirus-negative diarrheal episode occurred during follow-up and the participant had no severe rotavirus-positive episodes.

Table 1
Summary of rotavirus vaccine clinical trials in low-income settings.

Vaccine	Dosing schedule	Surveillance type	Study site	Age during follow-up	Primary per-protocol population (Vaccine/Placebo)	Country specific per-protocol population (Vaccine/Placebo)	Reference
Rotarix (RV1)	6, 10, 14 weeks or 10,14 weeks	Active: Scheduled weekly home visits and clinic visits	South Africa	<1 Years	2974/1443	1944/960	[2]
			Malawi			1030/483	
			South Africa	1–<2 Years	*	686/332	[3]
			Malawi			814/380	[4]
RotaTeq (RV5)	6, 10, 14 weeks	Passive: clinic visits	Ghana Kenya Mali	<2 Years	2404/2385	940/930 573/577 891/878	[5]
RotaTeq (RV5)	6, 10, 14 weeks	Passive: clinic visits	Bangladesh Vietnam	<2 Years	995/988	557/561 438/427	[6]

* Vaccine efficacy was estimated separately in South Africa and Malawi for the second year of this study.

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