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Analysis of the Universal Immunization Programme and introduction of a rotavirus vaccine in India with IndiaSim

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A B S T R A C T

Background and objectives: India has the highest under-five death toll globally, approximately 20% of which is attributed to vaccine-preventable diseases. India's Universal Immunization Programme (UIP) is working both to increase immunization coverage and to introduce new vaccines. Here, we analyze the disease and financial burden alleviated across India's population (by wealth quintile, rural or urban area, and state) through increasing vaccination rates and introducing a rotavirus vaccine.

Methods: We use IndiaSim, a simulated agent-based model (ABM) of the Indian population (including socio-economic characteristics and immunization status) and the health system to model three interventions. In the first intervention, a rotavirus vaccine is introduced at the current DPT3 immunization coverage level in India. In the second intervention, coverage of three doses of rotavirus and DPT and one dose of the measles vaccine are increased to 90% randomly across the population. In the third, we evaluate an increase in immunization coverage to 90% through targeted increases in rural and urban regions (across all states) that are below that level at baseline. For each intervention, we evaluate the disease and financial burden alleviated, costs incurred, and the cost per disability-adjusted life-year (DALY) averted.

Results: Baseline immunization coverage is low and has a large variance across population segments and regions. Targeting specific regions can approximately equate the rural and urban immunization rates. Introducing a rotavirus vaccine at the current DPT3 level (intervention one) averts 34.7 (95% uncertainty range [UR], 31.7–37.7) deaths and $215,569 (95% UR, $207,846–$223,292) out-of-pocket (OOP) expenditure per 100,000 under-five children. Increasing all immunization rates to 90% (intervention two) averts an additional 22.1 (95% UR, 18.6–25.7) deaths and $45,914 (95% UR, $37,909–$53,920) OOP expenditure. Scaling up immunization by targeting regions with low coverage (intervention three) averts a slightly higher number of deaths and OOP expenditure. The reduced burden of rotavirus diarrhea is the primary driver of the estimated health and economic benefits in all intervention scenarios. All three interventions are cost saving.

Conclusion: Improving immunization coverage and the introduction of a rotavirus vaccine significantly alleviates disease and financial burden in Indian households. Population subgroups or regions with low existing immunization coverage benefit the most from the intervention. Increasing coverage by targeting those subgroups alleviates the burden more than simply increasing coverage in the population at large.

1. Introduction

India has the largest number of under-five deaths in the world [1]. Vaccine-preventable diseases are a major contributor to the burden, causing approximately 20% of under-five deaths in Southeast Asia [2]. In 1985 India launched its Universal Immunization Programme (UIP), which provides free vaccines for measles, poliomyelitis, tuberculosis (BCG), hepatitis B, and diphtheria, pertussis, tetanus (DPT). Despite these efforts, each year more than 50,000 children under the age of five die from measles in India (44% of global under-five measles deaths) [3]. India accounts for 56% (2525) of global diphtheria cases, 18% (44,154) of pertussis cases, and 23% (2404) of tetanus cases [4]. The UIP has yet to incorporate existing vaccines against mumps, pneumococcal disease and rotavirus.

In the Global Immunization Vision and Strategy (GIVS) from 2005, the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) set a goal for all countries to achieve 90% national vaccination coverage and 80% coverage in every district by 2010 [5]. The UIP has fallen short of these targets. In 2007 only 53.5% of children were fully vaccinated, and vaccination

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coverage varied considerably across the country [6]. Immunization coverage is predicted to have improved in recent years, but full coverage remains below 70% in urban areas and below 60% in rural areas [7].

Rotavirus vaccines were first introduced in national immunization programs in 2006 as a key intervention to address the burden of diarrheal disease. By January 2014, 53 countries had introduced rotavirus vaccines [8]. These vaccines have the potential to significantly alleviate the disease and financial burden in India, where each year approximately 113,000 under-fives die from rotavirus (39% of diarrhea cases). Indians spend between $37.4 million and $66.8 million annually on direct medical costs of rotavirus diarrhea hospitalizations in children under five (457,000–884,000) and outpatient treatment (2 million visits) [9]. In 2014 Indian regulators licensed the Indian-made vaccine 116E following a successful Phase 3 trial [10,11].

In this paper we evaluate the health and financial effects of interventions introducing a rotavirus vaccine to the immunization program and increasing the immunization coverage of the DPT3 and measles vaccines. We build on IndiaSim [12], a simulated agent-based model (ABM) of the Indian population and health system, and use household-level data on immunization decisions. We simulate three intervention scenarios: (i) the introduction of the rotavirus vaccine at the current DPT3 level; (ii) an increase in DPT3, measles, and rotavirus vaccination coverage to 90% (the GIVS target) randomly across Indian households; and (iii), targeted state-level and rural–urban implementation that increases coverage in sub-regions that are below 90% immunization coverage in the baseline scenario.

Our analysis does not include the benefits of poliomyelitis immunization. India is polio-free and any changes in the coverage level of the poliomyelitis vaccine will not yield additional health or economic benefits. We also omit the BCG vaccine from the analysis: the burden of miliary tuberculosis is low [13], and BCG coverage is high in India [14].

2. Methods

2.1. Population sample

IndiaSim is populated with data from the District Level Household Survey (DLHS-3, conducted during 2007–08) of India [6]. DLHS data are representative at the district level and cover more than 720,000 households and 3.8 million individuals from 601 districts. The survey data include indicators on demographics, household socioeconomic status, household vaccination choices of UIP vaccines, and other indicators of health-seeking behavior. The simulations are based on a randomly selected subset of 128,000 households comprising approximately 750,000 individuals.

2.2. Disease, vaccination, and treatment data

Table 1 presents the input data on the epidemiology, treatment, and prevention of DPT, measles, and rotavirus. DPT and measles incidences are calibrated using the case-fatality rates (CFR) and the GBD 2010 mortality rates [15]. Rotavirus incidence [16] is distributed across wealth quintiles according to Rheingans et al. [17], and CFR is calibrated to that incidence and the mortality rate [18]. We do not include comorbidity of diseases because of a paucity of data.

In the absence of data to parameterize a demand function for treatment of vaccine-preventable diseases, we assume that everyone who contracts a vaccine-preventable disease seeks treatment. We do not model the effect of treatment on disease transmission. We assume that the baseline level of treatment utilization results in the realized baseline incidence and mortality rates in the population. In addition, we assume that the demand and supply of treatment for individuals with disease is equivalent across all simulation scenarios. Treatment costs for DPT and measles are estimated from the National Sample Survey (NSS) 60th round schedule 25 [19], and treatment costs for rotavirus are from Tate et al. [9]. All costs in the model are in 2013 US dollars.

Total routine immunization cost is the sum of costs for vaccines, personnel, vehicles and transportation, cold chain equipment and maintenance, and program and other recurrent costs, including planning, supervision, monitoring, and surveillance. The data were collected from the Ministry of Health and Family Welfare (MoHFW) by personal communication. We use the WHO comprehensive multi-year planning (cMYP) for immunization tool to analyze the data and assume that interventions are introduced in 2016. Costs include program as well as vaccine costs and are not separable by vaccine type.

Baseline vaccination coverage rates are from 2011 estimates [14].

2.3. Income data

The gross domestic product (GDP) per capita for India is from the World Bank [20]. The distribution across wealth quintiles is from NSS expenditure data. The state-level GDP per capita is from the Indian government's Press Information Bureau [21].

2.4. Model

IndiaSim is an iterative, stochastic ABM. The model comprises 67 regions, representing the urban and rural areas of 34 Indian states and districts. Nagaland is not included in the model because it is omitted from DLHS-3, and the urban area of Andaman and Nicobar is dropped because of a low number of observations. Each region comprises a set of representative households. A set of characteristics describes each household (socioeconomic indicators) and its individuals (age and sex). An iteration of a simulation represents a day (the timestep of the model).

Individuals in the model are in one of several disease states: they are healthy or they suffer from diphtheria, pertussis, tetanus, measles, and/or rotavirus. They contract diseases based on a stochastic function of their characteristics (age, sex, and wealth quintile) and their immunization history. Those suffering from disease seek treatment at public or private facilities based on the average treatment-seeking rates by income quintile in the DLHS-3 data. Births in the model are based on a household-level probit regression model that is bounded to the state-level fertility rates [12]. Deaths not related to the five diseases in the model are determined on the basis of WHO life tables [22].

We assume that households that immunized previously born children in the baseline DLHS-3 data will immunize any children born during the simulation with those vaccines. To increase the urban and rural sub-region rates to 2011 estimates, we select a random set of households to also vaccinate. In the intervention scenarios, to scale up the coverage rates, the model makes additional households vaccination compliant. The method of selecting these extra households varies across scenarios (e.g., random or targeted by state and region).

The model was programmed in C++.

Table 1
Disease and intervention parameters.

Variable	Base-case estimate	Sensitivity range	Source
Diphtheria			
Incidence (per 100,000)			Based on [15] and CFR
<1 year	42.2	29.5–54.8	
1–5 years	18.3	12.8–23.8	
CFR	0.012	0.008–0.016	[37]
Cost of seeking treatment			
Public facilities	$0.35	$0.25–$0.46	[19]
Private facilities	$0.37	$0.26–$0.49	
Treatment cost			
Public facilities	$3.51	$2.45–$4.56	[19]
Private facilities	$4.59	$3.21–$5.97	
DPT3 vaccination relative risk reduction	0.955	0.921–0.989	[38]
Pertussis			
Incidence (per 100,000)			Based on [15] and CFR
<1 year	2123.2	1486.3–2760.2	
1–5 years	313.4	219.4–407.5	
CFR			[39]
<1 year	0.037	0.026–0.048	
1–4.9 years	0.010	0.007–0.013	
Cost of seeking treatment			[19]
Public facilities	$0.72	$0.50–$0.93	
Private facilities	$0.77	$0.54–$1.00	
Treatment cost			[19]
Public facilities	$5.83	$4.08–$7.58	
Private facilities	$7.63	$5.34–$9.92	
DPT3 vaccination relative risk reduction	0.840	0.680–1.00	[40]
Tetanus			
Incidence (per 100,000)			Based on [15] and CFR
<1 year	637.1	446.0–828.2	
1–5 years	3.2	2.2–4.1	
CFR			[41]
<1 months	0.864	0.648–1.000	
1 month–5 years	0.328	0.230–0.427	
Cost of seeking treatment			[19]
Public facilities	$0.55	$0.38–$0.71	
Private facilities	$0.58	$0.41–$0.76	
Treatment cost			[19]
Public facilities	$3.54	$2.48–$4.60	
Private facilities	$4.63	$3.24–$6.02	
DPT3 vaccination relative risk reduction	1.000	.990–1.00	[42]
DPT3 vaccination baseline coverage	76.8%		Based on [6,14]
Measles			
Incidence (per 100,000)			Based on [15] and CFR
<1 year	4776.9	3343.9–6210.0	
1–5 years	2723.3	1906.3–3540.3	
CFR	0.015	0.011–0.020	[45]
Cost of seeking treatment			
Public facilities	$1.24	$0.87–$1.61	[19]
Private facilities	$1.32	$0.92–$1.72	
Treatment cost	$5.92	$4.14–$7.69	
Vaccination relative risk reduction	0.840	0.83–0.87	[43]
Vaccination baseline coverage	82.2%		Based on [6,14]
Rotavirus			
Incidence (per child-year)			Based on [9,16,17]
<6 months quintile I	1.38	0.96–1.79	
Quintile II	1.17	0.89–1.52	
Quintile III	0.97	0.68–1.25	
Quintile IV	0.76	0.53–0.98	
Quintile V	0.50	0.35–0.65	
6 months–1 year quintile I	2.08	1.46–2.70	
Quintile II	1.81	1.27–2.35	
Quintile III	1.53	1.07–1.99	
Quintile IV	1.15	0.80–1.49	
Quintile V	0.76	0.53–0.98	
1–2 years quintile I	1.74	1.22–2.26	
Quintile II	1.44	1.00–1.87	
Quintile III	1.24	0.87–1.61	
Quintile IV	0.94	0.66–1.22	
Quintile V	0.59	0.42–0.77	
2–5 years quintile I	1.11	0.78–1.44	
Quintile II	0.94	0.66–1.23	
Quintile III	0.78	0.55–1.01	
Quintile IV	0.59	0.42–0.77	
Quintile V	0.38	0.27–0.50	

Table 1 (*Continued*)

Variable	Base-case estimate	Sensitivity range	Source
CFR	0.0009	0.00063–0.00117	Based on incidence and [18]
Outpatient cost of seeking treatment	$0.36	$0.25–$0.46	
Outpatient treatment cost	$3.12	$2.18–$4.05	[9]
Inpatient cost of seeking treatment	$3.70	$2.59–$4.81	
Inpatient treatment cost	$74.26	$51.99–$96.54	
Vaccination relative risk reduction	0.56	0.420–0.700	[44]
Vaccination baseline coverage	0.00%		
UIP cost per DPT3 child			Based on cMYP and personal communication with MoFWH
Baseline	$22.50	$15.75–$29.25	
Intervention one	$27.00	$18.90–$35.10	
Intervention two/three	$23.50	$16.45–$30.55	

2.5. Analysis

2.5.1. Simulated results from one year are analyzed in R

Analysis variables fall into four categories, which consider the intervention's associated effect on disease burden, intervention costs, cost-effectiveness, and financial impact. The effect on disease burden includes both deaths and disability-adjusted life years (DALYs) averted (we discount at 3% and use uniform age-weights that value any extra year of life equally). Cost-effectiveness is measured by dollars per DALY averted incremental to the baseline scenario. The financial impact measures follow Verguet et al. [23] and include the out-of-pocket (OOP) expenditure averted from the baseline scenario, which measures the savings of the population that result from the intervention, and the money-metric value of insurance, which measures the value of protection from expenditure on disease treatment (including the costs of seeking care). The money-metric value of insurance here differs slightly from Verguet et al.'s analysis. Our analysis period is one year as we study a cross-section of the under-five population, while they study a birth cohort, which is susceptible to disease over the first five years of life. Given this, we include only one year of disposable income in the calculation as opposed to five years. Additionally, we evaluate the value of insurance of an intervention with respect to the baseline by subtracting one from the other. We analyze health and financial burden alleviated across India by wealth quintile, state, and rural versus urban areas.

2.6. Sensitivity analysis

To quantify the uncertainty of the model, we conduct a 100-simulation Latin hypercube sampling (LHS) sensitivity analysis over a plausible range of the input parameters (Table 1). For each disease, the parameters analyzed include the incidence, CFR, vaccine efficacy, vaccine cost, and treatment cost. Ninety-five percent uncertainty ranges for our mean estimated outcomes are calculated on the basis of this sensitivity analysis and reported in parentheses.

3. Results

In the baseline, immunization coverage is 77% for DPT3, 82% for measles, and there is no coverage for rotavirus. From DLHS-3 data, we find that baseline coverage increases by wealth for DPT3 and measles. The rural-to-urban immunization coverage ratio is 1.09 for DPT3 and 1.05 for measles (Fig. 1, row 1). Baseline DPT3 coverage is lowest in Arunachal Pradesh and Uttar Pradesh where 53% and 55% of under-fives are vaccinated (Fig. 2, column 1). Another nine states vaccinate less than 80% of their children; all of them are relatively poor states, with the exception of Gujarat (77% coverage). Eight states have DPT3 coverage above 90%. Measles vaccination coverage in six states is less than 80%; as with DPT3, coverage is lowest in Arunachal Pradesh (58%) and Uttar Pradesh (60%). Twelve states are above 90% coverage for measles, and Himachal Pradesh and Maharashtra are above 95% coverage.

Our interventions decrease the coverage disparity between wealth quintiles, rural and urban populations, and states. Intervention two reduces the urban-to-rural vaccine coverage ratio for all three vaccines to 1.03 (Fig. 1, row 1), though a total of 9 states do not achieve 90% coverage for all vaccines, and measles coverage remains below 80% in Arunachal Pradesh and Uttar Pradesh (Fig. 2). Intervention three equates urban and rural coverage (i.e., the urban-to-rural vaccine coverage ratio is approximately 1) and makes coverage in each state at or above 90% for all three vaccines.

In the baseline scenario, India at large has 88.7 (95% uncertainty range [UR], 85.1–92.4) rotavirus deaths per 100,000 under-fives; the rate is more than 60% higher in rural areas than in urban areas (96.6 versus 59.8). Intervention one averts 34.7 (95% UR, 31.7–37.7) deaths and 995 (95% UR, 910–1081) DALYs per 100,000 under-fives per year, roughly 44,500 deaths and 1.28 million DALYs throughout the country. The number of deaths averted per 100,000 under-fives is 25.2 (95% UR, 19.9–30.5) in urban populations and 37.3 (95% UR, 33.8–40.8) in rural populations (Fig. 1, row 2). Intervention two averts another 22.1 deaths (95% UR, 18.6–25.7) per 100,000 under-fives and 630 (95% UR, 522–737) DALYs per 100,000 for all of the related diseases. Intervention three averts slightly more deaths and DALYs than intervention two. Typically, the reduced burden is highest for the poor and in rural areas (Fig. 1, row 2); this trend is more pronounced in intervention three than in intervention two.

Fig. 3 (total deaths averted from the baseline across all under-fives) and the first row of Fig. 4 (DALYs averted across all under-fives in one year) map the disease burden alleviated in all interventions. In all states with sufficient data, introducing the rotavirus vaccine (intervention one) averts more than 15 rotavirus deaths and 450 DALYs per 100,000 under-fives, though the standard deviations are high. The intervention averts more than 45 deaths per 100,000 in Karnataka, Uttarakhand, Andhra Pradesh, Himachal Pradesh, West Bengal, Jammu and Kashmir and Bihar and more than 1500 DALYs per 100,000 in Jammu and Kashmir, Karnataka and Andhra Pradesh. Intervention one costs almost $93 million per year for all of India. The total intervention costs are mapped in Fig. 4, row 2. In intervention one, the cost per 100,000 under-fives ranges from $26,127 (95% UR, $16,996–$35,257) in Arunachal Pradesh to $212,878 (95% UR, $185,763–$239,994) in Delhi; the cost per 100,000 under-fives in Uttar Pradesh is low relative to other states (approximately 48,500), but the state has the highest overall costs (approximately $14.1 million), taking into account the entire under-five population. The urban-to-rural cost ratio is 1.17 (95% UR, 1.09–1.27) per 100,000 under fives.

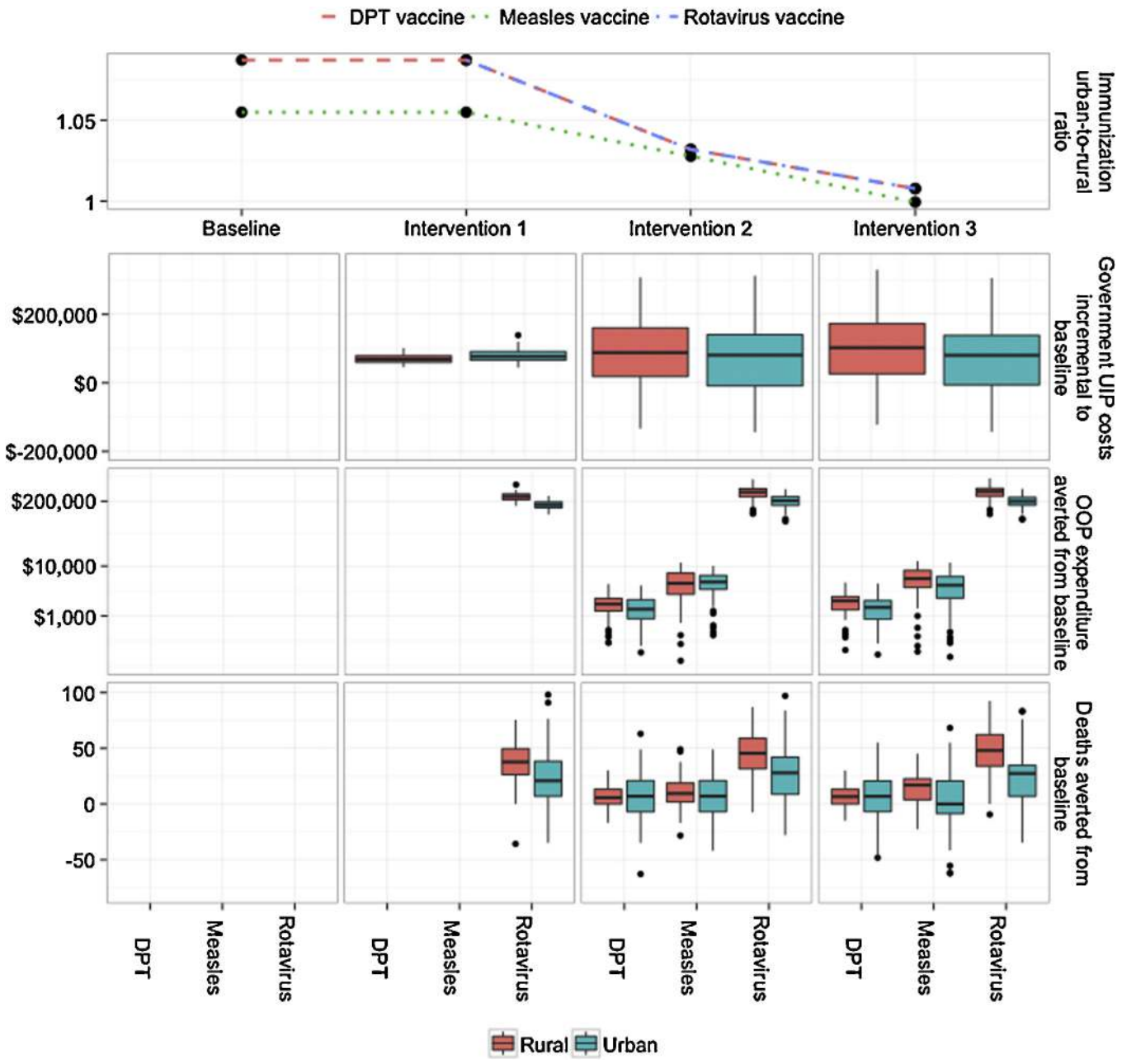

Fig. 1. Analysis by rural and urban populations per 100,000 under-fives in each.
Results are for 100 simulations. Confidence intervals around the mean are from the sensitivity analysis. OOP = out-of-pocket.

In interventions two (randomly increasing all three vaccines to 90% coverage) and three (increasing all three vaccines to at least 90% coverage in each region), states with low coverage rates in intervention one achieve the greatest additional reductions in burden (Figs. 3 and 4, row 1). For example, Uttar Pradesh has the second lowest coverage in intervention one, and it averts an additional 427 (95% UR, 275–580) rotavirus-related DALYs per 100,000 under-fives per year in intervention two and 548 (95% UR, 372–724) per 100,000 in intervention three. Approximately 665,000 DALYs are averted for all five diseases in Uttar Pradesh in intervention three.

The intervention costs incremental to the baseline in intervention two for all five diseases are $137,926 (95% UR, $120,787–$155,065) per 100,000 under-fives in Uttar Pradesh ($41 million for its entire population) and above $30,000 in all other states. In intervention three, the cost incremental to the baseline is above $100,000 in nine states, including Uttar Pradesh, where the cost is $186,454 (95% UR, $167,960–$204,948) per 100,000; the cost for all under-fives in Uttar Pradesh is approximately $53 million (Fig. 4, row 2). The urban-to-rural cost ratio is 0.88 (95% UR, 0.54–1.41) in intervention two and 0.75 (95% UR, 0.47–1.17) in intervention three (Fig. 2).

Most of the OOP expenditure averted results from the reduced rotavirus burden (Figs. 2 and 5, row 3): $232,354 (95% UR, $224,029–$240,678) averted per 100,000 under-fives in intervention one, with an additional $49,489 (95% UR, $40,861–$58,118) and $56,295 (95% UR, $47,599–$64,991) averted in interventions two and three, respectively. The OOP averted for DPT (approximately 1800) and measles (approximately 5500) is highest in

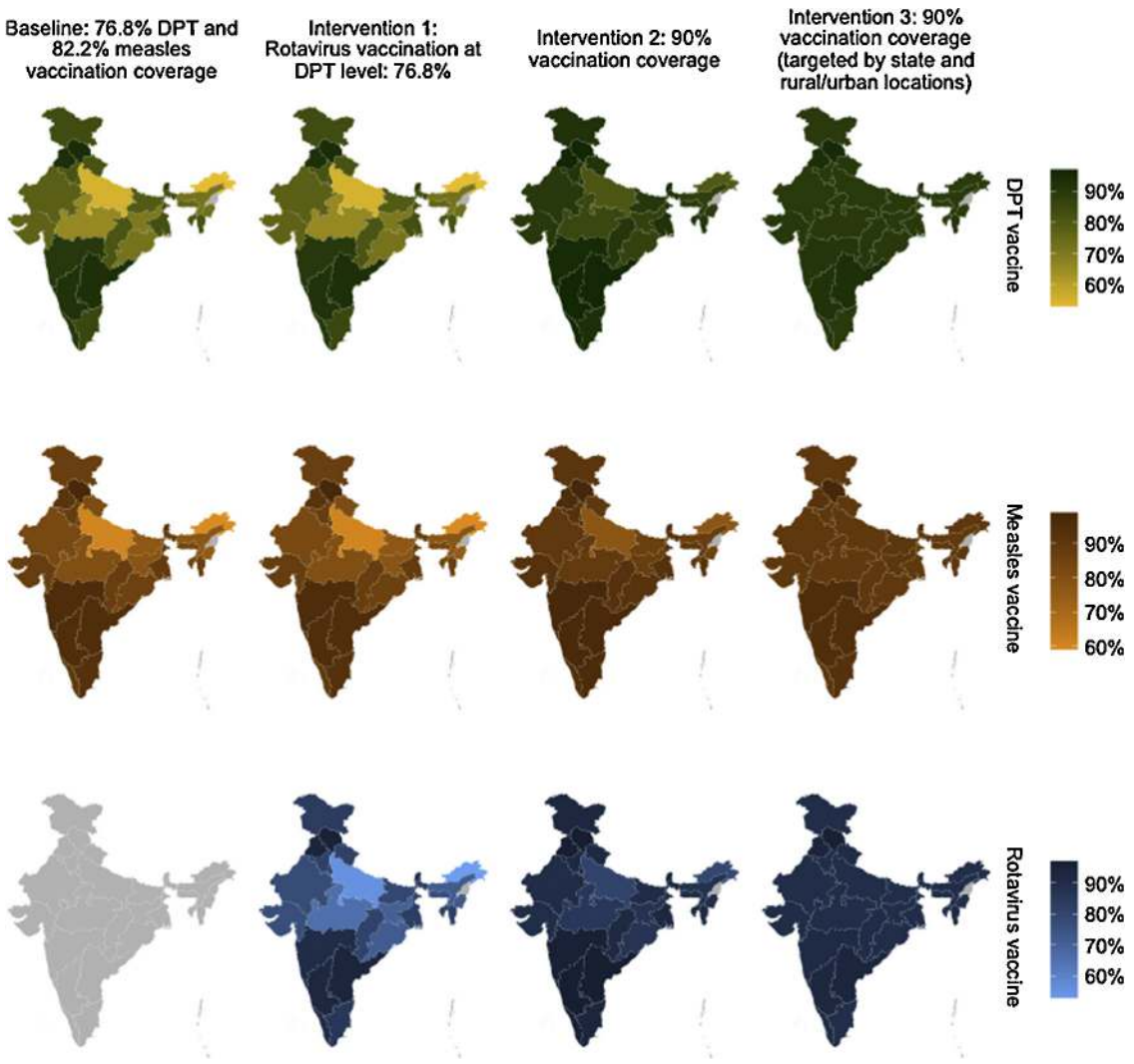

Fig. 2. Under-five immunization coverage.
Results are for 100 simulations. Rotavirus immunization is not available in the baseline scenario, and therefore the map is greyed out. Additionally, states with a low sample population are greyed out.

intervention three (Fig. 4, row 3?). The urban-to-rural ratio of OOP expenditure averted decreases from intervention one through intervention three (Fig. 1, row 4; e.g., the rotavirus ratio decreases from 0.70 to 0.48).

The interventions are cost saving in all states that have sufficient data. If we exclude OOP expenditure averted and only consider the intervention costs, the incremental dollars per DALY averted in intervention one is $70.89 (95% UR, 95% UR, $61.51–$80.28) with respect to the baseline. For interventions two and three, the incremental dollars per DALY averted are $30.47 (95% UR, −$4.36–$65.28) and $36.97 (95% UR, $7.96–$65.97) with respect to intervention one. Excluding OOP expenditure averted, the dollars per DALY averted are below $110 in all states (with sufficient sample size) in all interventions.

The value of intervening is highest for rotavirus. In intervention one, the money-metric value of insurance for rotavirus ranges from $521 (95% UR, $280–$761) per 100,000 under-fives in Delhi to $6756 (95% UR, $6318–$7196) in Bihar (Fig. 5). It is highest in intervention three in Bihar (approximately $7500 per 100,000 under-fives) and Uttar Pradesh (approximately $5400 per 100,000). The values for DPT and measles are at or below $250 per 100,000 under-fives in all states in all interventions. In all interventions, the money-metric value of insurance decreases as wealth increases.

4. Discussion

In this paper we present an ABM analysis for introducing a rotavirus vaccine to the UIP and increasing UIP coverage to the 90% goal set in the GIVS. We analyze the effects across the wealth distribution, the rural and urban population distribution, and states. The results do not present the exact benefits and costs that would be realized by implementing the intervention scenarios, but they highlight the variation across population segments. The model is a useful tool to understand which strategy and populations to target when allocating scarce resources.

Immunization is one of the most cost-effective interventions for improving health outcomes [24]. Even in a high-quality health system, immunization policy addresses an important market failure: individuals tend to under-vaccinate, and government intervention is needed to fix that failure. Though India has succeeded in eliminating polio, it has achieved less through routine immunization. Targeted immunization campaigns may be simpler to implement than routine immunization. For example, the pulse polio campaign involved a single-dose immunization. Routine vaccinations, however, may require a more complex immunization delivery schedule if several doses are required.

UIP coverage remains low in India, especially in certain sectors of the population. Targeting expansion in these subpopulations in

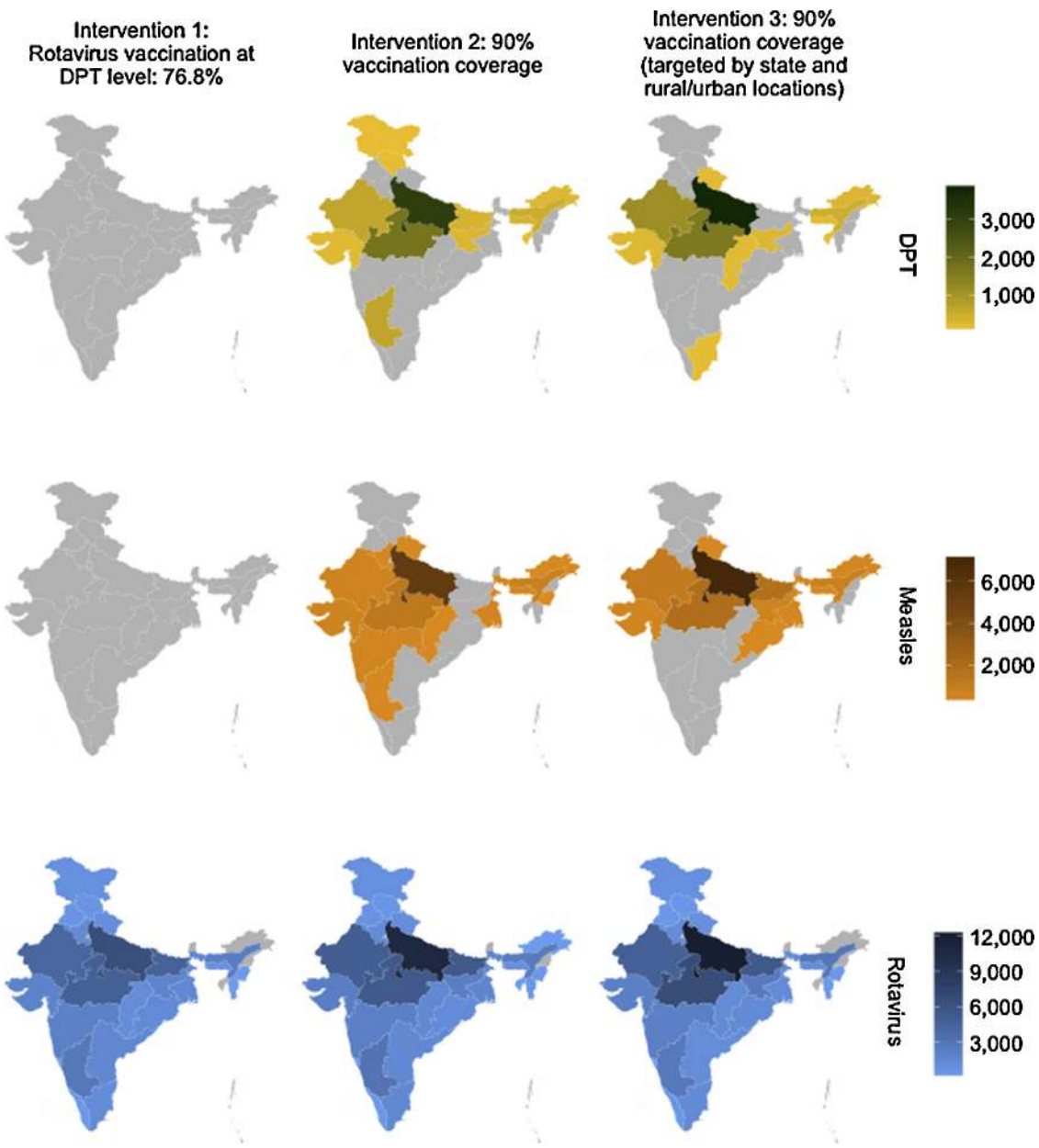

Fig. 3. Total under-five deaths averted from baseline.
Results are for 100 simulations. DPT3 and measles vaccination coverage does not change in intervention one, and therefore the map is greyed out. States in which immunization coverage is 90% or above in the baseline are greyed out in intervention three. Additionally, states with a low sample population or a high standard deviation are greyed out.

intervention three averts a greater burden than the random vaccination distribution in intervention two. This is partially because coverage is slightly higher than 90% in intervention three (a few states have higher-than-90% coverage in the baseline and maintain that coverage rate in intervention three). However, the simulation results also show that often the areas that suffer the highest disease burden and that have the greatest potential marginal gains to vaccination are the areas that currently under-vaccinate the most. Although rural areas have lower rotavirus immunization coverage than urban areas in intervention one, rural areas avert more rotavirus deaths in that scenario. Moreover, interventions tend to have a greater financial benefit for those segments of the population. Poor and rural areas avert more deaths and OOP expenditure than urban areas.

Demand and supply both contribute to low immunization rates. Lack of education contributes to low immunization demand. In a UNICEF survey of vaccination coverage in India, the most-cited reasons for non-immunization included “did not feel the need,” “not knowing about vaccines,” and “not knowing where to go for immunization” [7]. Additionally, rural areas have poor access to health care facilities. Where facilities are available, they often suffer from staffing issues and poor quality of service, which also decreases health care demand [25].

The Indian immunization delivery system relies heavily on community health workers (CHWs) to mobilize and vaccinate the rural population [26]. Strengthening CHW programs can increase immunization coverage [26,27] and encourage age-appropriate immunization [28]. Research suggests that providing incentives to families can also improve vaccination rates [29]. However, effects of these strategies have been little studied.

Although India is not currently reaching its target immunization coverage with the UIP, it recognizes the potential of new vaccines.

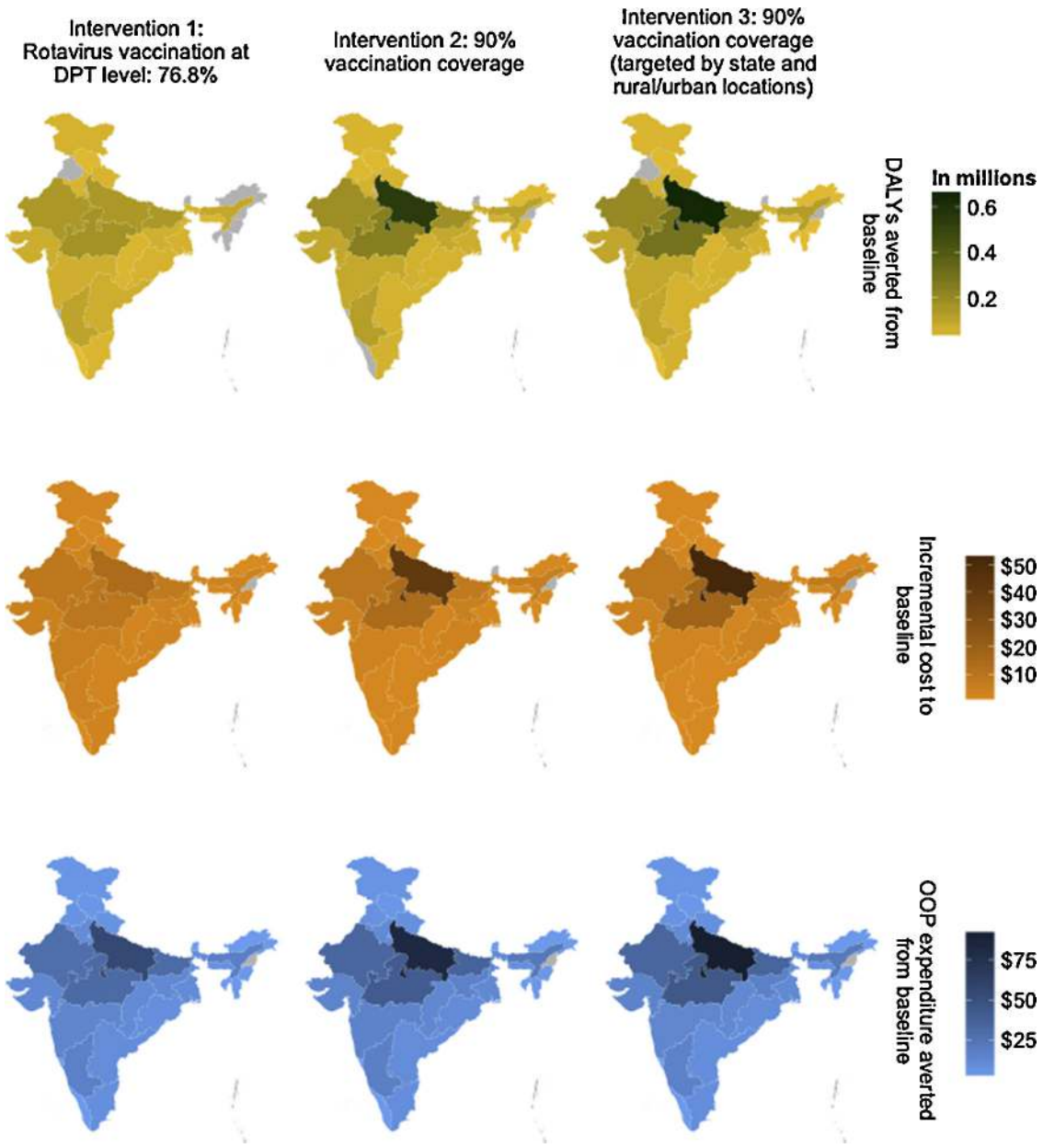

Fig. 4. Health and financial impact (totals by state).
Results are for 100 simulations. States with a low sample population or a high standard deviation are greyed out. Values are in millions. OOP expenditure averted assumes 100% demand for treatment. All interventions remain cost-effective if OOP expenditure averted is excluded. DALYs = disability-adjusted life years; OOP = out-of-pocket.

It has introduced a new pentavalent vaccine in a few states [30] and plans to roll it out across the country in 2014–15. Given the resource constraints, research into which vaccines alleviate the greatest burden is important. A rotavirus vaccine is a compelling choice. Rotavirus puts a heavy burden on the Indian population, especially on under-two year olds, and does not significantly decrease with improvements in hygiene and sanitation [31].

Our analysis of a rotavirus vaccine shows that its introduction can significantly reduce rotavirus burden. We predict that introducing the vaccine at the DPT3 level will avert approximately 44,500 under-five rotavirus deaths per year in India. Increasing rotavirus immunization coverage to 90% in our model averts approximately another 8500 and 9500 deaths in interventions two and three, respectively; all three interventions are cost saving. Our results for intervention one are similar to other cost-effectiveness models [32,33]. Our DPT3 coverage, which is estimated for 2011, is higher than that of Esposito et al. [33]. The similar result despite the disparity in vaccination coverage is because of different model assumptions. Our death rate is lower and our vaccine efficacy is slightly higher. A recent report by the International Vaccine Access Center (IVAC) at Johns Hopkins Bloomberg School of Public Health [34] uses a baseline death rate much lower than ours (approximately 54,000 versus 113,000) and estimates approximately 22,000 rotavirus deaths averted at 72% vaccination coverage. Their cost averted differs significantly from our OOP averted, though in addition to different model parameters they include components we do not (e.g. lost productivity). Verguet et al. [23] estimate (with DLH-3 vaccination rates) the OOP expenditure averted for a 1 million birth cohort and the money-metric value of insurance for 1 million households. Their cohort averts $1.8 million OOP expenditure over the first five years of life and the money-metric value of insurance is $16,000 for 1 million households. We estimate that

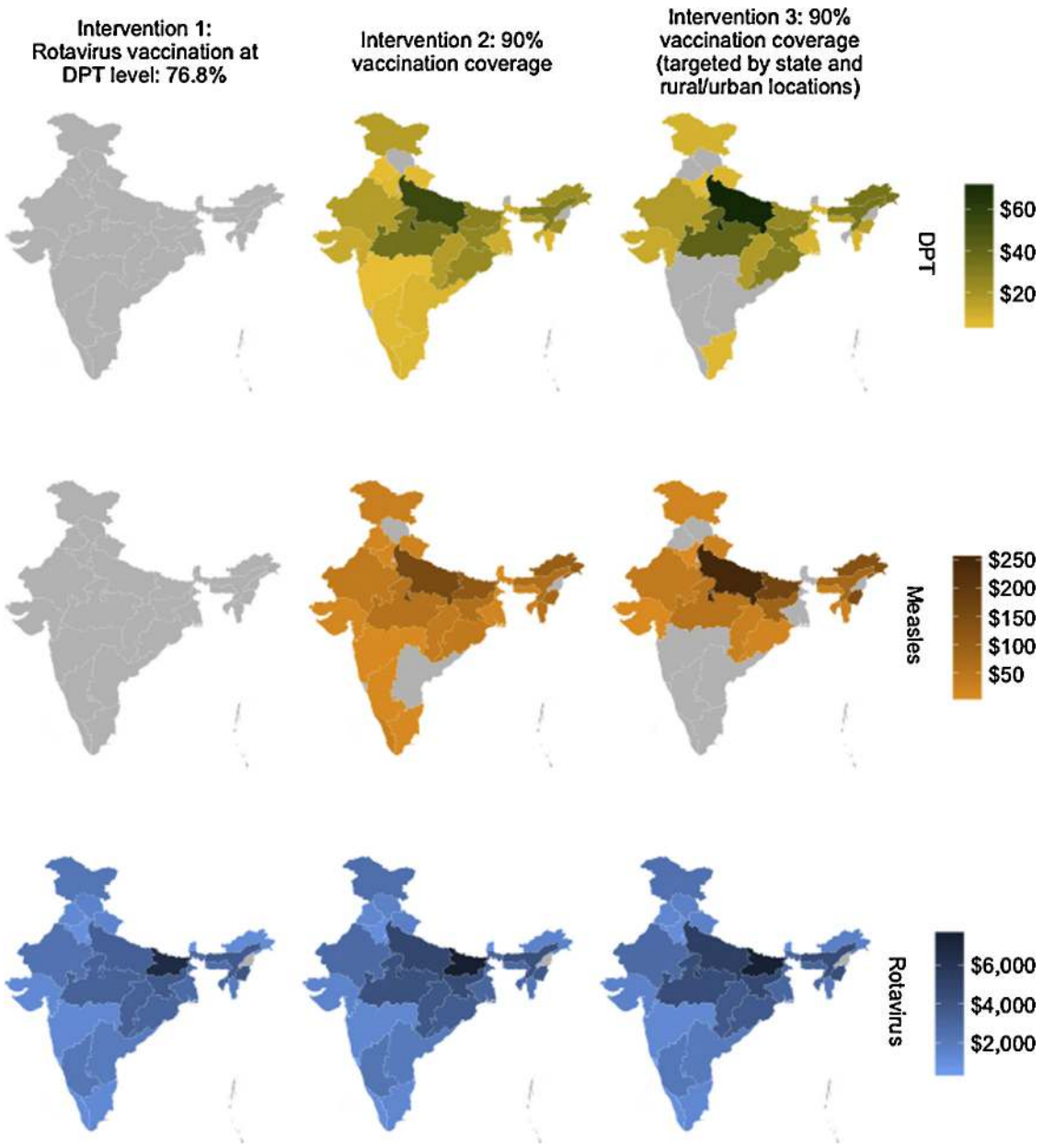

Fig. 5. Money-metric value of insurance per 100,000 under-fives.
Results are for 100 simulations. DPT3 and measles vaccination coverage does not change in intervention one, and therefore the map is greyed out. States in which immunization coverage is 90% or above in the baseline are greyed out in intervention three. Additionally, states with a low sample population or a high standard deviation are greyed out. Money-metric value of insurance = the value of protection from the risk of expenditure on disease treatment (including the costs of seeking care). It is the amount the population is willing to pay to avoid that risk.

approximately $2.3 million OOP is averted and a money-metric value of insurance of $23,500 summed over the wealth quintiles in a cross-section 1 million population of under-fives. We sum over wealth quintiles for comparability with their study, though wealth quintiles do not include an equal number of under-five year olds. Our results are similar, but the comparison is not exact due to the differing model populations and assumptions. The most significant difference in model assumptions of the two analyses is the age distribution of the under-five population.

The cost-effectiveness results here are more optimistic than other analyses [32,33] because of our assumption of 100% treatment demand. If we do not consider OOP averted, we have a lower bound estimate of cost-effectiveness, and the interventions remain very cost-effective by WHO's cost-effectiveness criteria [35]: the cost per DALY averted is less than India's per capita GDP.

The regional detail in the model is an additional reason for the differences between our findings and past analyses. As discussed, the marginal gains from immunization are often highest in areas that currently vaccinate the least. Introducing rotavirus according to DPT3 vaccination coverage (the same households) maintains that trend.

A major challenge to realizing the potential benefits described here is the low investment in routine immunization [36]. In 2011–12 the MoHFW spent approximately $233 million on routine immunization. Continuing the UIP at current coverage rates would cost approximately $438 million in the intervention year (cMYP and personal communication with MoHFW). The estimated cost for the polio campaign during the intervention year is approximately $108 million. Under the model assumptions, introducing a rotavirus vaccine at DPT3 levels costs another approximately $93 million, or

roughly a 17% increase on top of the total costs of the existing routine immunization and the polio campaign. Intervention three will cost approximately $129 million more than would be spent in the baseline ($53 million of which would be spent for Uttar Pradesh). A significant increase in immunization program funding is needed both to introduce the new vaccines and to increase immunization coverage in India.

The study is limited by the parameters we use. Though our analysis focuses on the distribution across population subgroups, the parameters do not capture all the covariates affecting these groups. For example, we do not capture the state fixed effects in many of our variables. We use the population distributions (by age, wealth, and sex) to extrapolate the values for specific subgroups. Additionally, we assume that the per-child UIP costs are distributed uniformly across states. Despite not fully capturing all the factors affecting the disease and expenditure distributions across the subpopulations, we feel that this research is a step in the right direction. Additionally, we do not model the infectious disease dynamics, which means we do not consider any additional benefits from herd immunity.

5. Conclusion

Introducing a rotavirus vaccine to UIP and increasing UIP coverage are cost-effective interventions that would greatly alleviate the disease and financial burden of vaccine-preventable diseases in India. The results presented here are useful for policy analysis, given the paucity of data on the interventions' effect size across different subsets of the population: at the state level, in the rural and urban populations, and across the wealth distribution. Additional research is needed to introduce an infectious disease model into the ABM used here and to take into account the state fixed effects.

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References

[1] World Health Organization, United Nations Children's Fund. Countdown to 2015, Maternal, Newborn and Child Survival: Building a Future for Women and Children; 2012. Geneva.
[2] World Health Organization. WHO estimates of disease burden and cost-effectiveness; 2014. Available at: http://www.who.int/immunization/monitoring_surveillance/burden/estimates/en/index.html [accessed 22.01.14].
[3] Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;6736:1–11.
[4] World Health Organization. WHO vaccine preventable diseases: monitoring system. 2013 global summary; 2013. Available at: http://apps.who.int/immunization_monitoring/globalsummary [accessed 01.04.14].
[5] World Health Organization. United Nations Children's Fund. Geneva: Global Immunization Vision and Strategy: 2006–2015; 2005.
[6] International Institute for Population Sciences (IIPS). District Level Household and Facility Survey (DLHS-3). 2007–08. Mumbai: IIPS; 2010.
[7] United Nations Children's Fund. Coverage Evaluation Survey; 2009. New Delhi.
[8] Country introduction | Maps and list – Rotavirus Vaccine Access and Delivery – PATH; 2014. Available at: http://sites.path.org/rotavirusvaccine/rotavirus-advocacy-and-communications-toolkit/country-introduction-maps-and-list/ [accessed 26.02.14].
[9] Tate JE, Chitambar S, Esposito DH, Sarkar R, Gladstone B, Ramani S, et al. Disease and economic burden of rotavirus diarrhoea in India. Vaccine 2009;27(Suppl. 5):F18–24.
[10] Madhi SA, Parashar UD. 116E rotavirus vaccine development: a successful alliance. Lancet 2014;6736:12–3.
[11] Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, Taneja S, et al. Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet 2014;6736:1–8.
[12] Megiddo I, Nandi A, Ashok A, Prabhakaran D, Laxminarayan R. Estimating the Health and Economic Benefits of Secondary Prevention of Cornary Heart Diseases in India; 2014 [submitted for publication].
[13] Swaminathan S. Protective efficacy of BCG. Indian J Pediatr 2004;71:1083–4.
[14] Pramanik S, Muthusamy N, Gera R, Laxminarayan R. Small area estimation of vaccination coverage rates by combining time series and cross sectional data; 2014 [submitted for publication].
[15] Global Burden of Disease Study 2010. Global Burden of Disease Study 2010 (GBD 2010) Results 1990–2010; 2013. Seattle.
[16] Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. BMC Public Health 2012;12:220.
[17] Rheingans R, Atherly D, Anderson J. Distributional impact of rotavirus vaccination in 25 GAVI countries: estimating disparities in benefits and cost-effectiveness. Vaccine 2012;30(Suppl.):A15–23.
[18] Morris SK, Awasthi S, Khera A, Bassani DG, Kang G, Parashar UD, et al. Rotavirus mortality in India: estimates based on a nationally representative survey of diarrhoeal deaths. Bull World Health Organ 2012;90:720–7.
[19] National Sample Survey Organisation. National Sample Survey 2004 (60th Round) – Schedule 25 – Morbidity and Healthcare. New Delhi: Ministry of Statistics and Programme Implementation (MOSPI); 2004.
[20] GDP per capita (current US$) | Data | Table; 2014. Available at: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD [accessed 05.02.14].
[21] Press Information Bureau. Statewise Per Capita Income and Gross Domestic Product at current prices; 2013. Available at: http://pib.nic.in/archieve/others/2013/dec/d2013121703.pdf [accessed 14.04.14].
[22] World Health Organization Life expectancy: Life tables India; 2013. Available at: http://apps.who.int/gho/data/view.main.60740 [accessed 26.02.14].
[23] Verguet S, Murphy S, Anderson B, Johansson KA, Glass R, Rheingans R. Public finance of rotavirus vaccination in India and Ethiopia: an extended cost-effectiveness analysis. Vaccine 2013;31:4902–10.
[24] World Health Organization. United Nation Children's Fund. The World Bank. State of the World's vaccines and immuniztion. 3rd ed. Geneva: World Health Organization; 2009.
[25] Streefland PH, Chowdhury a M, Ramos-Jimenez P. Quality of vaccination services and social demand for vaccinations in Africa and Asia. Bull World Health Organ 1999;77:722–30.
[26] Patel AR, Nowalk MP. Expanding immunization coverage in rural India: a review of evidence for the role of community health workers. Vaccine 2010;28:604–13.
[27] Prinja S, Jeet G, Verma R, Kumar D, Bahuguna P, Kaur M, et al. Economic analysis of delivering primary health care services through community health workers in 3 North Indian States. PLoS ONE 2014;9:e91781.
[28] Awofeso N, Rammohan A, Iqbal K. Age-appropriate vaccination against measles and DPT-3 in India – closing the gaps. BMC Public Health 2013;13:358.
[29] Banerjee AV, Duflo E, Glennerster R, Kothari D. Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without incentives. BMJ 2010;340:c2220.
[30] Gupta SK, Sosler S, Lahriya C. Introduction of Haemophilus influenzae type b (Hib) as pentavalent (DPT-HepB-Hib) vaccine in two states of India. Indian Pediatr 2012;49:707–9.
[31] World Health Organization. Report of the meeting on future directions for rotavirus vaccine research in developing countries; 2000. Geneva.
[32] Rose J, Hawthorn R. Public health impact and cost effectiveness of mass vaccination with live attenuated human rotavirus vaccine (RIX4414) in India: model based analysis. BMJ 2009;339:b3653.
[33] Esposito DH, Tate JE, Kang G, Parashar UD. Projected impact and cost-effectiveness of a rotavirus vaccination program in India, 2008. Clin Infect Dis 2011;52:171–7.
[34] Constenla D. Estimating the economic impact of Hib, PCV and RV vaccines in India: a state- and national level analysis. International Vaccine Access Center (IVAC), Johns Hopkins Bloomber School of Public Health; 2014.
[35] World Health Organization (WHO). WHO Guide to Cost-Effectiveness Analysis; 2003. Geneva.
[36] Laxminarayan R, Ganguly NK. India's vaccine deficit: why more than half of Indian children are not fully immunized, and what can—and should—be done. Health Aff 2011;6:1096–103.
[37] Bitragunta S, Murhekar MV, Hutin YJ, Penumur PP, Gupte MD. Persistence of diphtheria, Hyderabad, India, 2003–2006. Emerg Infect Dis 2008;14:1144–6.
[38] World Health Organization. Diphtheria vaccine. Wkly Epidemiol Rec 2006;81:24–31.
[39] Crowcroft N, Stein C. How best to estimate the global burden of pertussis? Lancet Infect Dis 2003;3:413–8.
[40] Heininger U, Cherry JD, Stehr K, Schmitt-Grohe S, Uberall M, Laussucq S, et al. Comparative efficacy of the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine and Lederle whole-cell component DTP vaccine in German children after household exposure. Pediatrics 1998;102:546–53.

[41] Patel JC, Mehta BC. Tetanus: study of 8,697 cases. Indian J Med Sci 1999;53:393–401.
[42] Center for Disease Control Prevention. Epidemiology and Prevention of Vaccine-Preventable Diseases. 12th ed. Washington, DC: Public Health Foundation; 2012.
[43] Sudfeld CR, Navar AM, Halsey Na. Effectiveness of measles vaccination and vitamin A treatment. Int J Epidemiol 2010;39(Suppl. 1):i48–55.
[44] Modi B. Rotavirus diarrhoea – current scenario and preventive strategies. Natl J Med Res 2013;3:104–5.
[45] Simons E, Ferrari M, Fricks J, Wannemuehler K, Ananad A, Burton A, et al. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. Lancet 2012;379:2173–8.