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Estimated Impact of Rotavirus Vaccine on Hospitalizations and Deaths from Rotavirus Diarrhea among Children <5 in Asia

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Summary

Objectives—Of the 215,000 global deaths from rotavirus estimated in 2013, 41% occur in Asian countries. However, despite a recommendation for global rotavirus vaccination since 2009, only eight countries in Asia have introduced rotavirus vaccine into their national immunization program as of September 2017. To help policy makers assess the potential value of vaccination, we projected the reduction in rotavirus hospitalizations and deaths following a hypothetical national introduction of rotavirus vaccines in all countries in Asia using data on national-level rotavirus mortality, <5 population, rotavirus hospitalizations rates, routine vaccination coverage, and vaccine effectiveness.

Methods—To quantify uncertainty, we generated 1,000 simulations of these inputs.

Results—Our model predicted 710,000 fewer rotavirus hospitalizations, a 49% decrease from the 1,452,000 baseline hospitalizations and 35,000 fewer rotavirus deaths, a 40% decrease from the 88,000 baseline deaths if all 43 Asian countries had introduced rotavirus vaccine. Similar reductions were projected in subanalyses by vaccine introduction status, subregion, and birth cohort size.

Conclusion—Rotavirus vaccines will substantially reduce morbidity and mortality due to rotavirus infections in Asia.

Keywords

rotavirus vaccines; rotavirus; diarrhea; Asia; routine vaccination; mortality

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Introduction

Rotavirus is estimated to cause 37% of diarrheal deaths among children <5 years old worldwide [1,2]. The disease burden is particularly severe in Asia; regional hospital-based surveillance detects rotavirus at the highest rate in the world in the Southeast Asian region and India has the largest national number of rotavirus deaths of any country [1]. Of the 215,000 estimated global deaths from rotavirus in 2013, 41% (n=89,000) occurred in Asia [1].

In more than a decade since licensure, rotavirus vaccines have been shown to dramatically reduce the morbidity and mortality of severe rotavirus disease [3]. In addition to two live, oral rotavirus vaccines available internationally (RotaTeq, Merck & Co., West Point, PA, USA and Co and Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) [4,5], there are four rotavirus vaccines manufactured in Asia [6]. Two of these rotavirus vaccines, Rotasiil (Serum Institute of India Pvt. Ltd., Pune, India) and ROTAVAC (Bharat Biotech International Ltd., Hyderabad, India), were recently licensed in India after phase 3 efficacy studies; ROTAVAC was recently approved and Rotasiil is being reviewed for World Health Organization (WHO) pre-qualification [7,8]. Additionally, locally licensed and manufactured vaccines are available in China (Lanzhou lamb, Lanzhou Institute of Biological Products Co. Ltd., Lanzhou, China) and Vietnam (Rotavin, PolyVac, Hanoi, Vietnam) [6,9,10].

The impact of rotavirus vaccines on morbidity and mortality could be significant in Asia because of the high burden of diarrhea disease and large birth cohorts in several countries, including China, India, Pakistan, Bangladesh and Indonesia. The combine birth cohort of these five countries represents 41% of the global birth cohort. Despite a WHO global recommendation for vaccine use since 2009, of the >80 countries that have introduced a rotavirus vaccine nationally worldwide, only eight are in the region (Figure 1) [11–14]. India and Pakistan began a planned phased introduction of rotavirus vaccines into the routine infant vaccination schedule in some states and districts in 2016, but full national implementation is expected to take several years in both countries. Bangladesh has been approved for rotavirus vaccine use and is expected to introduce the vaccine in 2018.

To help policy makers assess the potential value of implementing rotavirus vaccination, we projected the reduction in rotavirus hospitalizations and deaths following a hypothetical national introduction of rotavirus vaccines in all countries in Asia.

Methods

We included countries and territories (referred to as “countries”) in this analysis that are in the Eastern Asia, Southern Asia, South-eastern Asia and Western Asia regional groupings defined by the Millennium Development Indicators (Figure 1) [15]. This classification was chosen because WHO regions that include Asian countries overlap with other continents. Countries were further stratified by their 2015 UNICEF <5 year old child mortality rates [16]. The lowest child mortality strata was defined ≤8 deaths per 1,000 live births, which is the 15th percentile among the included countries; medium child mortality as >8–22 deaths

per 1,000 live births; and high child mortality as >22 deaths per 1,000 live births (50th percentile among included countries). For sub analyses, we categorized countries by vaccine introduction status, child mortality strata, the Millennium Development Indicator subregions, World Bank income groupings, and Gavi eligibility [12,15–18]. The eight countries that had introduced vaccine nationwide before 2015 were included in the 'introduced' group (Bahrain, Iraq, Jordan, Qatar, Saudi Arabia, United Arab Emirates, Uzbekistan, Yemen), and two of these countries (Uzbekistan and Yemen) received Gavi support. Gavi eligibility includes countries currently eligible for Gavi support and countries that received Gavi support for rotavirus vaccine introduction; Gavi provides financial support to countries with a mean per capita gross national income of < $1,580 over the previous 3 years[18].

Literature reviews

Using the PRISMA guidelines, we conducted systematic literature reviews to determine the rate of rotavirus hospitalizations in Asian countries and the vaccine effectiveness of rotavirus vaccines in Asian countries [19]. For hospitalizations rates, we searched PubMed for articles published 1 January 1998– 30 June 2017 whose titles included "rotavirus" and any of the following terms: "burden", "hospitali*", "incidence", "epidemiology", "surveillance". We limited results to these years for contemporary data. We limited articles to those that presented a rate of rotavirus diarrhea hospitalization among children <5 years old in an Asian country included in this analysis. In articles that presented more than one rate of rotavirus hospitalizations among children <5 years old, for example, from two different cities or two different countries, all of the published rates were included. We excluded rates from other age groups. Once the literature review was complete, rates were summarized as a median and interquartile range (IQR) by child mortality strata.

For vaccine efficacy and effectiveness (VE), we searched PubMed for articles published 1 January 2006– 30 June 2017 whose titles included "rotavirus" and "vacc*" and "eff*". Rotarix and RotaTeq were licensed in 2006. We included VE against severe rotavirus disease or hospitalization among children <5 years old for any rotavirus vaccine, except the Lanzhou vaccine because the recommended schedule for administration is substantially different than the other rotavirus vaccines. Articles were included if they presented a pre- or post-licensure VE estimate from at least one Asian country included in this analysis. Once the literature review was complete, rates were summarized as a median and IQR by child mortality strata.

Model construction

Following the methods of Shah et al [20], the expected number of rotavirus hospitalizations was calculated as follows:

$$Expected\ Hospitalizations = Hospitalization\ Rate \times < 5\ population$$

Where the <5 population is the national population of children <5 years old in 2015 and hospitalization rate is the strata-specific hospitalization rate calculated from the literature review [16,21].

The number of rotavirus hospitalizations prevented was calculated as follows:

$$Hospitalizations\ Prevented = VE \times Coverage \times Expected\ hospitalization$$

Where expected hospitalizations is the number of expected rotavirus hospitalizations calculated above, VE is the strata-specific VE calculated from the literature review, and coverage is 2016 DTP3 national coverage estimated in the WHO/UNICEF joint reporting form (JRF); if the 2016 estimate was not available, 2015 was used [22]. DTP3 coverage estimates from the Hong Kong Ministry of Health and UNICEF Palestine fact sheet supplemented the JRF data [23,24].

The number of rotavirus deaths prevented was calculated as follows:

$$Deaths\ Prevented = VE \times Coverage \times Expected\ Deaths$$

Where expected deaths is the number of rotavirus deaths in children <5 year of age in 2013 estimated by WHO [1], VE is the strata-specific VE calculated from the literature review, and coverage is 2016 DTP3 national coverage estimated in the WHO/UNICEF JRF; as above, if the 2016 estimate was not available, 2015 was used [22]. Hong Kong and Palestinian Territories were not included in this portion of the analysis as the expected rotavirus mortality was not available [23,24].

Simulations

To quantify uncertainty, we generated 1,000 simulations of the model inputs. Country-specific rotavirus deaths were randomly selected on a normal distribution from the published point estimate and 95% confidence interval (CI). Hospitalization rate point estimates were randomly selected on a uniform distribution from the hospitalization rate IQR calculated for the appropriate child mortality strata. Similarly, VE point estimates were randomly selected on a uniform distribution from the VE IQR calculated for the appropriate child mortality strata. From the 1,000 simulations, we calculated the median and the point estimate at the 2.5 and 97.5 percentiles as the CIs for the expected and prevented hospitalizations and deaths.

Results

We reviewed 893 articles for hospitalization rates in Asian countries selected for this analysis. Twenty-one articles from 14 countries met our inclusion criteria (Table 1). The median hospitalization rate per 100,000 was 395 (IQR: 200, 542) in low child mortality countries, 277 (IQR: 181, 521) in medium child mortality countries, and 337 (IQR: 240, 633) in high child mortality countries. We reviewed 363 articles for VE in Asian countries. Ten articles from eight countries met our inclusion criteria (Table 2). The median VE was 94% (IQR: 92%, 96%) in low child mortality countries, 64% (IQR: 63%, 81%) in medium child mortality countries, and 49% (IQR: 33%, 55%) in high child mortality countries.

Across the 43 Asian countries included in this analysis, we estimate there were 1,452,257 (95%CI: 1,142,109, 1,776,186) hospitalizations and 88,889 (95%CI: 84,014, 93,478) deaths

due to rotavirus annually. With hypothetical universal introduction of rotavirus vaccine, 710,580 (95%CI: 546,045, 889,358) fewer hospitalizations and 35,865 (95%CI: 30,427, 41,370) fewer deaths would occur (Table 3). This represents a 49% (95%CI: 43, 55) and 40% (95%CI: 35, 46) reduction over the expected number of hospitalizations and deaths, respectively. Of the rotavirus hospitalizations prevented, 95% were in countries that had not yet introduced rotavirus vaccine (676,538; 95%CI: 511,378, 855,881) and 54% were in high child mortality countries (383,007; 95%CI: 276,114, 516,655). Of the rotavirus deaths prevented, 96% were from countries that had not yet introduced rotavirus vaccine (34,540; 95%CI: 29,173, 40,010) and 89% were in high child mortality countries (32,080; 95%CI: 26,721, 37,673). Of the projected rotavirus hospitalizations that would be prevented with universal rotavirus vaccine implementation, 44% were in Gavi eligible countries and 81% of projected rotavirus deaths prevented were in Gavi eligible countries.

The largest percent reductions in rotavirus hospitalizations and deaths over the expected numbers were found in the East Asia sub-region, which includes China, Hong Kong, Democratic Republic of Korea, Republic of Korea, and Mongolia. The East Asia region accounted for 22% of rotavirus hospitalizations and 4% of rotavirus deaths in Asia. There were 71% (95%CI: 63%, 79%) fewer hospitalizations and 70% (95%CI: 61%, 77%) fewer deaths. The largest absolute reductions in rotavirus hospitalizations and deaths were in the South Asia sub-region, which includes Afghanistan, Bangladesh, Bhutan, India, Iran, Maldives, Nepal, Pakistan, and Sri Lanka. The South Asia region accounted for 52% of rotavirus hospitalizations and 79% of rotavirus deaths in Asia. There were 302,069 (95%CI: 202,474, 436,550) fewer hospitalizations and 26,981 (95%CI: 21,753, 32,407) fewer deaths. Country-specific point estimates and 95%CIs are presented in Supplementary Table 1.

Discussion

Our model predicted in excess of 710,000 fewer rotavirus hospitalizations and 35,000 fewer rotavirus deaths if all 43 Asian countries introduced rotavirus vaccine, a more than 40% decrease over the baseline estimate of approximately 1,452,000 hospitalizations and 88,000 deaths. Similar to other summary analyses of rotavirus VE, we found a gradient of decreasing VE with increasing national child mortality [25]. Despite estimated VE of just 49% in high child mortality countries, our findings show the largest absolute number of reductions would occur in these 20 countries, underscoring the public health values of even partially effective rotavirus vaccines in high burden settings.

Countries with large birth cohorts may have an out-sized influence on our findings. For example, 30% of all rotavirus hospitalizations prevented were in China represent and over 50% of all rotavirus deaths prevented were in India. These findings underscore the importance of implementing vaccination in these large countries to achieve maximum public health impact. However, when excluding countries with birth cohorts >1,500,000 (that is Bangladesh, China, India, Indonesia, Pakistan, and the Philippines) the percent reductions are slightly higher than that of the region overall, with a 55% reduction in hospitalizations and a 42% reduction in deaths. The country-specific analyses show reductions of at least 32% in diarrhea related morbidity and mortality in all countries.

This analysis has several limitations. The literature identified by the systematic review was not robust enough to calculate hospitalization rates or VE by age group. As rotavirus diarrhea hospitalizations tend to be highest in the youngest children and decrease in older children, the rates presented here cover the entire age group and likely underestimate rotavirus hospitalizations in the youngest children and overestimate hospitalizations in older children. Similarly, there is some evidence that VE decreases in the second year of life in high child mortality settings; the systematic review did not find enough age group-specific VE estimates in Asia to assign VE by age. This may have biased these results, however we cannot speculate on the magnitude or direction. Secondly, we did not account for subnational introductions or the current use of private market vaccination in our baseline hospitalization and death estimates. While this would inflate the estimated number of hospitalizations and deaths, it would not change the percent reductions. In calculating reductions, we used DTP3 and most countries globally to date have introduced a 2-dose vaccine. This may have underestimated coverage and therefore underestimated impact. Our model also does not account for potential indirect effects of introducing rotavirus vaccine. Finally, expected rotavirus mortality estimates were not available for Hong Kong and the Palestinian Territories, therefore they were excluded from the mortality analysis. Due to their size and Hong Kong's very low child mortality, we do not think this has influenced our overall estimates.

These findings support consideration of rotavirus vaccine to help alleviate diarrheal disease burden. However, there is still a need to examine ways to improve effectiveness of rotavirus vaccines in medium and high child mortality settings to receive even further benefits from vaccination. As countries in Asia prepare for rotavirus vaccine introduction, this analysis supports the importance of high coverage and strengthening of the immunization systems to deliver childhood vaccines on schedule. In some early introducing countries in other regions, initial rotavirus vaccine coverage lagged behind that of routine infant vaccines recommended for concomitant administration, reducing the potential of the vaccines to impact disease morbidity and mortality [26–28]. Although uptake has been slow in Asia so far, rotavirus vaccines are starting to gain traction in the region. Over the next five years, many of these estimated impacts will become real as countries incorporate rotavirus vaccines into their routine immunization programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Issues

- Of the 215,000 estimated global deaths from rotavirus among children <5 years old in 2013, 41% occurred in Asian countries. The Southeast Asian region has the highest rate of rotavirus detection in the world and we estimated more than 1,452,000 annual rotavirus hospitalizations among children <5 years old in Asian countries.
- There are four rotavirus vaccines manufactured in Asia: Rotasiil (Serum Institute of India), ROTAVAC (Bharat Biotech), Lanzhou (China) and Rotavin (Vietnam), in addition to two internationally available rotavirus vaccines. Despite this availability, only eight Asian countries have introduced a rotavirus vaccine into their national vaccination program.
- Our model predicted more than 710,000 fewer rotavirus hospitalizations and 35,000 fewer rotavirus deaths if all 43 Asian countries introduced rotavirus vaccine, a greater than 40% decrease over the baseline. Similar reductions were projected in sub-analyses by vaccine introduction status, child mortality strata, sub-region, income level, and birth cohort size.

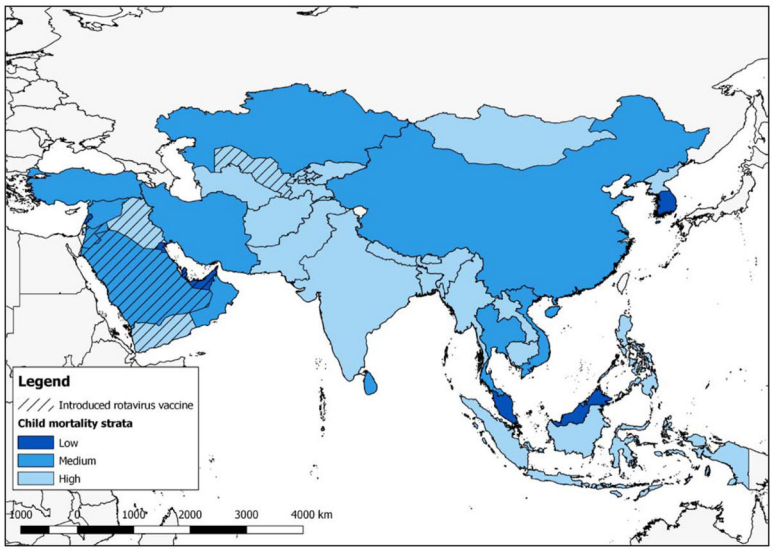

Figure 1.

Map of countries in Asia as defined by the Millennium Development Indicators, by child mortality strata and rotavirus vaccine introduction status.

Table 1

Summary of published rotavirus hospitalization rates among children 0–59 months of age in Asian countries

Country	Surveillance years	% Rotavirus positive	Hospitalization rate (per 100,000)	Reference
Low child mortality				
Hong Kong	1987– 1996	26	200	[29]
Hong Kong	1997– 2011	39	542	[30]
Hong Kong	2001– 2003	30	810	[31]
Malaysia	1999–2000	50	330	[32,33]
Malaysia	2013	45	122	[34]
Singapore	2005– 2008	*Not reported*	459	[35]
Median (IQR)			**395 (200, 542)**	
Medium child mortality				
China	2007– 2008	34	210	[36]
China	2002	20	151	[37]
China	2012–2013	30	144	[38]
Kazakhstan	2007–2009	30 (28, 32)	260	[39]
Kyrgyzstan	2005–2007	26 (24, 27)	362	[40]
Kyrgyzstan	2005–2009	24 (23, 25)	680	[39]
Turkey	2007	29	293	[41]
Vietnam	1998– 2003	55	1,500	[32,42]
Median (IQR)			**277 (181, 521)**	
High child mortality				
Bangladesh	2000–2006	33	1,080	[43]
Bhutan	2010–2012	33	240	[44]
India	2000– 2001	24	337	[45]
India	2002– 2003	27	652	[46,47]
India	2008	*Not reported*	633	[47]
Pakistan	2005– 2007	16	230	[48]
Pakistan	2005– 2007	18	560	[48]
Philippines	2005– 2006	30	281	[49]
Uzbekistan	2005–2009	26 (25, 27)	210	[39]
Median (IQR)			**337 (240, 633)**	

Table 2

Summary of published rotavirus vaccine effectiveness estimates in Asian countries

Country	Vaccine	Outcome	Vaccine effectiveness (95%CI) [1]	Study Type	Reference
Low child mortality					
Hong Kong	Rotarix	Hospitalization	93 (60, 99)	Clinical Trial	[50]
Hong Kong	Rotarix and RotaTeq	Hospitalization	91 (69, 97)	Observational	[51]
Hong Kong, Taiwan, Singapore	Rotarix	Severe diarrhea	96 (85, 99)	Clinical Trial	[52]
Hong Kong, Taiwan, Singapore	Rotarix	Hospitalization	95 (84, 99)	Clinical Trial	[53]
Median (IQR)			**94 (92, 96)**		
Medium child mortality					
China	Rotarix	Hospitalization	81 (44, 95)	Clinical Trial	[54]
Lebanon	Rotarix and RotaTeq	Hospitalization	63 (41, 76)	Observational	[55]
Vietnam	RotaTeq	Severe diarrhea	64 (8, 91)	Clinical Trial	[56]
Median (IQR)			**64 (63, 81)**		
High child mortality					
Bangladesh	Rotarix	Severe diarrhea	23 (0, 41)	Clinical Trial	[57]
Bangladesh	RotaTeq	Severe diarrhea	43 (10, 64)	Clinical Trial	[56]
India	ROTAVAC	Hospitalization	55 (40, 66)	Clinical Trial	[58]
India	ROTAVAC	Hospitalization	54 (35, 67)	Clinical Trial	[7]
Median (IQR)			**49 (33, 55)**		

[1] Full-series vaccine effectiveness

Table 3

Estimated expected and prevented numbers of rotavirus hospitalizations and deaths in children <5 years of age in Asian countries with hypothetical introduction of rotavirus vaccine into national immunization programs.

	Rotavirus hospitalizations						Rotavirus deaths					
	Expected		Prevented		% Prevented		Expected		Prevented		% Prevented	
	n	95%CI	n	95%CI	%	95%CI	n	95%CI	n	95%CI	%	95%CI
All countries[1]	1,452,257	1142109, 1776186	710,580	546045, 889358	49	43, 55	88,889	84014, 93478	35,865	30427, 41370	40	35, 46
Introduction status												
Introduced[2] (n=8)	73,332	56463, 90626	33,210	25460, 41737	46	39, 52	3,436	3238, 3645	1,327	1119, 1556	39	33, 45
Not introduced (n=35)	1,380,365	1067841, 1703794	676,538	511378, 855881	49	43, 55	85,474	80591, 90014	34,540	29173, 40010	41	35, 46
Child mortality strata												
Low (n=7)	22,206	15952, 29011	20,207	14624, 26360	91	90, 92	49	46, 52	44	41, 47	90	88, 91
Medium (n=16)	433,218	286624, 575540	301,210	197527, 417547	71	64, 77	5,335	5031, 5656	3,683	3300, 4118	69	63, 75
High (n=20)	992,953	748982, 1261353	383,007	276114, 516655	39	33, 44	83,478	78615, 88124	32,080	26721, 37673	39	33, 45
Subregion[3]												
Central Asia (n=5)	31,715	23105, 39886	15,396	11117, 20215	49	43, 55	1,380	1272, 1490	620	516, 732	45	38, 52
Eastern Asia (n=5)	319,143	178741, 456421	225,136	124677, 335519	71	63, 79	3,444	3143, 3767	2,392	2037, 2799	70	61, 77
South-Eastern Asia (n=11)	242,118	181975, 299303	111,180	85083, 141229	46	40, 52	10,767	10406, 1154	4,556	3982, 5125	42	37, 47
Southern Asia (n=9)	760,632	526894, 1011612	302,069	202474, 436550	40	33, 47	70,168	65235, 74661	26,981	21753, 32407	39	32, 46
Western Asia (n=13)	97,989	76699, 118962	51,149	40336, 63942	53	47, 58	3,133	2961, 1428	1,231	1048, 1428	39	34, 45
Income group[4]												
High (n=10)	25,904	18517, 33068	21,019	15145, 26799	82	76, 86	79	73, 86	58	50, 66	73	66, 80
Upper Middle (n=10)	408,150	263628, 548453	278,338	177342, 393494	69	62, 76	4,953	4631, 5301	3,105	2723, 3543	63	57, 69
Lower Middle (n=20)	971,245	726294, 1245855	389,167	283448, 523905	40	34, 46	78,349	73458, 82871	30,608	25350, 36175	39	33, 46
Low (n=3)	42,264	30232, 55073	15,769	10521, 21884	38	31, 44	5,500	5050, 5989	1,981	1529, 2455	36	28, 44
Gavi Eligibility												
Ineligible (n=31)	652,031	490018, 814420	396,348	289085, 516507	61	55, 67	13,225	12754, 13725	6,687	6080, 7367	51	46, 55
Eligible (n=12)	802,488	564372, 1055169	310,934	209491, 442674	39	32, 46	75,630	70735, 80151	29,158	23767, 34637	38	32, 45

[1] All countries for which model inputs were available; rotavirus mortality information was unavailable for Hong Kong and Palestinian Territories.

[2] National rotavirus vaccine introduction before 2015: Bahrain, Iraq, Jordan, Qatar, Saudi Arabia, United Arab Emirates, Uzbekistan, Yemen

[3] Millennium Development Goals definition

[4] World Bank definition