Modeling the impact of geographic targeting of rotavirus vaccination in India on rotavirus diarrhea mortality in children under 5 years of age

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Abstract

Modeling the impact of geographic targeting of rotavirus vaccination in India on rotavirus diarrhea mortality in children under 5 years of age

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Background:

Rotavirus causes around 329,000 diarrhea deaths annually around the world, almost a third of which are in India. The rotavirus vaccine is a relatively recent but important vaccine; an India-manufactured rotavirus vaccine was licensed for use in India in 2014. A total of 15 out of 31 Indian states and union territories have substantial rollout of this vaccine, while the remainder are just beginning to deploy the vaccine as of 2019. Targeting vaccination deployment to areas based on disease burden has been found to be more cost-effective than population-based deployment in Sub-Saharan Africa; this study seeks to explore this concept of geographic targeting of vaccinations in India. Quantifying the potential impact of various rotavirus vaccination targeting strategies on mortality in the states and union territories of India from 2020-2040 is key to determining the best strategies for vaccine rollout as these states begin to scale-up coverage.

Methods and Findings:

The objective of this study was to simulate different vaccination scenarios and quantify their impact on mortality, compared to a reference scenario based on historical vaccine coverage. The reference scenario is the mean of the observed rotavirus vaccine scale-up in the 15 states that have already introduced the vaccine in substantial numbers. The other three scenarios add the same number of vaccines on top of the reference scenario, but distributed in different ways. One scenario simply distributes the extra vaccines according to population in each state (population-based), one distributes based on diphtheria-tetanus-pertussis (DTP3) vaccine coverage (target DTP3 coverage), and the other distributes based on rotavirus diarrhea mortality rate levels (target rotavirus mortality). These vaccine scenarios were used to estimate under-5 rotavirus diarrhea mortality rates from 2020-2040 while holding other drivers of health to recent trends. In this study, approximately 163 million more vaccinations than in the reference scenario were distributed in each of the targeting scenarios. A total of 151,001 (59,343, 302,650) under-5 deaths from 2020-2040 were estimated in the reference scenario, compared to 125,050 (48,272, 251,358) in the population-based scenario, 119,260 (45,686, 240,953) in the DTP3 targeting scenario, and 116,152 (44,278, 234,991) in the rotavirus targeting scenario. The highest number of averted deaths is most likely to be achieved by using the strategy of vaccine distribution according to past rotavirus diarrhea mortality.

Conclusions:

This study suggests that geographic targeting based on historical disease burden would lower the number of deaths from rotavirus diarrhea seen in India from 2020-2040. As India progresses in advancing rotavirus vaccination, it is key to consider the distribution strategy of these vaccines. Targeting based on disease burden could lower the number of deaths seen from rotavirus diarrhea by thousands compared to distributing according to population. The largest reduction in deaths is seen in the next few years, making swift action in high-burden areas essential.

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Thank you to my committee, who have helped to guide me through an extremely complicated project across many inputs and methods. The expertise on everything from statistical details to vaccination knowledge was invaluable.

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Specific Aims:

1) Create future rotavirus vaccine coverage scenarios based on different geographic targeting strategies in states and union territories of India from 2020-2040 to characterize current trends in subnational vaccine deployment and possible alternative scenarios
2) Determine the impact of the different rotavirus vaccine coverage scenarios on the number of under-5 deaths from rotavirus diarrhea in the states and union territories of India

Background/Significance:

Rotavirus caused around 185,000 diarrhea deaths in children under 5 years of age worldwide in 2017, and 29,000 of these were in India (Roth et al.). India has the highest number of deaths from rotavirus in the world, in addition to high rates of hospitalization and outpatients resulting from infection. Rotavirus remains the leading etiology of diarrheal deaths in India and many other places, despite the availability of a vaccine (Roth et al.). The vaccine is on the WHO list of recommended national routine vaccination programs, especially for areas with high levels of rotavirus such as India. (World Health Organization). India licensed the specific vaccine "Rotavac" for use in 2014, which is largely manufactured for India by Bharat Biotech International. Fifteen of the 31 states and union territories of India have rolled out the vaccine, while the other half are starting to introduce substantial coverage programs as of the end of 2019 (GBD 2017 Risk Factor Collaborators). These states that are just starting to deploy the vaccine are the focus of this work, as there are many ways that the vaccines could be distributed as these states begin to scale up coverage.

Tate et al. estimated that India spent around 41-72 million USD on medical costs from rotavirus in 2009. This does not take into account the indirect and societal costs around the deaths and nonfatal burden of rotavirus, which would create an even higher burden if accounted for. When looking at India's administration of a domestically-produced rotavirus vaccine, Rose et al. found that the cost per rotavirus DALY averted was around $56 USD, which is considered highly cost-effective as it is less than the GDP per capita for India (Robinson). Additionally, most of the benefit in mortality reduction was found in those directly receiving the vaccine, rather than through effects of herd immunity. This study looked at nationwide vaccination, but it may be possible to achieve greater cost-effectiveness through targeted vaccination.

In order to optimize public health impact of immunization programs, Lee et al. recommended targeted distribution of vaccines based on a variety of demographic factors. They analyzed the impact of geographic targeting in sub-Saharan Africa for the oral cholera vaccine and found that targeting vaccine distribution areas by historical cholera burden was more effective than population-based distribution of cholera vaccines (i.e. distributing according to population). Targeting cholera vaccine distribution based on high levels of sanitation risk was also more effective than the population-based distribution. This evidence suggests that targeted strategies would be useful for other vaccines as well as locations outside of sub-Saharan Africa. As India continues scaling up coverage of rotavirus vaccine in the states and union territories that are beginning to introduce the vaccine, it is key to determine what strategy of vaccine deployment would be most effective given limited resources. This paper aims to address the question of how best to geographically target vaccines in India by comparing different vaccine coverage scenarios: reference (vaccination coverage trends continue according to expected scale-up), population-based scale-up according to population size (increase vaccination levels compared to reference across all states by population), targeting high burden areas (focusing on increasing vaccination levels in states with high rotavirus burden), and targeting low diphtheria-tetanus-pertussis vaccine (DTP3) coverage areas (focusing on increasing vaccination levels in states with low current DTP3 vaccine coverage). While forecasting methods often make strong assumptions about other drivers of health based, such as holding them constant or having a simple linear increase, here the framework from Foreman et al. (2018) is used to estimate mortality while holding other risk factors and drivers of health to change based on recent trends to allow for more accurate representation of what would be expected for these drivers in the future.

Methods:

Data:

This analysis required five types of inputs: (1) rotavirus vaccine coverage by Indian state or union territory; (2) estimates of rotavirus vaccine effectiveness; (3) rotavirus under-5 mortality rates; (4) other drivers of health and risk factors from 1990 to 2040; and (5) population to 2040.

Vaccine coverage by state and effectiveness is taken from GBD 2017 estimates (GBD 2017 Risk Factor Collaborators). The methods for these estimates are described in detail in Lozano et al. In brief, data from household-level surveys and administrative reports of immunization coverage are extracted for all available locations. After adjusting for administrative bias, trends are estimated using spatiotemporal Gaussian process regression to synthesize point estimates from the various data sources so that a single complete time series is derived for each vaccine. Rotavirus efficacy is also estimated via a meta-review process described in Traeger et al. These methods allow strengths of the various data sources to be included while accounting for missing data and inconsistencies between the various sources.

Rotavirus diarrhea mortality rates are also taken from GBD 2017 estimates (Troeger et al.). This mortality is modeled as an etiology of overall diarrhea deaths. Each diarrheal etiology is attributed to overall diarrhea using a counterfactual approach. The relative reduction in diarrhea mortality if there was no exposure to a given etiology (population attributable fraction, or PAF) is calculated from the proportion of severe diarrhea cases that are positive for each etiology. These PAFs can add up to over 100% of total diarrhea mortality, as there may be multiple pathogens causing diarrhea. This is estimated via a multiplication of the proportion of severe cases times one minus the inverse of the odds ratio of diarrhea given the presence of the pathogen. The odds ratio is calculated via a mixed effects conditional logistic regression model for ages under 1 year and 1-4 years. The proportion is then modeled using the meta-regression tool DisMod-MR to estimate the proportion of positive diarrhea cases by etiology for each location-year-age-sex combination. The PAF is then multiplied by the overall diarrhea mortality (estimated via the Cause of Death Ensemble modelling platform CODEm (Foreman et al. *Modeling Causes*), including a rotavirus vaccine covariate) to obtain estimates of the mortality rate for each diarrheal etiology, including rotavirus.

The framework for mortality forecasts utilizes sociodemographic index (SDI) as the primary driver of health to account for current demographic trends, and assumes that similar trends in the underlying mortality will continue given that current trends in demographic factors continue. Sociodemographic index is a summary index of lag-distributed income, mean years of education, and total fertility rate.

Past estimates of SDI are derived from GBD 2017 methodology (Roth et al., Lozano et al.), while forecasts use the framework of Vollset et al. Ensemble modeling is used in the creation of LDI forecasts, where demographic indicators are used in conjunction with time series terms (autoregressive terms, autocorrelated residuals) to capture recent trends that are projected forward. Out-of-sample comparisons then select best-performing models, whose estimates are averaged to obtain final estimates. Education forecasts used a weighted annualized-rate-of-change method to project past rates of change forward in to the future. Age-specific fertility rates (ASFR) were modelled using forecasted completed cohort fertility by age 50. The implied ASFR using a series of cohort age-specific models was then calculated. The geometric mean of these three measures is then taken after scaling them to be on the same index. The result of the geometric mean is SDI. More details on the methodology can be found in Vollset et al.

Information on other risk factors was included via population-attributable-fractions (PAFs) of those risk factors relating to rotavirus diarrhea mortality. PAFs are the proportional reduction in population disease or mortality that would occur if exposure to a risk was reduced to zero, which is essentially a measure of how much mortality of diarrhea rotavirus is due to a given risk factor and could be eliminated if that risk factor was changed to an ideal level (theoretical minimum risk exposure level). The PAF is a transformation of the summary exposure value (SEV), which is a measure taking both the exposure of a population to a risk factor and the severity of the risk's contribution to disease burden into account. The SEVs were forecasted using an annual change in the logit of the SEV for each location-age-sex-year combination. The annualized rate of change was then calculated via the weighted mean of the first difference over time, where the weights are determined by a recency-weighting parameter (chosen via out-of-sample comparisons). All risk factors for diarrhea rotavirus other than lack of rotavirus vaccination were unsafe water source, unsafe sanitation, no access to handwashing facility, non-exclusive breastfeeding, low birth weight, short gestation, child stunting, child underweight, vitamin A deficiency, child wasting, zinc deficiency, and discontinued breastfeeding. More details on the risk factor methodology can be found in Foreman et al. (2018).

Population estimates used the methodology of Vollset et al. In brief, this means using a cohort-component method of projection to project population at time t+1 from time t using migration and a Leslie matrix (which is a discrete, age-structured matrix used to increment population growth). Each time point represented a one-week age interval in order to capture changes in the youngest age groups more accurately than common one-year or five-year time steps. Note that for all of the inputs going into the future except for the vaccines (described in the next section), the "reference" scenario is used, which represents the expected trends in the future assuming that past trends continue. Other scenarios are not used so that the only differences between the scenarios in this work are due to the differences in vaccine targeting.

Scenarios:

This analysis uses current trends in the 15 states that have introduced the rotavirus vaccine before 2019 to determine an average rate of coverage scale-up. The average scale-up is used as a reference scenario in the states and union territories that introduced in 2019. In other words, the expected scale-up of the newly-introducing states and union territories is equal to the average scale-up of the 15 states introducing before 2019. From this, an envelope of excess vaccinations was calculated to determine a set amount of vaccines to distribute in each of the other three scenarios (population targeting, DTP3 coverage targeting, and rotavirus mortality targeting). These other three scenarios therefore all have the same amount of vaccines to distribute, but do so in different ways to determine the impact of different targeting strategies.

To determine the reference scenario, it is assumed that the scale-up of rotavirus vaccine coverage in the newly-introducing states will be the mean of the scale-up in the 15 states that have introduced before 2019. The 15 states that introduced before 2019 have their scale-up curves of vaccination forecasted via spatio-temporal Gaussian process regression using lag-distributed income as a covariate, where the dependent variable is the ratio of rotavirus to diphtheria-tetanus-pertussis vaccine (DTP3). DTP3 is used as it is a vaccine that has been introduced worldwide and is in most vaccination programs, thus providing a good indicator for the overall strength of the vaccine distribution system of a given location. DTP3 forecasts are made via a simple linear model in log space with sociodemographic index as the covariate. Rotavirus forecasts in these 15 states thus depend on 1) projected scale-up relative to DTP3 and 2) projected changes in DTP3 coverage based on SDI. The mean of these combined past and forecasted scale-up curves is used as the reference scenario for the half of states and union territories that are just beginning to introduce, with the introduction date set to 2020 for these locations.

The second issue of what number to increase coverage by beyond the reference scenario is captured via the envelope of excess vaccinations. This envelope represents the total number of complete rotavirus vaccination series that could be expected beyond reference if funding for scale-up was increased (such as via supplementation from Gavi or other entities). To calculate this envelope, the fastest scale-up observed in the earlier-introducing states is used as a "best-case" scenario for the half of states that are just beginning to introduce. The total number of vaccines used in the reference scenario is subtracted from the total number of vaccines used in this "best-case" scenario and then multiplied by a scale factor of 0.7 to obtain the envelope of excess vaccinations. The scale factor is used to reduce the number of vaccinations to a more plausible amount, as increasing coverage in all states to the fastest scale-up would be unreasonable. The envelope of excess vaccinations is used as a national bound on the number of vaccines that can be added beyond reference in the three additional scenarios; each non-reference scenario has the same number of vaccines to add on top of reference, but each scenario distributes them among the states differently.

Reference scenario:

The reference scenario represents vaccination coverage that follows recent trends, as described above. The states that are starting to introduce rotavirus vaccination all have the same scale-up in the reference scenario, which is the mean scale-up of the states that have introduced rotavirus vaccination earlier. It is worth noting that for the states that have introduced rotavirus vaccination earlier, the coverage across all four scenarios is the same (based on the spatio-temporal Gaussian process regression described previously).

Target high rotavirus mortality scenario:

For this scenario, states are targeted based on their rotavirus mortality rates in 2017. The state with the highest mortality is scaled-up to the fastest observed scale-up rate from the Indian states that introduced rotavirus vaccination earlier. The number of vaccines used by this state is then subtracted from the envelope of excess vaccinations. This is repeated for the state with the next highest rotavirus mortality in 2017 and continues down the list until the envelope would be depleted by introducing in another state. The increase in coverage for this last state is increased by an amount such that the envelope of excess vaccinations is not exceeded (i.e. fastest scale-up minus mean scale-up all multiplied by the scale factor to reduce the number of vaccinations across years to the required level).

Target low DTP3 coverage scenario:

The methods for this scenario are the same as those for targeting high rotavirus mortality, except that the order of states is determined by the lowest DTP3 coverage in 2017.

Population-based scenario:

The envelope of excess vaccinations is distributed to the newly-introducing states in proportion to their population. All states and union territories are thus scaled up to the same coverage percentage in each year.

Mortality:

Mortality results utilize the framework of Foreman et al (2018). After future coverage estimates are generated, these will be turned into a summary exposure value (SEV) by taking one minus the coverage percentage (as a decimal). The SEV is defined as a population's exposure to a risk factor that takes into account the extent of exposure by risk level and the severity of that risk's contribution to disease burden. The SEV is bounded by 0 and 1. For a binary risk factor (such as vaccine coverage, where a person either has complete coverage or does not) the SEV is equivalent to the prevalence. These SEVs for each scenario will then be converted into population attributable fractions (PAFs), which are the proportion of cases that are attributed to a given risk factor (or group of risk factors). In this case, that would be if the "lack of vaccine coverage" SEV was reduced to zero, i.e. vaccine coverage was increased to 100%. The PAF for a given risk-cause combination is defined in Equation 1:

$$\mathrm{PAF}_{rc} = \frac{\mathrm{SEV}_{rc}(\mathrm{RR}_{\mathrm{max}} - 1)}{1 + \mathrm{SEV}_{rc}(\mathrm{RR}_{\mathrm{max}} - 1)}$$

Equation 1: PAF defined from summary exposure value and relative risk

where RR_{max} is the relative risk of lack of rotavirus vaccination on rotavirus diarrhea mortality rate; notably, the relative risk is zero for those age groups above age 5 as the vaccine is primarily effective in reducing under-5 mortality. The PAF for rotavirus vaccine is then combined with the other risk factor PAFs for rotavirus (all held to the reference scenario) via the following equation:

$$\mathrm{PAF}_c = 1 - \prod_{j \in R} \left[1 - \mathrm{PAF}_{rc} \prod_{i \in R} (1 - \mathrm{MF}_{jic}) \right]$$

Equation 2: Total PAF for a given cause defined from the individual cause-risk PAFs and mediating factors.

where MF_{jic} would be the mediating factors; however, there are no mediating factors for risk factors of rotavirus diarrhea, so it becomes a simple multiplication across the cause-risk specific PAFs (PAF_{rc}). This total PAF for rotavirus is then transformed into a scalar, which is a choice about how to incorporate risk attribution into mortality rates, and is defined as:

$$S_c = \frac{1}{1 - m_c^A / m_c^T} = \frac{1}{1 - \mathrm{PAF}_c}$$

Equation 3: Scalar defined from risk-attributable mortality and total mortality, which is also the PAF.

where m_c^A represents the risk-attributable mortality for rotavirus and m_c^T represents the total mortality for rotavirus diarrhea. This scalar is multiplied by the forecasted underlying mortality rate to obtain total rotavirus mortality. Underlying mortality is obtained via the mixed-effects model described in Foreman et al (2018). Finally, a random walk model with attenuated drift is run on the residuals of the results of the mixed-effects model combined with the scalar in order to incorporate information about residual trends. This results in four scenarios for the mortality rate from 2020-2040 for under-5 age groups where the differences between the scenarios are due only to the differences in vaccination coverage.

Results:

Vaccine scenarios:

The total envelope of excess vaccinations calculated from 2020-2040 was 63,467,852 complete rotavirus vaccination series. The states targeted by the DTP3 scenario were Uttar Pradesh, Gujarat, Maharashtra, Karnataka, and Bihar, while the states targeted by the rotavirus mortality scenario were Bihar, Uttar Pradesh, Jharkhand, Chhattisgarh, Punjab, Gujarat, Uttarakhand, and Telangana. The number of complete rotavirus vaccination series delivered from 2020-2040 in the 16 states and union territories can be seen in Table 1:

	Reference	**Target High Rotavirus**	**Target Low DTP3**	**Population-based**
Bihar	47,843,997	58,029,744.8	56,979,025.6	54,974,020.5
Chhattisgarh	7,922,561	9,685,856.6	7,922,560.7	9,156,867.8
Delhi	3,697,338	3,697,338.2	3,697,338.2	4,268,363.1
Goa	240,321	240,321.2	240,321.2	277,461.0
Gujarat	16,294,549	19,889,390.5	19,889,390.5	18,810,937.9
Jammu and Kashmir	3,774,938	3,774,938.0	3,774,938.0	4,337,903.3
Jharkhand	10,683,086	13,040,925.7	10,683,086.1	12,333,573.9
Karnataka	12,219,181.8	12,219,181.8	14,970,992.4	14,145,449.2
Kerala	6,805,676.0	6,805,676.0	6,805,676.0	7,841,551.3
Maharashtra	22,610,373.8	22,610,373.8	27,671,937.1	26,153,468.1
Punjab	5,696,909.1	6,957,438.7	5,696,909.1	6,579,279.8
Telangana	7,031,483.0	7,837,710.0	7,031,483.0	8,149,014.1
Union Territories other than Delhi	597,832.3	597,832.3	597,832.3	692,022.4
Uttar Pradesh	73,421,953.9	89,610,227.8	89,610,227.8	84,753,745.6
Uttarakhand	2,346,675.5	2,866,992.6	2,346,675.5	2,710,897.5
West Bengal	17,877,955.9	17,877,955.9	17,877,955.9	20,697,661.5

Table 1: Number of complete rotavirus vaccination series distributed from 2020-2040 in each scenario. Shading represents the increase from the reference scenario; more shaded indicates higher number of complete vaccination series than the reference scenario and lightest shading indicates the same number of complete vaccinations as the reference scenario.

Note that more states were targeted in the rotavirus mortality scenario due to the lower average population of these states. This results in the vaccination coverage scenarios seen in Figure 1.

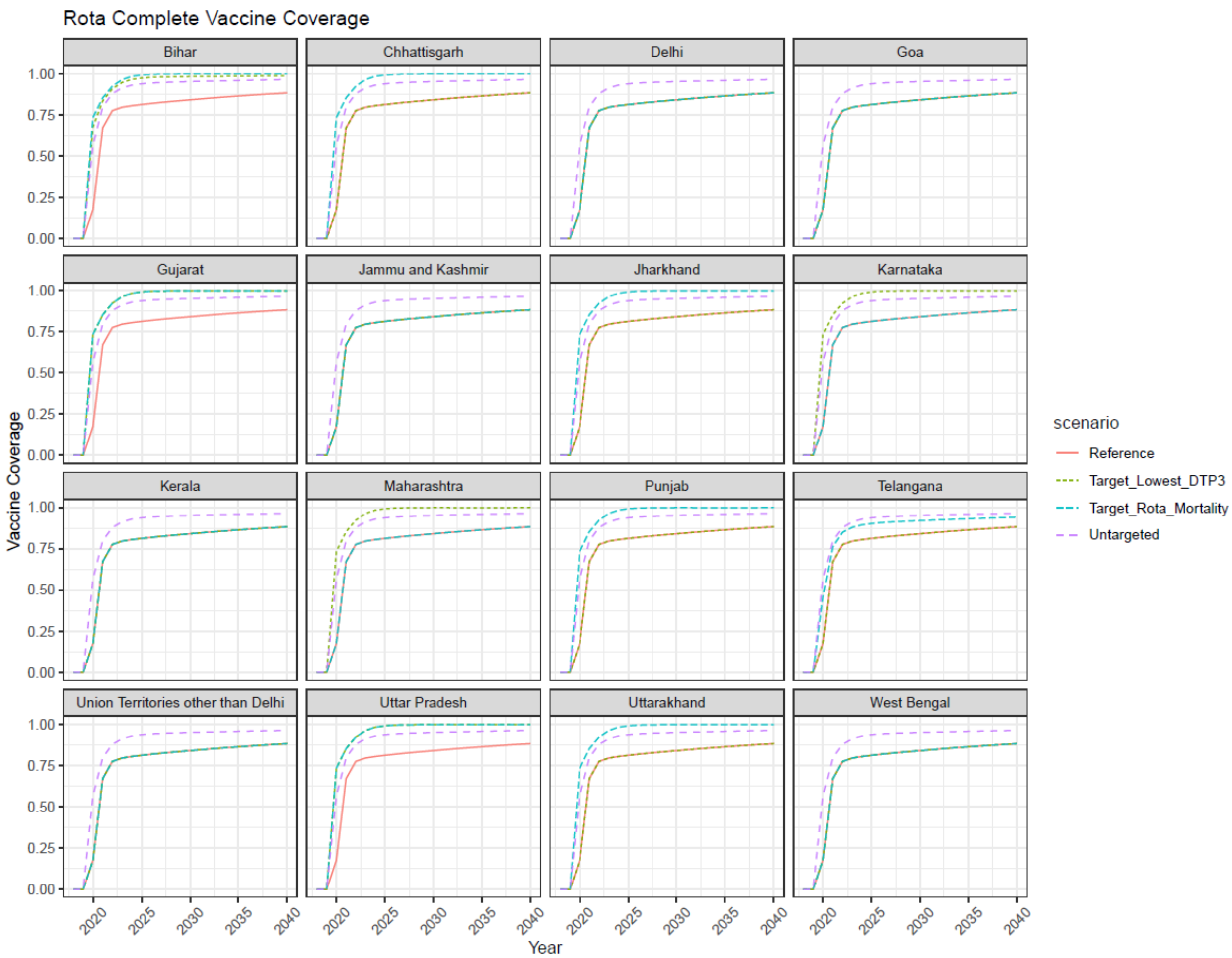

Figure 1: Vaccination coverage in the 16 states and union territories of India that are just beginning to introduce rotavirus vaccination. One represents 100% coverage, while zero represents 0% coverage.

From Figure 1 it can be seen that the reference scenario is the same across all states, as is the population targeting scenario. When states are not targeted in a scenario, they overlap with reference (e.g. Uttarakhand is not targeted in the DTP3 targeting scenario, and therefore the DTP3 scenario coverage overlaps the reference scenario). In Bihar, the coverage for the DTP3 targeting scenario is slightly lower than the coverage for the target rotavirus mortality scenario. This is due to the fact that Bihar was the last state that the DTP3 scenario was able to target before reaching the envelope of excess vaccinations, and therefore had to be scaled down slightly so as not to exceed the envelope.

Mortality:

The vaccine scenarios created resulted in the national under-5 (U5) mortality rate for rotavirus diarrhea in India seen in Figure 2. Mortality is highest in the reference scenario, while it is lowest in the rotavirus mortality targeting scenario. Both the rotavirus mortality targeting scenario and the DTP3 coverage targeting scenario resulted in lower mortality nationwide than the population-based scenario.

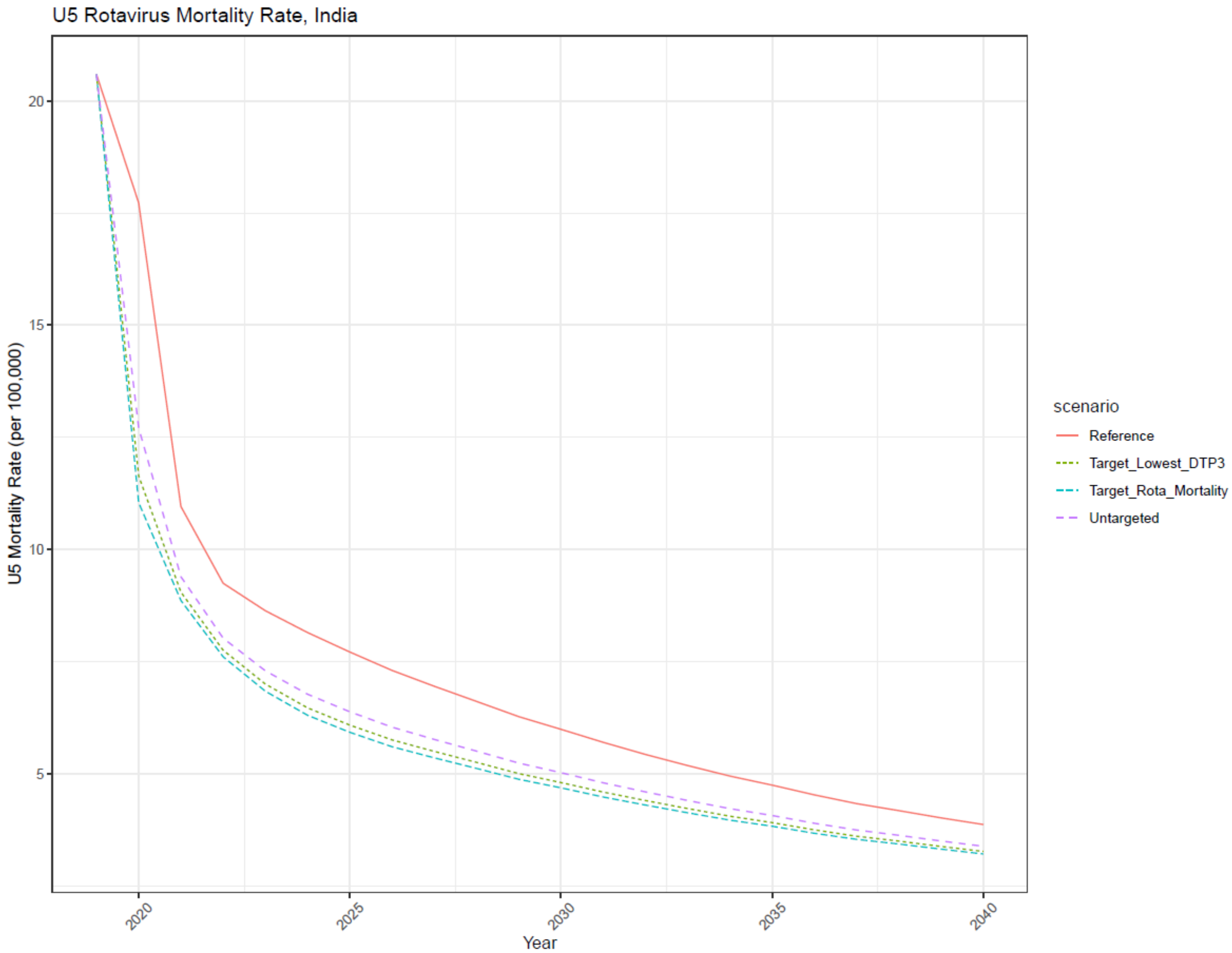

Figure 2: Under-5, all-sex rotavirus mortality rate for India from 2019-2040 for the four vaccine coverage scenarios.

This can be further seen in Figure 3, which breaks down the mortality rate by state and union territory. Bihar and Uttar Pradesh have the highest mortality rates overall, followed by Jharkhand. The effect of the slightly higher coverage in Bihar for the rotavirus mortality targeting scenario described in the previous section can be seen in the slightly lower mortality rate in Bihar for the rotavirus mortality targeting scenario as compared to the DTP3 targeting scenario.

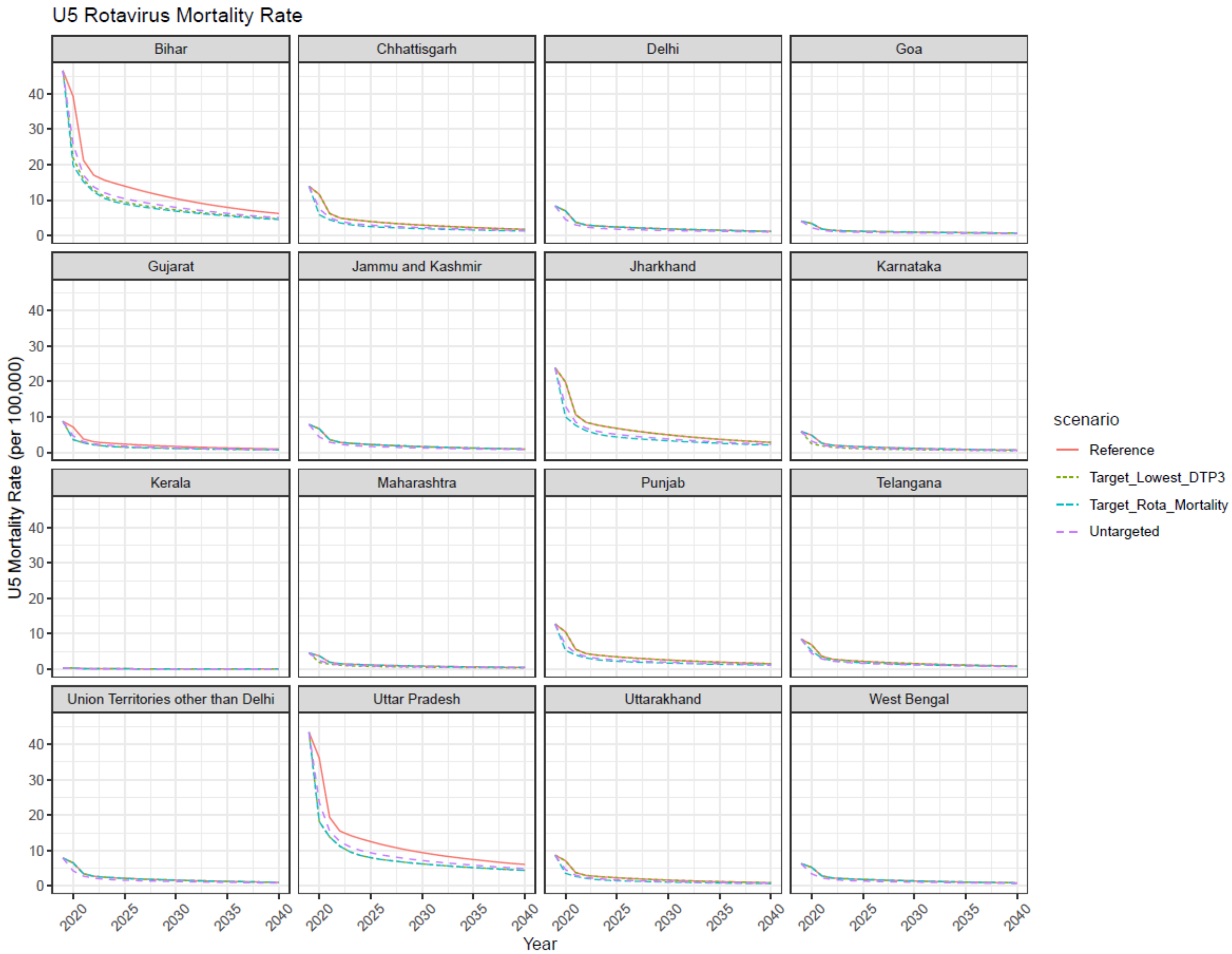

Figure 3:Under-5, all-sex rotavirus mortality rate for states and union territories of India for the four vaccine coverage scenarios.

Looking at it a different way, the amount of deaths averted as compared to the reference scenario is highest in the rotavirus mortality targeting scenario and lowest in the population-based scenario (Figure 4).

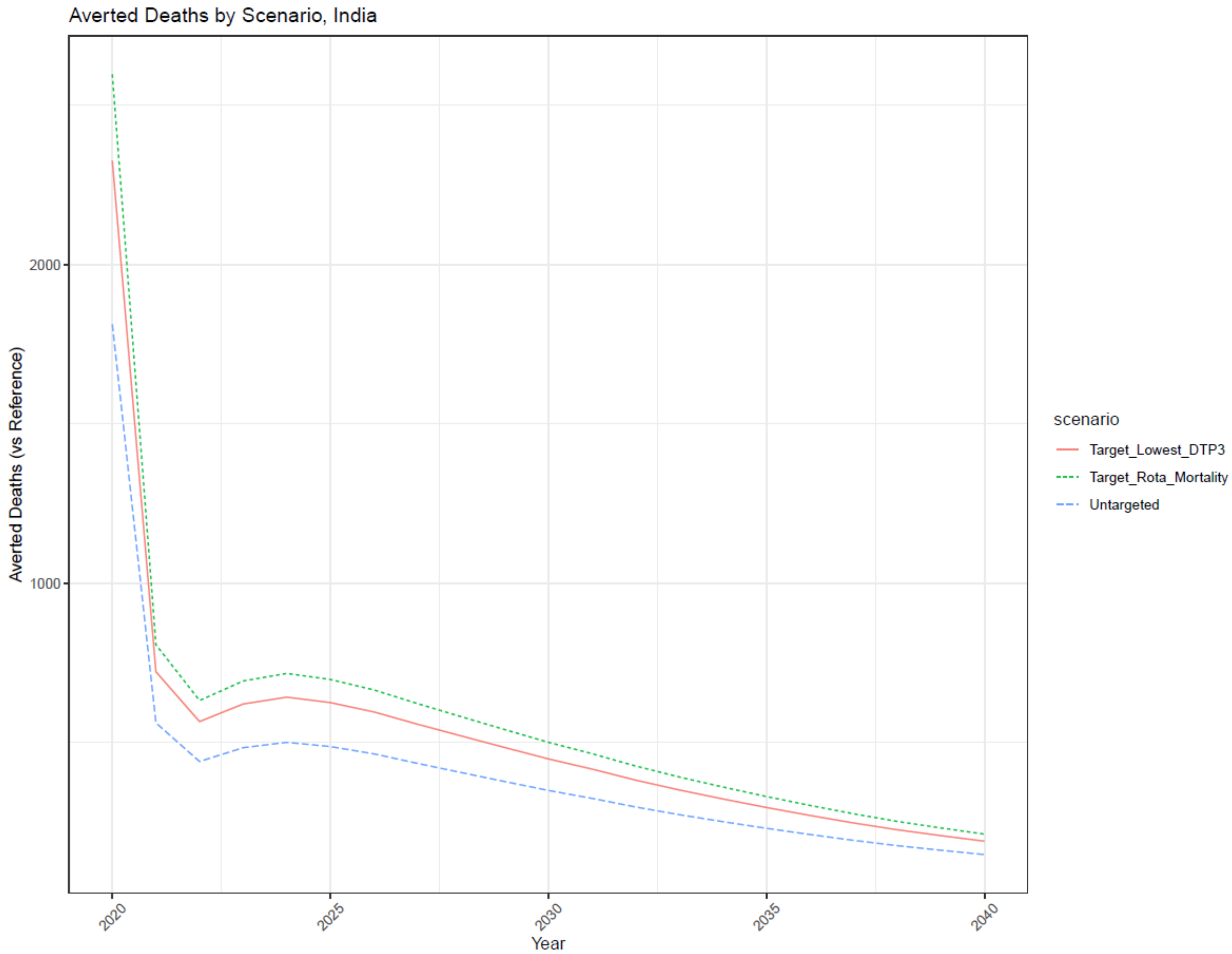

Figure 4: Averted under-5, all-sex deaths in India for the three scenarios compared to the reference scenario, 2020-2040.

The majority of averted deaths came from Bihar and Uttar Pradesh, with some in Jharkhand, as these states have both high rotavirus diarrhea mortality rates and high populations. The highest number of averted deaths come from the first few years after 2019, and slowly decrease from there. The overall under-5, all-sex deaths in each scenario can be seen in Table 2.

Scenario	U5 Deaths 2020-2040, Mean	U5 Deaths 2020-2040, Lower	U5 Deaths 2020-2040, Upper
Reference	151,001	59,343	302,650
Population-based Distribution	125,050	48,272	251,358
Target Low DTP3 Coverage	119,261	45,686	234,991
Target Rotavirus Mortality	116,151	44,278	239,810

Table 2: Under-5, all-sex deaths from rotavirus diarrhea from 2020-2040 in each scenario

Again, the reference scenario has the highest mortality, followed by the population-based scenario. The rotavirus mortality targeting scenario has the fewest deaths, with a mean of almost 10,000 fewer deaths nationwide than the population-based scenario. Even the population-based scenario has nearly 30,000 fewer deaths than the reference scenario.

Discussion:

The results of this study indicate that targeting distribution of rotavirus vaccines based on historical rotavirus burden is more effective than distributing vaccines in proportion to population. These findings corroborate the results of the work from Lee et al., extending to a new vaccine and a new location. However, even the population-based scenario is a significant improvement compared to the reference scenario, indicating a need for investment in rotavirus vaccination above what might be expected. The results of this study indicate the crucial need for investigation of the best ways to distribute vaccines within a country; relying solely on existing infrastructure and distributing vaccines to areas according to population will not be nearly as effective as focusing vaccine coverage on those areas that have a high historical burden of rotavirus diarrhea. The highest amounts of averted deaths were seen in the first few years, indicating a need for swift action in order to avert the most diarrhea rotavirus deaths.

One major strength of this study is the utilization of a forecasting framework that does not make strong assumptions about other drivers of mortality. Underlying rotavirus diarrhea mortality is forecasted using forecasted sociodemographic drivers and past trends, while other risk factors for rotavirus diarrhea are also forecasted and incorporated into the risk-attributable mortality. Thus, observed decreases in each scenario can be isolated to the impact of altering vaccine coverage; the positive effects of the increasing vaccine coverage are beyond what would be expected given the already decreasing rotavirus mortality in India and improvements in risk factors such as sanitation. Another strength is the utilization of observed trends in vaccination deployment in the 15 states introducing rotavirus vaccination before 2019 to create expected patterns of vaccination in the newly introducing states. This allows for a comparison reference scenario that is fairly realistic when looking at possible improvements in vaccine dispersal. Finally, the work can be easily extended to other vaccines and locations modeled in the GBD framework. Many scenarios of vaccination could be created to analyze potential effects, more granular locations could be used, and comparisons to scale-up of other vaccines could be made.

Limitations of this study include large uncertainty on the number of deaths that can be expected, lack of cost-effectiveness information, and population circularity. Since uncertainty is derived from all non-vaccine coverage elements (covariates for underlying mortality, other risk factors, random walk, and relative risk for lack of vaccine coverage), the bounds are uncertainty about the exact number of rotavirus deaths that will result given uncertainty about the levels and effects of other factors contributing to rotavirus mortality. The effect of rotavirus vaccination on rotavirus diarrhea mortality is known to be strong, and it is not plausible that higher rotavirus vaccination could lead to higher rotavirus mortality. The lower bound on reference should thus not be taken to mean that the reference scenario could have fewer rotavirus deaths than the other scenarios, but as uncertainty within each scenario about the exact number of rotavirus deaths that will result. Nevertheless, there is high uncertainty about the number of deaths that will result in a given scenario; the results should be interpreted as a general indication that geographic targeting is more effective than population-based distribution, not as a concrete statement that targeting by rotavirus mortality will prevent a certain number of deaths more than a population-based strategy. This study is focused on the epidemiological impact of different vaccination scenarios, and does not take into account the cost of the vaccine delivery across the different scenarios. This means that in comparing the scenarios, the costs will not truly be equal even though the number of excess doses is the same across scenarios. Different states have different supply chain and cold chain concerns that would affect the cost. The next steps would be to address feasibility of delivery and other aspects of implementation, potentially at smaller subnational units than states and union territories which can be extremely large in India. It is also worth noting that the same population is used for all scenarios. The different mortality rates of rotavirus resulting from different coverage would lead to different denominators in the forecasts of vaccines distributed and mortality. However, in order to minimize circularity in this framework and to standardize the number of vaccines distributed across scenarios, it was necessary to use one population that did not change depending on the scenario to produce the scenarios based on coverage and number of vaccines distributed across state populations. This study also focuses on scaling complete rotavirus vaccination, but there would also be some effects from non-complete rotavirus vaccination to be expected.

To minimize the mortality from rotavirus, distributing rotavirus vaccines based on past rotavirus mortality rates is better than distributing according to population in the states and union territories of India. It is key to boost the number of rotavirus vaccines distributed above the mean scale-up seen in states that have already introduced the vaccine in prior years so that tens of thousands of deaths can be averted.

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