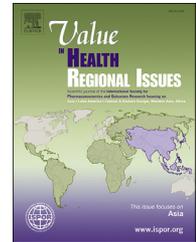




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## Economic Evaluation

# Budget Impact Analysis of Rotavirus Vaccine Adoption in the Childhood Immunization Schedule of Iran

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### ABSTRACT

**Objectives:** To examine the budget impact of introducing the RotaTeq® vaccine (Merck and Co Inc, West Point, PA) to the national immunization program in Iran. **Methods:** The pre- and postvaccine introduction costs were compared. The total annual costs included the vaccination and diarrhea treatment costs. The health outcome was the estimated annual cases of the disease. To evaluate the net budget impact, the annual prevaccine introduction cost was reduced from the postvaccine introduction cost. The sensitivity analysis was done to reduce the uncertainties. **Results:** The total cost of vaccination for 5 years would be more than \$184 million. Nevertheless, the financial savings would be about \$45 million and

\$7.5 million because of the reduction in the number of patients after vaccination in inpatient and outpatient sectors, respectively. So the incremental cost would be \$131 450 210 during 5 years of immunization. **Conclusions:** The results show that the inclusion of rotavirus vaccine in the national vaccination program would have a significant effect on health budgets and would raise government expenditure.

**Keywords:** budget impact, immunization, Iran, rotavirus vaccine

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## Introduction

Rotavirus is a major cause of gastroenteritis in children. Globally, it causes millions of gastroenteritis episodes per annum; almost all children will have at least an infection by the age of 5 years.<sup>1</sup> Although the exact burden of the disease is not clear in Iran, it is expected to cause about 35% cases of gastroenteritis; in fact, 39% of hospital admissions and 31% of outpatient cases are due to rotavirus.<sup>2</sup>

Currently, 2 types of vaccines are available in global markets: RotaTeq® (Merck and Co, Inc, West Point, PA) and the monovalent Rotarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium). Despite their differences in the strains, the vaccines have no significant difference in overall efficacy or in serotype-specific efficacy.<sup>3</sup>

Rotavirus infection naturally produces a low level of protection and the vaccine strengthens this protection. Therefore, the goal of the vaccine is mostly to prevent moderate and severe disease. Rotavirus vaccine considerably decreases the number of hospitalized children.

Therefore, this vaccine should be used in countries with high rotavirus-related morbidity and mortality rates.<sup>4</sup>

The incidence of rotavirus is similar in the developed and developing world; improvements in hygiene, sanitation, and water supply have little to do in the prevention. This underscores the importance of introducing rotavirus vaccines in national immunization programs. Nevertheless, the economic impact of the introduction of the vaccine in a given country has to be studied,<sup>5</sup> because the disease burden and health and economic situations are different from country to country and these factors are critical to decision making.

Budget impact analysis is an important part of health technology assessment that besides cost-effectiveness analysis can inform decision makers about a new health technology if its adoption is affordable considering the resource and budget constraints of the context.<sup>6</sup> So far, 2 cost-effectiveness studies have been conducted in Iran that show that vaccination against rotavirus is cost-effective.<sup>7,8</sup>

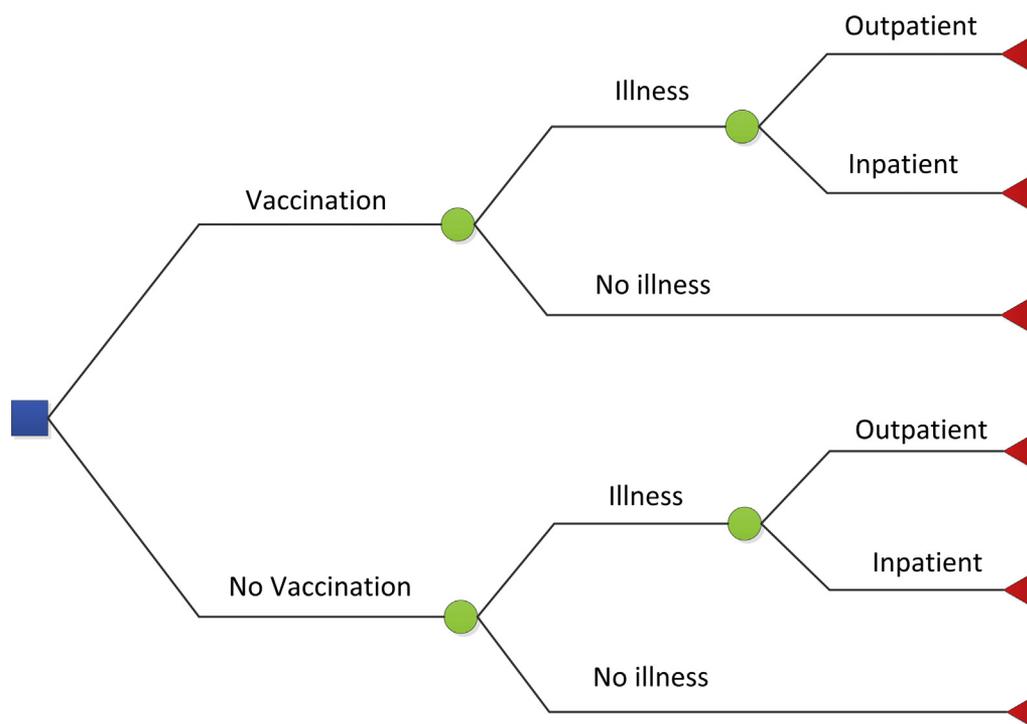
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**Fig. 1 – Decision tree model to figure out the possible outcomes and probabilities.**

The Ministry of Health is responsible for providing vaccines free of charge to all Iranian children in the national immunization program, and so considering the estimated incidence of rotavirus and the results of the aforementioned cost-effectiveness studies, the Iranian Ministry of Health currently decides to introduce this new vaccine to the national immunization program. Therefore, the aim of this study was to analyze the budget impact of rotavirus vaccine introduction and to inform decision makers in the case of actual costs.

## Methods

The pre- and postvaccine introduction costs were compared. Pre-vaccine costs include the direct cost of treating patients with rotavirus gastroenteritis in outpatients and admissions. Post-vaccine costs, including the total cost of vaccination and the direct cost of treating patients, the number of rotavirus-induced gastroenteritis cases, and consequent treatment costs are expected to decrease after the addition of the vaccine in the national immunization program.

We used a decision tree model to figure out the possible outcomes and probabilities (Figure 1). In this model, the square is a decision point, circles are probabilities, and triangles are

outcomes. The decision point is deciding whether to use rotavirus vaccine. In both options, there are 2 probabilities—children who get sick and those who do not. To calculate patient treatment cost, we considered 2 probabilities—patients who get treated as outpatients or inpatients. To calculate the number of both inpatients and outpatients per year, the distribution of the disease in the first 5 years of life is considered: 45% of the cases occurred in children aged 0 to 11 months, 40% in those aged 12 to 23 months, and 5% in each of the other years.<sup>9</sup> According to a systematic review and meta-analysis, the efficacy of RotaTeq in general cases (severe and nonsevere cases) and hospitalized cases (severe cases) was reported to be 70% and 90%, respectively.<sup>10</sup> In this study, the outpatient efficacy of the vaccine was assumed to be 70%, whereas the inpatient efficacy was assumed to be 90%. All patients were expected to recover from the gastroenteritis.

In Iran, 97% of people are covered by health insurance.<sup>11</sup> Ninety-three percent of total inpatient costs are paid by the government and insurance.<sup>12</sup> Therefore, the perspective of this study was the health system.<sup>13,14</sup> Medications and healthcare tariffs were assumed to be the same in all kinds of insurance.

The study period in budget impact analysis is usually between 1 and 5 years. In general, this time should be able to show the effect of the new intervention on costs and outcomes.<sup>6</sup> Because rotavirus diarrhea prevalence is more in children younger than 5

**Table 1 – Vaccine information used to calculate cost of vaccination.**

Parameter	Base	Scenarios		Source(s)
		Low	High	
Wastage rate (%)	5	1	5	Assumption/World Health Organization
Vaccination coverage (%)	96.51	96.51	100	Leelahavarong, <sup>6</sup> Motlagh et al, <sup>22</sup> Kolahi et al <sup>23</sup> /Assumption
Cold chain (\$)	Not included	Not included	25 096.50	Calculated
Vaccine price (\$)	7.00	6.30	7.70	Ministry of Health

**Table 2 – Cost of vaccination during 5 y.**

Vaccination program	Cost per FIC including wastage (\$)	Vaccination coverage	Population	Total cost (\$)
Year 1	21.21	0.9651	1 598 000	34 091 396 + 8 522 849 cost of reserve stock
Year 2	21.21	0.9651	1 624 000	34 646 074
Year 3	21.21	0.9651	1 648 000	35 158 085
Year 4	21.21	0.9651	1 672 000	35 670 096
Year 5	21.21	0.9651	1 696 000	36 182 107
Total	–	–	–	184 270 607

FIC indicates fully immunized child.

years, it is necessary to consider the cost and outcomes for 5 years to determine the effect of vaccination in reducing the number of cases; so 5-year costs from March 2018 to February 2023 were considered separately in this study. The study population was based on birth in this period. To estimate the population, we used the information in the national organization for civil registration; thus, the number of births of the past 16 years was considered,<sup>15</sup> and according to the population growth rate in these years, the number of births of the following years was estimated. There was no discount for the cost estimation according to the principles of budget impact analysis. The calculations in this study were done using Excel software. According to the official exchange price in 2017, the mean price of \$1 was 34 216.50 Iranian rials.<sup>16</sup>

### Vaccination Costs

To estimate the annual vaccination cost, we used the World Health Organization (WHO) guideline.<sup>17</sup> Total vaccine cost per year is estimated as  $c = p \times n$ , where  $p$  is the price per dose of the new vaccine and  $n$  is the number of doses supplied. The number of doses supplied for the first year is estimated as  $n = i \times b \times d \times [1/(1 - w)] \times [1 + r]$ , where  $i$  is immunization coverage rate,  $b$  is birth cohort,  $d$  is number of doses per fully immunized child,  $w$  is wastage rate (%), and  $r$  is reserve stock (%). To estimate the number of doses needed for other years, the same formula will be used but the reserve stock should be excluded:  $n = i \times b \times d \times [1/(1 - w)]$ .

According to the Iranian Ministry of Health, RotaTeq costs \$7 per dose to import in Iran, so the cost of this brand was calculated in this study. Because RotaTeq is prescribed at 2, 4, and 6 months after birth, the national immunization coverage of this period (96.51%) was used, on the basis of a survey of health and population patterns in Iran.<sup>18</sup>

According to WHO, wastage rate is considered to be 5%,<sup>8</sup> but given the fact that the rotavirus vaccine is orally administered and is presented in single-dose plastic tubes, a wastage rate of 1% was also included in the scenario analysis.

RotaTeq and Rotarix vaccines, unlike the first rotavirus vaccine that caused intestinal intussusception, are not associated with this complication.<sup>3</sup> A systematic review and meta-analysis showed that there was no significant difference between the case and control groups in relation to other complications such as fever, irritability, and swelling<sup>10</sup>; therefore, the present study does not cover the costs of side effects. Personnel costs were not considered because RotaTeq is coadministered with the pentavalent vaccine, which is already in the immunization program.

Rotavirus vaccines should be stored at 2°C to 8°C, and so there is a need for a cold chain to optimize the vaccine delivery in the country. Currently, in Iran this chain exists to supply other vaccines of the national immunization program. Because the rotavirus vaccine has a significant volume per dose, we may need to increase the volume in parts of the existing chain. We used the WHO guideline to calculate the cold chain volume. Maximum inventory volume (IVmax) of each vaccine used for routine immunization (in cubic meters) is  $IV_{max} = (P \times 1/R \times 100/(100 - W) \times (100 + SS)/100 \times V \times D)/1\,000\,000$ , where  $P$  is the target population,  $R$  is the reorder frequency (the number of times that vaccine is scheduled to be received by a city),  $W$  is the wastage rate,  $SS$  is a safety stock,  $V$  is vaccine volume per dose (in cubic meters), and  $D$  is the number of doses per fully immunized child. The resulting volume is equivalent to the net volume; in practice, to store this volume of vaccine, a larger volume of space is needed. To convert the net volume to the actual volume, we had multiplied the result of the formula by the grossing factor.<sup>19</sup> Vaccine volume per dose is 17.1 cm<sup>3</sup>.<sup>20</sup>

**Table 3 – Estimated rotavirus disease cases before and after inclusion of RotaTeq vaccine in the childhood immunization schedule in 5 y.**

Patients	No rotavirus vaccine	With rotavirus vaccine	Estimated event averted
Inpatients	194 993	19 499	175 494
Outpatients			
Total outpatients	6 285 174	1 885 552	4 399 622
Patients who have at least 1 visit (70%)	4 399 622	1 319 887	3 079 735
Public sector			
General practitioner visits	747 936	224 381	523 555
Pediatrician visits	356 369	106 911	249 458
Private sector			
General practitioner visits	985 515	295 655	689 860
Pediatrician visits	1 751 050	525 315	1 225 735

## Medical Costs

Direct medical costs included costs of outpatient and inpatient treatment. The average cost of each inpatient episode was estimated on the basis of medical records of 40 patients younger than 5 years, who were hospitalized for viral diarrhea in the children's medical center in Tehran, Iran, from March 2015 to February 2017. The length of the admission period varied from 1 to 5 days, and so weighted average costs were calculated. The weighted average costs of these years were \$139.72 (95% confidence interval \$107.95–\$171.49) and \$158.59 (95% confidence interval \$121.83–\$195.35), respectively. As noted, costs had risen by about 13.5% over the past 2 years; so to estimate hospitalization costs in the studied years, the coefficient of 13.5% annual increase was considered. Because the study perspective was government and insurance organizations, and the insurance covers 93% of hospitalization costs, estimated costs were multiplied by 93%.

About outpatient treatment costs, costs of prescribing drugs and physician visits were included. According to a systematic review, the weighted average duration of diarrhea for children younger than 5 years is estimated to be 4.3 days (4.3–4.4) in developing countries<sup>21</sup>; therefore, the outpatient treatment cost is considered for 4 days. A study on children with acute diarrhea in Iran showed that only 70% of patients with diarrhea refer to the doctor and the rest 30% do not see any physician and use home remedies, and so they were not included in the calculation. Physician referral distribution among 70% of patients who visit a doctor was as follows: the specialist (public 8.1%; private 39.8%), the general practitioner (public 17%; private 22.4%), and the health houses and health centers (12.7%),<sup>22</sup> where some medical services are provided free of charge under the government's supervision. The staffs of health houses and health centers have a fixed monthly salary and a fixed quota of free drugs; the government incurs no additional costs. Therefore, 12.7% of referrals were not included in the calculations.

On the basis of the perspective of the study, only public sector referrals were included to calculate physicians' visit costs because the government does not supply the private sector. Nevertheless, the number of referrals to both the public and private sectors was considered to calculate the cost of prescriptions because it was assumed that all patients are insured.

To calculate the outpatient treatment cost, visit fees and prescription costs were considered. For prescription, only the costs of drugs covered by insurance were considered; the general practitioner's prescription and visit costs were different from those of the specialists (\$1.00 vs \$1.70 for prescription costs and \$3.20 vs \$4.10 for visit costs, respectively). Because the tariffs over the past 3 years had increased by 15% and once again by 5% annually, we considered an average annual increase of 10% to estimate the visit costs in the studied years. We assumed that the drug costs remained constant over the study period.

## Sensitivity Analysis

To reduce some uncertainties, sensitivity analysis was designed with different scenarios. In the low scenario, the cold chain cost was not included, because the current volume of the cold space of cities is not known accurately and in practice, there may not be a need to increase the volume. In this scenario, the vaccine coverage rate and the wastage rate were considered to be 96.51% and 1%, respectively. The direct medical cost was the same as in the base scenario. The vaccine price was assumed to have a 10% increase and a 10% decrease in the low and high scenario, respectively. This scenario was an estimate of minimum costs.

In the high scenario, a 100% immunization coverage and an expansion of the cold chain by a refrigerator in each city were assumed. Therefore, the cost of the cold chain was calculated by assuming that all cities need to add a refrigerator. Wastage rate

was also assumed to be 5%. In calculating the direct medical costs, all patients were assumed to refer to physicians in the high scenario, whereas in the base scenario only 70% of patients were assumed to refer to physicians and 30% to not see any physicians and use home remedies. This scenario was an estimate of maximum costs.

## Results

Table 1 presents the information that was used to estimate the costs of vaccination. The cost to fully immunize a child including the wastage was \$21.21 and the total vaccination cost during the 5-year period in the base calculation was \$184 270 607 (Table 2).

We used 2864 annual incidences per 100 000<sup>7,18,23</sup> and 90% efficacy to calculate the number of inpatient cases, and also 92 315 annual incidences per 100 000<sup>7,18,23</sup> and 70% efficacy to calculate the number of outpatient cases aged 1 to 59 months. Table 3 presents the number of admissions and outpatient visits before and after the inclusion of the rotavirus vaccine in the childhood immunization schedule. The rotavirus vaccine would prevent approximately 175 494 inpatient cases and 4 399 622 outpatient cases during the 5-year period.

On the basis of the estimated number of patients and the cost of treatment per patient, the total patient treatment cost was calculated. The total inpatient and outpatient treatment costs during the 5-year period were reduced from \$50 331 405 and \$10 745 903 to \$5 033 141 and \$3 223 771, respectively, after the introduction of the vaccine. Therefore, the financial savings would be about \$45 million and \$7.5 million, respectively. The vaccination program cost was about \$184 million. Nevertheless, the inclusion of the vaccine saved about \$52.5 million in health-care costs over 5 years; so, the total incremental cost was \$131 450 210 (Table 4).

## Sensitivity Analysis

As presented in Table 5, both scenarios showed that the inclusion of the rotavirus vaccine in the national immunization schedule of Iran increased the financial burden on the government. The total net budget impact in these 2 scenarios was \$106 million and \$154 million, respectively.

## Discussion

The aim of the present study was to evaluate the financial consequences of adding the rotavirus vaccine to the national immunization program. The total vaccination cost during the 5-year period was \$184 million, but saved approximately \$52.5 million in healthcare costs because of the reduction of disease cases and treatment costs.

According to the Iranian Ministry of Health, the total cost of national vaccination in 2017 was \$42 633 598. The results of this study, however, revealed that the cost of providing the rotavirus vaccine in the first year (2018) would be about \$42 million. These data confirm that the cost of rotavirus vaccine introduction into the national immunization program is much higher than the national vaccine budget and increases government expenditure. According to the 2018 budget bill, \$100 million from the National Development Fund has been spent to import pneumococcal and rotavirus vaccines in the country.<sup>24</sup> This further strengthens our results.

Scenario analysis with the aim of reducing uncertainties, considering the vaccine price, direct medical costs, wastage rate, coverage, and the cold chain cost, was conducted. We initially carried out a basic analysis with data that we found to be more realistic and then analyzed 2 scenarios as minimum costs and

**Table 4 – Budget impact results.**

Annual cost outcomes (\$)	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Before vaccination						
Vaccination costs	0	0	0	0	0	0
Disease care costs	4 932 813	10 489 987	12 591 998	15 069 114	17 993 395	61 077 308
Total costs	4 932 813	10 489 987	12 591 998	15 069 114	17 993 395	61 077 308
After vaccination						
Vaccination costs	42 614 244	34 646 074	35 158 085	35 670 096	36 182 107	184 270 607
Disease care costs	697 217	1 454 679	1 715 074	2 018 092	2 371 849	8 256 911
Total costs	43 311 462	36 100 753	36 873 159	37 688 188	38 553 956	192 527 518
Budget impact						
Vaccine budget impact	42 614 244	34 646 074	35 158 085	35 670 096	36 182 107	184 270 607
Disease care budget impact	–4 235 596	–9 035 309	–10 876 924	–13 051 023	–15 621 546	–52 820 397
Net budget impact	38 378 649	25 610 766	24 281 161	22 619 073	20 560 561	131 450 210

maximum costs. All scenarios showed an increase in government expenditure with the introduction of the vaccine; of course, the most important factor is the vaccine price, which is very expensive. These costs might be reduced by facilitating the local production of the vaccine within the country in the long run.

Despite the fact that budget impact analysis is a helpful tool to devise policy and decision making, there are a few studies in the field of rotavirus vaccine in the world. According to a systematic review conducted in 2017, 60 cost-effectiveness studies were done on rotavirus vaccine in low- or middle-income countries, whereas only 6 budget impact studies could be found, of which 5 have been conducted alongside the cost-effectiveness studies.<sup>25</sup> Of course, 6 budget impact analysis is newfound in comparison with cost-effectiveness studies, and this might justify why a few studies are conducted. Cost-effectiveness studies have limitations alongside strengths; one of these constraints is uncertainties regarding thresholds that determine a study to be cost-effective. There is an important question on whether current cost-effectiveness thresholds for low- and middle-income countries are useful.<sup>26</sup> In general, decision makers need realistic consequence estimates that provide a new intervention with a defined budget and budgetary period.<sup>27</sup> In Iran, 2 cost-effectiveness studies have been done on the introduction of rotavirus vaccine into the national immunization program. One of them was conducted on the RotaTeq vaccine. On one hand, the results of this study showed that lost disability-adjusted life-years due to rotavirus gastroenteritis would be 138 161 over 10 years, which would

be reduced by vaccination to 76 591. On the other hand, the cost per disability-adjusted life-year averted would be about \$2868, which is considered as a cost-effective program from the government's perspective.<sup>7</sup> The other study evaluated both the RotaTeq and Rotarix vaccines and revealed that these interventions would be cost-effective on the basis of the thresholds considered to be cost-effective by the WHO for these types of studies.<sup>8</sup> A similar budget impact analysis was done in Iran to assess the financial burden of introducing *Haemophilus influenzae* type b vaccine as a part of the pentavalent vaccine in the immunization program. This study also showed that the inclusion of a new vaccine would increase the financial burden on the government. In fact, the inclusion of the pentavalent vaccine was expected to increase the government health expenditure by only \$43.4 million over a 5-year period.<sup>28</sup>

The management and planning organization in Iran defines the budget required for annual national vaccination, and so this type of study can be helpful for policy makers in this area. The most important limitation of this study was the lack of reliable and accurate data on the rotavirus gastroenteritis incidence in Iran. This limitation emanates from the poor documentation of the health system and unavailability of studies on the burden of rotavirus-induced gastroenteritis in the country. The other limitation comes from the lack of accurate knowledge about the efficacy of the vaccine in Iran. In this study, the efficacy was taken from a meta-analysis article and it is unpredictable whether the vaccine in Iran would have the same efficacy.

**Table 5 – Sensitivity analysis results.**

Scenario	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Base scenario						
Vaccine budget impact	42 614 244	34 646 074	35 158 085	35 670 096	36 182 107	184 270 607
Disease care budget impact	–4 235 596	–9 035 309	–10 876 924	–13 051 023	–15 621 546	–52 820 397
Net budget impact	38 378 649	25 610 766	24 281 161	22 619 073	20 560 561	131 450 210
Low scenario						
Vaccine budget impact	36 803 211	29 921 609	30 363 801	30 805 992	31 248 183	159 142 797
Disease care budget impact	–4 235 596	–9 035 309	–10 876 924	–13 051 023	–15 621 546	–52 820 397
Net budget impact	32 567 615	20 886 301	19 486 877	17 754 969	15 626 638	106 322 400
High scenario						
Vaccine budget impact	48 570 789	39 488 842	40 072 421	40 656 000	41 239 579	210 052 729 + 25 097 cold chain cost
Disease care budget impact	–4 541 500	–9 643 829	–11 560 736	–13 817 793	–16 480 311	–56 044 168
Net budget impact	44 029 290	29 845 013	28 511 685	26 838 207	24 759 268	154 033 658*

\* Considering the cold chain cost in total.

## Conclusions

The results show that the inclusion of rotavirus vaccine in the national vaccination program would have a significant effect on health budgets and would raise government expenditure. Source of financial support: This research was supported by the Faculty of Pharmacy, Tehran University of Medical Sciences (Tehran, Iran).

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