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Evaluation of cost-effectiveness of live oral pentavalent reassortant rotavirus vaccine introduction in Ghana

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ABSTRACT

Background: Globally, rotavirus gastroenteritis is the most common identifiable cause of severe diarrhea in children under 5. Recently introduced rotavirus vaccines from Merck & Co. and GlaxoSmithKline have the potential to save hundreds of thousands of lives. Efficacy results in Ghana suggest Merck & Co.'s live oral pentavalent rotavirus vaccine (RotaTeq®) prevents 65.0% of severe gastroenteritis due to rotavirus infection in children under 5. The announcement by Merck and GSK to make their rotavirus vaccines available for developing nations at reduced prices provides Ghana with the opportunity to introduce rotavirus vaccines into the national immunization program after investigation of the medical, economic and political implications.

Methods: We estimated the average costs of treating children with diarrhea in the Ashanti region of Ghana as inpatients and outpatients. Using these results, data from rotavirus surveillance studies, and recent rotavirus vaccine efficacy evaluation, we estimated the cost-effectiveness of introducing RotaTeq in Ghana.

Results: Based on our prospective calculations, we estimated an average inpatient and outpatient costs of $233.97 and $17.09, respectively, for treating childhood diarrhea. Using the 2003 birth cohort, RotaTeq introduction could save 1554 lives and avert 93,109 disability-adjusted life-years (DALYs) annually. At a market price of $5 per dose, introducing RotaTeq would have a base-case cost of $62.26 per DALY averted, at a market price of $3.50 per dose, a base-case cost of $39.59 per DALY averted and at market cost of $1 per dose, a base-case cost of $1.81 per DALY averted. All three values are below the 2009 Ghana per capita GDP. Thus, RotaTeq introduction into Ghana will be very cost-effective. Sensitivity analyses suggest these results are robust.

Conclusions: RotaTeq vaccination for children under five in Ghana would be a highly cost-effective public health intervention. Ghanaian health officials should seek GAVI funding and evaluate how to maximize RotaTeq access.

1. Introduction

Diarrheal diseases claim the lives of 1.8 million children each year world-wide [1]. Surveillance studies suggest that globally, rotavirus gastroenteritis is the most identifiable cause of diarrheal disease in children less than 5 years of age, accounting annually for more than 500,000 deaths and 55% of hospitalizations [2–5]. Rotavirus infection is transmitted by fecal–oral route and manifests as severe diarrhea in young children who lack previous exposure. Nearly all deaths due to rotavirus infection occur in the developing world, yet, children are infected at similar rates globally [1,6,7]. This indicates that rotavirus infection will continue to be transmitted regardless of sanitary improvements [8]. Thus, attention has now turned to vaccines, which have the greatest potential for reducing the burden of disease by preventing infection [6].

Two live oral rotavirus vaccines, an attenuated single human serotype [Rotarix (GlaxoSmithKline)] [9] and a pentavalent human-bovine reassortant [RotaTeq (Merck & Co.)] [10], have been developed and are being used in the United States, Europe, and Latin America. Data from the US indicates that rotavirus infection in children has been reduced by 86% within 3 years of vaccine introduction [11,12]. Therefore, rotavirus infection is now considered a vaccine preventable illness. The World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) has recommended that rotavirus vaccines be included in all national immunization programs, following the release of regional efficacy and cost-effectiveness data [13]. Lack of regional specific efficacy data has, however, delayed vaccine introduction into Africa and

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Asia. Fortunately, efficacy results for Rotarix and RotaTeq have recently begun to emerge in these regions [14,15].

In the Republic of Ghana, diarrheal diseases account for 12.2% of childhood mortality and the hospitalization of thousands of children annually [16]. Nearly half of the diarrheal disease hospitalizations of children under 5 in Ghana are caused by rotavirus gastroenteritis [17–20]. Recent studies in Ghana demonstrated that a rotavirus vaccine (RotaTeq) was 65.0% effective against severe cases of rotavirus gastroenteritis and 56.4% effective against all cases of rotavirus gastroenteritis [14]. These results, coupled with incidence data, suggest that introducing the RotaTeq vaccine into Ghana will prevent thousands of infections and deaths annually.

In 2005 Ghana introduced a National Health Insurance Scheme (NHIS), which requires that providers cover 95% of care for members including children [21]. This expanded access to healthcare for children, along with high existing coverage rates for other childhood vaccines such as DPT, will likely enable a successful vaccine introduction [22]. Ghana, however may be unable to fund RotaTeq introduction at current developed-country market values. Merck has recently announced that it will initially offer RotaTeq to UNICEF, a procurement partner of the GAVI Alliance, for $5 per dose and then for $3.50 per dose once purchase volume exceeds 30 million doses [22] which may make Ghana suitable for funding assistance [23,24].

Our study estimated the costs of treating children below 5 years of age presenting with diarrhea at an inpatient and outpatient facility in the Ashanti region of Ghana. We then estimated the expected costs and DALYs averted by introducing the vaccine into Ghana. Using these results, we calculated whether introducing RotaTeq into Ghana will be cost-saving and/or cost-effective.

2. Methods

2.1. Study overview

Our analysis was adapted from models developed and utilized by Rheingans et al. [25,26]. We used the same methods for evaluating health burden, direct costs, cost-effectiveness, and vaccine coverage. To evaluate the cost-effectiveness of rotavirus vaccines, specifically RotaTeq, introduction in Ghana, we used rotavirus surveillance data, our prospective calculation of healthcare costs associated with treating children under 5 with diarrhea, the efficacy of RotaTeq in clinical trials in Ghana [14], and the cost of vaccine introductions. Our assessment focused on one nation rather than six global regions, thus differing from Rheingans et al. [25,26], nor did we adjust coverage based on risk. Furthermore, our evaluation was done from the perspective of the health care provider, so we did not include societal costs. In our sensitivity analyses base-case values of incidence and cost data were subjected to $\pm$25% and $\pm$50% variance. Changes in health outcome following the introduction of RotaTeq were measured in Disability Adjusted Life Years (DALYs) averted [27], and were based on expected events and costs for a 2003 birth cohort until 5 years of age. Monetary values were collected in 2009 Ghana cedis, and were expressed in 2009 $US using an exchange rate of 1.44 Ghana cedi to 1.00 $US.

2.2. Health burden of rotavirus

The burden of disease was estimated as the expected number of rotavirus-associated hospitalizations, outpatient visits, deaths and DALYs during the first 5 years of life for the 2003 Ghanaian birth cohort using data from northern Ghana and surveillance data from 2003 to 2008 [18–20,28]. The number of children in the 2003 birth cohort that were treated for rotavirus infection in outpatient clinics was estimated to be 12.1 times the number that were hospitalized due to rotavirus [8]. For mortality data, we used the WHO published 2004 Ghanaian childhood rotavirus mortality data [29].

DALYs were calculated to quantify the years of life lost due to premature mortality (YLL) and years lived with a disability (YLD) [27]. Most severe diarrhea occurs in children 1.5 years of age, so the YLL due to rotavirus is equivalent to the average life expectancy of a 1 year old multiplied by the number of deaths [30]. YLD is calculated by multiplying the average duration of the condition by the severity weight measures valuation of loss of healthy life [31]. Parental days of missed work were not included in our analysis.

2.3. Medical costs of treating rotavirus gastroenteritis

The prospective study was conducted in accordance with the human studies principles of the Noguchi Memorial Institute for Medical Research at the University of Ghana, and the Agogo Presbyterian Hospital in Agogo, Ghana and was approved by University of Ghana IRB. We estimated the direct medical costs of treating children under 5 years old with diarrhea using subjects who had $\geq$3 watery stools in the 24 h prior to visit, and whose guardians gave informed consent. The number of subjects that presented with mild to severe dehydration during our study was 52 outpatients and 15 inpatients.

Using this information and the monetary values obtained from administrators of Agogo hospital, we calculated the costs of hospitalization, diagnostics, pharmaceuticals, hospital personnel and capital expenditures on buildings and equipment. The average length of stay was generated from the results of the prospective study and published global data [32,33]. We then calculated the cost per bed-day using WHO protocol for estimating the economic burden of rotavirus diarrhea [33]. The total cost per outpatient visit was calculated by adjusting the WHO-CHOICE Ghana estimate proportionally to the inpatient cost per bed-day obtained in the prospective study [34]. Using treatment costs, cost per bed-day and cost per visit, we calculated the total average cost per inpatient and outpatient visit. A previous study conducted in northern Ghana predicted lower inpatient and outpatient visit costs, therefore, these values were used in the sensitivity analyses to account for uncertainty [35]. The economic burden of rotavirus infection in Ghana was then estimated by multiplying the cost of treating each event by the number of times each event occurred.

2.4. Estimating costs and efficacy of RotaTeq introduction

The costs of introducing RotaTeq include the price of the vaccine, the number of doses, the cost of administration, and the expected loss from waste. Merck announced that RotaTeq will be available for $5 per dose or $3.50 per dose to UNICEF [23]. Furthermore, GAVI Alliance suggests that rotavirus vaccines could eventually be procured at $1 per dose in developing nations, based on tiered pricing [24]. Thus we calculated the incremental cost-effectiveness ratio (ICER) at $5 per dose, $3.50 per dose and $1 per dose. Since RotaTeq will be administered simultaneously with DPT, a low incremental administration cost of $0.35 per dose was assumed [36].

Our analysis incorporated the predicted RotaTeq coverage level and the efficacy of RotaTeq against a range of disease severities. RotaTeq coverage should mimic the current DPT coverage level in Ghana (84.6%) because they will be administered together [3,16]. We applied lower bounds of 57% and 63% coverage to assess how the proposed age-limitations would affect the cost-effectiveness of RotaTeq introduction [37].

This study used the clinical trial efficacy results of RotaTeq in Ghana [14] to estimate what proportion of rotavirus-related events occurred in the 2003 birth cohort could have been averted if the vaccine had been introduced. We used the vaccine efficacy against severe diarrhea (0.65) as measures of efficacy against

hospitalizations and deaths, but this likely provides a conservative estimate for deaths [26]. Efficacy rates were not altered to account for partial series administration because partial administration of RotaTeq was still found to be highly effective at preventing severe rotavirus disease [38].

2.5. Cost-effectiveness analyses

The ICER value indicates the monetary investment needed to avert each DALY. It was calculated by dividing the incremental cost (IC) of RotaTeq introduction by the number of DALYs averted. The incremental cost was measured by comparing the annual cost of managing rotavirus infections before and after RotaTeq introduction without including the potential cost of side effects associated with vaccination. The number of DALYs averted was estimated by comparing the number of deaths and infections before and after RotaTeq introduction. Thus the ICER value is measured in $US per DALY averted. We compared the ICER values to the 2009 Ghana per capita GDP to evaluate the cost-effectiveness of RotaTeq introduction into Ghana [24,25]. An intervention with an ICER value less than the GDP per capita is considered very cost-effective, an intervention with an ICER value between one and three times GDP per capita is considered cost-effective, and an intervention with an ICER value more than three time the GDP per capita is not considered cost-effective [39]. We assumed a willingness-to-pay threshold equal to the 2009 Ghana per capita GDP.

2.6. Discounting and sensitivity analyses

This assessment used 3% annual discounting over a 5 year period, because present costs carry more weight than future costs [27]. We also discounted health effects because the value of a unit of consumption decreases over time. The ideal discount rate for health effects is widely debated, yet this study used a 3% discount rate per annum [40,41]. To test the sensitivity of these results, we applied 0% and 6% annual discount rates to costs and effects.

One-way sensitivity analyses were done by varying individual base-case input values, to compensate for parametric uncertainties and to evaluate how changes in individual parameters affect the cost-effectiveness of introducing RotaTeq. Input variables included mortality, hospitalization and outpatient rates; vaccine coverage, cost and efficacy; treatment and program costs; and discounts (Table 1).

In order to show the potential maximum ICER, we conducted a multi-way sensitivity analysis and measured whether the ICER could cross our defined potential willingness-to-pay threshold if multiple parameters were altered. This was assessed by simultaneously using the least economically optimal upper or lower bounds for each parameter.

3. Results

3.1. Treatment costs

A total of 67 patients were interviewed. 52 were outpatients, including 27 boys (52%) and 25 girls (48%), with a mean age of 15.93 months. 15 were inpatients, including 11 boys (73%) and 4 girls (27%), with a mean age of 10.38 months. Patients were diagnosed based on their symptoms without confirmatory cultures. We documented the treatment and diagnostic tests required for treating each patient; 87% were treated for diarrhea as well as malaria, dysentery, sepsis and/or other infections. We then calculated the average cost of treating each inpatient and outpatient including costs of pharmaceuticals and diagnostic tests. The average inpatient stayed for 4.3 days and received $68.25 worth of treatment and diagnostic tests. The average outpatient required fewer treatments and diagnostics, receiving $6.18 worth of treatment and diagnostic tests.

The capital and recurrent costs of running the hospital were calculated using data obtained from administrators of Agogo hospital. The cost per visit allocated to hospital bed-day was $16.11, the staff cost was $15.63, and the overhead cost was $9.69. Thus the average cost per bed-day at inpatient facilities in Ghana was estimated at $41.43. After adjusting the WHO-CHOICE proportion of inpatient and outpatient visit costs [34], the mean cost of treating inpatients with diarrhea was $233.97 per child and the mean cost of treating outpatient children was $17.09 per patient.

3.2. National health and economic burden of rotavirus infection

We estimated that in the 2003 Ghana birth cohort; 7804 hospitalizations, 94,671 outpatient visits, 2826 deaths and 169,446 DALYs were the results of rotavirus infection. In order to administer three doses of RotaTeq to 84.6% of the 2003 birth cohort 1,342,315 doses of RotaTeq were needed (1,491,461 doses after 10% waste was accounted for [42]). With this level of RotaTeq administration, hospitalization and outpatient visits due to rotavirus infection are expected to drop to 3513 and 46,055, respectively. As a result, deaths and DALYs would be reduced by about 55% to 1272 and 76,337, respectively.

We then used the health burden data and patient costs to estimate the total economic burden of rotavirus-induced disease before and after vaccine introduction. Table 2 details the intervention cost and net cost before and after the introduction of RotaTeq using three possible vaccine price scenarios. This framework estimated that $3,248,976 was spent treating children in the 2003 birth cohort with rotavirus, and predicted that $1,731,085 equal to 53.3% of treatment costs would have been averted if RotaTeq had been introduced.

3.3. Cost-effectiveness

The total costs of introducing RotaTeq at $5, $3.50 or $1 per dose were $7,527,846, $5,417,235 or $1,899,550, respectively. Using these values, we calculated that the corresponding incremental cost (IC) of introducing RotaTeq using the three possible prices/dose is $5,796,761, $3,686,150 or $168,465 respectively (Table 2). The vaccine would need to cost less than $1.16 per dose to be cost-saving, so at all prices (with $0.35 program costs), introducing RotaTeq into Ghana is not cost-saving.

Assuming 65% efficacy against death and 56.4% against all infection, 1554 deaths (55.0%) would have been averted and 93,109 years of healthy life (54.9%) would have been regained. Thus, the incremental cost-effectiveness ratio (ICER) is $62.26 per DALY averted at $5 per dose, $39.59 per DALY averted at $3.50 per dose or $1.81 per DALY averted at $1 per dose, all of which are well below the per capita GDP, without including additional societal costs. The values used to calculate these ICER's are detailed in Table 2 and indicate that introducing RotaTeq into Ghana is very cost-effective.

3.4. Sensitivity analysis

Sensitivity analyses were conducted to account for uncertainty in inputs and to determine how robust the cost-effectiveness analysis results were. The parametric ranges used in one-way sensitivity analyses are detailed in Table 1. Fig. 1 depicts the range of ICER values that correspond with upper and lower bounds in the one-way sensitivity analyses. Fig. 1A represents the ICER values at Merck's pledged price of $5 per dose. The parameters that most heavily influenced the ICER were price per dose, RotaTeq efficacy against severe disease, and rotavirus death. Similar effects are seen in

Table 1
Epidemiologic, clinical, and economic variable estimates utilized in the cost effectiveness evaluation of RotaTeq introduction in Ghana.

Parameter	Base case	Range for uncertainty analysis	Source
Epidemiologic			
2003 Birth cohort	528,887	–	[28]
Life expectancy of 1–4 year olds, years	63.2	–	[28]
Clinical			
Coverage rate (based on DTP3 vaccine rate)	0.846	0.57–0.99	[22]
RotaTeq efficacy against severe rotavirus, %	0.65	0.325–0.724	[14]
RotaTeq efficacy against all rotavirus, %	0.564	0.355–0.819	[14]
Proportion of children treated as inpatients with rotavirus	0.014755	0.011066–0.018445	[32–34]
Proportion of children treated as outpatients with rotavirus	0.179	0.172–0.22	[34]
Number of rotavirus deaths in Ghana, 2004	2826	2337–3316	[29]
Discounting health effects	0.03	0.00–0.06	[27,40,41]
Economic, US$			
Price per dose	5.00	0.10–10.00	[23,24]
Program cost per dose	0.35	0.18–0.53	[33]
Vaccine wastage rate	0.1	0.05–0.15	[33]
Average total inpatient cost	233.97	65.14–268.10	[33,35]
Average total outpatient cost	17.09	3.86–22.55	[33–35]
Discounting costs	0.03	0.00–0.06	[27]

Note: DTP3, 3-dose diphtheria, tetanus, and pertussis.

Table 2
Costs and cost-effectiveness of RotaTeq introduction in Ghana.

	Price per dose, US$		
	5.00	3.50	1.00
(A) Cost of treatment without vaccination program[a]	3,248,976	3,248,976	3,248,976
(B) Cost of vaccination program alone[b]	7,527,846	5,417,235	1,899,550
(C) Total cost of vaccination program and remaining treatment[c]	9,045,737	6,935,126	3,417,441
(D) Additional cost of vaccination program (C–A)[d]	5,796,761	3,686,150	168,465
(E) ICER, US$ per DALY averted[e]	62.26	39.59	1.81

[a] All costs in 2009 US dollars, 3% annual discounting where appropriate.
[b] Calculated as product of price per dose and number of doses.
[c] Sum of total expenditure on RotaTeq vaccination and remaining cost of treating inpatients and outpatients with rotavirus.
[d] The total cost of a vaccination program and additional treatment less the costs of treatment alone, without a vaccination program.
[e] ICER, incremental cost-effectiveness ratio. Additional cost of the vaccination program (D) divided by 93,109 DALYs averted assuming 3% annual discounting.

Fig. 1B, which depicts the ICER values at Merck's projected future price of $3.50 per dose; the ICER varied most when RotaTeq efficacy against severe disease and rotavirus death values were changed. Fig. 1C shows the ICER value at GAVI Alliance's projected price of $1 per dose, which was most heavily affected by changes in total outpatient and inpatient costs and changes in RotaTeq efficacy against severe rotavirus. Despite variation, all one-way sensitivity analyses yielded ICER values that were below the GDP per capita, supporting the conclusion that RotaTeq introduction in Ghana is very cost-effective. In addition, the use of least optimal values for each parameter in our multi-way sensitivity analysis predicted that introducing RotaTeq into Ghana would in the worst case scenario, cost $320.94 per DALY averted, an ICER value that is well below the annual per capita GDP.

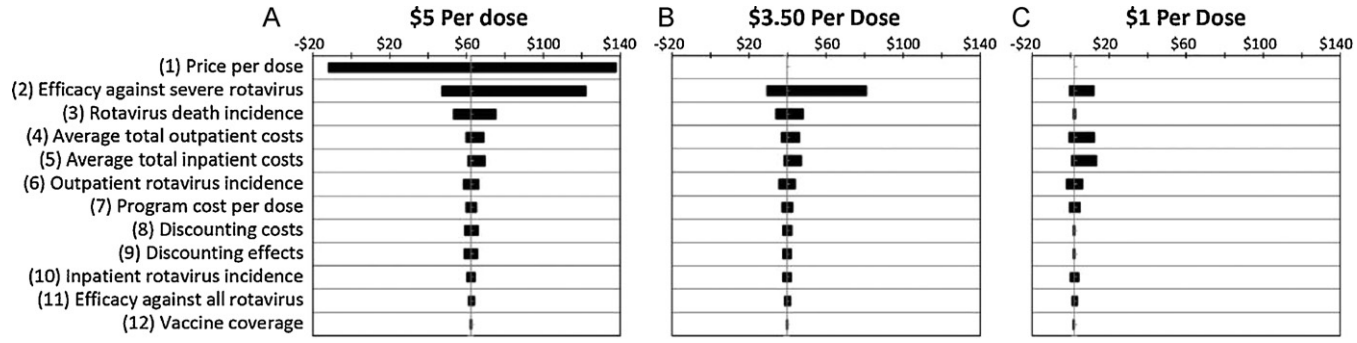

Fig. 1. *One-way sensitivity analysis of ICER values at various prices.* In order to account for uncertainty in input values, one-way sensitivity analyses were conducted for each of the three prices: (A) the original Merck Price ($5/dose) – base ICER $62.26 per DALY, (B) the Merck reduced price ($3.50/dose) – base ICER $39.59 per DALY, and (C) the GAVI anticipated price ($1/dose) – base ICER $1.81 per DALY. The range of ICER values obtained by varying each input variable individually are depicted above by the black boxes. In all analyses, the introduction of RotaTeq is cost effective. Values below $0 represent cost-saving interventions. Variability in the ICER values is generally smaller with lower RotaTeq prices. (1) Price per dose sensitivity analysis was only conducted from the $5/dose reference (A) from $0.10 to $10.00. (2) RotaTeq efficacy against severe infection was varied from 35.5% to 81.9%. (3) The rotavirus death incidence was varied from 2337 to 3316. (4) The average total outpatient cost per episode was varied from $3.86 to $22.55. (5) The average total inpatient cost per episode was varied from $65.14 to $268.10. (6) The rotavirus outpatient incidence was varied from 47,336 to 142,007. (7) The program cost per dose was varied ±50% from $0.18 to $0.53. (8) Discounting costs and (9) health effects were varied ±100% from 0% to 6%. (10) Inpatient rotavirus incidence was varied from 5853 to 9755. (11) RotaTeq efficacy against all types of rotavirus infection was varied from 32.5% to 72.4%. (12) Vaccine coverage rates were varied from 57% to 99%. References for each of the above variables are included in Table 1. All appropriate values are in $USD.

4. Discussion

Over 500,000 children die annually from rotavirus gastroenteritis, and the majority of the deaths could be averted with the introduction of rotavirus vaccines into national immunization programs. Recent strides made by the international health community highlight the need for these vaccines globally. We have the resources and knowledge necessary to provide children in developing nations with life-saving vaccines, and thus policy makers must now push for the immediate introduction of rotavirus vaccines. The GAVI Alliance Accelerated Vaccine Introduction Initiative (AVI) has set as one of its objectives the rapid and large-scale introduction of pneumococcal conjugate and rotavirus vaccines into GAVI-eligible countries [43]. A key component of this initiative is to establish reduced prices and an increased supply of vaccines. At a 2011 pledging conference, GAVI obtained US $4.3 billion in pledges from various donors, which helped to fill their funding gap. The implications of this milestone are enormous and may enable immunizing of over 250 million children by 2015 [44]. GlaxoSmithKline has agreed to make Rotarix available to GAVI for $2.50 per dose, and Merck has pledged to offer RotaTeq to UNICEF for $5 (and eventually $3.50) per dose [23], significantly below the current lowest market price. These prices are likely to lead to $150–500 million in savings through 2020, will generate a dynamic supply base, and will enable more children to receive vaccinations globally.

We present Ghana as a case study for evaluation of the cost-effectiveness of RotaTeq introduction into Sub-Saharan Africa. At $5, $3.50 or $1 per dose, the ICERs generated in base-case and sensitivity analyses were all well below Ghana's 2009 GDP per capita of US $695 [45]. Our results support cost-effectiveness trends seen in other developing countries. When ICER and GDP per capita values from 8 Latin American countries were compared, there was nearly an identical ratio between Ghana and the most cost-effective rotavirus vaccine introduction in a Latin American country (Honduras) [25,45]. Furthermore, when extreme changes due to variation in cost-effectiveness models were mimicked, RotaTeq introduction into Ghana was still a very cost-effective intervention. Several recent studies compared cost effectiveness models [46] and demonstrated equivalent results in other countries [47–50]. This assessment did not analyze Rotarix introduction because no Rotarix efficacy data exists in Ghana. The ICER changed insignificantly (<5%) when RotaTeq program costs were altered to mimic the administration of two doses rather than three, and thus, differences in efficacy and price per dose will determine cost-effectiveness variance between the two vaccines.

There are a few limitations to this study. First, a small number of subjects from one location were included in the assessment of treatment costs. However, our sensitivity analyses used values ±50% the base-case as well as the visit costs estimated by Aikins et al. [35] in northern Ghana, and found that in all instances, the ICER values were still well below the GDP per capita. These findings suggest that the introduction of RotaTeq into Ghana will be very cost-effective regardless of differences in treatment costs, and that analyses involving more subjects will yield similar conclusions. Another limitation of this study concerns the recommended scheduled RotaTeq age administration cut-offs. Arvay et al. [37] state that children in the Kassena-Nankana District of Ghana often received DPT later than the RotaTeq age-limit cutoffs. If administration of the first dose was required by 12 weeks of age, coverage levels are predicted to drop to 63% and if doses 2 and 3 were required by 32 weeks of age, coverage levels are predicted to drop to 57% [37]. If these cut-offs were instituted, the reach of RotaTeq would be reduced; 507 (32.6%) fewer lives would be saved and 30,376 (32.6%) fewer DALYs would be averted. Nevertheless, these rates changed the ICER values minimally, and we expect RotaTeq introduction will be very cost-effective regardless of age based administration cut-offs. Furthermore, we used conservative mortality rates and excluded indirect medical costs attributed to disease, and thus RotaTeq introduction may be even more cost-effective than predicted here.

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