Vaccination against rotavirus

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Summary

The third African Union Agenda 2063 (healthy and well-nourished citizens) cannot be achieved without the prevention or control of diarrhoea which is a major leading cause of death especially in children under 5. This study employed a simulation based decision analytic Markov model using retrospective data from eight Africa countries that have high diarrhoeamortality rate to evaluate the cost-benefit of implementing rotavirus vaccination in Africa to prevent diarrhoea. The median BCR obtained was 44.

Background

Diarrhoea remains one of the simplest diseases to prevent and manage but yet remains a major killer of children under 5 years(UNICEF, 2018). In a recent survey, it was ranked as the fifth leading cause of death globally and still ranks as the third leading cause of death among childhood diseases. Africa remains the continent with the second highest prevalence and mortality after Asia (WHO/IHME, 2017).

Gastroenteritis (a bowel infection) is a common cause of diarrhoea in both adults and children although the disease can result from other causes such as food allergy, medication or irritable bowel syndrome. Gastroenteritis can be caused by virus (rotavirus), bacteria (Escherichia coli, campylobacter) and parasite (giardiasis). These infections are contacted particularly in areas with poor standards of public hygiene typical in developing nations. Rotavirus vaccine protects against rotavirus infections, the leading cause of severe diarrhoea among young children(WHO, 2013). The vaccine can prevent up to 96% of severe diarrhoea (Soares-Weiser et al., 2010).

Statement of Problem

With healthcare budgets decreasing and costs of interventions increasing, governments and health organisations are under pressure to ensure that they achieve the best value for money while maintaining high quality healthcare delivery. Payers and decision-makers require information about the impact of an intervention on diarrhoea prevention to know if it would be worthwhile to scale-up the treatment in Africa. As decision-makers desire to get the best value for money, they are faced with the challenge of choosing the best preventive approach for childhood diarrhoea among several alternatives.

Study Justification

The third African Union Agenda 2063 (healthy and well-nourished citizens) cannot be achieved without the prevention or control of diarrhoea which is a major leading cause of death especially in children under 5. Considering rotavirus vaccination as an option that can prevent diarrhoea based on WHO recommendation and other research findings (Okafor & Ekwunife, 2017), it will be necessary to determine if the benefits of vaccinating the greatest number of African children at risk out-weighs the cost if implemented. Besides, WHO-CHOICE recommends economic evaluation in order to inform the best option in terms of maximum health gain with minimal expenditure, hence the need for a cost-benefit analysis of implementing rotavirus vaccination.

Study Objective

The principal objective of this study was to evaluate the cost-benefit of implementing rotavirus vaccination in Africa to prevent diarrhoea. Also to determine if there would be need for scale-up of the vaccination program in Africa.

Methods

This study employed a simulation based decision analytic Markov model using retrospective data from eight Africa countries (Chad, Angola, Somalia, DR Congo, Benin, Nigeria, Burundi and Cameroun) which have highdiarrhoea mortality rate of at least 10% for children under 5 and with high prevalence of diarrhoea(WHO/MCEE, 2018).

The intervention used in the study was a monovalent rotavirus vaccine (RV1). The RV1 requires two doses for complete vaccination whereas the pentavalent rotavirus vaccine (RV5) requires 3 doses for complete vaccination. The RV1 will save time and cost and thus, was used in our evaluation. The cost calculation was carried out for population under one year since the vaccination with RV1 is for children between 6 to 32 weeks of age. We used DTP3 coverage rate for each of the countries as the intervention target rate(WHO/UNICEF, 2018). Effectiveness of the vaccine (relative risk ratio) was obtained from Cochrane data base(Madhi et al., 2010). The transition probabilities of moving to the different health states (Asymptomatic, moderate or severe diarrhoea) were obtained from literature (Walker et al., 2013), (Lamberti, Fischer Walker, & Black, 2012), (UNICEF, 2015), while the transition probabilities to diarrhoeal death at under 1 year, 1 – 4 years, and under 5 years old children were obtain from 2017 GBD (Institute for Health Metrics and Evaluation, 2018).

The WHO 'Guidelines for estimating costs of introducing new vaccines into the national immunization system was adopted to estimate the resource use and costs associated with rotavirus vaccine implementation (World Health Organization Department of Vaccines and Biologicals, 2002), (Tan-Torres Edejer et al., 2003). Mixed (top-down and bottom-up) costing approach was used in the analyses. Cost was estimated from the payer's perspective which includes: cost of the vaccine (2 doses), logistic cost (which include salaries to health care professionals and health assistants, cost of vaccine storage in cold chain, vaccine transportation and vehicles maintenance), advocacy and social mobilization cost, surveillance cost, wastage and management cost. Cost of RV1 was obtained from international drug price indicator guide(WHO/MSH, 2015). Cost of tradable and non-tradable items were obtained from WHO-CHOICE(WHO, 2005), (WHO-CHOICE, 2008). The cost of providing health education to the mother/caregiver on 'diarrhoea prevention' by health professionals on vaccination days was built in their salary. Surveillance, advocacy and social mobilization cost per child was obtained from a demonstration study in Malawi (Madsen et al., 2014).Cost of utilities and equipments were calculated for period of 44 years (2020 – 2063) and annuitized.

The benefit of the intervention was measured in terms of Disability Adjusted Life Years (DALY) averted. DALY was calculated as the sum of the years of life lived with disability (YLD) from morbidity and the years of life lost (YLL) from mortality. The infant mortality, diarrhoeal mortality, percentage of diarrhoeal death, diarrhoeal infant mortality rate, diarrhoeal incidence and disability weights were obtained from 2017 GBD and (Troeger et al., 2017), (Troeger et al., 2018), (Institute for Health Metrics and Evaluation, 2018), (WHO, 2016). In calculating the monetary value of a DALY, we used the Harvard led guideline for conducting Benefit-Cost Analysis project(Robinson, Hammitt, & O'Keeffe, 2019). The valuation was based on ''value of statistical life year'' (VSLY) with one DALY avertedvalued at 1.3 times the GNI per capita of a country in sub-Saharan Africa.

Cost of vaccination was calculated for each country and averaged. The benefit was also calculated and averaged for each country based on the percentage of children at risk and the GNI per capita. The benefit was estimated over of the children's first 5 years (260 weeks) of life. The cost and benefit (YLD and YLL) were discounted at the rate of 5%. The median benefit-cost ratio per child will be used to estimate BCRs for other African countries.

Probabilistic Sensitivity Analysis (PSA) was used to assess simultaneous uncertainty in many variables. This approach is well suited to express overall parameters uncertainty (Briggs, Claxton, & Sculpher, 2006). To assess how simultaneous change of several variables affects the cost and benefit, a Monte-Carlo simulation (1000 iterations) was performed (a type of multivariate sensitivity analysis). This technique runs a large number of simulations by repeatedly drawing samples from probability distributions of input variables. Beta and gamma distributions were used for relative risk ratio and unit cost respectively.

Results

Cost of the Intervention

From the excel calculation sheet total cost of vaccination per child vary from country to country although not too significant. See table 1 and appendix 1 below for details.

Benefit of the Intervention

The benefit in DALY averted was obtained as the difference between the 'vaccination scenario' and 'no vaccination scenario'. DALY averted also varied from country to country. The BCR for Nigeria, Angola, Benin, Burundi, Somalia, Cameroon, Chad and DR Congo were: 126, 100, 30, 13, 13, 64, 58, and 17respectively. The median BCR was 44. Details are shown in table 1 and appendix 1.

The Monte Carlo simulation performed showed that the result was insensitive to the parameters.Thus, the result is deemed robust.

TABLE 1: UNIT COST, BENEFIT AND BCR FOR RV1 INTERVENTION IN 8 DIFFERENT COUNTRIES

Country	Mean Cost	Mean Benefit	BCR
Nigeria	5.31	668.72	126
Angola	8.58	853.41	100
Benin	7.02	211.90	30
Burundi	4.87	62.55	13
Somalia	6.32	83.23	13
Cameroon	5.68	363.21	64
Chad	7.50	438.12	58
DR Congo	5.79	96.07	17
Median BCR			**44**

The population of Africa in 2018 was approximately 1,288 million (World Population Review, 2018),(Worldbank, 2017). Based on annual birth of 35 per 1000 in Africa (World Population Data Sheet, 2018),(WorldBank, 2018) the number of children at risk of having rotavirus diarrhea and needs the vaccine is about 45 million children each year. Thus, with a BCR = 44 the estimated benefit of vaccinating all children is $12 billion per year (45 million * $44 per dollar spent on vaccination * $6.08 per vaccination per child), while total cost is $0.27 billion per year (45 million * $6.08 per vaccination per child).

Discussion

As the recent GBD 2017 shows the importance of diarrhoea disease especially in Africa, African leaders are faced with the challenge of rational decision making in allocation of fund due to scarce resources. This study provides estimate and implications that will guide decision making.

Some factors have the potential to affect the BCRs. A key factor is the cost of vaccination in each country. A high rate of diarrhoeal death will cause an increase in the benefit component (averted DALY) with use of RV1. High vaccination coverage has the advantage of increasing total benefit and reducing overall cost per infant because some cost components are fixed regardless of the number of infants to be vaccinated.

This study showed that there is a huge benefit if the vaccination program is scaled-up in Africa to reach all children. It will be more beneficial to leverage on already existing vaccination network in each country to save time and logistic cost. Similar results will be obtained for LIC, LMIC and UMIC in Africa. However, some factors can affect the replication of this result which includes corruption, unfavourable policies and poor power supply. The three-year GNI per capita of some UMICs and LMICs like Angola and Nigeria are above the GAVI threshold ($1500), hence they will not be eligible for GAVI support (WorldBank, 2017b). This can affect the scale-up in these regions. The African continental free trade agreement (AfCFTA) will positively affect the implementation of this program, reducing the huge variations in cost across some African countries.

Rotavirus vaccine needs a cold chain system from production to end user consumption. A major contributing factor to the cost of the vaccine is the cost of shipment in cold chain and wastage during transportation. Logistic managers always have a problem of maintaining their 'reserve stock' before new reorder and this can increase the risk of out-of-stock, over-stock, early expiration of some batches due to bulk supply etc. Although the WHO has a guideline for estimating vaccines needed per annum, the accuracy cannot be

guaranteed due to unforeseen circumstance. In a bid to lower the cost of scale-up, it will be worthwhile to establish one or two WHO-GMP certified vaccine manufacturing plants in Africa. This will reduce the cost of transportation, wastage cost, excessive stocking which leads to early expiration. The set-up of these plants will ease the production planning and maintain good stock level at all time. Since the project will be effective for at least 40years based on African Union projection, the plant set-up will in the long-run be highly beneficial as they will not only produce RV1 but also other vaccines like DTP, Pneumococcal vaccines etc needed in the regions.

The analyses have some limitations. Due to short-time frame, we could not conduct a one-way sensitivity analysis but a PSA. It will be worthwhile in further research to study how the individual parameters can affect the result. This will provide useful information for decision making. BCR for countries in North and Southern African were not evaluated. This would have given a clearer picture of the variation across the different African regions. There was no country specific data for effectiveness of the rotavirus vaccine for the eight countries. Thus we worked with regional estimate. Future study should consider use individual country effectiveness data.

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Appendix 1.

Table showing key components of the analyses

	Nigeria	Angola	Benin	Burundi	Somalia	Came-roon	Chad	DR Congo	
	Projected 2018	Projected 2018	Projected 2018	Projected 2018	Projected 2018	Projected 2018	Projected 2018	Projected 2018	
Crude birth rate per 1000 population	37.93	40.88	36.23	41.3	42.76	35.25	42.28	41.2	WB (WDI)
Infant mortality rate per 1000 live birth	62.66	51.73	62	40.9	77.49	53.64	71.83	68.04	WB (WDI)
Population	195.9M	30.8M	11.5M	11.2M	15.0M	25.2M	15.5M	84.1M	WB (WDI)
Births	7.4M	1.3M	0.4M	0.5M	0.6M	0.9M	0.6M	3.5M	
Infant deaths	465,535	65,155	25,798	18,876	49,729	47,679	47,006	235,663	
Population u1 yr	7.1M	1.2M	0.4M	0.4M	0.6M	0.9M	0.6M	3.4M	GBD 2017
Infant deaths (all causes)	330,000	37,985	13,900	12,500	23,000	22,870	36,454	89,048	GBD 2017 (approx. for 2018)
Diarrheal death under 1	55,000	5,750	1,900	1,600	4,020	4,150	8,950	11,400	GBD 2017
Diarrheal Mortality rate under 1	0.0077	0.0047	0.0047	0.0036	0.0065	0.0048	0.0145	0.0034	
Diarrheal death by age 1 - 4	48,088	4,231	1,684	1,434	2,577	3,524	11,087	7,493	GBD 2017
Diarrheal Mortality rate by age 1 - 4	0.0068	0.0035	0.0042	0.0032	0.0042	0.0041	0.0179	0.0022	
Diarrheal death by age 5	103,922	10,191	3,604	3,037	6,670	7,904	20,028	19,464	GBD 2017
Diarrheal Mortality rate by age 5	0.0146	0.0083	0.0090	0.0068	0.0108	0.0091	0.0324	0.0058	
% diarrheal deaths under 1	17%	15%	14%	13%	18%	18%	25%	13%	
Diarrheal infant mortality rate	7.56	5.88	5.52	4.71	6.36	5.27	13.3	6.25	Approximate
Diarrheal incidence	20.8M	4.3M	1.1M	2.5M	1.9M	3.1M	3.0M	15.8M	GBD 2017
YLDs	28,958	6525	1320	1800	2982	4597	5670	17,500	GBD 2017
YLDs	43,860	9870	3297	3520	4066	6030	5111	29,597	Markov Model Calculation
Diarrheal prevalence	33.5M	6.7M	2.3M	3.6M	292.7M	4.6M	4.6M	21.9M	GBD 2017
Income Classification	**LMIC**	**UMIC**	**LIC**	**LIC**	**LIC**	**LMIC**	**LIC**	**LIC**	GBD 2017
Disability weight (Moderate/Severe)	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	0.188/ 0.247	GBD 2017
Vaccination coverage (DTP3)	57%	59%	76%	90%	41%	79%	41%	81%	WHO-UNICEF 2018
Cost per child full immunization	5.31	8.58	7.02	4.87	6.32	5.68	7.50	5.79	Estimate
Effectiveness of vaccine	0.698	0.698	0.698	0.698	0.698	0.698	0.698	0.698	Madhi et al, 2010
DALY averted per case	0.262	0.195	0.187	0.172	0.206	0.194	0.503	0.151	Estimate
GNI per capita	1,960	3370	870	280	311	1440	670	490	Estimate
Value of DALY averted	668.72	853.41	211.90	62.55	83.23	363.21	438.12	96.07	Estimate
BCR	**126**	**100**	**30**	**13**	**13**	**64**	**58**	**17**	Estimate