Estimated impact and cost-effectiveness of rotavirus vaccination in Senegal:

A country-led analysis

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1. INTRODUCTION

Recent case-control studies conducted in Africa have confirmed that rotavirus is the leading cause of acute, moderate to severe diarrhea among children under 5 years of age presenting at healthcare facilities. [1] This supports the regional rotavirus surveillance coordinated by the African Regional Office of the World Health Organization (WHO), which reports that approximately 38% of cases reporting to hospital with acute diarrhea were rotavirus-positive. [2] Rotavirus is estimated to be responsible for about 5% of all deaths in young African children. [3]

In the area of child health, many life-saving interventions, such as oral rehydration therapy and micro-nutrient supplementation, that prevent and manage diarrhea are available and have been proven to be effective [5]. Unfortunately, utilization and coverage of these inexpensive and effective interventions are low in most countries in Africa [6, 7], although efforts are underway to improve uptake. Furthermore, strategies such as improving water quality and sanitation, food quality, and hygiene are generally long-term and linked to socio-economic empowerment and development of communities. In addition, these strategies have not had a great impact in reducing the incidence of rotavirus diarrhea [3]. Rotavirus immunization, on the other hand, is available and has been shown to have a dramatic effect on reducing diarrheal hospitalizations, [8] diarrheal deaths,[9, 10] and to be cost-effective[11-16]. Thus, since 2009, WHO has recommended the introduction of rotavirus vaccination into the national Expanded Program on Immunization (EPI), particularly in countries with high diarrheal mortality. [17] In addition, Gavi, the Vaccine Alliance, (GAVI) has prioritized support for

rotavirus vaccine to low-income countries, and many countries in the African region are introducing rotavirus vaccine. [18]

Currently, two rotavirus vaccines are available commercially and are pre-qualified by WHO for procurement by UNICEF. [3] A pentavalent, reassortant vaccine containing the common human rotavirus antigens, RotaTeq™ (Merck Research, Whitehouse, Pennsylvania, USA) is available as an oral, 3-dose, live attenuated vaccine. The monovalent rotavirus vaccine, Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium) based on a human rotavirus strain, is licensed as an oral, 2-dose, live attenuated vaccine. Both vaccines are expected to provide similar benefits at similar cost for low-income countries. So, for simplicity, just one product--the monovalent vaccine, was evaluated.

In addition to the substantial morbidity, there is growing evidence of the economic burden created by diarrheal disease [19-24]. In particular, where resources are limited, such as in sub-Saharan Africa, it is critical for national authorities to be informed of the economic implications for their strategic choices. Consequently, cost-effectiveness analysis (CEA) has become an increasingly necessary criterion among other policy issues in new vaccine introduction strategy. This has been addressed by the Pan American Health Organization's (PAHO's) ProVac Initiative in Latin American countries and is now being disseminated under its auspices to other WHO regions [25]. The current initiative was launched in Senegal; the ProVac International Working Group (IWG) is helping to pave the way for better child health (saving lives and preventing diseases) by enabling national decisions-makers to identify and use more consistent and reliable evidence to support the decision-making process regarding vaccines.

2. MATERIALS AND METHODS

2.1 Model

The TRIVAC model, developed by researchers from the London School of Hygiene and Tropical Medicine (LSHTM), is built in Microsoft Excel with support from PAHO's ProVac Initiative and GAVI's *Haemophilus influenzae* type b (Hib) Initiative. TRIVAC is purposefully designed for use at country level, and allows national teams to perform cost-effectiveness analyses of vaccines for three diseases: pneumococcal, rotavirus, and Hib. Version 2.0 of the model was used for this analysis. The model includes the following categories of input parameters: demographics, burden of disease, vaccine schedule, vaccine efficacy, vaccine costs, health services utilization, and health services costs. Model inputs and their values are shown in Tables 1 - 5. Detailed model structure and methodology have been published previously [26].

Annual birth cohorts were followed for a five-year period, and the costs and health outcomes incurred by these populations were estimated under scenarios with and without rotavirus vaccine. Results are reported for one single cohort for the year 2019, when the vaccination program is expected to be fully scaled up, and for 20 cohorts from 2014-2033.

The analysis was conducted from both healthcare system and societal perspectives. Household out-of-pocket costs for direct medical expenses were included in the societal perspective, but non-medical and indirect costs were not included. All costs and health outcomes were discounted at 3% per year.

2.2 Demographic data

Data on number of live births per year, infant mortality rate, mortality rates for children under 5, and life expectancy at birth were gathered from local sources where available.

National data on mortality rates were drawn from Demographic and Health Surveys and Situation Economique du Senegal (Economic Situation of Senegal) reports, [27-29] whereas United Nations Population Division (UNPOP) data were used for births and life expectancy.

2.3 Disease burden

There are no Senegal-specific estimates for incidence of rotavirus gastroenteritis (RVGE), so we assumed a rate of 10,000 per 100,000 in children under 5, based on the pooled estimate from a global meta-analysis [30]. To estimate RVGE hospitalizations, we assumed an incidence rate of 500 per 100,000 in children under 5 globally, which is consistent with estimates from Kenya [31] and several countries in Latin America [32]. To estimate overall severe RVGE incidence, we divided RVGE hospital incidence (500 per 100,000 per year in children under 5) by the percentage of those with access to care in Senegal. The non-severe RVGE incidence was calculated by subtracting the severe RVGE incidence from the overall incidence of RVGE (10,000 per 100,000 in children under 5).

The proportion of diarrheal deaths due to rotavirus was estimated from Senegal-specific and regional surveillance data. [33-37] Estimates from these studies ranged from 26% to 41%; 34% was used as the base-case estimate, and the range was explored in the scenario analysis. Using this proportion, the number of deaths due to rotavirus in children under 5 was calculated by multiplying the diarrheal disease deaths in Senegal for the year 2010 by the proportion attributable to rotavirus. It is estimated that there were nearly 1,000 deaths due to rotavirus in 2010, equivalent to 45 per 100,000 per year [38]. This was adjusted to the year of anticipated

vaccine introduction (2014) by assuming the same percentage of mortality in children under 5 would be due to rotavirus over the period from 2010 to 2014.

2.4 Vaccine schedule and coverage

Senegal is expected to initially introduce the monovalent rotavirus vaccine. The vaccine requires two doses and will be administered within the current EPI infant vaccination schedule. Therefore, DTP1 and DTP2 coverage levels were used as proxies for rotavirus vaccine coverage projections, and were provided by the latest vaccine coverage survey conducted in February 2013 by the Directorate of Preventive Medicine within the Ministry of Health.[39]

An adjustment factor (relative coverage), was applied to the coverage estimates to account for the likelihood that children at the highest risk of dying from rotavirus disease are less likely to be vaccinated. The relative coverage was determined by dividing the DTP coverage in the lowest wealth quintile by the DTP coverage in the entire population.

2.5 Vaccine efficacy

Many pivotal studies of rotavirus vaccines conducted worldwide have demonstrated good efficacy against severe rotavirus cases. Data for this analysis in Senegal were based on the large, randomized, controlled trial of the monovalent rotavirus vaccine (Rotarix™) carried out in South Africa and Malawi [40] using 2 and 3 doses of the vaccine. The overall vaccine efficacy in preventing severe RVGE was 61.2% (95% confidence interval [CI]: 44% to 73.2%). In preventing severe RVGE among infants who received two doses of vaccine, the overall efficacy of the vaccine was 58.7% (95% CI: 35.7% to 74.0%); in those who received three doses, the overall

vaccine efficacy was 63.7% (95% CI: 42.4% to 77.8%). In Senegal, the efficacy rate used was the pooled data from both countries at two doses, which corresponds to 58.7 % efficacy (95% CI: 35.7% to 74.0%).

The protective effect of rotavirus vaccines has been shown to decline over time. For most efficacy and effectiveness studies a reduction is reported after one year, and again after two years [41]. Waning vaccine protection was determined in this analysis by comparing second-season efficacy (42%) against first-season efficacy (59%) from the pooled Malawi/South Africa clinical trial data. This gives 29% waning protection per year, calculated as follows: $[(59\% - 42\%) / 59\%]$.

2.6 Vaccine and systems costs

Vaccine cost per dose includes the vaccine price, handling, and delivery fees. As a GAVI-eligible country in the intermediate co-financing group, Senegal will benefit from support for vaccine; its co-pay agreement starts at \$0.20 per dose and increases by 15% annually [42]. Handling and delivery fees obtained from GAVI applications are 3% and 2%, respectively. A wastage rate of 5% was included in the calculation of vaccine price.

Estimates for the incremental systems cost to deliver each dose of rotavirus vaccine were derived from the Senegal Project Optimize study conducted in 2013 for cold-chain costs per dose, in addition to detailed costing work conducted in Ethiopia [43, 44]. The incremental cost estimate was \$0.50 per dose, including start-up costs such as training and communication as well as ongoing costs for supervision, cold chain, transportation and supplies. The cost

125 assumes that the existing immunization program staff in the health facilities were used for the
126 introduction.

127 *2.7 Health services utilization*

128 The health delivery system is divided into three major levels of care. The first line of care
129 is provided by facilities called health posts. Services are oriented toward promotional and
130 preventive activities and serve a large proportion of the rural population.

131 The second line of care consists of health centers and district hospitals. These
132 intermediate-level healthcare facilities provide basic curative healthcare services, including
133 maternal and dental care.

134 The third line of care is comprised of regional and national hospitals, including teaching
135 facilities. Many medical and surgical specialties such as cardiology, internal medicine,
136 pediatrics, gynecology, neurology, and neurosurgery can be found at these facilities.

137 In order to determine the distribution of visits and admissions for diarrheal disease
138 across health facility levels, we used WHO-CHOICE [45] estimates and local reports [46], then
139 conducted phone interviews with five district public health doctors working in four different
140 regions of Senegal (Fatick, Thies, Diourbel, and Kaolack). (WHO-CHOICE is an initiative that,
141 among other things, identifies healthcare interventions that are most cost-effective.)

142 District and regional hospitals are estimated to provide services to approximately 70% of
143 severe rotavirus cases, while 20% are seen in national hospitals, and the remaining cases in
144 lower levels of care. Non-severe cases, by contrast, were seen primarily in health posts and

health centers (75%), while the remainder were seen in district, regional, and national hospitals.

2.8 Health services costs

Government costs per inpatient bed-day and the cost per outpatient visit are available from WHO-CHOICE [47]. Since the additional disease-specific costs are not included in these estimates, for all diseases we inflated CHOICE estimates by 25% to account for the cost of disease-specific drugs, diagnostics, and procedures. This fraction is based on the fraction reported in a recent South African pneumonia costing study [48]. Household costs were assumed to be equivalent to the percentage of total health expenditure which is out-of-pocket, based on estimates from the WHO Global Health Expenditure Database [49]. In Senegal, 34% of healthcare expenditures are borne by households. The formula used to estimate the household cost per visit or admission was: $\text{[Government cost per case / (1 - \% of total cost borne by households)]} - \text{Government cost per case}$. Household costs included direct medical expenses, but not direct non-medical or losses in productivity.

2.9 Sensitivity analysis

Scenario analysis was performed to assess the impact of changes in specific model input values on the cost-effectiveness -- cost/DALY (disability-adjusted life year) averted of rotavirus vaccination. Variables included incidence of disease, mortality, vaccine efficacy, waning protection, vaccine coverage, relative coverage, vaccine systems costs, vaccine prices, cost of healthcare services and percentage discounting.

3. RESULTS

3.1 Health impact of vaccination

The outcomes presented in Table 6 reflect the projected health outcomes under scenarios with and without a rotavirus vaccination program. Introduction of rotavirus vaccine in Senegal could result in a reduction of more than 2 million cases of rotavirus and nearly 190,000 DALYs and avert more than 8,500 deaths from 2014 to 2033. Once the program is fully implemented, vaccination is estimated to avert over 80,000 cases and prevent more than 450 deaths per year, equivalent to 42% of all rotavirus deaths.

3.2 Cost and cost-effectiveness of vaccination

The healthcare costs with and without vaccination are shown in Table 7. The costs averted due to vaccination are higher from the societal perspective due to the inclusion of household out-of-pocket costs. The cost-effectiveness of rotavirus vaccination is \$92 and \$73 per DALY averted from the health provider and societal perspectives, respectively (Table 8).

3.3 Scenario analysis

Figure 1 presents the results of varying select model input values on the cost-effectiveness of vaccination. The base case from a provider perspective is \$92 per DALY averted. Under all scenarios involving the most influential factors, results vary from \$50 to \$170 per DALY averted—all well below the cost-effectiveness threshold of \$1,040, the GDP per capita

for Senegal [50]. This suggests that the model results are robust to changes in the value of all major variables.

4. DISCUSSION

The results of this evaluation suggest that rotavirus vaccination would be highly cost-effective and would substantially reduce child illness and deaths due to rotavirus in Senegal. The analysis was performed using local data where possible, and relied on regional and global estimates when national data were not available or practical to collect. Limited data on the burden of rotavirus in Senegal were available, but those data were assessed together with national and regional data from other African countries to broaden and strengthen the body of evidence.

Although analyses that project costs and benefits into the future aim to use the best available data to achieve highly valid results, limitations will always be present. Healthcare costs were estimated from WHO-CHOICE; although this is a good source of data in the absence of costs collected directly at the national or sub-national level, future evaluations should seek to incorporate these local costs as they become available. A small sample of local costs gathered from a survey of physicians and facilities were explored within the scenario analysis and the changes observed had little effect on the cost-effectiveness of vaccination. Local data were available on cold-chain systems costs from a recent project in Saint Louis, Senegal. Since cold-chain and related transportation costs are the most significant portion of vaccine systems costs, the local data were valuable in assessing these costs. However, the data were modeled for one region and extrapolated nationally for this analysis. Variations in systems costs were also

204 explored in sensitivity analysis and cost-effectiveness results were robust to a doubling of the
205 base case estimate.

206 Results obtained in this study are consistent with the cost-effectiveness of rotavirus
207 vaccine from previous studies done in many developing country settings worldwide, [14, 16, 51-
208 54] and in particular, consistent with a cost-effectiveness study conducted in Malawi[14].
209 Vaccine program cost-effectiveness for both perspectives in Senegal would be similarly
210 favorable to results from Malawi, which demonstrated \$74.73 per DALY averted.

211 The study was performed by local researchers, with input data and results reviewed and
212 approved by a local group of experts, which contributes to the relevance and validity of the
213 analysis. Engaging local experts in the collection and validation of model inputs and results is
214 very likely to increase the acceptability of the evidence for local policy-makers. This in turn may
215 improve the likelihood that the evidence will be incorporated into decision-making about the
216 adoption and ongoing support of vaccination programs in Senegal.

217 Senegal recently made the decision to introduce rotavirus vaccines with GAVI support.
218 Over time, the country is expected to contribute a greater share of the vaccine price.
219 Eventually, Senegal may graduate from GAVI eligibility and incur the full price of vaccine. As
220 Senegal and other countries take on an increasing share of costs, analyses that elucidate the
221 benefits and costs of new vaccines are likely to become even more relevant to the decision-
222 making process.

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Table 1. Input parameters for estimating disease burden

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Annual incidence per 100,000 aged 1-59m:				
Rotavirus (non-severe) cases	7,523	6,816	8,330	Assumption, derived from [1-3]
Rotavirus (severe) cases	2427	2,184	2,670	Assumption, derived from [1-3]
Rotavirus deaths ^a	45	40	50	[4]
Disability weight for DALY calculations				
Rotavirus (non-severe) cases	0.12	-	-	[5]
Rotavirus (severe) cases	0.12	-	-	[5]
Mean duration of illness (in days)				
Rotavirus (non-severe) cases	6	-	-	Assumption
Rotavirus (severe) cases	6	-	-	Assumption
Age distribution of disease cases and deaths				
<3m:	6.6%	-	-	[6, 7]
3-5m:	19.4%	-	-	[6, 7]
6-8m:	31.9%	-	-	[6, 7]
9-11m:	19.8%	-	-	[6, 7]
12-23m:	21.8%	-	-	[6, 7]
24-35m:	0.5%	-	-	[6, 7]
36-47m:	0.0%	-	-	[6, 7]
48-59m:	0.0%	-	-	[6, 7]

^a Derived from diarrheal disease mortality estimates for Senegal. In the absence of vaccination, this ratio is assumed to decline in each successive birth cohort in line with the general trend in mortality among children under age 5. This is done by assuming that the fraction of deaths under age 5 caused by the disease remains fixed over time.

Table 2. Input parameters for estimating health service costs (all costs are presented in 2013 US \$)

Parameter	Estimate	Scenarios		Source/s
		Low	High	
OUTPATIENT VISITS				
Government cost per outpatient visit ^a				
Rotavirus outpatient visits	\$3.50	\$1.75	\$5.25	[8]
Household cost per outpatient visit ^b				
Rotavirus outpatient visits	\$1.36	\$0.68	\$2.04	Assumption, derived from [8]
INPATIENT ADMISSIONS				
Government cost per inpatient admission ^c				
Rotavirus admissions	\$64.50	\$32.25	\$96.75	[8]
Household cost per inpatient admission ^d				
Rotavirus admissions	\$33.23	\$16.61	\$49.84	Assumption, derived from [8]

^a Government costs per outpatient visit include all cost components including drugs and diagnostics.

^b Household costs per outpatient visit include all direct medical out-of-pocket payments. Productivity losses and travel expenses are not included.

^c Government costs per inpatient admission include the cost per bed-day multiplied by the expected length of stay (6 days), and the cost of drugs and diagnostics.

^d Household costs per inpatient admission include all direct medical out-of-pocket payments. Productivity losses and travel expenses are not included.

Table 3. Input parameters for estimating rotavirus vaccine (RV) coverage and timeliness

Parameter	Estimate	Source/s
3m	73.4%	[6, 9]
6m	88.1%	[6, 9]
9m	91.8%	[6, 9]
12m	94.7%	[6, 9]
24m	96.7%	[6, 9]
3m	34.7%	[6, 9]
6m	78.5%	[6, 9]
9m	85.9%	[6, 9]
12m	89.9%	[6, 9]
24m	94.7%	[6, 9]

Table 4. Input parameters for estimating RV1 program costs

Parameter	Estimate	Alternate Scenario	Source/s
Vaccine dose price projection			
2014	\$0.20	\$2.50	GAVI [10]
2015	\$0.23	\$2.38	GAVI [10]
2016	\$0.26	\$2.26	GAVI [10]
2017	\$0.30	\$2.14	GAVI [10]
2018	\$0.35	\$2.04	GAVI [10]
2019	\$0.40	\$1.93	GAVI [10]
2020	\$0.46	\$1.84	GAVI [10]
2021	\$0.53	\$1.75	GAVI [10]
2022	\$0.61	\$1.66	GAVI [10]
2023	\$0.70	\$1.58	GAVI [10]
2024	\$1.50	\$1.50	Assumption
2025	\$1.50	\$1.42	Assumption
2026	\$1.50	\$1.35	Assumption
2027	\$1.50	\$1.28	Assumption
2028	\$1.50	\$1.22	Assumption
2029	\$1.50	\$1.16	Assumption
2030	\$1.50	\$1.10	Assumption
2031	\$1.50	\$1.05	Assumption
2032	\$1.50	\$0.99	Assumption
2033	\$1.50	\$0.94	Assumption
Other vaccine dose costs			
International handling (% of vaccine price)	3%	--	Assumption
International delivery (% of vaccine price)	2%	--	Assumption
Wastage (% of doses discarded etc) ^a	5%	--	Assumption
Incremental system costs of introduction^b			
Incremental system cost per dose	\$0.50	\$0.35 - \$1.00	[11, 12]

Table 5. Input parameters for estimating the health impact of RV1

Parameter	Estimate	Scenarios		Source/s
		Low	High	
Vaccine efficacy vs rotavirus (non-severe) cases				
	47.0%	30.0%	60.0%	[13]
Vaccine efficacy vs rotavirus (severe) cases				
	59.0%	36.0%	74.0%	[14]
Other vaccination impact assumptions				
% relative coverage ^a	94.0%	80.0%	100%	Assumption
% decrease in dose efficacy per yr ^b	28.8%	21.6%	50.0%	Assumption
% contribution of herd effect in <5yrs ^c	110%	100%	120%	Assumption

^a Relative coverage is the coverage in those at risk of getting the disease (i.e., effective coverage) relative to coverage in the entire birth cohort (i.e., overall coverage). Overall coverage is multiplied by relative coverage to obtain a more realistic estimate of effective coverage.

^b To account for waning duration of clinical vaccine-induced protection, TRIVAC uses a waning matrix with age bands (<3m, 4-5m, 6-8m, 9-11m, 12-23m, 24-35m, 36-47m, 48-59m) repeated in the rows and columns of the matrix. The direct protection at the start of each age band is represented by the diagonal from top-left to bottom-right of the matrix. Protection is re-calculated for each age band as the child gets older (moves from left to right in each row). Adjusted protection by age is calculated by adding together the revised protection estimates for each column.

^c Rather than endogenous modeling of transmission dynamics, the % of direct protection for children under 5 yrs is multiplied by a herd effect factor (e.g., 120%) to give the % of total protection in the cohort of interest before age 5 yrs. This excludes any herd effect in individuals aged 5 yrs+ and is therefore very conservative.

Table 6. Health benefits (20 cohorts vaccinated over the period 2014-2033)

	No vaccine (Status quo)	RV1 With vaccine	Averted
Total non-severe cases <5yrs	3,280,936	2,194,481	1,086,455
Total severe cases <5yrs	1,051,476	614,092	437,384
Total deaths <5yrs	15,772	9,192	6,580
Total deaths<5yrs (undiscounted)	20,456	11,952	8,503
DALYs	457,460	267,180	190,280
YLDs - DALYs due to morbidity	8,470	5,490	2,980
YLLs - DALYs due to mortality	448,990	261,680	187,300

Health benefits are discounted at 3% per year unless otherwise indicated.

Table 7. Economic benefits (20 cohorts vaccinated over the period 2014-2033)

	No vaccine (status quo)	RV1 With vaccine	Averted
TOTAL GOV. HEALTH SERVICE COSTS	\$18,849,182	\$11,208,602	\$7,640,580
Total outpatient visit costs	\$3,831,449	\$2,437,821	\$1,393,628
Total inpatient admission costs	\$15,017,733	\$8,770,781	\$6,246,952
TOTAL SOCIETAL HEALTH SERVICE COSTS	\$28,064,115	\$16,668,266	\$11,395,849
Total outpatient visit costs	\$5,309,974	\$3,379,203	\$1,930,772
Total inpatient admission costs	\$22,754,141	\$13,289,063	\$9,465,078

Costs are discounted at 3% per year.

Table 8. Discounted cost-effectiveness of RV (20 cohorts vaccinated over the period 2014-2033)

	RV1	
	Government perspective	Societal perspective
<i>Cost-effectiveness compared to no vaccine</i>		
Net cost of vaccine introduction	\$17,570,000	\$13,810,000
Costs of vaccine introduction	\$25,210,000	\$25,210,000
Health service costs avoided	\$7,640,000	\$11,400,000
DALYs averted	190,280	190,280
YLDs averted - DALYs due to morbidity	2,980	2,980
YLLs averted - DALYs due to mortality	187,300	187,300
US\$ per DALY averted	\$92	\$73
<i>Cost-effectiveness threshold</i>		
1 x GDP per capita (2012) - WHO threshold for 'highly cost-effective'	\$1,032	\$1,032
3 x GDP per capita (2012) - WHO threshold for 'cost-effective'	\$3,095	\$3,095

Costs and DALYs are discounted at 3% per year.

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Figure 1. US\$ per DALY averted for base-case scenario and alternative scenarios: Government perspective and societal perspective