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ORIGINAL ARTICLE

Cost-effectiveness analysis of rotavirus vaccination among Libyan children using a simple economic model

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Background: Rotavirus infection is a major cause of childhood diarrhea in Libya. The objective of this study is to evaluate the cost-effectiveness of rotavirus vaccination in that country.

Methods: We used a published decision tree model that has been adapted to the Libyan situation to analyze a birth cohort of 160,000 children. The evaluation of diarrhea events in three public hospitals helped to estimate the rotavirus burden. The economic analysis was done from two perspectives: health care provider and societal. Univariate sensitivity analyses were conducted to assess uncertainty in some values of the variables selected.

Results: The three hospitals received 545 diarrhea patients aged ≤ 5 with 311 (57%) rotavirus positive test results during a 9-month period. The societal cost for treatment of a case of rotavirus diarrhea was estimated at US\$ 661/event. The incremental cost-effectiveness ratio with a vaccine price of US\$ 27 per course was US\$ 8,972 per quality-adjusted life year gained from the health care perspective. From a societal perspective, the analysis shows cost savings of around US\$ 16 per child.

Conclusion: The model shows that rotavirus vaccination could be economically a very attractive intervention in Libya.

Keywords: diarrhea; rotavirus; cost-effectiveness; vaccination; Libya

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Rotavirus is an important cause of diarrhea in children, with globally more than 110 million cases, 2 million hospitalizations, 25 million outpatient visits, and 450,000 deaths annually. The incidence rate of rotavirus infection is often similar in developing and developed countries. Meanwhile, the mortality rate is much higher in the developing than in the developed world, as more than 80% of all the rotavirus deaths occur in the developing countries (1–6). The disease is manifested by watery diarrhea causing severe dehydration. As the virus destroys intestinal villi, the diarrhea may stop only when the villi have regenerated. The disease may lead to hospitalization and even death. During epidemic seasons, rotavirus is responsible for about 20–40% of all hospital admissions and 20% of the diarrhea deaths (6). These percentages were recently confirmed for Libya (7, 8). Adequate rehydration is the therapeutic strategy against the disease, but it does not affect disease spread. This diarrhea poses a high economic burden on the health care system and on the families because of the

high hospitalization and medical costs and because of work absenteeism of family members who normally care for the children (9–12).

Two safe and effective rotavirus vaccines on the global market, available since the end of 2005, can prevent diarrhea events in young children by more than 80% (13–18). These two vaccines against rotavirus infection have also been licensed in Libya. One is a two-dose vaccine, called Rotarix® (GlaxoSmithKline, Biologicals, Rixensart, Belgium), which can be given at the age of 2 and 4 months, and the other is a three-dose vaccine, called RotaTeq® (Merck, Whitehouse Station, NJ, USA), which can be given at 2, 4, and 6 months (15, 18). Introduction of the rotavirus vaccine into the National Immunization Program (NIP) of Libya could prevent many diarrhea events in children and may offset much of the health care cost (19–21). In Libya, the disease leads to a massive use of public hospital services, which provide free treatment. This study assessed the cost-effectiveness of introducing the rotavirus vaccine into the NIP in Libya. We present

theoretical modeling results with best estimates to measure the cost-effectiveness of the vaccine using a Libyan cohort, age ≤ 5 . The findings may support the decision of administering rotavirus vaccination into the NIP. We considered two different perspectives for the analysis. One is the health care system and the other is societal, including all the different cost items in the equation.

Subjects and methods

This is a theoretical modeling study that helps to define the economic value of rotavirus vaccination in Libya. We used the available country-specific data whenever possible. In the absence of country-specific data, assumptions were made. These assumptions were tested in sensitivity analysis. In the next paragraphs, we present the data collected at the national level, describe the model used, and present the assumptions put forth in the model. We also define the sensitivity analysis that was undertaken.

Data collection

We collected data during the period from August 2012 to April 2013 (9 months) to determine the proportion of rotavirus cases among children with diarrhea aged ≤ 5 in three public hospitals of two cities, Zliten and Khoms, located in the north-western part of Libya. Stool samples were collected from suspected cases in hospital care and in outpatient clinics to test for rotavirus. A suspected case was defined as a child aged ≤ 5 with episodes of diarrheal illness (loose stools more than three times a day) (18, 22). Once the sample was taken by the nurse, it was stored in a fridge at the hospital, and collected samples were transported once a week to the National Laboratory by car in fridge boxes. The samples were analyzed at the National Laboratory because the relevant tests were not routinely performed at the study hospitals. To identify rotavirus infections (group A), we used an immunoassay kit ProSpect Rotavirus Test (Oxoid Ltd, UK). The kit was provided by the World Health Organization, which also provided training for the laboratory staff on how to use the test.

Cost items

The confirmed rotavirus cases in the hospital setting were used to estimate the hospitalization cost and the indirect cost paid by parents. Since public hospitals provide health services free of charge, the overall cost for treating diarrhea is poorly documented because there are no bills of payment to refer to. We estimated the hospital cost by including the bed-day cost, the drug cost, and the laboratory test cost during hospitalization. The bed-day cost was estimated from staff salary, furniture, equipment, food, laundry, disposal, cleaning, utilities, and maintenance. Details of drugs and laboratory tests administered to the patients were retrieved from the patient files, and

their costs were obtained from the central pharmacy and the main laboratory at the hospital, respectively. Details of the expenditure involved were also collected from the pediatric ward in the year 2012. Furthermore, the total number of bed-days at the pediatric ward in 2012 was considered to determine the cost per bed-day. Cost per consultation of the general practitioner and that of the pediatrician in the outpatient clinic was determined according to expert opinion (23). Rate of inflation in Libya was obtained from the World Bank [4.7%, (24)]. It was used to estimate the current cost of treatment of a rotavirus patient.

Details of indirect cost was collected from interviews with the parents ($n = 130$). When a child was discharged from hospital care or from an outpatient clinic, each parent was asked to participate in an interview about all the costs they incurred due to the disease. The interview was voluntary and involved no payment. Each interview took about 15 min, and the same person interviewed all the participants. The information collected consisted of transportation cost from home to the medical or hospital and back, household cost, which included the extra cost families have when relatives and friends come to visit in order to provide support. These visits necessitate provision of food and beverages. Moreover, there is loss of income due to absence from work during the illness.

The model

A simple disease-specific decision tree model was used to assess the cost-effectiveness of rotavirus vaccination for a birth cohort estimated at 160,000 children. The model was developed in MS Excel and has already been published for the economic assessment of rotavirus vaccination in other countries, including Turkey (25). The model compares two theoretical situations of non-vaccinated and vaccinated children during the risk period from birth to the age of 5. It subdivides the disease condition into four health states: mild (staying home), moderate (seeking medical advice), severe (being hospitalized), and death. The model was selected because it is easy to use, transparent, and has a limited number of variables to work with ($n = 20$). The model also allows performing sensitivity analysis and budget impact estimates. The outcome is close to the more extended Markov cohort models that are more precise in some aspects of the vaccine impact related to vaccine compliance and completion (25).

Cost-effectiveness calculation

The cost for the rotavirus vaccine is presented as a condition for being cost-effective. It included the cost of the vaccine with the cost of administration per child and per full course. Vaccine administration cost was estimated considering the cost for staff, training, and transportation related to the rotavirus vaccine. Cold chain cost was excluded since rotavirus vaccine could utilize the same

storage used for other vaccines. The vaccine coverage rate is assumed to be the same as for the DPT vaccine in 2013, which was estimated at 98% for a three-dose vaccine because rotavirus vaccination can be given at the same age together with the DPT vaccine (26).

The model is used to evaluate under baseline conditions the effect of the vaccine on any rotavirus diarrhea event, medical visits, hospitalizations, and deaths. In addition, the model allows calculation of the cost-effectiveness of rotavirus vaccination when introduced into the NIP by comparing non-vaccinated and vaccinated situations. The model does this from different perspectives. One perspective is the health care system, where only the cost incurred by that institution is considered, and the other is the societal situation, which includes all costs from whatever source. The rate of rotavirus diarrhea in the birth cohort of ≤ 5 years old is based on the definition of diarrhea as set by the WHO criteria. The rates of medical visits and hospitalizations of the birth cohort were assumed based on literature review as well as on the deaths reported due to rotavirus in the birth cohort (7). Finally, we introduced a quality-adjusted life years (QALY) assessment per health state in the model equivalent to the one used in the Turkish model (25). The QALYs gained from avoiding cause-specific deaths is based on the life expectancy at birth for Libya (27). QALYs were selected here as we could easily refer to the reported literature on how QALYs were estimated for each health state in the model. The incremental cost-effectiveness ratio (ICER) was calculated per QALY gained, as well as per diarrhea event avoided, death avoided, hospitalization avoided, and medical visit avoided.

Sensitivity analysis

An extended univariate sensitivity analysis was performed on the key variables in the model assuming a range testing of 20% change (above and under) in order to identify the robustness of the ICER result. A 20% change should be able to identify a more meaningful value change for some of the variables selected. This is certainly the case when the baseline value such as vaccine efficacy has a high starting value. The results are presented as a tornado diagram of the 15 most influential variables considered separately from a health provider and from a societal perspective.

Approval

Approval for the study was given by the University of Malaya Medical Ethics Committee (IRP 908.6). Health authorities in the places of the study and National Center for Disease Control (NCDC) provided the permissions to carry out the study. Parents signed a consent form for the interview.

Results

Data collection

During the 9 months of data collection at the three hospitals, there were 545 cases of diarrhea in children aged ≤ 5 , of which 311 were due to rotavirus (57%). Most of the rotavirus cases were inpatient (77%). No deaths due to rotavirus diarrhea occurred at the hospitals during that period. The proportion of rotavirus diarrhea in each hospital and for inpatient and outpatient is presented in Table 1.

Costs

Total treatment cost for a rotavirus patient was estimated from hospitalization and patient data (Table 2). The average treatment cost for a rotavirus case was estimated at US\$ 661. The provider cost was US\$ 475, representing 72% of all the cost, while the contribution of patient cost was US\$ 186 (28%). The per diem (bed-day cost) was the highest cost item (50%), while the lowest cost item (5%) was the laboratory test. The analysis also indicates that all the cost data are much skewed, with big outliers to the right when we look in particular at the upper range values in Table 2. The average duration for hospital stay is around 3.02 days.

The household cost includes the cost of extra diapers and specific hygienic items for the child, as well as the hospitality cost for relatives or friends visiting due the child's illness.

Overall data input

The required variables with their baseline values for measuring the effect and the cost-effectiveness of rotavirus vaccination in children using the model are shown in Table 3.

For 25 values (highlighted in the table), a minimum and a maximum estimate were calculated based

Table 1. Proportion of rotavirus diarrhea in children aged ≤ 5

Place	Diarrhea cases	Rotavirus cases	Proportion rotavirus (%)
Zliten city	281	167	59
Khoms city	264	144	55
Hospitals	410 (75%)	239 (77%)	58
Outpatient clinic	135 (25%)	72 (23%)	53
Total number	545	311	57
Male	315	179	57
Female	230	132	57
0– <1 years old	336	175	52
1– <2 years old	142	91	64
2– <3 years old	46	33	72
3– <4 years old	10	6	60
4– ≤ 5 years old	11	6	55

Table 2. Cost of rotavirus treatment among children aged ≤ 5

Variable	Cost (US\$)			
	Mean	SD	Range	Median
Provider cost				
Per diem	332.69 (50%)	254.04	68–2,045	284
Medication	108.61 (16%)	226.26	15–3,284	66
Laboratory tests	33.94 (5%)	12.41	16–108	32
Patient cost				
Transportation	74.012 (11%)	80.27	10–912	60
Household	70.99 (11%)	80.52	19–557	30
Lost income (indirect cost)	40.68 (6%)	152.96	0–1,440	0
Total cost per patient	660.92	580.31	141–6,389	623

These costs were estimated in 2012 and adjusted with an annual inflation rate of 4.7% to 2014; SD = standard deviation.

on a 20% value change. These data were used in the sensitivity analysis.

Outcome and offsets

The effect of rotavirus vaccination and the cost analysis measured by the model for one cohort aged ≤ 5 is reported in Table 4. Introducing the vaccine would avoid 47,000 diarrhea events with a decrease of 3,400 hospitalizations, and 20,100 outpatient visits. Deaths related to rotavirus infection would be reduced by nine cases.

The model predicts that the universal rotavirus vaccination could offset more than 2 million US\$ in direct medical costs. The highest cost-offset is in hospitalizations avoided (1.6 million US\$) followed by the offset in medical visits (380,000 US\$).

ICER of rotavirus vaccine

The ICER in the base cases is US\$ 8,972 per QALY gained. This is below the Libyan per capita GDP of US\$ 10,132 in 2012 (24). Being under that threshold identifies the new intervention as being highly cost-effective according to the WHO's definition of cost-effectiveness (31, 32). Similarly, the ICER result per hospitalization avoided is US\$ 642, per outpatient visit avoided is US\$ 110, and per diarrhea event avoided is US\$ 47. For each death avoided the vaccine results in an extra cost of US\$ 245,734 (Table 5).

Including indirect cost

Including the indirect cost in the equation will heavily impact the economic value of the vaccine when considering the patient perspective. These indirect costs include three factors: the transport cost to and from the medical care unit, the household cost, and the loss of production. Table 6 reports the impact of each factor on the total cost of vaccination. As can be seen, it leads to important savings in the range of 16 US\$ per child of the

birth cohort, especially because of the reduction in the household cost, with more than 2.5 million US\$ cost gain. Under such circumstances, there is benefit for each family unit to pay for the vaccine because the cost of transportation plus the household cost is much higher than the vaccination cost.

Sensitivity analysis

For the health care perspective, we analyzed and tested the ICER results on many different variables. Figure 1 shows the results presented as a tornado diagram. This diagram indicates from high to low which variable has the greatest/smallest impact on the outcome measure as indicated in the X-axis above. For instance, the highest impact on the ICER result, as expected, is the vaccine price. The discount factor that takes into account the value decrease of the QALY per year (equivalent to the inflation rate) heavily impacts the QALY result on life expectancy. It is the next impact driver on the ICER result. The blue color indicates that a lower value for the variable is selected than the baseline. The red color indicates a higher value. So, the lower the price of the vaccine, the lower will be the ICER result. In contrast is the red color of death cases (the third variable). If that value is in red color (higher), the ICER result will decrease because there are more deaths to be avoided and therefore more benefit to be expected.

The sensitivity analysis for the societal perspective is analyzed on a different outcome measure than the ICER, because from the overall analysis in Table 6, we observed important cost savings. So the outcome measure selected is a cost difference and not an ICER result. Figure 2 presents the tornado diagram. Surprisingly, the cost of the vaccine is no longer the first driver of the analysis. Instead, the prevalence of the disease, the vaccine coverage rate, and the cost incurred by a household are the big influencing factors. There is a clear difference in what matters most depending on whether one considers a narrow perspective (health provider only) or a broader view (society as a whole).

Discussion

This study aimed to evaluate the economic value of rotavirus vaccination in Libya from the healthcare providers' perspective and from a societal perspective. Given the limited available data to estimate the disease burden, interpolation of data from various sources, with several assumptions, had to be made to perform the cost-effectiveness analysis. A simple decision tree model was selected to calculate the ICER for a group of children aged ≤ 5 .

The percentage of diarrhea cases in children in three major hospitals in Libya attributable to rotavirus infection was 57%. This is similar to many studies conducted in other countries, such as Oman (70%) and Iran (58%) (7).

Table 3. Input variables for estimating the cost-effectiveness of rotavirus vaccination with baseline, minimum (Min), and maximum (Max) values

Variables	Baseline	Min	Max	Source
Annual birth cohort	160,000			(28)
Vaccination coverage rate	98%	78%	100%	(26)
Inflation rate	4.7%	3.8%	5.6%	(24)
Cost per consultation GP (US\$)	15			Local expert opinion
Cost per consultation pediatrician (US\$)	29			Local expert opinion
Proportion going to the GP	70%			(7)
Cost for medical visit (US\$)	$15 \times 0.7 + 29 \times 0.3 = 19.2$	15.4	23.0	Calculated
Cost of prescribed drugs (US\$)	108.61			This study
Cost for hospital day care (US\$)	332.69			This study
Cost for lab test (US\$)	33.94			This study
Cost hospitalization (US\$)	$108.61 + 332.69 + 33.94 = 475.24$	380	570	Calculated
Cost labor woman per day (US\$)	34	27.2	40.8	This study
Proportion working mothers	35%	28%	42%	(29)
Days lost mild	3	2.4	3.6	(7)
Days lost moderate	1	0.8	1.2	(7)
Days lost severe	3	2.4	3.6	(7)
Cost indirect loss mild/event (US\$)	$34 \times 3 \times 0.35 = 36$			Calculated
Cost indirect loss moderate/event (US\$)	$34 \times 1 \times 0.35 = 12$			Calculated
Cost indirect loss severe/event (US\$)	$34 \times 3 \times 0.35 = 36$			Calculated
Cost for transportation severe (US\$)	74	59.2	88.8	This study
Cost for household (US\$)	70.99	56.8	85.2	This study
Cost vaccine per course (US\$)	27	21.60	32.40	This study
Disutility mild	-0.00016	-0.00013	-0.00020	(25)
Disutility moderate	-0.00068	-0.00055	-0.00082	(25)
Disutility severe	-0.00575	-0.00460	-0.00690	(25)
Life expectancy	75	60	90	(27)
Proportion mild	40%	32%	48%	(23)
Proportion moderate	15.1%	12.1%	18.1%	Local expert opinion
Proportion severe	2.44%	2%	2.9%	Local expert opinion
Proportion deaths	0.0055%	0.0044%	0.0066%	(7)
Vaccine efficacy against mild	75%	60%	90%	(30)
Vaccine efficacy against moderate	85%	68%	100%	(30)
Vaccine efficacy against severe	90%	72%	100%	(30)
Vaccine efficacy against death	100%	80%	100%	(30)

Cost of rotavirus diarrhea treatment was collected primarily from the patients who sought treatment for rotavirus infection. These were a good approximation of the true cost incurred for the disease treatment. In this study, treatment cost for rotavirus disease was US\$ 661 per patient, which is similar to that reported in Algeria (US\$ 650) (33). It is lower than that in Belgium (US\$ 1,005), Norway (US\$ 2,382), and Portugal (US\$ 2,172), but much higher than that in Egypt (US\$ 19), Vietnam (US\$ 20), and Brazil (US\$ 200) (11, 12, 33). Using the same coverage rate of DPT as for rotavirus vaccine of 98%, (26, 34), the model showed a large reduction in rotavirus infection of 47,040 for the birth cohort. This may offset 2 million US\$ in direct treatment cost. The ICER per event avoided was US\$ 47, but per QALY gained it was

US\$ 8,972. Both values are below the Libyan per capita GDP of US\$ 10,132 in 2012 (24). If we accept that the GDP per capita is the appropriate threshold for being cost-effective, we can say that the vaccine is good value for money, and that rotavirus vaccination is highly cost-effective using the WHO criteria for an intervention, and below the Libyan GDP per capita in 2012 (31, 32, 35). Similarly, the rotavirus vaccine was highly cost-effective in many countries, such as Vietnam, Indonesia, and Japan (36–38). In other countries, such as the Latin American countries, Thailand, and the Caribbean, rotavirus vaccination could also be cost-effective should the price of the vaccine be lower (39, 40). Most studies showed through sensitivity analysis that the price of rotavirus vaccine is a big driver of the cost-effectiveness result (39). Also, in

Table 4. Health outcomes and cost of treatment of rotavirus patients in no vaccination and vaccination scenarios

Variable	No vaccination	Vaccination	Difference
Efficacy of rotavirus vaccination	No.	No.	No. (%)
Birth cohort	160,000	160,000	
Rotavirus diarrhea events	64,000	16,960	– 47,040 (74)
Outpatient visits	24,160	4,035	– 20,105 (83)
Rotavirus diarrhea hospitalization	3,904	461	– 3,443 (88)
Rotavirus-related deaths	9	0	– 9 (100)
Cost of rotavirus cases	US\$	US\$	US\$
Total costs without vaccine	2,318,272	296,286	– 2,021,986
Total costs per patient	14	2	– 12
Vaccine costs	–	4,233,600	4,233,600
Outpatient visit	463,872	77,467	– 386,405
Hospitalizations	1,854,400	218,819	– 1,635,581
Total direct cost with vaccine	2,318,272	4,529,886	2,211,614
QALYS			
Mild condition	– 10.52	– 2.78	7.7
Moderate condition	– 16.54	– 2.76	13.8
Severe condition	– 22.46	– 2.65	19.8
Deaths	– 205.2	0	205.2
Total	– 254.7	– 8.20	246

Belgium, France, Ireland, England, and Wales, the cost-effectiveness of rotavirus vaccination was sensitive to the assumption of the vaccine price (41–44).

The findings from this analysis provide evidence for the expected benefit of the introduction of the rotavirus vaccine in Libya. Generalization of the findings related to the estimate of the disease burden has to be made with caution because the study was hospital based and cases of mild rotavirus infection in the population were not captured. The vaccine will avoid the latter cases and therefore improve the economic results. Real-life conditions will see a dramatic reduction in hospitalizations within the first 2 years after the introduction of the vaccine, with a high uptake because of the herd effect it will cause. The use of the model with imputation of some data from the literature helped to provide a sensitive estimate. But the ICER of rotavirus vaccination shows that it is highly cost-effective. Hence, the decision to incorporate the vaccine into the NIP of Libya is justified, and priority should be given to continuing allocation of a budget for this preventive program.

Table 5. Incremental cost-effectiveness analysis of rotavirus vaccination

Variables	NV	V	Difference	ICER (US\$)
Incremental cost/QALY				
Cost (US\$)	14.49	28.31	13.82	
QALYs	– 0.00159	– 0.00005	0.00154	8,972
Incremental cost/death avoided				
Cost (US\$)	14.49	28.31	13.82	
Deaths	0.000056	0	0.000056	245,734
Incremental cost/hospitalization avoided				
Cost (US\$)	14.49	28.31	13.82	
Hospitalization	0.0244	0.0029	0.0215	642
Incremental cost/outpatient visit avoided				
Cost (US\$)	14.49	28.31	13.82	
Outpatient visit	0.151	0.0252	0.1257	110
Incremental cost/diarrhea event avoided				
Cost (US\$)	14.49	28.31	13.82	
Diarrhea event	0.400	0.106	0.294	47

NV = no vaccination; V = vaccination; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

One limitation of this study is that it does not capture the total burden of the disease in the analysis. Another is that many assumptions had to be introduced in the model to keep it running. A more complete epidemiologic analysis of the disease burden would have helped understanding the management of the disease in the whole country, including remote areas.

An additional part of the study that is not presented in other cost-effectiveness analyses reported for that region is the collection of data on money spent on visits by relatives and neighbors who come to provide support during the stressful situation. During those visits, the cost incurred on drinks and cookies negatively impact the budgets of the families, which are already reeling under the cost of treatment. Those household costs were estimated here at 71 US\$ per event, which is much higher than the vaccination cost (see Table 3). This part of household cost has been underreported in the literature

Table 6. Including the indirect cost (US\$) in the economic evaluation of the vaccine

Cost type	NV	V	Difference
Transport cost (US\$)	288,896	158,893	– 130,003
Household cost (US\$)	6,535,623	3,978,223	– 2,557,401
Productivity loss (US\$)	2,711,677	1,669,970	– 1,041,707
Direct medical cost (US\$)	2,318,272	3,446,646	1,128,374
Total cost (US\$)	11,854,468	9,253,732	2,600,736
Total cost/child (US\$)	74.09	57.83	– 16.25

NV = no vaccination; V = vaccination.

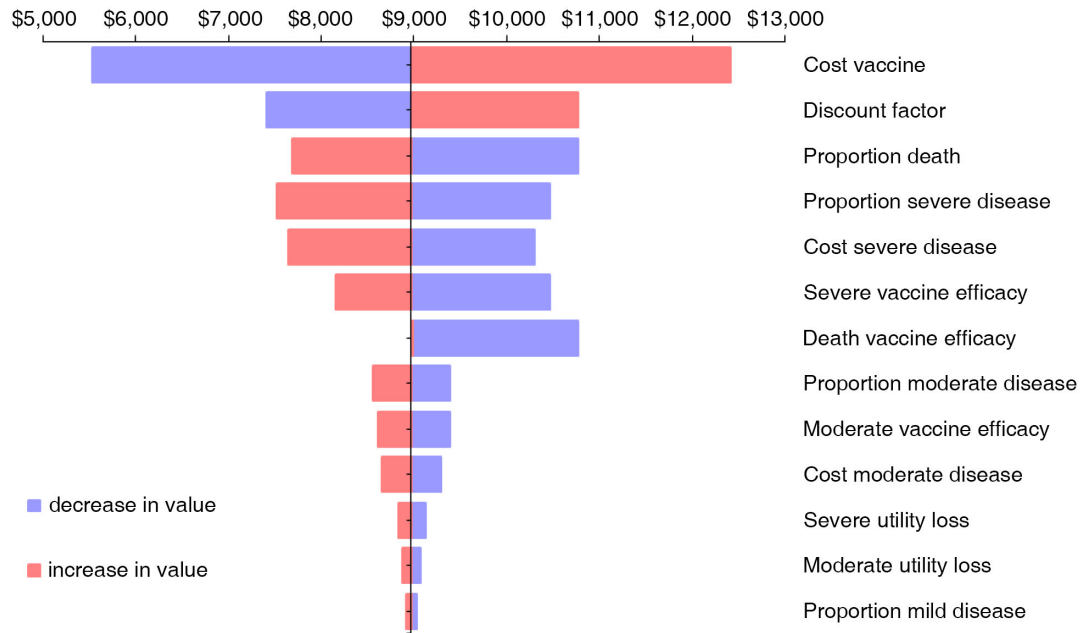


Fig. 1. Sensitivity analysis (tornado diagram) of the incremental cost per QALY gained analyzed from the health provider perspective (example: the lower the cost of the vaccine, blue color, the lower the cost-effectiveness result; the color changes at the baseline value of \$8,972, see Table 5).

and is not included in economic evaluations of the vaccine. Vaccination could help saving the family some money. Moreover, those visits are a means for spreading the disease. So, there are at least two hidden reasons of additional benefit by introducing the vaccine: an important reduction in social cost burden for the parents and the limitation of the spread of the virus.

Conclusion

Rotavirus infection represents 57% of hospital treated diarrhea in Libyan children aged ≤ 5 . Introduction of rotavirus vaccination is expected to alleviate a significant burden of the disease and is highly cost-effective in Libya. The decision by the government to incorporate this vaccine into the NIP is justified.

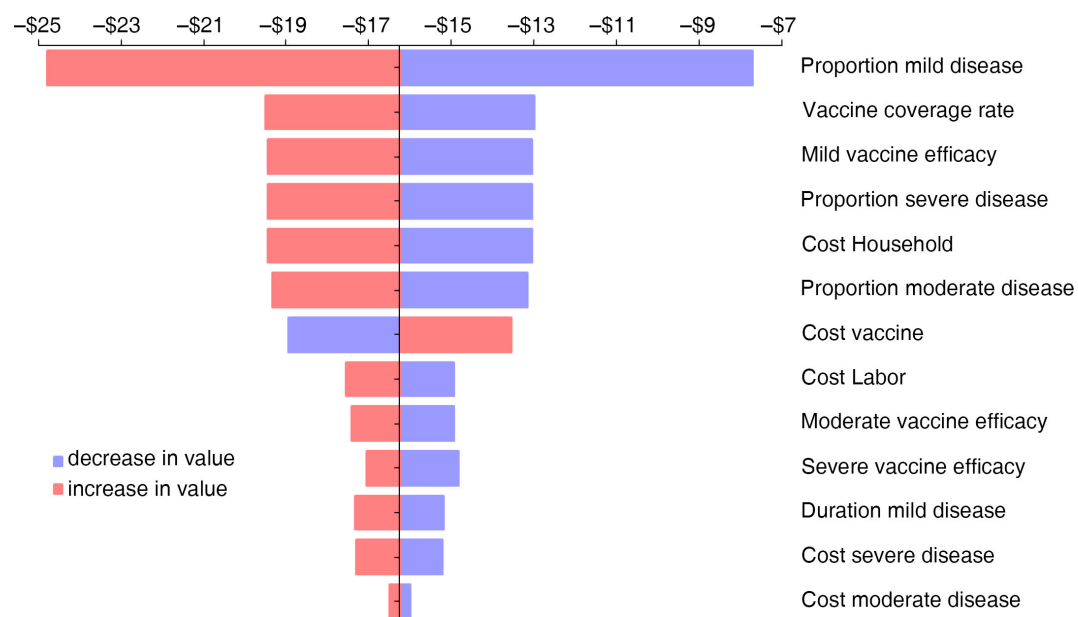


Fig. 2. Sensitivity analysis (tornado diagram) on the cost difference per child in the birth cohort (Vaccination – No Vaccination) analyzed from a societal perspective (example: the lower the proportion of mild disease, blue color, the lower the cost savings on the X-axis).

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