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RESEARCH

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Coverage and distributional benefit–cost of rotavirus vaccine in Uganda: an analysis of routine health facility aggregated data

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Abstract

Introduction Owing to the lack of local cost and clinical effectiveness data in sub-Saharan Africa, economic evaluations of the rotavirus vaccine are still limited in the region. In this study, we utilize different data sources, including aggregated routine health information system data to examine the net benefits of the rotavirus vaccine in Uganda. We also present ways in which health facility data can be used to assess subnational vaccination coverage as well as the effect of the vaccine on diarrhoea hospitalization.

Methods We used monthly health facility data collected between 2015 and 2021 to study the relationship between rollout of rotavirus vaccine and diarrhoea hospitalization. We gathered information from empirical studies on the cost of diarrhoea (household and health facility) and vaccine administration to estimate the costs averted due to the rotavirus vaccine. As household costs, we considered out-of-pocket payments associated with the episodes of diarrhoea and the productivity loss associated with time spent on treatment and with mortality using a human capital approach. Finally, we employed an interrupted time series analysis to examine the effect of rotavirus vaccine on diarrhoea hospitalization. Costs are presented in 2018 US dollars.

Results As of 2021, nationwide coverage of the first and second doses of the rotavirus vaccine (RV) in Uganda was estimated at 89% and 65% respectively, with variations observed across the regions. The study revealed a decrease in diarrhoea hospitalization by 1% for each 1% increase in RV coverage. Moreover, the study showed that diarrhoea hospitalization reduced by 2% for each additional month post- vaccine rollout. Excluding productivity losses due to mortality, the analyses of costs averted due to the RV reveal that between 2018 and 2021, Uganda saved approximately $57 million ($7 per capita) in expenses associated with diarrhoea. The return on investment (ROI) due to RV was calculated to be $1.48 per dollar invested. When including mortality costs, the net benefit reached up to $3 billion in economic cost ($385 per capita), and an ROI of $78 overall. Furthermore, the study demonstrated that RV provided substantial health benefits, particularly for socially disadvantaged groups. Excluding mortality costs, the ROI for the two most disadvantaged groups ranged from $1.71 to $2.03 per dollar spent, while for the remaining groups, it ranged from $1.10 to $1.14.

Conclusion This manuscript stresses the importance of RV in alleviating the burden of diarrhoeal diseases and associated costs in Uganda. The study not only emphasizes the tangible benefits derived from the vaccine

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but also highlights the role of routine aggregated healthcare information systems in systematically monitoring the effectiveness and coverage of interventions.

Keywords Rotavirus, Vaccine, Health information system, Benefit–cost analysis, Sub-Saharan Africa

Introduction

Ending preventable causes of child death, such as diarrhoea, is one of the global health priorities in the current sustainable development goals (SDG) framework [1]. While there has been a global decline in morbidity and mortality due to diarrhoea, diarrhoea remains among the leading causes of mortality among children younger than 5 years of age [2]. In Africa, diarrhoea remains among the top diseases that burden health facilities and families [3]. The recurrent episodes of diarrhoea lead to catastrophic health expenditure as well as a long-term economic burden on individuals and families. For instance, some of the studies on the cost of diarrhoea done in developing countries indicate an average of $79 for each hospitalised episode of diarrhoea [3, 4].

Diarrhoea is due to a variety of pathogenic microorganisms, such as protozoa, bacteria, and viruses [5, 6]. Rotavirus accounts for 36–46% of diarrhoea cases [7–10]. The mortality rate due to rotavirus is estimated at 20 per 100,000 children younger than 5 years and about 80% of rotavirus deaths occur in sub-Saharan Africa [6]. Additionally, close to 40% of diarrhoea hospitalization in Africa is due to rotavirus [11]. The introduction of the rotavirus vaccine has significantly contributed to reduced mortality and morbidity due to rotavirus, and as such, WHO recommended having rotavirus vaccines included within the national immunization programs for countries where mortality rates in children were still high, especially in sub-Saharan Africa and South and Southeast Asia [12]. As such, several African countries including Uganda have introduced rotavirus vaccines into their national immunization programs. However, access to the rotavirus vaccine, as has been the case for other vaccines, is affected by different factors such as household socioeconomic status, mother's literacy, and geographical location [13, 14]. Furthermore, due to factors independent of vaccine coverage—such as malnutrition, differences in gut microbiota, and co-infections, the effectiveness of rotavirus vaccines in preventing new cases varies across countries, ranging from about 85% to 100% in high- or middle-income countries and from about 48% to 61% in low-income countries [15, 16]. Aliabadi et al. 2019 note the presence of rotavirus in 38% of admitted acute diarrhoea cases in countries that have not introduced rotavirus and 23% in countries that have introduced the vaccine [17].

In Uganda, the rotavirus vaccine was introduced in 2018 in all public health facilities, free of charge. The rotavirus vaccine is part of the normal routine immunization package, which is given at ages 6 weeks and 10 weeks. Nonetheless, the rotavirus vaccine alone may not accelerate progress toward reducing mortality and morbidity due to diarrhoea. Indeed, progress in reducing mortality and morbidity due to diarrhoea has been partly associated with the implementation of programmes towards addressing key environmental risks for diarrhoea and scaling up interventions to prevent or treat acute diarrhoea [2]. As alluded to earlier, like in other low-income countries, access to the rotavirus vaccine in Uganda is affected by different factors including household socioeconomic status, mother's literacy, and geographical location [13, 14].

Owing to the lack of local cost and clinical effectiveness data in sub-Saharan Africa, the economic evaluations of the rotavirus vaccine are still limited in the region. In this study, we used a novel approach of bringing different data sources together to examine the net benefits of the rotavirus vaccine in Uganda. We used the monthly aggregated health facility data collected between 2015 and 2021 to study the effect of the rotavirus vaccine on diarrhoea hospitalization. We used the information from different studies on the cost of diarrhoea (household and health facility) and vaccine administration to estimate the costs averted due to the rotavirus vaccine.

Methods

Model parameters and data sources

We used District Health Information Systems (DHIS) data collected between 2015 and 2021 to address the three study objectives. Furthermore, the analysis used data inputs for vaccine coverage, the prevalence of diarrhoea disease—specified as acute (ambulatory) or persistent (hospitalized) cases, the proportion of diarrhoea cases likely caused by rotavirus, the cost of the immunization program, the direct and indirect costs associated with treatment, the indirect cost due to mortality, a composite ranking of the households by level of "(composite) disadvantage for immunization", and other sociodemographic variables such as district of residence and urban/rural residence.

We used the most recent (2016) Uganda Demographic and Health Survey (DHS) to generate "disadvantage

quintiles" using the VERSE Equity Toolkit methodology [18, 19]. The disadvantage quintiles rank households using a composite index based on sociodemographic variables known to *unfairly* affect the distribution of vaccines in the population: the district of residence, whether the household lives in an urban or rural area, the household's wealth, the sex of the child, maternal education level, and whether it is covered by health insurance [19]. The VERSE Equity Toolkit's composite ranking was previously applied to examine vaccine equity in Uganda using historical DHS data [20]. We then estimated the level of coverage of the Diphtheria-Pertussis-Tetanus vaccine (DPT) and the distribution of diarrhoea cases by disadvantage quintile.

Once we determined the distribution of vaccines and cases by level of "disadvantage", we used Uganda's Ministry of Health DHIS-2 data to estimate the (actual) monthly totals per district for the number of rotavirus vaccine doses (first and second doses), DPT (first and second doses), acute (ambulatory) diarrhoea case/s, persistent (hospitalized) diarrhoea cases for the period January 2014 to December 2021. The proportion of acute and persistent cases attributable to rotavirus is estimated at 40% from the literature [7, 8]. In Uganda, the DHIS-2 is used as a management system for aggregating health facility reports. At the facility level, the data are aggregated from paper-based recording and reporting. The monthly reports are then sent to the district or subcounty health office where the data are entered into a web-based DHIS-2 system. However, most of the public and non-for-profit hospitals enter the data directly into DHIS-2 system. We address our assessment of the data quality in the next section. The case fatality rate for rotavirus diarrhoea is estimated at 2.5% among children in low- and middle-income countries [21]. Details of the sources of cost data are indicated in Table 1

We then obtained data on the economic cost of diarrhoea treatment, including the government costs (medical treatment in a public facility) and the household's direct medical and non-medical, and indirect costs incurred by the child's caregiver from an earlier study [4]. The government cost included all treatment costs, medications, facility overhead, and labour. The household medical costs included any cost incurred at a public or private facility, including pharmacies and informal providers. Non-medical costs focused on travel costs: transportation, meals, and lodging (for the caregiver). Indirect costs associated with the treatment used the human capital approach, combining the time spent seeking healthcare with the head of the household's average income [4]. The indirect cost associated with mortality, *i.e.*, the productivity loss due to the premature death of the child due to diarrhoea, was derived from the same source [4] and World Bank estimates, comparing an estimation using primary data (Eq. 1) and the Gross Domestic Product (GDP) per capita for 2018 (Eq. 2) [24]. The latter method is used to assess the return on investment of immunization programmes [25]. All costs are presented in 2018 US dollars. We used an annual discount rate of 5%.

Indirect cost associated with mortality using primary data (Method 1).

$$\begin{aligned} \textit{Productivity loss per child death} = & \textit{Average income per year} \\ & \times \textit{Labour force participation rate} \\ & \times \textit{Number of productive years} \end{aligned} \quad (1)$$

Indirect cost associated with mortality using GDP per capita (Method 2).

$$\begin{aligned} \textit{Productivity loss per child death} = & \textit{GDP per capita} \\ & \times \textit{Labour force participation rate} \\ & \times \textit{Number of productive years} \end{aligned} \quad (2)$$

The immunization programme costs are the sum of the UNICEF vaccine price for the rotavirus vaccine and Portnoy et al.'s estimation of the economic cost of vaccine delivery [22, 23]. All costs are reported in 2018 US dollars ($1 = 3,727 Ugandan Shillings) [26].

Assessing and addressing the quality of health facility data

Before the analysis, we assessed the quality of data by examining the completeness of reporting, consistency over time and improbably extreme outliers in the reported monthly data from each district. Internal inconsistencies were checked by comparing the correlation between the first dose of the rotavirus vaccine and the Pentavalent vaccine and between the second dose of the rotavirus vaccine and DPT. Extreme outliers were identified using a modified Z-score which is a standardized score of observations measuring the deviation from the median, obtained by dividing the difference from the median by the median absolute deviation [27]. Monthly data with a score greater than five times the standard deviation from the annual median were identified as extreme outliers. Extreme outliers and missing data were replaced with the median value of the calendar year. The formula for identifying outliers is [27]:

Identification of outliers.

$$\begin{aligned} & Median - 1.4826 \\ & \times 5 \times MAD < X_{ij} < Median + 1.4826 \times 5 \times MAD \end{aligned} \quad (3)$$

Table 1 Immunization programme and diarrhoeal disease cost inputs

Variable	Estimates (2018 USD)	Source
Cost of the immunization programme (per dose)	$4.00	
Vaccine price (per dose)	$2.20 (€1.88)[1]	[22]
Administrative cost (per dose)	$1.79	[23]
Cost of acute diarrhoea (per ambulatory case)	$15.66	[4]
Government costs[2]	$4.41	
Household costs	$11.25	
Out-of-pocket payments[3]	*$6.22*	
Indirect costs associated with treatment	*$5.03*	
Cost of persistent diarrhoea (per hospitalized case)	$62.68	[4]
Government costs[2]	$8.26	
Household costs	$54.42	
Out-of-pocket payments[3]	*$27.63*	
Indirect costs associated with treatment	*$26.79*	
Indirect costs associated with mortality (per death)	(See methods below)	
Based on primary data estimates		[4]
Discounted (5%) over 48 years		
Deaths in 2018	*$13,005.43*	
Deaths in 2019	*$11,737.40*	
Deaths in 2020	*$10,593.01*	
Deaths in 2021	*$9,560.19*	
Undiscounted	*$63,147.19*	
Based on GDP per capita estimates		World Bank
Discounted (5%) over 48 years		
Deaths occurring in 2018	*$7,840.43*	
Deaths occurring in 2019	*$7,730.16*	
Deaths occurring in 2020	*$7,555.10*	
Deaths occurring in 2021	*$7,491.80*	
Undiscounted	*$27,181.12*	

[1] Assuming an exchange rate of €1 = $1.15 (2018) https://www.exchangerates.org.uk/EUR-USD-spot-exchange-rates-history-2018.html Accessed on 23 September 2022

[2] Government costs are averaged per case of diarrhoea for cases treated in public and private healthcare facilities (overall)

[3] Households' out-of-pocket payments include direct medical and non-medical costs

With

$$MAD = Median(|X_{ij} - X\sim|)$$

where X_{ij} is the value of the observation for a particular period (year) and the MAD is defined as the median absolute deviation, where $X\sim$ is the annual median for indicator i in district j.

To address the issue of incomplete reporting by facilities, we adjusted for incomplete reporting by facilities based on the number of service outputs provided at nonreporting health facilities compared with those that reported. This adjustment considers the prevalence of health facilities, particularly private ones, that offer immunization services but fail to submit reports to the district health office. The adjustment was done using the following expression (Eq. 4).

Adjustment of facility-based data from the DHIS-2.

$$n_{adjusted} = n + n\left(\frac{1}{c} - 1\right) * k \quad (4)$$

where n is the number of service outputs, c is the reporting completeness, k is the adjustment factor. If we consider the missing reports an indication that no services were provided during the reporting period, then $k=0$, and no adjustments are made for incomplete reporting. However, if facilities provided services but not at the same level, k is between 0 and 1. If services are assumed to be provided at the same rate in non-reporting facilities as in reporting facilities, then $k=1$. Important considerations in the selection of a value of k are the extent to which large health facilities and private health facilities are reporting and engaged in the provision of specific

services. In this study, we assumed that 25% of immunization and treatment of diarrhoea were done in non-reporting health facilities, which are normally private health institutions.

Coverage estimation

To calculate the coverage of the first dose of the rotavirus vaccine, we utilized the first dose of DPT coverage and the number of attendances for DPT-1 to establish the number of surviving infants at 6 weeks (denominator) (Eq. 5). The DPT-1 vaccine is administered simultaneously with the rotavirus vaccine and is known to have almost universal coverage, as reported by the DHS Program in 2016.

$$Child\ population_t = \frac{DPT1\ attendance_t}{DPT1\ coverage_t} * 100 \quad (5)$$

Estimating the effect of rotavirus vaccine on health facility admissions for diarrhoea

While a few doses of the rotavirus vaccine were distributed through the private sector before 2018—when the vaccine was introduced in Uganda's Expanded Programme for Immunization, we assumed coverage of zero for the rotavirus vaccine until 2018. We calculated the prevalence of acute (ambulatory) and persistent (hospitalized) cases of diarrhoea from 2015 to 2018. We ran a negative binomial regression model of acute, persistent and all cases of diarrhoea as outcomes controlling for various factors (Eq. 6). We then used the expected number of acute and persistent diarrhoea cases to estimate the annual changes in the number of cases due to the rotavirus vaccine, given the annual coverage of the vaccine.

$$\begin{aligned} H_i =& \propto_i + \beta_1 VaccineCoverage_i \\ &+ \beta_2 VaccineRollOut_i \\ &+ \beta_3 HealthFacilities_i \\ &+ \beta_4 Under5Pop_i \\ &+ \beta_5 VaccinationPeriod_i \end{aligned} \quad (6)$$

where $VaccineCoverage_i$ — *annual rotavirus vaccine*; $VaccineRollOut_i$—whether the rotavirus vaccine has been rolled out: Value = 0 for 2015–2017 or Value = 1 for 2018–2021; $HealthFacilities_i$—Number of health facilities in a district; $Under5Pop_i$— Under-5 total population per district; and $VaccinationPeriod_i$—The time (number of years) since the rotavirus vaccine was rolled out.

We estimated the number of deaths associated with acute and persistent diarrhoea using the global WHO estimate of 2.5% case-fatality ratio for low- and middle-income countries [21]. Whether the rotavirus vaccine provides additional protection against death is still a matter of discussion [28, 29]. We opted to model two scenarios when accounting for the productivity loss associated with mortality: the first where the vaccine offers no additional protection against death beyond preventing cases, and the second where the vaccine is fully protective against death (see Eq. 7).

Estimation of the number of deaths per year

$$\begin{aligned} Number\ of\ deaths =& Number\ of\ cases \\ &\times Case\ Fatality\ Ratio \\ &\times Vaccine\ protection \end{aligned} \quad (7)$$

where *Number of cases* — *Number of acute and persistent cases (expected or observed)*; *Case Fatality Ratio* — *The proportion of all cases (acute and persistent) leading to death* (= 2.5%); *and Vaccine protection*—Whether the rotavirus vaccine has been rolled out: Value = 0 if the vaccine provides full protection (100%) against death or Value = 1 if the vaccine does not provide any additional protection against death.

Distribution of immunization benefits

The distributional impact of vaccination was modelled by comparing healthcare and health outcomes across the disadvantage quintiles generated with a composite index. The healthcare outcome referred to the coverage of the rotavirus vaccine for doses 1 and 2, and the proportion of children who have access to treatment for diarrhoea. Health outcomes included the proportion of acute and persistent diarrhoea cases, the proportion of deaths, and the economic cost associated with morbidity and mortality. We used relative differences in DPT 1 coverage across quintiles and applied the same relative differences to rotavirus coverage.

The difference in expected (without vaccine) and observed (with vaccine) cases by quintile provided the basis for the benefits associated with the rotavirus vaccine (Eqs. 8 and 9). All costs were discounted to present value at an annual rate of 5%.

Total benefit of rotavirus vaccination.

$$\sum_t^T (E_t - [O_t + Vac_t]) \quad (8)$$

where:

$$E_t = \sum_t^T E_{ht} * C_{treat} \Big/ (1+r)^t$$

$$O_t = \sum_{t}^{T} O_{ht} * \frac{C_{treat}}{(1+r)^t}$$

$$vac_t = \sum_{t}^{T} vac_{ht} * \frac{C_{treat}}{(1+r)^t}$$

Distributional benefit for quintile "i" at time "t".

$$\sum_{t=1}^{T} \frac{E_{ti}}{(1+r)^t} - \frac{O_{ti}}{(1+r)^t} \quad (9)$$

E_t is the expected cost based on the expected number of diarrhoea hospitalized cases at time tE_{ht}- Expected number of diarrhoea OPD cases at time tO_t is the observed cost based on the actual number of diarrhoea hospitalized casesO_{ht}—expected number of diarhoea OPD cases at time tC_{treat} is the cost of treating diarrhoea casesVac_t is the cost of vaccination based on the administered total number of doses at time tVac_{ht}- number of children vaccinated at time t

Results

Assessing the quality of data

Overall, the completeness of monthly health facility reports for the main forms that report the number of diarrhoea cases and immunization was at least 90% in all reporting periods and was observed to be closer to 100% for the 2020 and 2021 reporting years (Supplement Fig. 1).

Trends in diarrhoea cases and children vaccinated with rotavirus vaccine.

In 2018, the vaccine's first dose national coverage was estimated at 58%, increasing to almost 90% in 2021 (Table 2). The national coverage of the second dose showed a similar increase from 32% in 2018 to 68% in

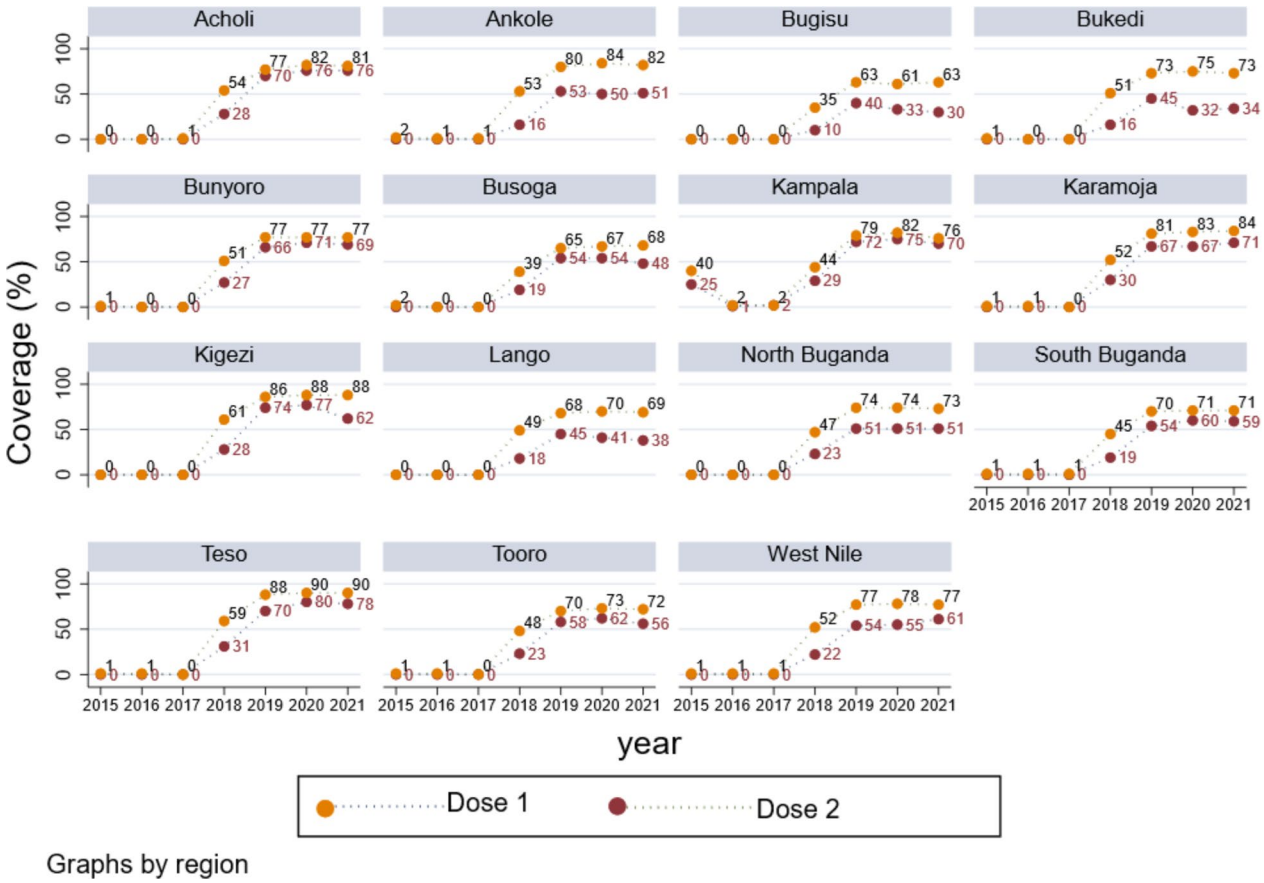

Fig. 1 Coverage of doses 1 and 2 of the rotavirus vaccine by regions

Table 2 Estimated coverage for rotavirus vaccine doses and DPT-3 in comparison with WHO estimates

Year	Rotavirus vaccine (dose 1)		Rotavirus vaccine (dose 2)		DTP vaccine (dose 1)**	DTP vaccine (dose 3)	
	Adj.DHIS-2	WUENIC	Adj.DHIS-2	WUENIC***	WUENIC	Adj.DHIS-2	WUENIC
2018	58.1%	–	26.7%	36.0%	97%	88%	93.0%
2019	89.4%	–	68.2%	87.0%	96%	88%	93.0%
2020	86.5%	–	65.0%	88.0%	94%	90%	89.0%
2021	88.9%	–	64.9%	87.0%	97%	89%	91.0%

Adj.—adjusted

WUENIC WHO and UNICEF estimates of national immunization coverage

**In our study, we used the 2016 Uganda Demographic Household Survey coverage of DPT-1 (95%) and assume no changes over the years

-Estimates not available

***Percentage of surviving infants who received the final recommended dose of rotavirus vaccine, which can be either the 2nd or the 3rd dose depending on the vaccine

2019. However, since 2019, the coverage for both doses seems to have plateaued, staying just below 90% and around 65% for the first and second doses, respectively. For validation check, we observed that the estimated DPT-3 values derived from our adjusted DHIS-2 data closely align with the estimations provided by both the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF).

A closer look at regional data (Fig. 1) shows strong variations between regions. For the first dose, Teso, Kigezi, and Karamoja regions display the highest coverage, ranging from 84% in Karamoja to 90% in Teso. Meanwhile, Bugisu and Busoga regions show the lowest coverage at 63% and 69%, respectively. For the second dose, Teso and Acholi regions present the highest rates at 78% and 76%, while Bugisu, Bukedi, and Lango have the lowest ones at 30%, 34%, and 38%. Acholi, Bunyoro, and Kampala regions have slightly lower coverage for the first dose than the top-performing regions, but they show

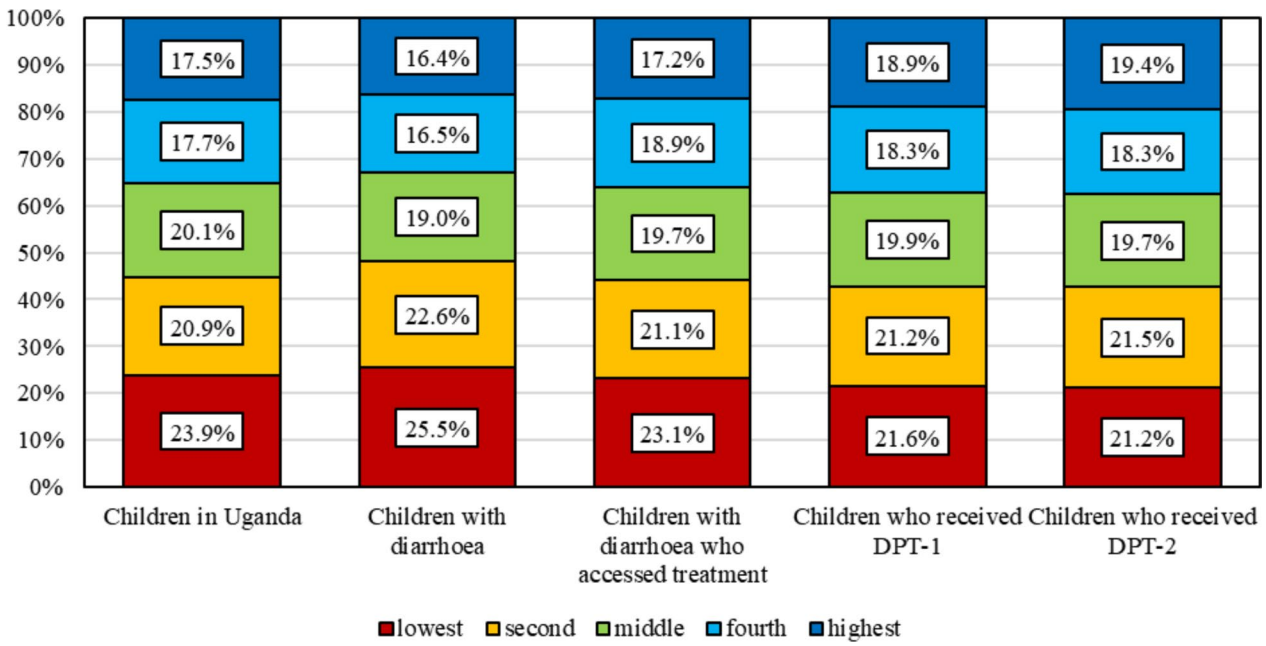

Fig. 2 Projected proportion of children, children with diarrhoea, and children with diarrhoea who accessed treatment by sociodemographic disadvantage

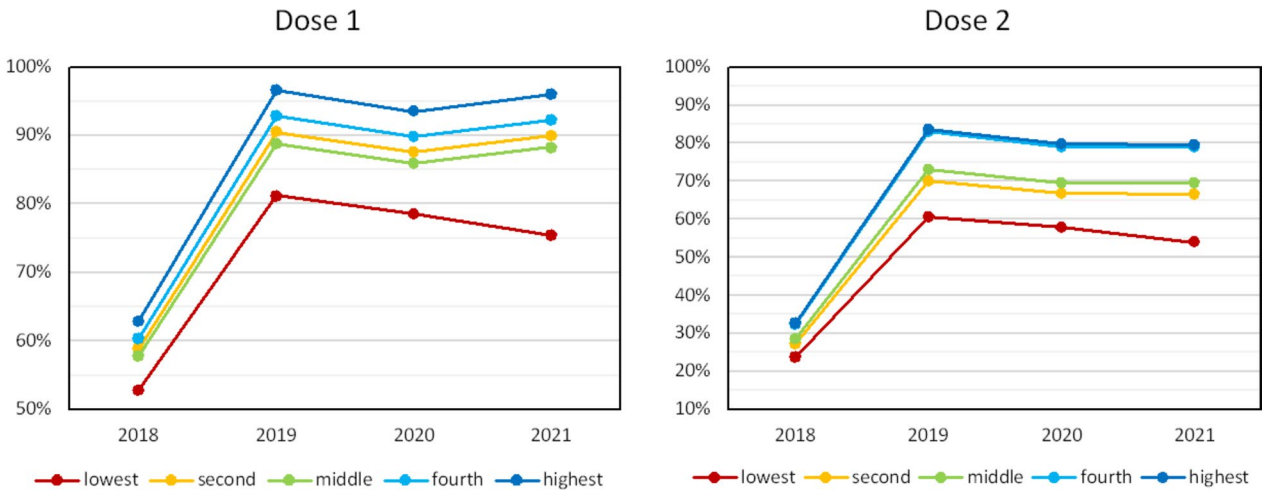

Fig. 3 Distribution of projected rotavirus vaccine doses 1 and 2 by sociodemographic disadvantage

Table 3 The evolution of diarrhea cases and deaths since the introduction

	All cases		Acute cases		Persistent cases	
	IRR	P	IRR	P	IRR	P
Rotavirus vaccine (dose 1) coverage	0.99	0.165	0.99	0.234	0.99	< 0.001
time—months	1.01	< 0.001	1.012	< 0.001	1.01	< 0.001
Number of months since rollout	0.98	< 0.001	0.98	< 0.001	0.98	< 0.001
0-before introduction	–	–	–	–	–	–
1-after introduction	0.90	0.021	0.89	0.018	1.01	0.911
Total number of health facilities	1.01	< 0.001	1.01	0.002	1.01	< 0.001
Population of under-five	1.01	< 0.001	1.01	< 0.001	1.01	< 0.001

IRR Incidence Rate Ratio, P- Probability value at 0.005 level of significancy

Table 4 Observed and expected number of diarrhoea cases

Year	Expected (sample prediction)			Observed			%
	All	Acute	Persistent	All	Acute	Persistent	All
2015	953,402	894,294	59,108	953,402	894,294	59,108	0
2016	1,774,428	1,662,915	111,512	1,749,880	1,640,932	108,948	1.4
2017	1,692,427	1,591,136	101,291	1,702,281	1,601,296	100,985	(–)0.6
Rotavirus vaccine introduced in the EPI in 2018: it is available in the public sector							
2018	2,218,042	1,985,920	232,122	1,525,899	1,438,138	87,761	31
2019	2,242,588	1,987,474	255,114	1,558,344	1,478,146	80,198	31
2020	2,502,746	2,185,794	316,952	1,330,739	1,275,870	54,869	47
2021	2,900,421	2,484,846	415,575	1,254,846	1,202,629	52,217	57

less than 10 percentage points differences in coverage between doses 1 and 2.

Sociodemographic distribution of diarrhoea cases and rotavirus vaccine doses

Based on the 2016 Uganda demographic health survey, the prevalence of suspected diarrhoea was observed highest among the most disadvantaged in Uganda (Fig. 2).

Every year since its introduction in the EPI schedule, the projected coverage for the rotavirus vaccine appears higher among the children belonging to households in the more privileged quintiles. Between 2019 and 2021, the projected rotavirus vaccine coverage was about 23 percentage points higher for the most privileged households compared to the most disadvantaged ones (Fig. 3).

A 1% increase in rotavirus vaccination (dose 1) coverage is associated with a 1% decrease diarrhoea hospitalization (Table 3). Similarly, for every additional month after the rollout of the rotavirus vaccine (dose 1), there is a 2% decrease in diarrhoea hospitalization (Table 3). Supplement Fig. 2 show a downward trend in the predicted number of cases as the number of months post-rotavirus vaccine (dose 1) rollout increase. Furthermore, diarrhoea hospitalization was 10% lower in the period when the first dose of the rotavirus vaccine was administered compared to when it was not universally administered (Table 2).

Comparing the observed and expected cases, the number of diarrhoea cases reduced by 31%, 31%, 47%, and 57% in 2018, 2019, 2020, and 2021 respectively (Table 4).

Cost–benefit analysis

The productivity loss (indirect cost) due to mortality is between 92 and 89% of the total cost, which is due to the significant valuation associated with an average of 48 years of life lost with each death (Fig. 4). While taking a true societal perspective accounting for the cost associated with mortality, we presented the costs including and excluding those indirect costs. The two methods used to appraise the indirect costs of mortality—either using primary data estimates or the GDP per capita estimates as valuation measures—are presented.

When considering the expenses (government and household) and the productivity loss associated with treatment, along with the immunization programme cost, and assuming all other factors remained constant, we estimated that diarrhoea costed the country about $129 million since 2018 with the introduction of the rotavirus vaccine. If the vaccine hadn't been introduced, we expected the cost to rise to $186 million (Fig. 5)—a $57 million net benefit (Fig. 6). When adding the indirect cost of mortality, we estimated the current cost at $1,925 or $1,326 million, depending on the valuation method chosen, either including or excluding the loss

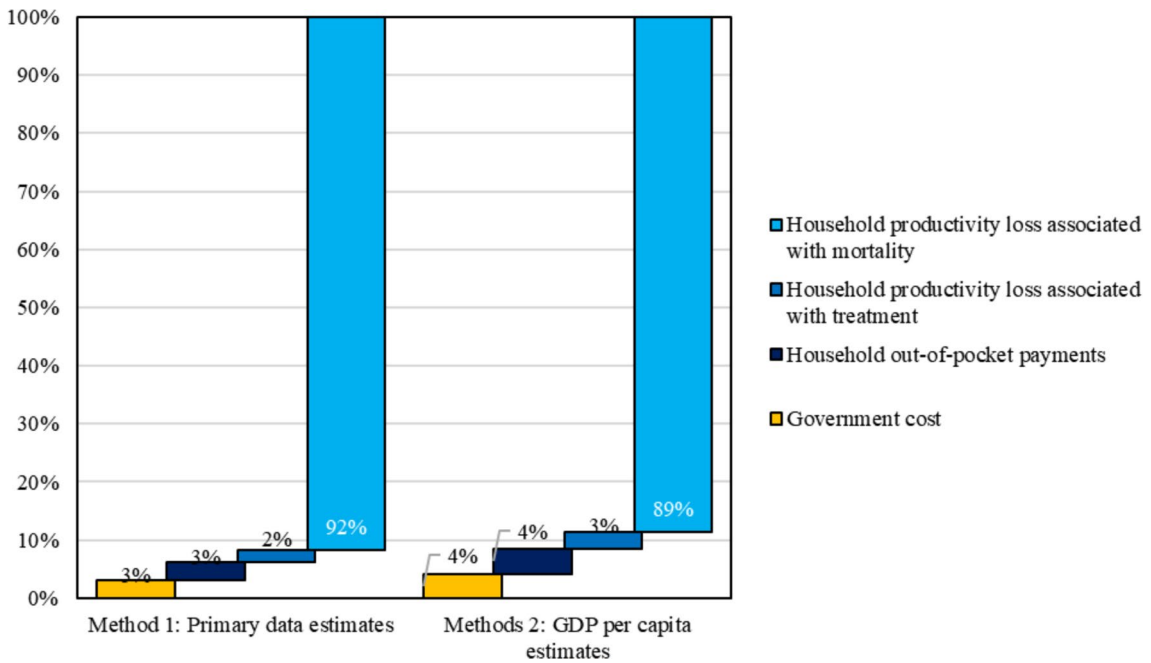

Fig. 4 Disaggregation of the total expected/observed cost by type of cost

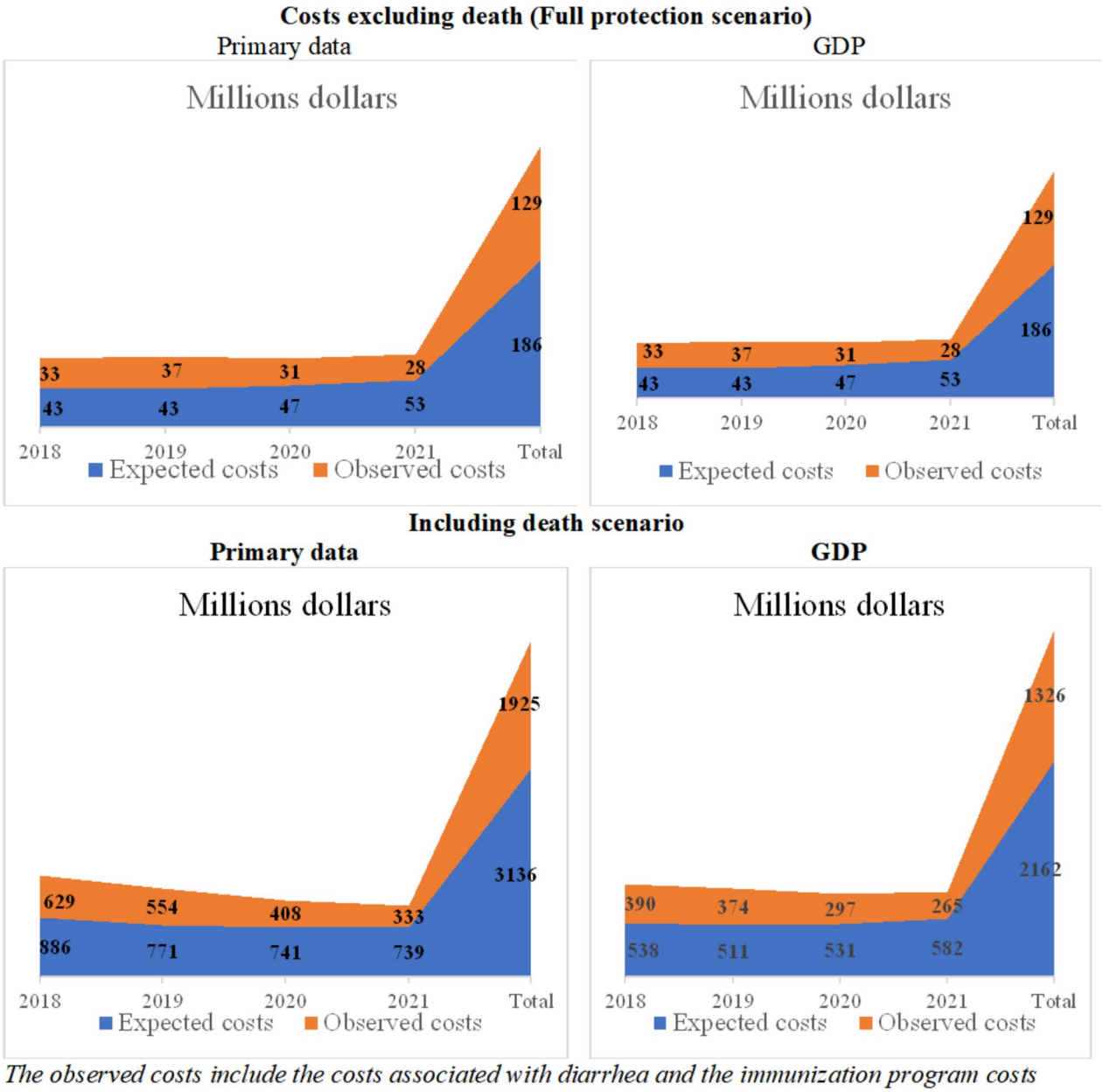

Fig. 5 Expected and observed costs due to diarrhoea, including or excluding productivity loss due to mortality generated using primary data estimates and the GDP per capita

of productivity due to deaths, given that the vaccine primarily prevents cases of illness. If the vaccine were 100% effective in preventing deaths, there would be no deaths, and the estimate would also be about $129 million.

However, the net benefit is not positive for all parties involved. Comparing the observed costs with the immunization programme in place against the expected costs without it, the government see an increase in overall spending of $21 million (Fig. 6). However, this increase is well compensated by the decrease in household out-of-pocket payments, which decreased by $40 million (Fig. 6). For each dollar invested in the rotavirus immunization programme, we see a return on investment of $1.48 without mortality costs and, with mortality costs, $30.40 (Method #1) or $20.68 (Method #2) if the vaccine does not provide any additional protection against death, and $77.92 (#1) or $52.68 (#2) if there is full protection against death (Fig. 7).

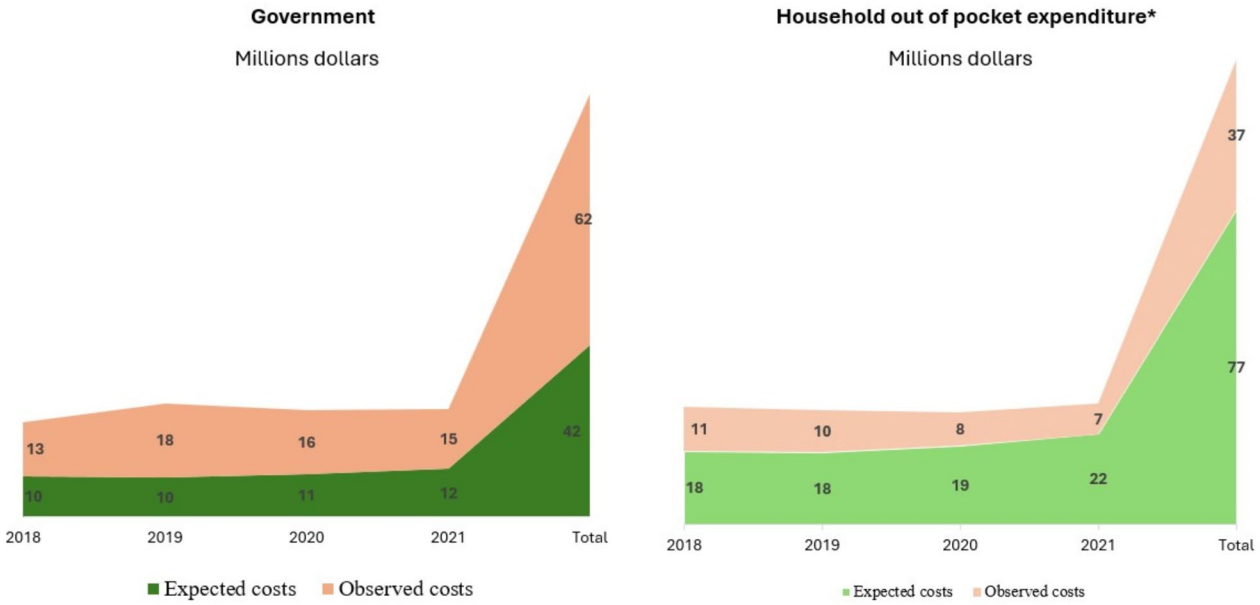

Fig. 6 Overall household and government cost

The largest net benefit and return on investment, regardless of the method to appraise mortality costs, occurs three years (2021) after the vaccine introduction. For each dollar invested in the vaccine, there is a societal return on investment between $40 and $135 (or $22 and $80, method #2) for 2018 (Fig. 7).

Due to the "pro-disadvantaged" distribution of diarrhoea cases and if we can assume that all those who reported diarrhoea should seek healthcare (oral rehydration solution therapy at minimum), we estimated that the benefits of the rotavirus immunization programme have been distributed to favour the most disadvantaged in Uganda (Figs. 8). Assuming equal household costs across the quintiles (to avoid overvaluing the more privileged groups), each dollar spent on the rotavirus vaccine programme yielded a significant return on investment when considering its impact on household out-of-pocket payments. On average, the first and second most disadvantaged groups had a return on investment of $1.28 and $1.14 per dollar spent, whereas the other three groups ranged between $0.88 and $0.99 (Fig. 8).

Discussion

Our study provides valuable information on the coverage and benefits of the rotavirus vaccine in Uganda. The improved coverage rates for the first and second doses of the vaccine, as well as the potential health and economic benefits of the vaccine, highlight the importance of continued investment in immunization programs. These findings are congruent with similar studies conducted in other countries, which have shown that rotavirus vaccination is an effective means of reducing the morbidity and mortality associated with diarrhoeal disease [16, 17, 30]. Economic benefits that contribute to the lowering of recurrent costs of curative care are especially critical in low- and middle-income countries that are struggling to meet their healthcare costs. According to the National Health Accounts for Uganda, 20% of the current health expenditure was attributed to preventive care compared to 55% of expenditure on curative care and yet 75% of the disease burden in the country is preventable. Increased allocation of funds towards preventive care can contribute to increased coverage of cost-effective interventions such as rotavirus vaccine.

Our study also revealed important disparities in vaccine utilization along socioeconomic and geographic lines. Such disparities contribute to lower coverage of the second dose of the vaccine and yet the effectiveness of the Rotavirus vaccine is higher among children who have received both doses of the vaccine [29]. This finding is consistent with previous research on immunization in Uganda, which has identified healthcare disparities along socioeconomic and geographic lines and high dropout rates especially for the newer vaccines [31, 32]. Overall, as of 2021, the coverage for the first and second doses

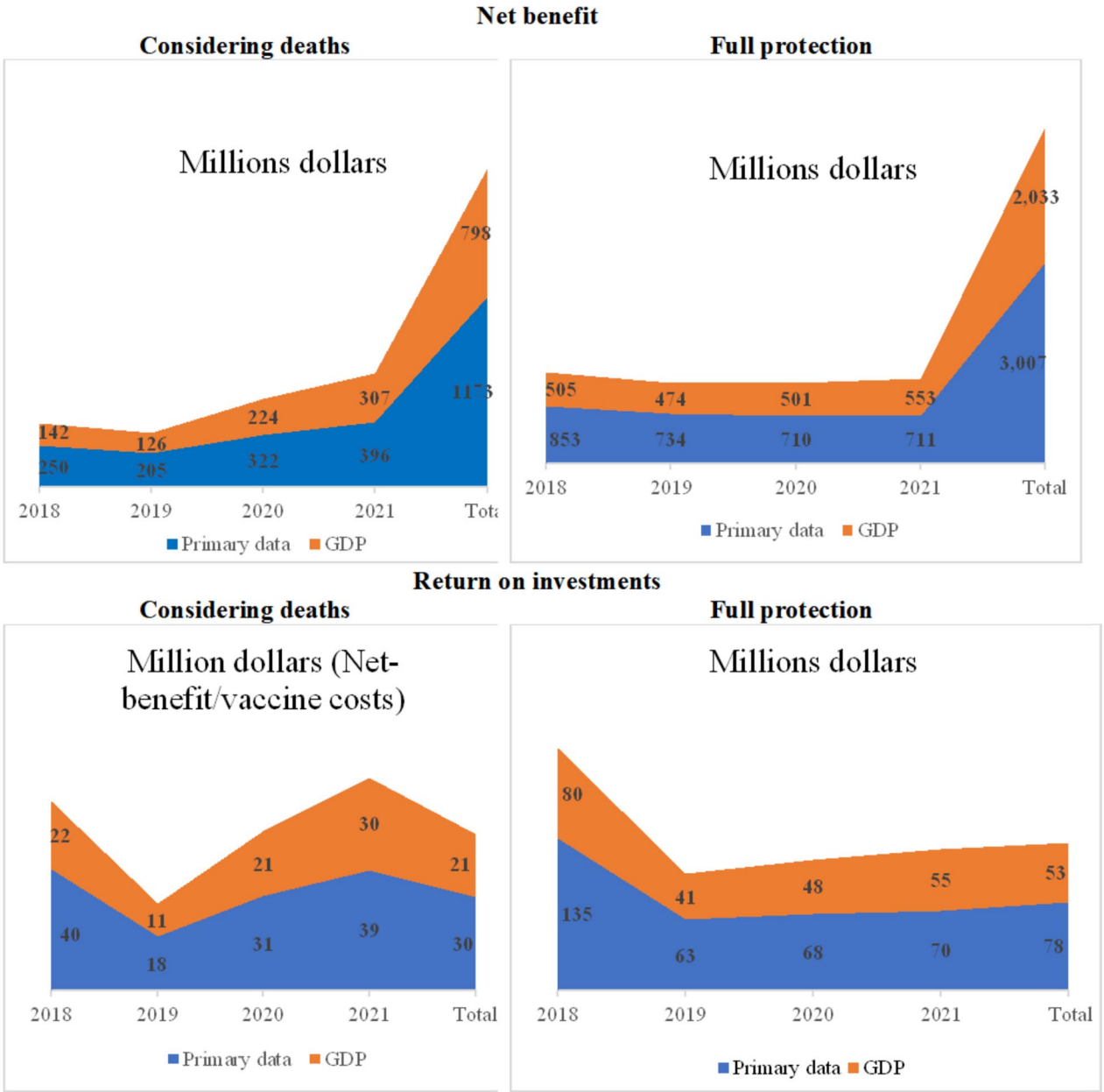

Fig. 7 Net benefit and return on investments

of the rotavirus vaccine was estimated at 89% and 65% nationwide [20].

The regions with the highest coverage were Teso (1st dose: 90%; 2nd dose: 78%), Kigezi (88%; 62%) and Karamoja (84%; 71%). While the regions with the lowest coverage were Bugisu (63%; 30%) and Busoga (68%; 48%). In the latest DHS (2016), Karamoja, Bukedi, and Kigezi also present high vaccine coverage for the first dose of the 10-valent pneumococcal vaccine (PCV), given when the child is 6 weeks old and relatively new (introduced in 2013). The lowest coverage for PCV in 2016 was found in Tooro (75%) and Lango (69%), with Busoga not far above (81%). Historically, the Karamoja region populated with nomadic pastoralists was difficult to reach for healthcare services. However, following the resurgence of several infectious diseases (*e.g.*, yellow fever, *Peste des petits ruminants*), the national government made special provisions to reach all "hard-to-reach" populations in the region, culminating with the Family Health Days implemented

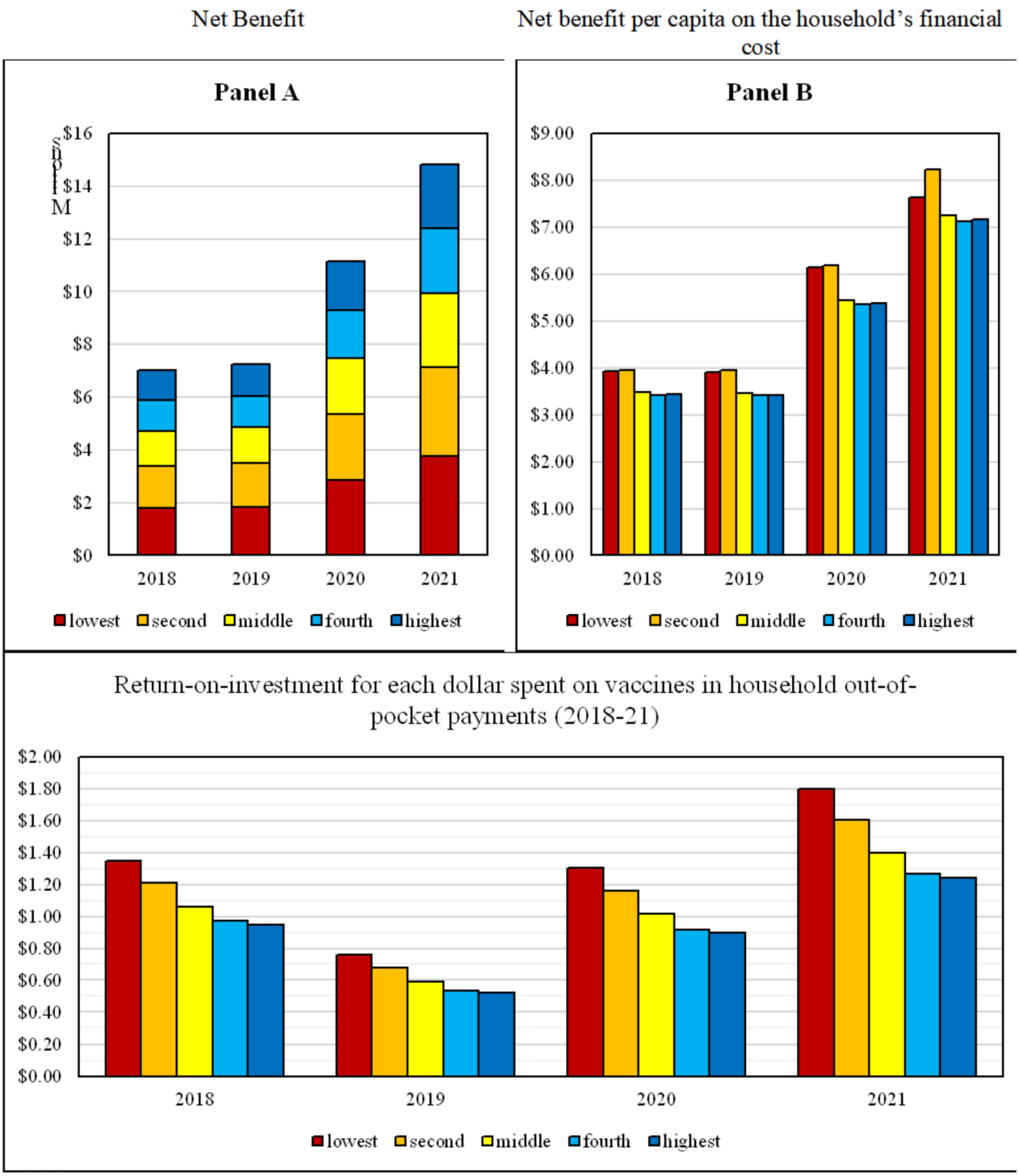

Fig. 8 Net benefit, net benefit per capita, on the household's financial cost (out-of-pocket expenditures only) and return on investment by level of sociodemographic disadvantage, excluding the immunization program cost

in 2011 and still ongoing [33–35]. A continued focus on these inequalities and implementing interventions that target the most vulnerable populations may be an important step in reducing the burden of disease caused by diarrhoeal disease. Indeed, our work demonstrated higher rates of return on investment for the most disadvantaged groups.

While the DPT-3 reported using our adjusted DHIS-2 data was consistent with the WHO/UNICEF estimates, the rotavirus estimates were inconsistent when comparing the estimates in the two sources. It is imperative to note, however, that discerning the reliability of either set of estimates poses a challenge, given that both sources derive their calculations from an array of assumptions. Despite the inconsistencies, it is noteworthy that both sets of estimates contribute valuable insights into the trends associated with access to the rotavirus vaccine. This paper, in particular, underscores the significance of routine health facility data as a pivotal tool in monitoring the coverage of health interventions.

Placing these results in the context of economic development, the annual net benefit we estimated for 2018 to 2021 represents between 0.58–0.98% and 1.75–2.59% of Uganda's GDP (between $3.29B and 4,05B in current US dollars), depending on the vaccine providing no or full protection against death. When excluding productivity loss due to deaths, the introduction of the rotavirus vaccine still generates a significant annual net benefit between 0.02% and 0.06% of the GDP. Pro-disenfranchised, this introduction also contributes meaningfully to the economy at a scale few other policies can offer. However, the high cost of adding such vaccines to the routine immunization systems of low-income countries cannot be ignored as countries transition from reliance on GAVI financial support towards self-financing [30]. The Uganda National Expanded Program for Immunization currently has six different vaccines, that protect children under five years from ten preventable diseases in its routine schedule, and it is constantly considering the introduction of more vaccines. Most of these vaccines are currently funded by GAVI. However, as countries transition from donor funding, it is expected that they will be able to support the vaccines on their routine immunization schedule. However, this may be difficult for countries such as Uganda which spends only 0.7% of their GDP on health resulting in a per capita expenditure of only $36, subsequently having chronic shortages in health funding [36]. Such countries can therefore consider lowering the public cost of vaccinations by recommending public funding of additional vaccines such as rotavirus vaccines to the most at-risk populations rather than targeting all children. Implementation of such strategies can be implemented through vouchers that can be awarded only to the target population. Vaccines should also be included as part of prepayment programs in countries with insurance to lower the need for public funding of vaccines.

Secondly, considering the reduced efficacy of rotavirus vaccine in countries with high child mortality [29, 37], the high cost of vaccines, and the transmission of rotavirus primarily through the oral faecal route [38], other interventions that can also contribute to reduced infection should also be prioritised by low- and middle-income countries. Work by Bwogi et al. (2016) in Uganda, found an association between the consumption of raw vegetables, family ownership of dogs and rotavirus infection [7]. Similarly, the Global Burden of Disease 2017—Diarrhoeal Disease Collaborators (2020), found that the largest declines in mortality due to diarrhoeal disease were due to exposure to unsafe sanitation, childhood wasting and low use of oral rehydration salts. Countries with a high burden of diarrhoeal disease should also step-up efforts to improve proper washing and preparation of vegetables before they are consumed, improved sanitation and hand hygiene as well as adequate nutrition as long-term strategies for reducing the incidence of diarrhoeal diseases.

Thirdly countries such as India have introduced rotavirus vaccination using domestically manufactured vaccines [30]. Developing countries should be supported to set up the infrastructure required to develop their vaccines to reduce reliance on external support for vaccinations. The use of routinely aggregated healthcare information systems is an important aspect of our study, as it highlights the potential for these systems to be leveraged in the monitoring evaluation of immunization and other public health interventions. The present study tracked vaccine coverage and disease prevalence using a combination of government data sources, typically readily available to public agents and local researchers. Significant improvements have been made in data reporting on these databases in recent years, particularly since the implementation of the DHIS2 facility data input and management system [39]. However, limitations in data quality, completeness, and accuracy persist and may hamper efforts to accurately measure vaccine coverage and effectiveness. Such challenges may limit the ability of researchers to conduct a similar analysis in other settings [40]. Nonetheless, the use of these data sources is an important step in improving the transparency of vaccine coverage and effectiveness data and may help to inform decision-making in the context of public health interventions.

Furthermore, while there are recurrent efforts to conduct cost-of-illness studies and economic evaluations providing "real-world" monetary valuations, they are only published sporadically and their method varies significantly, limiting modellers' ability to integrate them into cost–benefit analyses [41]. As cost data from the patient's perspective are not typically regularly collected in government systems, researchers must rely on ad-hoc evidence to build relevant and accurate value estimates. In sync with WHO guidance on conducting cost-effectiveness analyses for diarrhoeal diseases, we recommend the

immediate application of new empirical cost estimates to economic evaluations such as this one to provide policy-relevant impact evaluations for large interventions such as immunization and, reversely, demonstrate the external validity of the new cost estimates [42]. Furthermore, we recommend using economic evaluations that account for distributional equity in health and economic outcomes to highlight the contribution of modern vaccine programs to supporting the disenfranchised as current cost-effectiveness studies often ignore financial risk protection afforded to households. Extended cost-effectiveness analyses have addressed this gap [43], but a distributional benefit–cost analysis can expand upon this by allowing for comparability across other sectors that do not have morbidity or mortality outcomes. Additionally, distributional benefit–cost analyses are in line with the universal health coverage framework posed by the WHO whose dimensions involve expanding coverage to the most vulnerable (captured by our distributional analysis, rather than the poorest), expansion of services offered (captured by our assessment of a new vaccine), and assessment of financial risk protection afforded (captured by our benefit–cost framework which includes the cost of illness for both the government and households).

Study limitation

Productivity loss was estimated through the human capital approach using the average annual income as reported by caregivers, which presents several biases [4]. First, questions about income are sensitive, and the reliability of self-reported income can vary. The surveys were conducted to ensure confidentiality and privacy to encourage caregivers to provide an accurate estimate. Second, income was mainly reported as daily, weekly, monthly, and seasonal estimates, with only a few caregivers reporting an annual income. The survey asked for the caregiver's best estimate of what they do in their preferred time unit, and data collectors calculated the annual amount from the provided estimate and asked caregivers to confirm it to limit this bias. Finally, we chose to give the same valuation (government cost, treatment cost, and productivity loss) to all cases across quintiles, despite evidence that these costs were greater in the higher quintiles, to avoid amplifying the weight of the more privileged group.

While the vaccine plays a significant role in reducing the burden of diarrheal disease, it is important to recognize that other factors, such as improvements in water, sanitation, and hygiene, as well as overall healthcare access, that contribute to the reduction in diarrhoea hospitalization were not considered in modelling projection.

Furthermore, the generation of the denominator relies on DPT-1 survey-based coverage estimates. However, the consistency in trends within the regions suggests that DPT-1 could be utilized as the optimal indicator for deriving the immunization coverage denominator. Additionally, the DPT-1 estimates are from the 2016 survey, which may not consider some of the changes. However, we note that substantial changes within a 5-year timeframe are usually unexpected for an indicator that has attained near-universal coverage. In fact, the recent 2022 Uganda Demographic Health Survey preliminary results indicate a 96% coverage for DPT-1 [44]. Furthermore, considering the challenges associated with private-sector reporting, our analysis does not incorporate the contribution of private health facilities. It is noteworthy that individuals from affluent socio-classes and urban residents typically access health services through these private channels. Therefore, the distribution of costs across socio-classes may not fully capture the dynamics of immunization coverage in segments of the population relying on private health facilities. Nonetheless, according to available evidence, close to 75% of the population accesses immunization services from public health facilities and therefore, the adjustment of our data to accommodate the remaining 25% of the population accessing immunization services from private health facilities could have potentially alleviated reporting bias. Lastly, it is essential to acknowledge that addressing outliers with median estimates, while a common statistical practice, may have inadvertently overlooked the occurrence and impact of diarrhoea outbreaks.

Conclusion

Our study contributes to the growing body of evidence supporting the value and impact of the rotavirus vaccine. The positive impact of the vaccine on reducing the burden of diarrheal diseases and the associated costs are both significant. Additionally, the rotavirus vaccine has demonstrated significant health benefits, particularly for socially disadvantaged groups. This emphasizes the importance of ensuring equitable access to vaccines as one means of addressing disparities in healthcare delivery. Moreover, our study has highlighted the potential of using routine health data for economic benefits analysis and assessing geographic disparities. By utilizing existing data sources, we have been able to uncover the economic advantages of investing in the introduction and scale-up of rotavirus vaccine over time. This information can guide decision-making and resource allocation towards immunization programs in Uganda. The evidence of a positive return on investment for the rotavirus vaccine, even when excluding indirect benefits and mortality impact underscores the importance of prioritizing and strengthening vaccination efforts.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12962-024-00586-5.

Supplementary Material 1.

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Author contributions
RMK, GB, and BP contributed to the conceptualization of the paper. RMK led the acquisition of data and data cleaning. RMK and GB led the analysis and the writing of the original draft of the manuscript. All authors reviewed and provided feedback on the draft and approved the final draft of the manuscript. All authors had final responsibility for the decision to submit for publication.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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