Age restrictions for rotavirus vaccination: evidence-based analysis of rotavirus mortality reduction versus risk of fatal intussusception by mortality stratum
SUMMARY

Background: To minimize potential risk of intussusception, the World Health Organization (WHO) recommends that rotavirus immunization should be initiated by age 15 weeks and completed before age 32 weeks. A large body of evidence now exists on the burden of fatal rotavirus disease and the safety and efficacy of rotavirus vaccines compared to the previous similar analysis done in 2009. These data were applied to assess and compare the potential benefits for mortality reduction from rotavirus versus the risk of fatal intussusception for an age restricted and unrestricted vaccination policy in WHO countries with low and high child mortality.

Methods: This analysis modeled the number of rotavirus deaths prevented by rotavirus vaccination and the number of intussusception deaths caused by vaccination when administered on the current restricted schedule versus an unrestricted schedule whereby rotavirus vaccine would be administered with DTP vaccine up to age 3 years. Countries were grouped by WHO child mortality strata. Inputs were stratum-specific estimates of rotavirus mortality, intussusception mortality, and predicted vaccination rates by week of age, and vaccine efficacy and vaccine-associated intussusception risk.

Findings: The model estimated that a restricted schedule would prevent 156,100 rotavirus deaths (5th–95th centiles, 110,100–201,800) while causing 288 intussusception deaths (99–688). Vaccination without age restrictions would prevent 199,200 rotavirus deaths (140,700–255,400) while causing 605 intussusception deaths (310–1,133).

Without the age restrictions vaccination would avert an additional 136 rotavirus deaths for every intussusception death caused by vaccine, for a net benefit of 42,800 additional deaths (30,400–53,200) prevented by vaccination. These additional deaths prevented under an unrestricted versus restricted schedule reflect an additional 21%-25% children who would potentially be eligible for rotavirus vaccine. The number of additional rotavirus deaths averted and intussusception deaths caused by vaccination varied by WHO mortality are as follows:

- B& C countries: 3,900 (3,600-4,000 versus 20 (11-30);
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-D-Americas: 500 (300-600) versus 2 (1-3);
-D-Asia: 20,100 (13,000-25,900) versus 169 (106-243)
-D&E-Africa: 18,400 (13,800-22,600) versus 125 (91-170)

**Interpretation:** In low and middle-income countries, the additional lives saved by removing age restrictions for rotavirus vaccination would outnumber the excess vaccine-associated intussusception deaths.
BACKGROUND

Rotavirus infection is the leading cause of fatal diarrhea among children younger than 5 years, accounting for 453,000 deaths in the year 2008 based on recently published World Health Organization (WHO) estimates.1 To curb this large toll of severe rotavirus disease, in 2006, the WHO recommended two rotavirus vaccines—Rotarix (GSK Biologicals) and Rotateq (Merck & Co.)—for use in Europe and the Americas, and in 2009, they expanded this recommendation to all children worldwide.2 These recommendations reflected the sequential availability of evidence of the good efficacy profile of rotavirus vaccines – first from clinical trials in high and middle income countries in the Americas and Europe in 2006 and then also from low income settings in Africa and Asia in 2009.3-7 Furthermore, because a previous rotavirus vaccine (RotaShield) was found to be associated with intussusception, a rare form of bowel obstruction,8 the pivotal pre-licensure trials in the Americas and Europe for both rotavirus vaccine were conducted in over 60,000 infants each and did not document an increase in vaccine-associated intussusception.3,4

Decision-makers worldwide have acted on these data and donor funding has also been made available for the poorest countries with the highest rotavirus mortality to purchase these vaccines.9 Remarkable progress has been realized in the past 5 years with some 30 high and middle income countries having introduced a rotavirus vaccine into their national immunisation program and many have already documented substantial declines in severe and fatal diarrheal disease as a result of vaccination.10-13 Recent data on the postlicensure safety of rotavirus vaccines generated from these countries has also shown evidence of a low level risk of intussusception (~1-2 excess cases per 100,000 vaccinated infants) in some countries but not in others.14,15 Based on considerations that this low level risk is greatly exceeded by the observed health benefits of vaccination, national and international policy and regulatory bodies have continued to support recommendations for use of rotavirus vaccine.14,15
WHO currently recommends that rotavirus vaccines should not be initiated for infants aged 15 weeks or older, with all doses being completed by 32 weeks. These age restrictions are driven by concerns about intussusception risk. Natural intussusception rarely occurs before 3 months of age and the incidence increases 10-fold between 3 and 6 months of age. Therefore, any potential vaccine-associated risk of intussusception, particularly with the first vaccine dose that has been primarily associated with risk, would translate to more excess cases if infants were vaccinated late, beyond 3 months of age. Similar findings were observed in the United States after use of RotaShield, prompting a debate of whether restriction of RotaShield to infants younger than 3 months of age would have averted withdrawal of the vaccine. A consequence of these strict restrictions is that those arriving late for immunisation would potentially not have access to the benefits of rotavirus vaccination. This is particularly relevant for the developing world, where substantial delays in the timing of childhood vaccination occur in many countries.

Previously, a scenario analysis assessed the benefits and risks of a rotavirus vaccination strategy with and without an age restriction. Since this analysis, new evidence has been published on several key parameters for the scenario analysis, including data on efficacy of rotavirus vaccines in Africa and Asia, the effect of rotavirus vaccines on diarrhea deaths, postlicensure data on risk of intussusception with current rotavirus vaccines, the release of updated estimates of rotavirus mortality by WHO, age-distribution of rotavirus disease by week of age, and updated data on timeliness of vaccination coverage in low and middle income countries. The availability of these new data and the imminent introduction of rotavirus vaccines in many developing countries in Africa during the next two years prompted us to revise our previous analysis to provide policy makers with the most up-to-date evidence to inform decisions of best approaches to global implementation of rotavirus vaccines.
METHODS

The current analysis focused exclusively on the benefits of rotavirus mortality reduction and risk of fatal intussusception in children < 5 years of age in 158 countries with a birth cohort of 123.6 million where 99.9% of the global rotavirus mortality occurs (i.e., low and middle-income countries). To explore the effect of age restriction in different parts of the world, we grouped these countries on the basis of child mortality rates, according to WHO mortality strata, and assigned to one of four groups: group B and C (countries with low child mortality), group D-Americas (countries in the Americas with high child mortality), group D-Asia (countries in Asia with high child mortality), and group D&E-Africa (countries in Africa with high child mortality). Group A countries with very low child mortality (i.e., high-income) represented <0.1% of the global rotavirus deaths and were excluded from this analysis (the point estimates of rotavirus and intussusception deaths related to vaccination in A countries are presented to illustrate this). The benefits of vaccination are the estimated number of rotavirus-associated deaths prevented through vaccination, on the basis of updated estimates of rotavirus mortality and region-specific vaccine efficacy. The risks are the expected number of excess intussusception-associated deaths occurring after vaccination, on the basis of baseline intussusception rates and vaccine-associated risk uncovered in recent studies.

Vaccination strategies and coverage estimates

For both immunisation strategies, restricted and unrestricted, the model assumed that rotavirus vaccine would be given at the same time as the diphtheria-tetanus-pertussis (DTP) vaccine and that vaccine coverage in the individual countries would be equal to the proportion of infants receiving each of the three DTP doses by week of age (i.e., proportion vaccinated, ρv) during the first 3 years of life. Under the restricted schedule, if infants received their first DTP dose by ≤14 weeks of age, we assumed they would receive all doses up to 32 weeks of age, but if they appeared after 14 weeks, they would remain unvaccinated. On the unrestricted schedule, vaccine would be administered according to the
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age-specific coverage rates for each of the DTP dose up to 3 years of age. The analysis does not allow catch-up immunization and assumes no improvement in timeliness with the introduction of rotavirus vaccine.

DTP coverage estimates are based on vaccination data from household Demographic Health Surveys (DHS)\textsuperscript{26} and the UNICEF Multiple Indicator Cluster Survey (MICS)\textsuperscript{27} that were administered in 48 countries between 1996 and 2009. To estimate coverage for countries without DHS or MICS data, overall WHO-UNICEF 2010 country-specific coverage estimates were converted into age-specific coverage rates using regression coefficients to predict lognormal curves of timeliness. These were derived from the available DHS/MICS survey data and extrapolated to countries without a survey. Timeliness was determined by WHO sub-region and adjusted for trends between the DHS/MICS survey year and 2010 using the WHO-UNICEF 2010 best estimates for DTP coverage data, drop-out rate between DTP1 and 3, the target age recommended in the country schedule, and the Gross Domestic Product per capita.\textsuperscript{28} This was done separately for DTP1 and DTP3. DTP2 timeliness assumed the average of the regression coefficients used for DTP1 and DTP3. Timeliness trajectories were weighted by the numbers of births in each country, as reported by the UN Population Division.\textsuperscript{29}

Assessment of benefits—base scenario

The number of rotavirus deaths prevented was obtained from $\lambda_{rv}\varepsilon_{rv}\rho_{rv}$, where $\lambda_{rv}$ is the number of rotavirus deaths by week of age, $\varepsilon_{rv}$ is the vaccine efficacy, and $\rho_{rv}$ is the proportion vaccinated by week of age.

Estimated numbers of country-specific rotavirus deaths ($\lambda_{rv}$) were obtained from WHO, using the 95% confidence intervals to define the triangular distributions around the point estimate (Table 1).\textsuperscript{1} Based on a WHO-sponsored review of published and unpublished studies on age-distribution of diarrhea mortality and rotavirus-associated hospitalizations by week of age, the model predicted 1-week gamma
age distributions for the first year of life and 4-week age categories thereafter for countries in different WHO regions.

Rotavirus vaccine efficacy (epsilon) against fatal rotavirus disease was estimated from clinical trials or vaccine effectiveness studies in each of the respective WHO region (Table 1). Because efficacy against rotavirus mortality could not be directly measured in the trials, efficacy estimates against the most severe rotavirus disease outcome reported in the study were applied. This is a reasonable approach given that three nationwide studies from Latin America have documented reductions in diarrhea deaths after vaccine introduction that have approximated reductions based on the efficacy of these vaccines against severe rotavirus disease. Beucase both rotavirus vaccines have performed similarly in clinical trials, the same overall efficacy was assumed for the 2-dose Rotarix and the 3-dose RotaTeq vaccine. The efficacy parameters were age-stratified (<1 year and >1 year of age) because studies have documented lower efficacy among children older than 1 year of age. Efficacy of partial vaccination (first dose) was also available from 1 country in the B&C region, and 1 country in the D-Americas region, but not for D-Asia and D&E-Africa. Thus, the point estimates for full vaccine efficacy for Asia and Africa were reduced by the same proportion as the reduction in efficacy between the full and partial series in D: Americas region. For the uncertainty analysis, the 95% confidence intervals from the respective studies were used to define the triangular distribution around the vaccine efficacy point estimates.

Assessment of risk—base scenario

Risk of intussusception has been documented after postlicensure use of Rotarix and RotaTeq in 4 different studies. Each of these studies identified an approximate 4 to 6-fold increase in risk relative to background during the first week after dose 1, a magnitude of risk that would not have been detected in the clinical trials. No effect modification of risk with age at vaccination was reported in these studies, but vaccine was largely administered on time. In 2 additional countries, no risk of
intussusception was identified after the first vaccine dose. The first, a Brazilian study, found no risk of intussusception with good precision (relative risk = 1.1; 95% CI= 0.3, 3.3). The second study, from the United States, also did not identify risk during the first week after dose 1 (relative risk = 1.2; 95% CI = 0.03, 6.8), but a risk of small magnitude similar to that detected in the other 4 studies could not be excluded in view of the wide CIs. In Brazil, a statistically significant 2-fold risk was also identified in the first week after dose 2.

To err on the side of risk, dose-specific pooled estimates of relative risk (RR) were used from each of the studies where risk of intussusception was identified (Table 1; Supplementary Table 1). The weighted average of the logarithm of the relative risk, \( \sum \log(RR_i) \omega_i / \sum \omega_i \), was used, where weight (\( \omega_i \)) for each study is the inverse of the variance computed from the reported 95% CIs. The variance of the weighted average RR is the inverse of the sum of the each weight (1/\( \sum \omega_i \)) and was used to compute the 95% CIs for the pooled risk estimate. For the uncertainty analyses, the 95% confidence intervals were used to define the triangular distribution around the RR estimates.

The average annual risk of natural intussusception was estimated from published studies. Because natural intussusception is a very rare disease, we restricted our review to studies reporting either national rates of intussusception or rates of intussusception from a minimum of 5 hospitals with known catchment population, stratified by age. The intussusception incidence in this review ranged from 18-88 per 100,000 infants. The age-distribution of intussusception in broader 3 month age-groups was similar between the different studies. However, intussusception incidence by week of age was needed for the risk-benefit analysis and was only available from the United States. Thus, to obtain intussusception incidence by week of age (\( \lambda_{ui} \)), the global intussusception incidence among infants were applied and a gamma curve was fit to intussusception surveillance data from the United States. For uncertainty analysis, parameters of the gamma curve for \( \lambda_{ui} \) were sampled from a normal distribution, assuming standard distribution is equal to 5% of the mid-parameter values.
Death caused by intussusception is uncommon in industrialized countries, occurring in < 1% of the cases. In a recently conducted national study from 16 hospitals in Mexico and 43 hospitals in Brazil (WHO group B&C), case-fatality for intussusception was 1% and 5%, respectively. One large study from 9 countries across Africa indicated an average case-fatality of about 12%. No reliable estimates of case-fatality were available for countries in D-Americas and D-Asia. Thus, the case-fatality ($\delta_{s}$) was conservatively estimated at 5% for B&C countries, 10% for D-Americas, 25% for D-Asia, and 25% for D&E-Africa. Fatality was sampled from a beta distribution, assuming standard deviation is equal to 5% of the mid parameter values to specify the upper and lower limits of $\delta_{s}$ in uncertainty analyses.

The number of intussusception deaths associated with vaccination, during the first week after dose 1 and 2, was obtained from $B\rho_{v}(\lambda_{is}RR_{i})\cdot \lambda_{is}\delta_{is}$, where $B$ is the number of births, $\rho_{v}$ is the proportion vaccinated by week of age, $\lambda_{is}$ is the intussusception incidence by week of age, $RR_{i}$ is the relative risk during the week after each dose, and $\delta_{is}$ the proportion of intussusception events that lead to death.

**Sensitivity analysis**

One-way sensitivity analysis was conducted to determine the impact on the benefit-risk ratios when assuming four conservative scenarios that would favor risk: 1) a relative increase of 20% in incidence and case-fatality of intussusception was assumed. 2) the impact of effect modification of risk by age at vaccination was explored by doubling estimates of relative risk of intussusception when dose 1 of rotavirus vaccine was administered to infants older than 14 weeks of age. 3) a scenario of low vaccine efficacy was assumed by inputting the lower 95% confidence intervals for each of the efficacy estimates. 4) the effect of a “pessimistic” situation was explored by combining all of the preceding three scenarios.

**Uncertainty analysis**

The above analyses yielded estimates of rotavirus deaths averted and intussusception deaths caused under age restricted and unrestricted vaccination strategies. A probabilistic uncertainty analysis
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was conducted to assess the potential impact of simultaneous variation each of model inputs ($\lambda_{rv}$, $\epsilon_{rv}$, $\rho_{rv}$, $\lambda_{is}$, RR) on the precision of the benefit risk estimates. The lognormal timeliness curves, gamma rotavirus and intussusception age curves were shifted by simultaneously sampling new shape, shift, and scale parameters for each run, with each parameter being sampled from a normal distribution with standard deviation equal to 5% of the original parameter value. Based on the error estimates and error distributions described for each of the model inputs, 1,000 simulations were conducted to obtain the median estimates of deaths averted and caused as well as the uncertainty ranges, defined as the 5-95 percentile, to provide an indication of the uncertainty in the estimates. All analyses were done with Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and SAS 9.2 (Cary, NC, USA).
RESULTS

In low and middle-income WHO countries (i.e., low and high child mortality stratum), about 453,000 rotavirus-associated deaths are estimated among children younger than 5 annually without a rotavirus vaccination program (Figure 1). The model projects that a rotavirus vaccination program under the current age-restricted schedule would prevent almost 35% or 156,100 of these deaths (5th–95th centiles, 110,100–201,800) if delivered at the same ages at which the DTP vaccine is currently being delivered in these countries (Table 2). Without the age restrictions, a program would prevent 44% or 199,200 deaths of all rotavirus deaths (140,700–255,400), which would represent 43,100 more deaths prevented (30,600–53,600) than with an age-restricted schedule. These additional deaths prevented under an unrestricted vaccination schedule reflect an additional 28%, 21%, 25%, and 22% of the children receiving DTP1 in the WHO B&C, D-Americas, D-Asia, and D-Africa countries, respectively, compared to the age-restricted schedule in these countries (Figure 2).

From the perspective of risk, a rotavirus vaccination program limiting vaccination to children < 14 weeks of age would cause about 288 intussusception deaths (99–688) (Table 2). A program without age restrictions would cause 605 intussusception deaths (310–1,133). Thus, a vaccination policy without any age restrictions for use of rotavirus vaccines in low and middle-income WHO countries would avert an additional 43,100 rotavirus-associated deaths and cause an additional 316 intussusception-associated deaths, compared to the current age-restricted strategy (Table 3). The median incremental benefit-risk ratio in all mortality stratum was nearly 136 lives averted for every death caused, ranging from 119-232 lives averted for every death caused across the different mortality stratum (Figure 3).

Under a scenario of effect modification of risk with age at vaccination and increased incidence and case fatality of intussusception, an unrestricted schedule would cause 641 (224–891) and 456 (304–641) excess deaths, respectively, while averting about 43,100 rotavirus deaths (30,600–53,600) (Table 3). A scenario where efficacy approximated the lower 95% CI in the clinical trials would avert an
additional 24,300 rotavirus deaths (22,200–26,500) under an unrestricted schedule. With pessimistic assumptions of high intussusception incidence and case fatality, high risk, and low efficacy, a vaccination program without age restrictions would prevent an additional 26 rotavirus deaths (24,300) for every intussusception death caused (923).
LIMITATIONS OF THE ANALYSIS

The benefit-risk estimates could be conservative and err on the side of risk for three reasons.

- Over 45 publications have documented remarkable declines in severe diarrhea and rotavirus disease, including deaths, since their introduction in national immunization programs worldwide. Many of these studies from different locations have demonstrated significant declines in unvaccinated members of the community, indicating indirect benefits of vaccination which were not accounted for in the model.\textsuperscript{13,51-53}

- It was assumed that some risk of intussusception exists in all countries worldwide, including with dose 2; however, risk of intussusception has varied by setting and robust studies in 2 large countries have not identified risk after dose 1.\textsuperscript{15,24}

- Eve in the base scenario, high rates of intussusception case-fatality were assumed in all WHO regions, about two-fold higher than those reported in the literature.

The benefit risk ratios might be inflated due to several factors.

- The base scenario assumed that the relative risk of intussusception relative to background does not increase with age. After the withdrawal of RotaShield, a debate persisted with regard to whether the relative risk of intussusception might have been higher for infants vaccinated beyond 14 weeks of age.\textsuperscript{17,18,20} While limited data from an evaluation in Mexico does not suggest effect modification of risk for current vaccines by age,\textsuperscript{15} we incorporated a scenario of increased risk with age at vaccination which indicated that vaccination would avert 66 rotavirus deaths for each excess intussusception death.

- The model might have overestimated vaccine coverage among children at the highest risk of dying from rotavirus as these might be the hardest to reach, thus inflating the mortality benefits of vaccination relative to the risks in our model. However, data from Mexico and Brazil, where
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substantial reductions in diarrhea deaths have occurred in all regions of both countries after the introduction of vaccine,\textsuperscript{11,12,34} provides some reassurance that vaccine is reaching those at the highest risk of dying.

- Limited data exist on the background intussusception incidence and case-fatality in low income settings of Africa and Asia. Thus, the base scenario used case-fatality estimates that were 2-fold higher than the estimates published in the literature. In the sensitivity analysis, intussusception incidence and case-fatality were further increased by 20%.

- Data on intussusception risk after vaccination is from middle and high income settings and no studies have assessed risk of intussusception in Africa and Asia. Data on differences in risk of intussusception after rotavirus vaccine in Mexico and Brazil suggest that factors interfering with rotavirus vaccine take (perhaps oral polio vaccine) might be associated with a reduced intussusception risk. Thus, in low-income settings of Africa and Asia, where rotavirus vaccine take is significantly lower than higher socioeconomic settings (where data on intussusception exist), risk of intussusception would not be expected to be greater.
SUMMARY

In summary, using emerging evidence on rotavirus and intussusception mortality and rotavirus vaccine efficacy, safety, and coverage, the model demonstrates the advantages and disadvantages of the age restrictions for rotavirus vaccine. The model estimated that a rotavirus vaccine schedule without any age restrictions would avert an additional 136 rotavirus deaths for each excess intussusception death caused by vaccination in low and middle income countries. These additional deaths reflect an additional 21%-25% children who would potentially be eligible for rotavirus vaccine, and overall would lead to a net 42,800 additional lives saved.
Figure 1: Age distribution of rotavirus deaths among children under 5, by WHO mortality stratum
Figure 2: DTP dose 1 vaccine coverage by week of age based on the Demographic Health Surveys and UNICEF Multiple Indicator Cluster Surveys, by WHO mortality stratum
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Figure 3 (Panels 1-5): Relationship between estimated number of rotavirus gastroenteritis deaths avoided versus intussusception deaths caused by rotavirus vaccination.*

*From 1000 simulations, each dot represents a potential estimate of rotavirus deaths prevented (y-axis) versus intussusception deaths caused (x-axis) given the uncertainty on the parameters in the model: rotavirus mortality, vaccine efficacy, vaccine coverage, intussusception incidence, intussusception risk from vaccine, and intussusception fatality.
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Panel 1: Global

Panel 2: B&C countries

Panel 3: D-Americas

Panel 4: D&E-Africa

Panel 5: D-Asia
Table 1: Vaccine efficacy estimates for WHO high mortality stratum regions, by outcome

<table>
<thead>
<tr>
<th>WHO mortality stratum</th>
<th>Estimate (lower bound, upper bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B &amp; C</td>
</tr>
<tr>
<td>Rotavirus mortality</td>
<td>26,700 (24,000-29,000)</td>
</tr>
<tr>
<td>Vaccine efficacy against RV deaths</td>
<td></td>
</tr>
<tr>
<td>First year of life</td>
<td>97% (84-100)</td>
</tr>
<tr>
<td>&gt; 1 year of life</td>
<td>97% (84-100)</td>
</tr>
<tr>
<td>Partial series</td>
<td>51% (26-67)</td>
</tr>
<tr>
<td>Relative risk of IS</td>
<td></td>
</tr>
<tr>
<td>Dose 1</td>
<td>5.5</td>
</tr>
<tr>
<td>Dose 2</td>
<td>1.7</td>
</tr>
<tr>
<td>Dose 3</td>
<td>1</td>
</tr>
<tr>
<td>IS incidence (range)</td>
<td>53.3 (17.7-88.2)</td>
</tr>
<tr>
<td>IS case fatality</td>
<td>5% (4-6)</td>
</tr>
</tbody>
</table>

RV = rotavirus; IS = intussusception

* Because vaccine efficacy against RV deaths was not available, the model input was efficacy against RV gastroenteritis of severity >=15 on 20 point Vesikari clinical scoring system, where >=11 denotes "severe" diarrhea and >=15 denotes "very severe" diarrhea.
<table>
<thead>
<tr>
<th>Vaccination strategy</th>
<th>Rotavirus deaths averted (95% CI)</th>
<th>Intussusception deaths caused (95% CI)</th>
<th>Benefit to Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age restriction†</td>
<td>No age restriction</td>
<td>Excess</td>
</tr>
<tr>
<td><strong>B &amp; C countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>17,100</td>
<td>21,000</td>
<td>3,900</td>
</tr>
<tr>
<td>5th percentile</td>
<td>14,700</td>
<td>18,300</td>
<td>3,600</td>
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<tr>
<td>95th percentile</td>
<td>19,500</td>
<td>23,500</td>
<td>4,000</td>
</tr>
<tr>
<td><strong>D: Americas</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2,100</td>
<td>2,600</td>
<td>500</td>
</tr>
<tr>
<td>5th percentile</td>
<td>1,500</td>
<td>1,800</td>
<td>300</td>
</tr>
<tr>
<td>95th percentile</td>
<td>2,700</td>
<td>3,300</td>
<td>600</td>
</tr>
<tr>
<td><strong>D: Asia</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>58,300</td>
<td>78,400</td>
<td>20,100</td>
</tr>
<tr>
<td>5th percentile</td>
<td>38,200</td>
<td>51,200</td>
<td>13,000</td>
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<tr>
<td>95th percentile</td>
<td>77,800</td>
<td>103,700</td>
<td>25,900</td>
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<tr>
<td><strong>D: Africa</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>78,900</td>
<td>97,300</td>
<td>18,400</td>
</tr>
<tr>
<td>5th percentile</td>
<td>55,200</td>
<td>69,000</td>
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<tr>
<td>95th percentile</td>
<td>102,100</td>
<td>124,700</td>
<td>22,600</td>
</tr>
<tr>
<td><strong>All stratum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>156,100</td>
<td>199,200</td>
<td>43,100</td>
</tr>
<tr>
<td>5th percentile</td>
<td>110,100</td>
<td>140,700</td>
<td>30,600</td>
</tr>
<tr>
<td>95th percentile</td>
<td>201,800</td>
<td>255,400</td>
<td>53,600</td>
</tr>
</tbody>
</table>

* Estimates of rotavirus deaths averted and intussusception deaths caused are based on efficacy, risk, case-fatality parameters in Table 1. Vaccination coverage is based on diphtheria-tetanus-pertussis (DTP) vaccination rates from household Demographic Health Surveys and UNICEF Multiple Indicator Cluster Surveys.

† Age restriction denotes dose 1 administration by 15 weeks and the full series by 32 weeks of age
Table 3. Additional lives saved versus deaths caused by loosening the age restrictions for rotavirus vaccines in WHO high and very high mortality stratum

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Lives saved</th>
<th>Deaths caused</th>
<th>Net Benefits</th>
<th>Benefit/Risk ratio**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base*</td>
<td>43,100 (30,600, 53,600)</td>
<td>316 (211, 445)</td>
<td>42,800 (30,400, 53,200)</td>
<td>136 (69, 254)</td>
</tr>
<tr>
<td>Base + higher intussusception rate and case-fatality†</td>
<td>43,100 (30,600, 53,500)</td>
<td>456 (304, 641)</td>
<td>42,600 (30,300, 52,900)</td>
<td>95 (48, 176)</td>
</tr>
<tr>
<td>Base + increase relative risk with age at dose 1‡</td>
<td>43,100 (30,600, 53,500)</td>
<td>641 (224, 891)</td>
<td>42,500 (30,400, 52,600)</td>
<td>67 (34, 239)</td>
</tr>
<tr>
<td>Base with low vaccine efficacy</td>
<td>24,300 (22,200, 26,500)</td>
<td>316 (211, 445)</td>
<td>24,000 (22,000, 26,100)</td>
<td>77 (50, 126)</td>
</tr>
<tr>
<td>Pessimistic§</td>
<td>24,300 (22,200, 26,500)</td>
<td>923 (596, 1283)</td>
<td>23,400 (21,600, 25,200)</td>
<td>26 (17, 44)</td>
</tr>
</tbody>
</table>

* Assumes point estimates for vaccine efficacy and intussusception risk and case-fatality estimates presented in Table 1
† Assumes 20% relative increase in incidence and case-fatality of intussusception compared to base scenario
‡ Assumes a doubling of relative risk of vaccine associated risk of intussusception among children receiving dose 1 beyond 15 weeks of age
§ Pessimistic scenario assumes base scenario with: 1) 20% increase in background incidence and case-fatality of intussusception compared to base scenario; 2) doubling of relative risk among children vaccinated with dose 1 beyond 15 weeks of age; and 3) lower 95% confidence limit for vaccine efficacy
### Supplemental Table 1: Pooled estimates of risk after dose 1 of rotavirus vaccine

<table>
<thead>
<tr>
<th>Country</th>
<th>Ref</th>
<th>Vaccine</th>
<th>Relative risk</th>
<th>lower 95% limit</th>
<th>upper 95% limit</th>
</tr>
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<tbody>
<tr>
<td><strong>DOSE 1</strong></td>
<td></td>
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<tr>
<td>Australia</td>
<td>9</td>
<td>pentavalent</td>
<td>3.9</td>
<td>1.5</td>
<td>9.9</td>
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<tr>
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<td>monovalent</td>
<td>4.1</td>
<td>1.3</td>
<td>13.5</td>
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<td>5.3</td>
<td>3</td>
<td>9.3</td>
</tr>
<tr>
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<td>monovalent</td>
<td>6.5</td>
<td>4.2</td>
<td>10.1</td>
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<tr>
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<td>monovalent</td>
<td>5.0</td>
<td>1.7</td>
<td>14.3</td>
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<tr>
<td><strong>Pooled estimate</strong>*</td>
<td></td>
<td></td>
<td><strong>5.5</strong></td>
<td><strong>4.1</strong></td>
<td><strong>7.5</strong></td>
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<td><strong>DOSE 2</strong></td>
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<td>monovalent</td>
<td>1.8</td>
<td>0.9</td>
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<td>2.6</td>
<td>1.3</td>
<td>5.2</td>
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<tr>
<td><strong>Pooled estimate</strong>*</td>
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<td></td>
<td><strong>1.7</strong></td>
<td><strong>1.2</strong></td>
<td><strong>2.4</strong></td>
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</tbody>
</table>

* We used the weighted average of the logarithm of the relative risk, \( \sum \log(\text{RR}_i) \omega_i / \sum \omega_i \), where weight (\( \omega_i \)) for each study is the inverse of the variance computed from the reported 95% CIs.\(^{(ref 60)}\) The variance of the weighted average RR is the inverse of the sum of the each weight (1/\( \sum \omega_i \)) and was used to compute the 95% CIs for the pooled risk estimate.
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