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Evaluation of the Indirect Effects of Rotavirus Vaccination Programs in World Health Organization Member States

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B.Sc. University of Iowa, 2018

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Abstract

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Rotavirus is a leading cause of diarrhea-related deaths in children under 5 years old, most of which occur in low-to-middle income countries (LMICs). Licensed rotavirus vaccines provide high levels of direct protection, but their indirect effect – the protection provided to unvaccinated individuals within a mixed-vaccinated population – is not fully understood. We aimed to quantify the population-level effects of rotavirus vaccination and identify factors that drive indirect protection. We used a transmission model to estimate the indirect effects of vaccination on rotavirus deaths in 112 LMICs. Indirect effects were estimated by quantifying the difference between predicted impacts if vaccination did (overall effects) or did not (direct effects) change the force of infection, and both scenarios were compared with a no vaccine scenario. We performed a linear regression analysis on model outputs to identify predictors of indirect effect magnitude. We also used logistic regression to understand predictors of negative indirect effects. Indirect effect sizes 8-years post-vaccine introduction ranged from 16.9% in the WHO European region to 0.97% in the Western Pacific region. Under-5 mortality rate and vaccine coverage were positively associated with indirect effect magnitude. Birth rate was negatively correlated. Of the 112 countries analyzed, 18 (16%) had at least one year with a predicted negative indirect effect. Negative indirect effects were more common in countries with higher birth rate and were less common in countries with higher under-5 mortality and higher vaccine coverage. These results suggest that the rotavirus vaccine provides indirect benefits to unvaccinated individuals within a partially-vaccinated population. The strength of this effect varies by country and depends on country-specific birth rate, under-5 mortality rate, and vaccine coverage. Rotavirus vaccination may have a larger impact than would be expected from direct effects alone.

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Chapter 1: Introduction

Introduction and Rationale

Rotavirus is a leading cause diarrheal disease and accounts for nearly 30% of diarrhea-related mortality in children under 5 years old globally, with approximately 128,500 childhood deaths in 2016 [1, 2]. Rotavirus infections primarily occur in children 4-24 months of age [3]. Rotavirus incidence has decreased drastically over time due to water, sanitation, and hygiene improvements and the introduction of rotavirus vaccines. In 2016, it is estimated that upwards of 28,000 child deaths were averted due to rotavirus vaccination [2].

There are currently four licensed rotavirus vaccines recommended by the World Health Organization – Rotarix, RotaTeq, Rotasiil, and Rotavac [4, 5]. All vaccines have demonstrated efficacy in preventing rotavirus infection in children [5]. However, the protection provided to unvaccinated individuals in a partially-vaccinated population – the indirect effect – is still not well-defined [6, 7].

Problem Statement

Although rotavirus affects children globally, the burden of rotavirus infections is highest for those living in low-to-middle income countries (LMICs). Over 90% of childhood rotavirus deaths occur in LMICs [8]. Additionally, children living in LMICs have a younger age of first infection than those living in high-income countries [3]. Rotavirus vaccines are becoming more widely available in LMICs, with Rotarix as the primary vaccine used [9]. However, the strength of protection provided by the vaccine to vaccinated individuals – the direct effect – decreases with decreased country income level [6]. Moreover, the indirect vaccine effect is influenced by sociodemographic factors such as birth rate, vaccine coverage, and background mortality, which also generally vary by country income level [10].

Purpose Statement

The purpose of this analysis is to quantify the modeled indirect effect of rotavirus vaccines in LMICs based on the Emory Rotavirus Model and further our understanding of the association of sociodemographic factors with indirect effect magnitude.

Research Aims

Aim 1: Estimate the direct, indirect, and overall effects of the rotavirus vaccine in LMICs

Aim 2: Assess sociodemographic predictors of indirect vaccine effect magnitude

Aim 3: Identify sociodemographic factors that are associated with negative indirect vaccine effect

Significance Statement

There is a clear need to define the strength of vaccine indirect effects in LMICs. There is also a need to understand how sociodemographic factors, such as those previously mentioned, influence indirect effect. This information could be used to tailor rotavirus immunization policy and strategy to a country's unique sociodemographic landscape and ultimately help close the gap in protection between LMICs and high-income countries.

Chapter 2: Literature Review

This chapter will review the theory underlying direct and indirect vaccine effects and how these theories apply to the rotavirus vaccine. It will also provide an overview of rotavirus biology and epidemiology, as well as the existing approved vaccines for rotavirus.

Theory of Direct and Indirect Vaccine Effects

With the advent of vaccines, vaccination campaigns, and disease eradication efforts, the concept of herd immunity is at the forefront of public health efforts [11]. The underlying idea of herd immunity is that the risk of infection for individuals in a population is reduced as people within the population gain immunity. Herd immunity is often described as a threshold – once a certain proportion of individuals are immune, through natural infection or vaccination, transmission of the pathogen will decline [11]. If a vaccine does not provide complete protection or the vaccine-induced immunity wanes over time, the threshold for herd immunity is relatively higher compared to a perfectly immunizing vaccine or infection [11].

Herd immunity is the result of both the direct and indirect protection conferred by vaccines [11]. The direct effect of a vaccine is the protection given to an individual from the immunologic response to a vaccine [12]. The magnitude of this effect is measured in randomized clinical trials, cohort studies, case-control studies, and case-population studies through comparing infection incidence in vaccinated and unvaccinated people [12]. Although vaccination provides a benefit to the recipient, it is ultimately the reduction in transmission of a pathogen that is responsible for providing indirect protection in the population [11]. If a vaccine only benefited the recipient by preventing symptomatic disease, indirect protection and herd immunity – some of the most impactful benefits of vaccines – would not occur [11].

The indirect effect of a vaccine is the protection conferred to unvaccinated individuals through a reduction of susceptibility within a population that contains vaccinated individuals, as well as the additional protection vaccinated individuals receive from less exposure to the pathogen [12]. For vaccines to provide indirect protection, the pathogen must be transmitted person-to-person. Pathogens with no capacity for person-to-person transmission, such as zoonoses or environmental pathogens, are not susceptible to indirect effects [12]. The strength of indirect effects is dependent on the transmissibility of the pathogen, the route of transmission (e.g., fecal-oral), the prevalence of the infection within the population, the type of immunity the vaccine elicits (humoral vs. cellular), and the level of vaccine coverage in the population [11]. Indirect effects can be measured by comparing disease incidence in a completely unvaccinated population to the incidence amongst unvaccinated individuals in a population that includes vaccinated individuals [12]. The total vaccine effect is the protection of a vaccinated individual in a vaccinated population relative to the protection of an unvaccinated individual in an unvaccinated population [13].

Indirect protection is population-specific and can vary depending on a variety of social and biological factors. The force of infection is a measure commonly used in infectious disease epidemiology to define the rate at which susceptible individuals become infected per unit time [14]. The force of infection can vary by locale based on social mixing patterns in the population [11]. If the force of infection in a certain population is particularly high, more individuals will need to be vaccinated to reach a certain level of indirect protection than if the force of infection was lower. Another determinant of indirect effects is local vaccination coverage [15]. To experience the protection of indirect effects of a vaccine, a high proportion of the population must be vaccinated. However, if every person in the population were to be vaccinated, then

protection would be almost entirely due to the direct effect of the vaccine and there would be no indirect protection conferred. Demographic factors such as birth rates and background mortality can also influence indirect protection. For example, a country with a higher birth rate will require higher vaccination coverage to reach herd immunity, as herd immunity is dependent on the proportion of susceptible individuals in a population [15]. Widespread pre-existing medical conditions in a population that decrease the direct effect of a vaccine can also decrease the indirect effect. For example, an observational study from 2007 found that HIV-1-positive children in Zambia experienced rapid waning immunity after receiving the measles vaccination, compared to their HIV-negative counterparts. 27 months post-vaccination, only 50% of HIV-1-positive children maintained a strong level of immunity, whereas 89% of HIV-negative children maintained their level of immunity [10]. In countries or regions where immunocompromising diseases are endemic or epidemic, indirect protection will be lessened.

Overview of Rotavirus Biology and Epidemiology

Rotavirus is a pathogen that causes diarrheal disease which accounts for 29.3% of diarrhea-related deaths in children under 5 years old [1]. In 2016, rotavirus-related disease killed 128,500 children worldwide [2]. More than 90% of these fatal child infections occur in low-income countries [8]. This non-enveloped double-stranded RNA virus is a member of the *Reoviridae* family and has seven major groups (Groups A-G), however most strains that infect humans are in Group A [8] [16].

Rotavirus is primarily transmitted fecal-orally in instances of close person-to-person contact, but can also be transmitted through contaminated food and water [17]. Fomites, particularly in healthcare settings, and respiratory droplets have also been known to transmit the

virus, but these routes are far less common [8]. Large amounts of virus are shed during diarrheal episodes, increasing the probability of transmission at these times [16].

The typical clinical manifestation of rotavirus infection includes symptoms such as non-bloody diarrhea, vomiting, fever, and malaise [18]. Infections can also be asymptomatic or sub-clinical [8]. Systemic infection is possible but rare [8]. Symptoms vary by age, with newborn infants (less than 1 month of age) typically having asymptomatic infections due to maternal immunity. Once maternal protection begins to wane, children are more likely to present with symptomatic infections. For this reason, incidence of symptomatic rotavirus is highest between 4 and 23 months of age [18]. Reinfection is common, but disease severity typically decreases with each subsequent infection [8]. Rotavirus infections are treated with oral and intravenous rehydration[8].

Rotavirus primarily affects young children, most frequently those between 4-24 months of age [3]. In a 2011 birth cohort study of 452 children living in Vellore, India, 56% of children had their first rotavirus infection in the first 6 months of age [19]. A similar study from 1996 on infants in Mexico found that of the 200 study participants, 34% had a primary infection by 6 months of age and 96% had a primary infection by two years of age. Furthermore, 69% had a second rotavirus infection and 42% had a third rotavirus infection by two years of age [20].

Although most common in children, adult rotavirus infections still occur, particularly within families with an infected child, long-term care facilities, and travelers [3]. Adult infections are often asymptomatic or sub-clinical [16], but may play a role in sustaining transmission. In general, children living in low-to-middle income countries develop their first rotavirus infection at a younger age than those living in high-income countries [3]. In countries with temperate climates like the United Kingdom and Japan, rotavirus transmission is seasonal

with peaks during the winter months, whereas countries with tropical climates like India and Nigeria experience transmission year round [3].

Direct and Indirect Effects of Rotavirus Vaccines

In 2006, the World Health Organization (WHO) recommended rotavirus vaccination be included as part of the standard immunization programs in the Americas and Europe. The recommendation was extended to all other world regions in 2009 [21]. As of 2021, 111 countries have introduced a rotavirus vaccine into their national immunization program [9]. During the first six years of rotavirus vaccination recommendation, the vaccine was primarily available in European countries and countries in the Americas. The vaccine did not become available to a majority of African countries until 2015, in Middle Eastern and Eurasian countries until 2018, and is still limited in Eastern Asian countries [9]. Four live oral rotavirus vaccines – RotaTeq, Rotarix, Rotasiil, and Rotavac – are currently licensed and recommended by the WHO. RotaTeq and Rotasiil are 3-dose pentavalent bovine-human reassortant vaccines [4, 5]. Rotarix and Rotavac are 2-dose monovalent human vaccines [4, 5]. Rotarix is the vaccine primarily used in low- and middle-income countries [9].

A literature review and meta-analysis of 60 studies comparing the effectiveness of rotavirus vaccines in children from countries with various child-mortality levels found that both RotaTeq and Rotarix effectively prevent rotavirus-related diarrhea. The vaccine efficacy was strongest (83-89%) in countries with lower child mortality [22]. Another meta-analysis of rotavirus vaccine effects in the United States found an 80% decrease in rotavirus-associated hospitalizations and 57% decrease in emergency department visits following vaccine introduction in 2006 [23]. However, the effectiveness of the vaccine does vary by country income-level. In high-income countries, the efficacy is between 84-90%, whereas in middle- and

low-income countries it drops to ~75% and ~50%, respectively [6]. Although there is strong evidence of vaccine-induced protection, clinical trial evidence suggests that immunity from RotaTeq and Rotarix wanes and a booster dose of these vaccines may be needed to maintain protection [4].

The direct effectiveness of the rotavirus vaccines has been measured extensively, but the extent of protection from indirect effects is still being elucidated [7]. A study using time series data on rotavirus gastroenteritis hospitalization in the United States found that there were significant indirect vaccine effects on hospitalization [7]. In this study, the indirect effect was measured by comparing rates of rotavirus in unvaccinated populations before the introduction of the vaccine and in the years following vaccination implementation. The reduction in incidence in children under 1 year of age was 79%, in unvaccinated adults aged 25-44 years was 56%, and in unvaccinated adults aged 45-64 years was 35% [7]. Comparative transmission dynamic modeling suggested that indirect protection was strongest in the first few years following vaccine introduction but may decrease due to factors such as waning immunity and the shift in age of first-infection to older age groups [24]. This phenomenon has been coined by McLean and Anderson as the "honeymoon effect" – a period of low disease incidence following the shift in age distribution of susceptible individuals due to vaccination or other infection control measures [25]. Based on these reasons, it is expected that low- and middle-income countries may experience less benefits from the indirect effects of the rotavirus vaccine. The extent of the differences amongst countries requires further study.

The Emory Rotavirus Model is a transmission model developed to estimate the impact of rotavirus vaccination on deaths, disability-adjusted life years, and severe rotavirus cases in low- and middle-income countries [26]. The model was calibrated using the Global Rotavirus

Surveillance Network (GRSN) dataset and has been validated [26]. This model estimated that the rotavirus vaccine could reduce death due to the infection by 50.4% by 2034 compared to a no vaccine scenario [26]. The study that initially described this model included an in-depth analysis of indirect vaccine effects in Pakistan, India, Nigeria, and Ethiopia (PINE countries) – countries with high rotavirus incidence [26]. The analysis found that most of the overall effect of vaccination was due to direct effects, but indirect effects also increased the impact of vaccination. Based on country-specific vaccine coverage, the estimated percent of deaths prevented due to direct and indirect effects were as follows: Pakistan (DE: 45.7%, IE: 9.6%), India (DE: 40.3%, IE: 17.8%), Nigeria (DE: 47.5%, IE: 1.2%), and Ethiopia (DE: 37.5%, IE: 8.7%). [26]. Although the direct effect remained fairly consistent across countries, the magnitude of the indirect effects varied [26].

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Evaluation of the Indirect Effects of Rotavirus Vaccination Programs in World Health Organization Member States

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Abstract

Rotavirus is a leading cause of diarrhea-related deaths in children under 5 years old, most of which occur in low-to-middle income countries (LMICs). Licensed rotavirus vaccines provide high levels of direct protection, but their indirect effect – the protection provided to unvaccinated individuals within a mixed-vaccinated population – is not fully understood. We aimed to quantify the population-level effects of rotavirus vaccination and identify factors that drive indirect protection. We used a transmission model to estimate the indirect effects of vaccination on rotavirus deaths in 112 LMICs. Indirect effects were estimated by quantifying the difference between predicted impacts if vaccination did (overall effects) or did not (direct effects) change the force of infection, and both scenarios were compared with a no vaccine scenario. We performed a linear regression analysis on model outputs to identify predictors of indirect effect magnitude. We also used logistic regression to understand predictors of negative indirect effects. Indirect effect sizes 8-years post-vaccine introduction ranged from 16.9% in the WHO European region to 0.97% in the Western Pacific region. Under-5 mortality rate and vaccine coverage were positively associated with indirect effect magnitude. Birth rate was negatively correlated. Of the 112 countries analyzed, 18 (16%) had at least one year with a predicted negative indirect effect. Negative indirect effects were more common in countries with higher birth rate and were less common in countries with higher under-5 mortality and higher vaccine coverage. These results suggest that the rotavirus vaccine provides indirect benefits to unvaccinated individuals within a mixed-vaccinated population. The strength of this effect varies by country and depends on country-specific birth rate, under-5 mortality rate, and vaccine coverage. Rotavirus vaccination may have a larger impact than would be expected from direct effects alone.

Introduction

Rotavirus is a leading cause of diarrheal disease that accounts for 29.3% of diarrhea-related deaths in children under 5 years old [1]. Over 90% of childhood rotavirus deaths occur in low-to-middle income countries (LMICs) [8]. Rotavirus primarily affects children 4-24 months of age. A majority of children in LMICs will have multiple rotavirus infections by the age of 2 years [20]. Generally, children in LMICs have a younger age of first infection than children in high-income countries [3]. For these reasons, the burden of rotavirus is unequally placed on those living in LMICs.

There are currently four live oral rotavirus vaccines (Rotarix, RotaTeq, Rotasiil, and Rotavac) that are licensed and recommended through the World Health Organization (WHO) [4, 5]. Rotarix is the primary vaccine used in LMICs [9]. All four vaccines have both been found to have strong efficacy in vaccinated individuals, otherwise known as the direct effect of the vaccine [5, 6]. However, the strength of the direct effect varies by country. A study of the effectiveness of rotavirus vaccines in countries with different income-levels found the vaccine was approximately 84% to 90% effective in high-income countries. This value drops to approximately 75% in middle-income countries and 50% in low-income countries [6].

The direct effect of rotavirus vaccines is well-established, but the indirect effect is less understood [7]. The indirect effect of a vaccine is the protection provided to unvaccinated individuals in a partially-vaccinated population [12]. Indirect effects can be measured by comparing the incidence of disease in an entirely unvaccinated population to the incidence amongst unvaccinated individuals in a partially-vaccinated population [12]. Biological and demographic factors, such as birth rate, vaccine coverage, and background mortality, can

influence the magnitude of indirect effects [10]. Because the direct effect is smaller in LMICs, it is expected that LMICs will also have less indirect protection from the rotavirus vaccine.

Transmission models have been developed to increase understanding of the long-term effects of rotavirus vaccination. The Emory Rotavirus Model is a transmission model developed to estimate the impact of rotavirus vaccination on deaths, disability-adjusted life years (DALYs), and severe rotavirus cases in LMICs [26]. The model estimated that rotavirus vaccine could reduce deaths due to infection by 50.4% by 2034 compared to the counterfactual scenario of no vaccination [26]. A study by Kraay et al utilizing this model performed an in-depth analysis of the vaccine effects in four countries with a high incidence of rotavirus: Pakistan, India, Nigeria, and Ethiopia. In all four countries, the overall effect of vaccination was primarily due to the direct effect, but the indirect effect did increase the impact of vaccination. The direct effect remained fairly consistent across the four countries but the magnitude of the indirect effect varied [26].

Due to the negative outcomes of rotavirus infection, particularly in young children, there is a need to expand rotavirus vaccination coverage. Before expanding coverage, it is important to understand the full effects of the vaccine to inform immunization program policy. In this study, we utilize the Emory Rotavirus Model to estimate the direct, indirect, and overall effects of the rotavirus vaccine from time of vaccine introduction to 12-years post-introduction in 112 LMICs. In addition, regression analysis is performed to identify country-level predictors of indirect effect magnitude.

Methods

The purpose of this study was to estimate the predicted indirect effects of the rotavirus vaccine in 112 World Health Organization member states. This analysis utilized estimates of

deaths due to rotavirus from the Emory Rotavirus Model by Kraay et al [26]. Additionally, we identified predictors of the magnitude of indirect effects and factors associated with negative indirect effects.

Demographic Factors of World Health Organization (WHO) Geographic Regions

Country-level socio-demographic factors were used in the Emory Rotavirus Model to estimate the number of deaths due to rotavirus infection and were also examined as predictors of indirect effect magnitude in the regression analysis. The median birth rate, under-5 mortality rate, and estimated vaccine coverage at 0-, 5-, and 8-years post-vaccine introduction of the countries by WHO geographic region are described in Table 1. Country-specific birth rates and under-5 mortality rates were provided by Montagu. Country-specific vaccine coverage estimates per year were provided by the Global Alliance Vaccine Initiative (GAVI). The median birth rates and under-5 mortality rates for each country were assumed to be constant between years within the model.

The WHO geographic regions include the African Region (AFR; 42 countries), Region of the Americas (AMR; 15 countries), Eastern Mediterranean Region (EMR; 13 countries), European Region (EUR; 16 countries), South-East Asian Region (SEAR; 10 countries), and the Western Pacific Region (WPR; 16 countries). AFR countries had the highest median birth rate (35.98 births per 1,000 people), followed by EMR (28.18 births per 1,000 people), WPR (25.03 births per 1,000 people), AMR (20.63 births per 1,000 people), SEAR (18.33 births per 1,000 people), and EUR (13.14 births per 1,000 people). AFR countries also had the highest median under-5 mortality rate with 72.1 deaths per 1,000 births, followed by SEAR (34.4 deaths per 1,000 births), EMR (32.0 deaths per 1,000 births), WPR (27.8 deaths per 1,000 births), AMR (20.4 deaths per 1,000 births), and EUR (15.0 deaths per 1,000 births).

Estimates from the year of vaccine introduction (Year 0), 5-years post-introduction (Year 5), and 8-years post-introduction (Year 8) were used in the linear regression analysis. At year of introduction, AMR countries had the highest median estimated level of coverage (38.0%), followed by AFR (31.0%), EMR (12.0%), EUR (10.5%), and SEAR and WPR (0.0%). SEAR and WPR countries had median coverage estimates of 0% due to late introduction of the vaccine in these regions and low uptake. All regions had a median coverage estimate of at least 75.0% by Year 5 and at least 82.1% by Year 8.

Emory Rotavirus Model

The Emory Rotavirus Model is an age-structured compartmental model that generates country-specific estimates of severe rotavirus cases, deaths, and disability adjusted life years (DALYs) due to rotavirus infection (Figure 1) [26]. The model considers three vaccine coverage scenarios: default, best-case, and no vaccination. The default scenario considers a gradual increase in vaccine coverage, with coverage plateauing at least at 90%. The best-case scenario models a faster increase in coverage, with coverage peaking at an optimal country-specific level. The no vaccine scenario does not account for any rotavirus vaccination coverage.

This model estimates deaths, severe cases, and DALYs due to rotavirus in children aged 0-4 years from years 2000-2034. The number of deaths was calculated by multiplying the number of severe rotavirus cases in each country per year by the case fatality ratio (CFR) for the country in each age group. Using data from the literature, the proportion of people expected to develop severe infections was estimated based on the number of infections an individual previously had (with second, third, or fourth rotavirus infections becoming less severe) and the average age of first infection in the population. The country-specific CFRs were estimated by dividing the country-specific number of expected deaths before the rotavirus vaccine became

available in 2005 by the estimated number of severe cases (CFR = expected deaths / number of severe cases). The estimates for the number of expected deaths used in this calculation came from the Global Burden of Disease Study [2]. DALYs were estimated based on the number of deaths and severe cases in each country.

Vaccine Effect Estimates

In this analysis, we utilized the output from the Emory Rotavirus Model to estimate the direct, indirect, and overall effect of the rotavirus vaccine 12 years after introduction of the vaccine. The estimated number of rotavirus deaths from the model was used as a metric to compare the effects of the rotavirus vaccine. Individual effects were estimated for 112 countries but, for simplicity, were presented in aggregate by World Health Organization geographic region.

To estimate the direct effect of the vaccine, we ran the model with the force of infection fixed to its pre-vaccination value, which served as a counterfactual of the overall incidence if vaccine introduction did not provide indirect benefits to unvaccinated individuals. The force of infection is the rate at which susceptible individuals become infected with a pathogen per unit time [27]. Introducing a vaccine into a population decreases the force of infection of the pathogen [27]. The estimated direct effect was then calculated by dividing the number of deaths in the default scenario with a fixed force of infection by the number of deaths in the no vaccine scenario (deaths in default scenario / deaths in no vaccine scenario).

The overall effect was estimated by dividing the number of deaths in the default scenario without a fixed force of infection by the number of deaths in the no vaccine scenario. The estimated indirect effect was the difference between the estimated overall effect and the estimated direct effect.

Predictors of the Magnitude of Indirect Effects

Due to the variation in indirect effects across countries, we also aimed to identify predictors of the magnitude of indirect effect. We used a linear regression model to assess the effects of various predictors on the indirect effect for each country. The predictors included in the model were birth rate, under-5 mortality, and rotavirus vaccine coverage. The values of these parameters came from the same sources as those used in the Emory Rotavirus Model.

A regression model was run with indirect effect at 0-years, 5-years, and 8-years post-vaccine introduction as the outcome to assess the impact of predictors over time. The 8-year timepoint was chosen as the final timepoint to assess because the effects were generally stable around this time period. However, they began to decrease in the Region of the Americas around year 10, because vaccine coverage was projected to drop around this time.

Predictors of the Negative of Indirect Effects

Negative indirect effect estimates can occur when the direct benefit of the vaccine is greater than the overall effect. This indicates a detrimental effect for unvaccinated individuals in a population by increasing the force of infection. A logistic regression model was run to assess the association between birth rate, under-5 mortality rate, and vaccine coverage and a country ever having an estimated negative indirect effect in the 12-year time span analyzed. Vaccine coverage for each model was averaged over the 12-year time period and that value was used in the model.

Ethical Considerations

This study did not require institutional review board approval because it did not include human subjects, nor was it a clinical investigation as defined by federal regulations. The data used was the output from the Emory Rotavirus Model, along with country-level socio-

demographic data. We were granted special permissions by GAVI to use the data included in the Emory Rotavirus Model.

Results

Estimation of Vaccine Effects by WHO Geographic Region

The vaccine effects of each individual country were estimated based on model output and are presented in aggregate by WHO geographic region. Overall, the Emory Rotavirus Model predicted a 47.8% to 56.1% reduction in rotavirus-related deaths 8-years post-vaccine introduction, i.e., the overall effect. AMR had the highest median overall effect (56.1%; 42.6% to 61.7%), followed by EUR (51.0%; 47.0% to 61.2%), SEAR (50.4%; 43.9% to 55.9%), EMR (48.6%; 38.3% to 62.1%), AFR (48.5%; 38.2% to 59.4%), and WPR (47.8%; 4.4% to 60.6%). The proportion of overall benefit from rotavirus vaccination due to the direct effect of vaccination varied widely amongst regions. In EUR, 33.1% of the median overall effect was due to the median indirect effect of the vaccine, followed by 28.3% in SEAR, 26.4% in AMR, 20.6% in EMR, 10.3% in AFR, and 2.0% in WPR. AFR had the largest median direct effect (43.2%) with a country-level range of 38.2% to 59.4%, followed by AMR (42.1%; 28.0% to 51.8%), WPR (41.2%; 3.9% to 60.2%), EMR (37.2%; 30.6% to 52.2%), SEAR (36.9%; 27.5% to 41.6%), and EUR (33.7%; 27.1% to 50.2%) (Table 2, Figure 2).

In all regions, the maximum indirect effect occurred shortly after vaccine introduction. Most countries in AFR (29 countries), AMR (7 countries), SEAR (5 countries), and WPR (13 countries) had their maximum estimated indirect effect during the year vaccine was introduced. Most countries in EMR (4 countries) and EUR (8 countries) experienced the maximum effect 1-year post-vaccine introduction. At 8-years post-vaccine introduction, EUR countries had the highest median overall percentage of deaths averted due to indirect effects (16.9%; 2.9% to

23.9%), followed by AMR (14.8%; 2.1% to 26.7%), SEAR (14.3%; 6.6% to 20.6%), EMR (10.0%; -3.5% to 17.3%), AFR (5.0%; -3.1% to 19.4%), and WPR (0.97%; -1.7% to 21.2%) (Table 2, Figure 3).

Predictors of Indirect Effect Magnitude

Birth rate had a negative correlation with indirect effect magnitude. At Year 0, for every 1-birth increase per 1,000 people, indirect effect decreased by 0.49% (95% CI: -0.63%, -0.36%). At Year 5, for every 1 unit increase in birth rate, indirect effect decreased by 0.64% (95% CI: -0.83%, -0.45%). At Year 8, for every 1 unit increase in birth rate, indirect effect decreased by 0.66% (95% CI: -0.84%, -0.48%) (Table 3). Year-specific vaccine coverage was a significant predictor in all three models and had a positive correlation with indirect effect magnitude. In Year 0, 5, and 8, for each 1% increase in vaccine coverage, indirect effect increased by 0.11% (95% CI = 0.090%, 0.14%), 0.10% (95% CI = 0.037%, 0.17%) and 0.12% (95% CI = 0.054%, 0.19%), respectively (Table 3). Under-5 mortality rate was a significant predictor of indirect effect magnitude at 5- and 8-years post-vaccine introduction, but not at year of vaccine introduction. At Years 5 and 8, as under-5 mortality rate increased by 1 death per 1,000 births, the indirect effect increased by 0.064% (95% CI = 0.010%, 0.12%) and 0.068% (95% CI = 0.016%, 0.12%), respectively (Table 3).

When assessing the independence assumption for the linear regression model, the birth rate and under-5 mortality rate appeared to be highly correlated ($r^2 = 0.812$). The variance inflation factor (VIF) was calculated for each model to assess the amount of multicollinearity between the variables. The VIFs for birth rate and under-5 mortality rate in each model were below the threshold for multicollinearity ($VIF \geq 5$) and ranged from 2.95 to 3.24 (Table 6). The VIFs for vaccine coverage in each model were below 1.5 (Table 6).

Predictors of Negative Indirect Effect

18 countries had at least one year of predicted negative indirect effect from the rotavirus vaccine during the 12-year timespan. (Table 4). Of these countries 50% were from WPR, 33% from AFR, 11% from AMR, and 6% from EMR. It is important to note that in the years these countries had predicted indirect negative effects, the value of the overall effect of the vaccine remained positive.

Crude associations of each variable and negative indirect effect were calculated (Table 5). For every 1% increase in mean vaccine coverage, the odds of having at least one year of negative indirect effect decreased by 4% (OR = 0.96; 95% CI = 0.94, 0.99). The crude association between birth rate (OR = 1.04; 95% CI = 0.99, 1.10) or under-5 mortality rate (OR = 1.00; 95% CI = 0.99, 1.02) and having at least one year of negative indirect effect was minimal.

The fully adjusted model included birth rate, under-5 mortality rate, and mean vaccine coverage (Table 5). In this model, the odds of having at least one year of negative indirect effect increased by 17% with every 1 unit increase in birth rate (OR = 1.17; 95% CI = 1.04, 1.31), decreased by 4% with every 1 unit increase in under-5 mortality rate (OR = 0.96; 95% CI = 0.93, 0.99) and decreased by 5% with every 1% increase in vaccine coverage (OR = 0.95; 95% CI = 0.92, 0.98).

As with the linear models, the variables of the logistic regression models were assessed for multicollinearity. The VIFs for birth rate, under-5 mortality, and mean vaccine coverage within the fully adjusted model were under the threshold of high multicollinearity (Table 6).

Discussion

Summary of Key Findings

At 8-years post-vaccine introduction, AMR countries were estimated to have the highest overall effect, AFR countries had the highest direct effect, and EUR countries had the highest indirect effect. The indirect effect was highest in all regions during the year of vaccine introduction and 1-year post-vaccine introduction. Lower birth rate and higher vaccine coverage were predictors of indirect effect magnitude at 0-, 5-, and 8-years post-vaccine introduction. Lower under-5 mortality rate was a predictor at 5- and 8-years post-vaccine introduction. Higher birth rate, lower vaccine coverage, and lower under-5 mortality were all associated with having a negative indirect effect.

Indirect Vaccine Effects Trends by Geographic Region

The estimates of the direct, indirect, and overall effects from the Emory Rotavirus Model indicated that the indirect effect increased the median overall effect of countries in all WHO geographic regions. The median indirect effect 8-years post-vaccine introduction by region ranged from 0.97% to 16.9%, which was lower than what was seen in high-income countries. Some individual countries had stronger effects, with impacts ranging from -3.5% to 26.7%. This trend has been observed in the literature, with one meta-analysis finding the indirect vaccine effect for high-income countries to be 52% on average [28]. The meta-analysis also found that the LMIC subgroup analyzed had an average indirect effect of 25%, which falls into the range calculated for LMICs in this study [28]. The difference in indirect effect values based on income-level may be based in high-income countries generally having a higher vaccine direct effect due to biological and environmental factors [29, 30]. In countries with higher direct effect, less vaccine coverage is needed to have indirect protection compared [28].

Predictors of Indirect Effect Magnitude

When analyzing the demographic characteristics of the countries in aggregate by geographic region across a 12-year timespan, higher indirect effects were predicted for regions with lower median birth rates and under-5 mortality rates. This aligns with previous studies that have shown birth rate to be a determining factor in rotavirus incidence [31]. A higher birth rate will decrease the indirect effect of vaccination because as more immune-naïve individuals - i.e., infants - enter the population, the number of susceptible individuals in the population increases [31]. This in turn can lead to a higher force of infection if there is not adequate vaccine coverage, as the proportion of susceptible individuals must remain lower than $1/R_0$ for herd immunity to remain in effect [11].

Increased vaccine coverage would act in a similar way to decreased birth rate, as it also decreases the number of susceptible people and transmission rates. This aligns with the results of the linear regression analysis, which indicated that as vaccine coverage increased by 1%, indirect effect magnitude increased by between 0.10% to 0.12%.

Under-5 mortality rate had a positive correlation with indirect effect magnitude. As under-5 mortality rate increased, indirect effect magnitude increased between 0.019% to 0.068% across the three time points. Although this result is logically sound, with a higher mortality rate leading to a reduced number of susceptible individuals, it contradicts what is seen in the indirect effect estimates. Countries with higher median under-5 mortality rates generally had lower median indirect effects. For example, countries in AFR had the highest median under-5 mortality rate of all the regions, with 72.1 deaths per 1,000 births. AFR countries also had the lowest estimated median indirect effect at 8-years post-vaccine introduction (5.0%). This discrepancy in the relationship between under-5 mortality rate and indirect effect magnitude could be due to the fact that the under-5 mortality rate used in the model was fixed, so decreases in this parameter

due to the rotavirus vaccine or other public health measures were not accounted for. Additionally, the model controlled for birth rate, which was highly correlated with under-5 mortality rate. Birth rate may be acting as a confounder between under-5 morality rate and indirect effect magnitude, resulting in a difference in the association.

Although other dynamic rotavirus modeling studies have been published, few consider multiple countries over an extended timespan. This makes it difficult to make cross-country and year comparisons [32]. A strength of this analysis is that the Emory Rotavirus Model includes estimates for 112 countries over up to 34 years post-vaccine introduction [26]. Using output from this model has allowed us to make robust longitudinal vaccine effect estimates that can be compared across countries and geographic regions. However, it is important to note that the relationships found in this analysis are associated with the predicted effects within a model system. Real-world associations may differ based on factors not accounted for in the model. Further research will be needed to better define the relationship between the parameters.

Predictors of Negative Indirect Effect

Of the 112 countries included in this analysis, 18 had at least one year with an estimated negative indirect effect. A negative indirect effect occurs when there is a higher death rate among unvaccinated individuals within a partially vaccinated population than there are when the population is entirely unvaccinated. This is cause for concern because it indicates that the vaccine is putting unvaccinated individuals in a partially vaccinated population at an increased risk of death due to rotavirus.

The factors underlying a negative indirect effect were the same as those that predicted a lower magnitude of indirect effect. Birth rate increased the risk of having at least one year of negative indirect effect and under-5 mortality rate and vaccine coverage decreased the risk.

These relationships are explained by the increase and decrease, respectively, in the number of susceptible individuals in the population due to the demographic factors.

Most of the countries with a predicted negative indirect effect were in WPR. Countries in this region introduced the vaccine later than other countries and had low vaccine uptake. Consequentially, many countries in WPR have a high number of children without access to rotavirus vaccine [9]. This highlights the importance of increasing access to rotavirus vaccination, particularly in regions with high birth rate.

Although there were countries with predicted negative indirect effects, it was a small proportion of all the countries examined (16%). Additionally, each country had at least two years of predicted positive indirect effect. Further research on the effect of these predictors on indirect effect value is needed, and the overall net benefit of the rotavirus vaccine is highly positive. Moreover, despite having negative indirect effects in some years, it is notable that the overall impact of vaccination was positive for each study year.

Study Limitations

This study has several limitations. First, the Emory Rotavirus Model assumes that rotavirus vaccinations are administered at 2 and 4 months of age. Although this is the recommended schedule for Rotarix (the most common vaccine used in low-and middle-income countries), vaccinations may be delayed due to natural infection or country-specific vaccination timelines [33], with administration up to 8 months of age being consistent with WHO recommendations [34]. However, the coverage estimates provided by GAVI do account for predicted lapses in coverage due to health system disruption caused by the pandemic, but do not account for how the timing of doses received may have changed during the pandemic.

Another limitation is that the regression model assumes that birth rate and under-5 mortality remains constant for each country. Year-specific birth rates are implicitly included in population size estimations used in the Emory Rotavirus Model, but the birth rate used in the linear and logistic regression models included in this paper do not change by year. The strength of associations estimated in the regression analyses may be affected by these assumptions, as the rates likely do vary year-to-year from the impact of immunizations, WASH interventions, and other country-specific public health measures. Finally, two parameters included in the regression models are highly correlated (birth rate and under-5 mortality rate). Because all estimates in this study are based on the outputs of a model that does include these variables, the effects shown may be skewed due to confounding.

Conclusion

The results described in this study suggest that rotavirus vaccination provides indirect protection to unvaccinated individuals in LMICs, increasing the predicted overall impact of vaccination. This highlights the importance of expanding and maintaining rotavirus vaccine coverage in these countries. The results also indicate that birth rate, under-5 mortality rate, and vaccine coverage affect the strength of the effect. Future studies should focus on validating these effects using real-world data to better support immunization policy decisions.

Tables and Figures

Figure 1: The structure of the Emory Rotavirus Model. After birth, children have maternal immunity to the virus and enter the "M" class. When maternal immunity wanes, children become fully susceptible to infection (S1 class). After a child becomes infected (I1 class), they will either become susceptible to subsequent infection (S2 class) or fully recover and gain immunity (R class). This continues until the child reaches a quaternary infection, in which they become fully recovered (R class). Infection becomes less severe with each previous infection. Immunity wanes and an individual will eventually become susceptible to infection again (re-enter S1 class). The orange arrows represent individuals who are vaccinated. After each dose of vaccine, the individual moves to the next class of susceptibility.

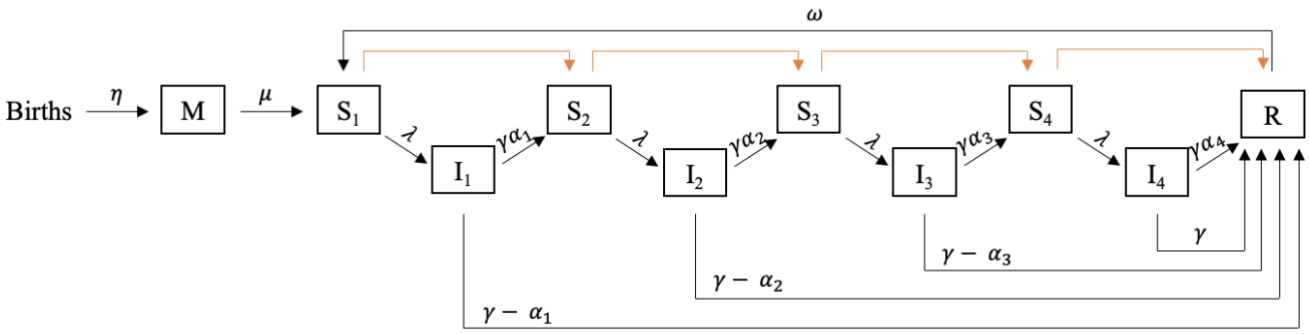

Table 1. **Median birth rate, under-5 mortality rate, and vaccine coverage of countries grouped by WHO geographic region**

	WHO Geographic Region					
	AFR	**AMR**	**EMR**	**EUR**	**SEAR**	**WPR**
Countries (n)	42	15	13	16	10	16
Birth rate[+] (Country-level range)	35.98 (20.75-47.50)	20.63 (10.82-25.63)	28.18 (18.71-42.30)	13.14 (8.66-32.12)	18.33 (10.84-29.32)	25.03 (12.31-33.56)
Under-5 mortality rate[++] (Country-level range)	72.1 (24.5-156.9)	20.4 (5.5-69.0)	32.0 (12.9-136.8)	15.0 (4.6-51.4)	34.4 (9.8-52.6)	27.8 (10.7-66.7)
Vaccine Coverage (%) (Country-level range)						
Year 0	31.0 (0.0-87.0)	38.0 (0.0-82.0)	12.0 (0.0-88.0)	10.5 (0.0-99.0)	0.0 (0.0-59.7)	0.0 (0.0-85.0)
Year 5	80.5 (53.6-98.0)	90.0 (48.0-99.0)	75.0 (49.1-98.9)	86.6 (48.0-98.8)	91.7 (77.6-98.2)	89.6 (0.0-99.0)
Year 8	82.1 (58.0-97.1)	90.0 (53.3-98.0)	87.1 (42.0-99.0)	91.5 (56.0-98.7)	88.6 (83.2-97.4)	89.1 (0.0-99.0)

+ = rate per 1,000 people

++ = rate per 1,000 births

Table 2. Median percent of rotavirus deaths averted 8-years post-vaccine introduction to due vaccine effects.

Region	Overall Effect (%) (Country-level range)	Direct Effect (%) (Country-level range)	Indirect Effect (%) (Country-level range)	Proportion of Benefit due to Indirect Effect (%)
AFR	48.5 (38.2-59.4)	43.2 (33.5-54.7)	5.0 (-3.1-19.4)	10.3
AMR	56.1 (42.6-61.7)	42.1 (28.0-51.8)	14.8 (2.1-26.7)	26.4
EMR	48.6 (38.3-62.1)	37.2 (30.6-52.2)	10.0 (-3.5-17.3)	20.6
EUR	51.0 (47.0-61.2)	33.7 (27.1-50.2)	16.9 (2.9-23.9)	33.1
SEAR	50.4 (43.9-55.9)	36.9 (27.5-41.6)	14.3 (6.6-20.6)	28.3
WPR	47.8 (4.4-60.6)	41.2 (3.9-60.2)	0.97 (-1.7-21.2)	2.0

Figure 2. Annual median direct effect (dashed line) and overall effect (solid line) up to 12 years post vaccine introduction by WHO geographic region

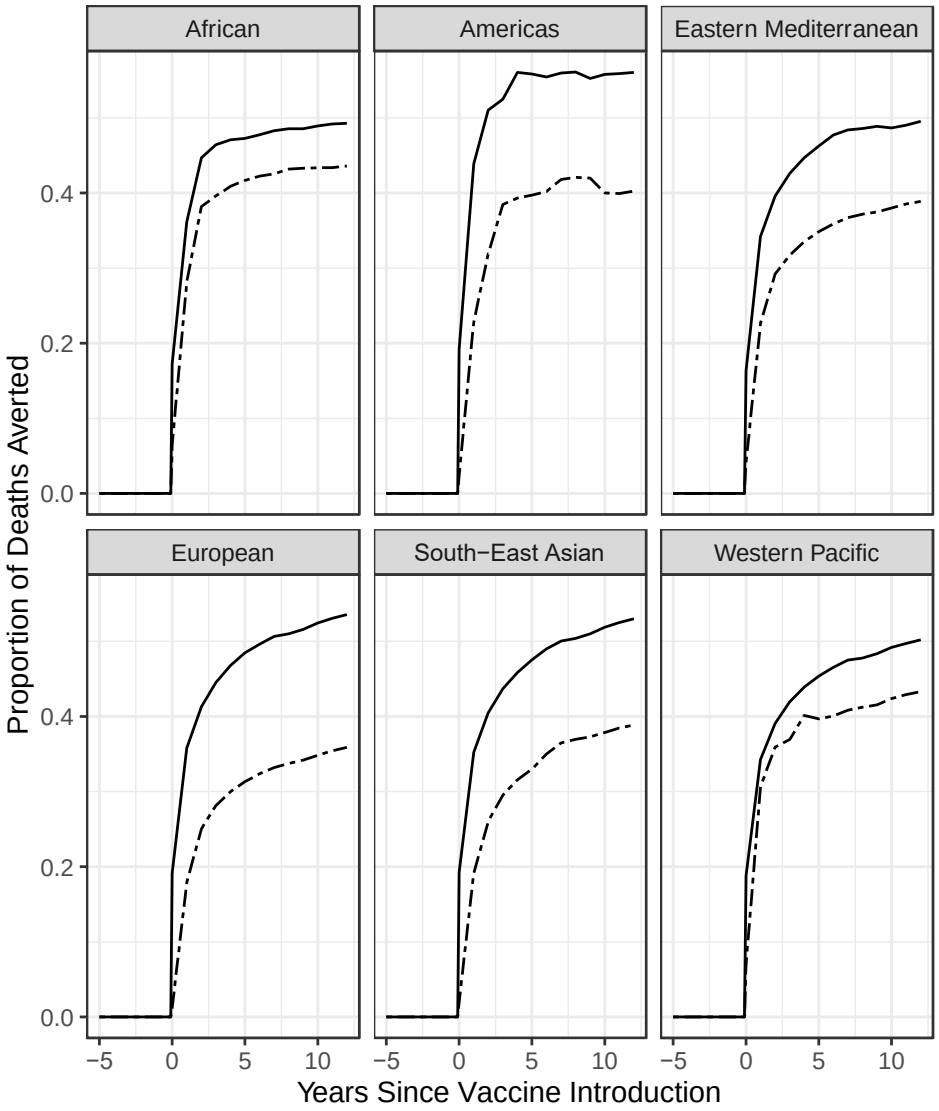

Figure 3. Distribution of country-level indirect effect values at 8 years post-vaccine introduction, grouped by WHO geographic region

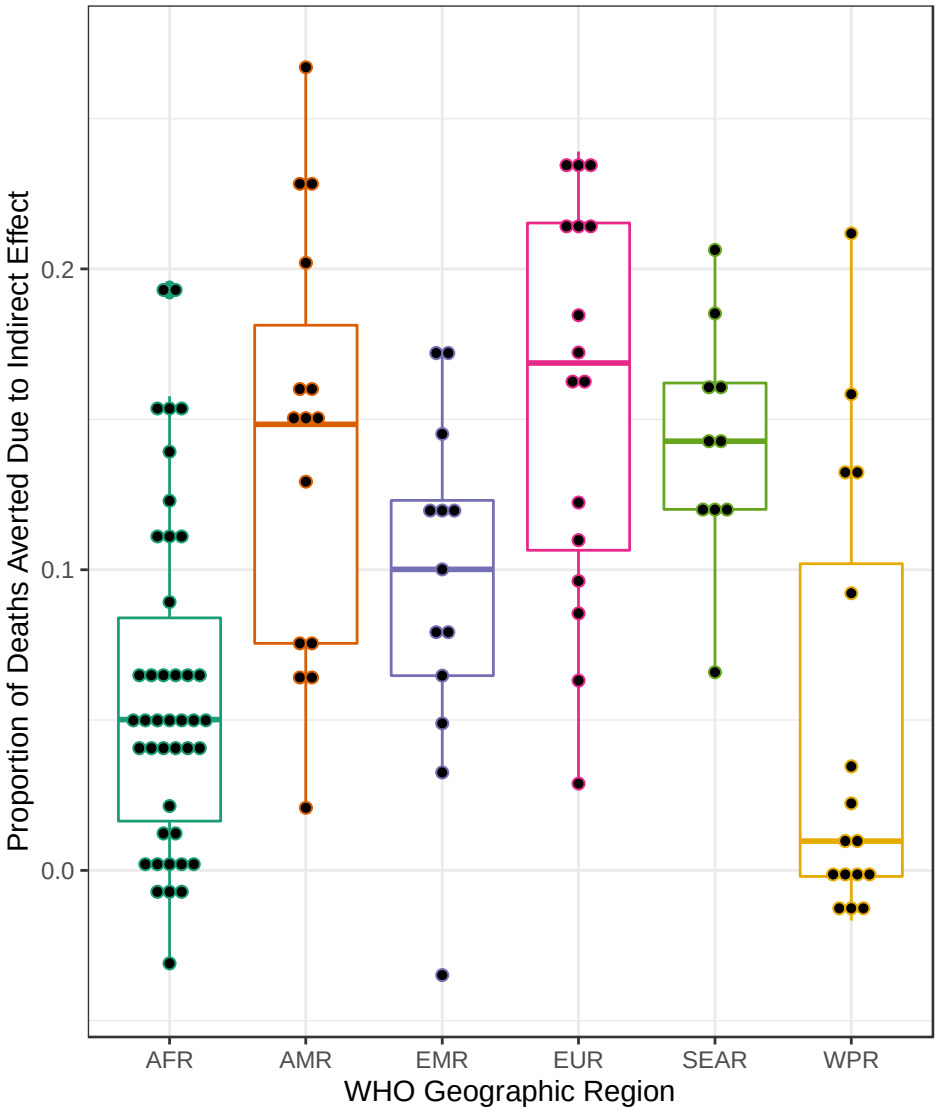

Table 3. Linear association between vaccine indirect effect and birth rate, under-5 mortality rate, and rotavirus vaccine coverage at 0-, 5-, and 8-years post-vaccine introduction.

	Years Post-Introduction of Rotavirus Vaccine					
	0 Years		5 Years		8 Years	
	Coefficient (95% C.I.)	**P-value**	**Coefficient (95% C.I.)**	**P-value**	**Coefficient (95% C.I.)**	**P-value**
Birth rate[+]	-0.49 (-0.63, -0.36)	<0.0001 **	-0.64 (-0.83, -0.45)	<0.0001 **	-0.66 (-0.84, -0.48)	<0.0001** *
Under-5 mortality rate[++]	0.019 (-0.018, 0.055)	0.31	0.064 (0.010, 0.12)	0.020*	0.068 (0.016, 0.12)	0.012*
Vaccine Coverage (%)	0.11 (0.090, 0.14)	<0.0001 **	0.10 (0.037, 0.17)	0.0027** *	0.12 (0.054, 0.19)	0.00061*
R-squared	0.61		0.47		0.50	
Adjusted R-squared	0.60		0.46		0.49	

** = significant at =0.01

* = significant at =0.05

+ = rate per 1,000 people

++ = rate per 1,000 births

Table 4. Countries with at least one year estimated to have a negative indirect effect post-vaccine introduction

WHO Region	Country	Year(s) Post-Vaccine Introduction w/ Negative IE Estimate	Birth Rate[+]	Under-5 Mortality Rate[++]	Mean Vaccine Coverage[+++] (%)
WPR					
	Fiji	2-3	21.98	22.4	95.5
	Federated States of Micronesia	1-12	23.21	34.7	43.6
	Kiribati	3-12	28.98	55.9	90.4
	Marshall Islands	1-9	23.21	36.0	48.0
	Philippines	2-9	22.27	28.0	2.8
	Tonga	2-8	25.35	16.7	91.4
	Tuvalu	8	25.35	27.1	72.5
	Vanuatu	2-12	30.81	27.5	69.4
	Samoa	2-12	25.43	17.5	50.8
AFR					
	Côte d'Ivoire	2-12	36.44	92.6	73.1
	Guinea	2-12	37.58	93.7	36.3
	Guinea-Bissau	2-12	36.82	92.5	78.2
	Niger	2-12	47.50	95.5	74.6
	Senegal	3-6	36.32	47.2	92.2
	Chad	2-12	43.73	138.7	37.9
AMR					
	Guatemala	4	25.63	29.1	76.6
	Venezuela	11-12	19.00	14.9	49.2
EMR					
	Syria	2-12	24.95	12.9	45.7

+ = rate per 1,000 people

++ = rate per 1,000 births

+++ = average of country-specific vaccine coverage from year of vaccine introduction to 12-years post-vaccine introduction

Table 5. Unadjusted and adjusted logistic association between birth rate, under-5 mortality rate, and mean vaccine coverage and negative indirect effect

	Unadjusted Associations		Fully Adjusted Associations*	
	Odds Ratio	**95% Confidence Interval**	**Odds Ratio**	**95% Confidence Interval**
Birth rate+	1.04	0.99, 1.10	1.17	1.04, 1.31
Under-5 mortality rate++	1.00	0.99, 1.02	0.96	0.93, 0.99
Mean Vaccine Coverage+++ (%)	0.96	0.94, 0.99	0.95	0.92, 0.98

*** =** Fully adjusted associations account for all variables in this table

+ = rate per 1,000 people

++ = rate per 1,000 births

+++ = average of country-specific vaccine coverage from year of vaccine introduction to 12-years post-vaccine introduction

Table 6. Variance inflation factor (VIF) values for each parameter in the linear and logistic regression models

	Birth Rate	Under-5 Mortality Rate	Vaccine Coverage
Linear Regression			
Year 0	3.26	3.07	1.12
Year 5	2.95	3.24	1.22
Year 8	2.95	3.19	1.18
Logistic Regression	3.05	3.41	1.25

Chapter 4: Conclusions and Implications

The study results suggest that the indirect effect of the rotavirus vaccine provides benefits to unvaccinated individuals in a partially-vaccinated population. The strength of the effect varies by country-specific birth rate, under-5 mortality rate, and vaccine coverage. Lower birth rate, higher under-5 mortality rate, and higher vaccine coverage are generally associated with a stronger indirect effect. These relationships arise from the decrease in the number of susceptible individuals in a population due to each of these factors.

The results of this study support the inclusion of rotavirus vaccination in national immunization programs. According to data from the International Vaccine Access Center, 62 countries have not yet decided on whether to introduce rotavirus vaccine in national immunization programs. Eighteen countries are in the planning stages of introducing the vaccine [9]. Most countries without rotavirus vaccination or in the planning stages are low-income. Based on our study, countries with high birth rates will need to achieve and maintain a high level of vaccine coverage to maximize the amount of indirect protection. However, countries with high birth rates also tend to have lower income. In 2019, the average birth rate in LMICs was over twice that of high-income countries [35]. LMICs that lack access to rotavirus vaccines could benefit from organizations such as the GAVI that provide financial support for introduction of vaccines to national immunization programs [36].

Future research is needed to fully define the impact country-specific factors have on indirect effects. Because the results of this study are based on model output, surveillance and other country-level empirical data should be analyzed before implementing any immunization policy changes. Additional sociodemographic factors should also be examined to better understand the drivers of indirect effect magnitude.

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