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ORIGINAL ARTICLE

Cost-effectiveness of rotavirus vaccination in Turkey

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Abstract *Background/Purpose:* Cost-effectiveness studies about rotavirus (RV) vaccination programs were performed in many countries due to the severe economic burden of RV infections. This study is an economic evaluation performed to assess the potential for introducing the RV vaccine to the Turkish National Immunization Program.
Methods: In this retrospective clinical study, the records and laboratory findings of a total of 4126 patients admitted to Turgut Ozal University Hospital, Ankara, Turkey with acute gastroenteritis were analyzed. A model described by Parashar et al. was used to obtain the annual episodes of diarrhea, hospitalization and outpatients visits in Turkey. Monovalent and pentavalent vaccination was assumed to protect in average 85% of RV acute gastroenteritis. All costs are expressed in 2012 United States (US) $, where US$1 equals 1.8 Turkish Liras (TL). Losses of labor costs were not taken into consideration.
Results: The vaccination program with 85% coverage was cost effective and cost saving compared to no vaccination. A projected birth cohort of 1.25 million children was followed until 5 years of age; a routine vaccination could potentially avert 210,994 cases of diarrhea treated in outpatient hospital facilities and 42,715 hospitalizations. The RV associated economic burden was obtained as US$17,909 million per year (US$14.33 per birth annually) in medical direct costs by using the national level of RV diarrhea disease burden estimates. For monovalent and pentavalent vaccination, assuming a cost of US$31.5 and US$38 per vaccine course, the cost of the vaccination program was estimated to be approximately US$37,878 million and US$45,475 million, respectively.

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Conclusion: At a cost per vaccine course of US$31.5 for monovalent and US$38 for pentavalent vaccine, routine RV vaccination could be potentially cost effective and also cost saving in Turkey. National RV vaccinations will play a significant role in preventing RV infections.

Introduction

Rotavirus (RV) is the most frequent cause of acute gastroenteritis (AGE) and AGE-related hospitalizations throughout the world in children under 5 years. Rotavirus-related gastroenteritis accounts for 10—20% of AGE and 25—55% of AGE-related hospitalizations.[1] Rotavirus diarrheas cause 111 million diarrheal episodes yearly worldwide, Due to this, 25 million outpatients and two million children stay in hospital.[2] Annually 611,000 children die due to severe RV diarrhea and 85% of deaths occurs in developing countries.[3] Incidence of RV which is distinguished from other gastroenteritis agents by not being related to socioeconomic conditions and hygiene measures is the same in developed and developing countries; while its mortality is high in developing countries; it leads to high morbidity and economic losses in developed countries.[3,4] Studies indicate that RV is one of the main causes of gastroenteritis among children aged between 0 years and 5 years in Turkey.[5] Rotavirus infections may be asymptomatic or cause nonspecific symptoms like diarrhea, vomiting, and fever. The frequency of RV infection increases in winter.[6]

Directly and indirectly, the annual cost of RV infections to the United States is $1 billion and to the Europe is €350 million, approximately.[7,8] Rotavirus infections cause economic burden both for the families and the countries not only due to hospitalizations but also as a result of outpatient clinic admissions and loss of labor.[9]

There is no particular therapy for RV infection. Immunization plays a significant role for RV related morbidity and mortality and currently two vaccines are available.[10] Rotarix (GlaksoSmithKline, Rixenrant, Belgium) and RotaTeq (Merck Sharp&Dohme Corp., Whitehouse Station NJ, USA), two vaccines developed against RV infections, are reported to reduce hospital and emergency room admissions by 90%.[9] These vaccines which have been used in many countries since 2006 are currently included in routine vaccination programs in more than 100 countries.[11] Studies about cost-effectiveness of routine vaccination continue as vaccine prices are so high in many countries all over the world.[12] It was difficult to use the health data of one country for another because of differences between epidemiology and health system of countries.[13] In this study, we aimed to calculate the financial burden of outpatients and hospitalized RV patients. According to financial burden results, we estimated the cost of RV vaccines in Turkey in which RV vaccines have not been included in routine vaccination programs yet.

Methods

In this study, records and laboratory data of 4126 patients younger than 5 years, who were admitted to the Department of Pediatrics, Faculty of Medicine, Turgut Ozal University, Ankara, Turkey with AGE between January 2005 and May 2012 were retrospectively analyzed. Rotavirus antigens were investigated in fresh stool specimens with the "qualitative immunochoromatographic" test (CerTest Rotavirus kit, Biotec, Zaragoza, Spain).

This study was estimated to cover three types of hospital (university, public, and private) costs available in Turkey and represented an average cost of gastroenteritis due to RV. All patients admitted to the Turgut Ozal University Hospital, Ankara, Turkey were assumed to be admitted to a public and a private hospital. This study was approved by the Human Subjects' Research Committees at the Faculty of Medicine, Turgut Ozal University.

A resolution analytical model has been developed to predict the effectiveness and cost effectiveness of RV in the childhood population (< 59 months of age) with the opportunity to focus the analysis on a risk based vaccination program. Demographic and epidemiological inputs were obtained from previously conducted study sources from different regions of Turkey and international literature.

To compare the costs of the vaccination versus non-vaccination situation and health outcomes, an incremental cost-effectiveness ratio (ICER) was estimated as the incremental cost per life year gained (LYG). Since there are no health utility data available in Turkey, the quality of life gained due to vaccination has not been evaluated. ICER compares the net cost of a health intervention with the benefit gained. The ICER was calculated for a range of vaccine prices [United States (US)$1—40 per vaccine course).

Bills of the in- and outpatients for RV gastroenteritis were analyzed in detail and direct medical costs were calculated as in the studies investigating economic burden of RV infections at University Hospital. After the interviews with government health officials and private hospital managers in Ankara in 2012, estimates of costs were obtained. Medical direct costs for RV-specific diarrhea were estimated for the 2012 Turkey birth cohort. Nondirect medical and indirect costs were not taken into account in the model. All costs are expressed in 2012 US$, where US$1 equals 1.8 Turkish Liras (TL).

A model described by Parashar[2] was used to obtain the annual episodes of diarrhea, hospitalization and outpatients visits in Turkey. Among the 1.25 million births annually in Turkey (7.5 million children younger than 5 years in 2012), the annual episodes of diarrhea in Turkey was estimated to be 13,371,800 among children younger than 5 years, corresponding to 94,817 hospitalizations and 1,182,046 outpatient visits (Table 1).[14] Rotavirus AGE comprised 21% of the outpatient AGE cases[15] and RV gastroenteritis among all children hospitalized for

Table 1 Estimated disease burden of rotavirus diarrhea without a national rotavirus vaccination program in Turkey for a 1-year birth cohort (n = 1.25 million).[a]

	Total diarrhea cases (n)	RV of all cause diarrheas (%)	RV without vaccination (n)
Hospitalization	94,817	53	50,253
Outpatient visit	1,182,046	21	248,229

[a] The model described by Parashar et al.[2]

gastroenteritis was 53% (32.4–67.4%).[14] There is no health utility data available in Turkey. Therefore, the data of deaths related with RV has not been evaluated and not taken into account in the model.

A two-dose vaccination program for monovalent and three-dose vaccination program for pentavalent RV vaccine total costs were calculated based on the number of vaccines required to vaccinate 1.25 million infants annually. The efficacy of the monovalent and pentavalent RV vaccines are 84%/90% for reduction in hospitalizations and 70%/85% for reduction in outpatients visits, respectively.[16] Vaccine coverage was estimated based on reports for other vaccines given at the same age (pneumococcal conjugate vaccine) in Turkey (81.6–89.5%).[17] We assumed the mean coverage rate of both vaccines was 85% in the national immunization program. Vaccination costs included the vaccine price and procedure fees for vaccine administration. To take RV vaccines into the National Vaccination Schedule a considerable cost reduction should be carried out by the Ministry of Health. Based on previous experience of the Ministry of Health with other vaccines (Prevenar-7 (Pfizer, Philadelphia, USA) and Prevenar-13 (Pfizer, Philadelphia, USA)) which were recently added into the Turkish National Vaccination Schedule, the cost of the RV vaccine course would be 1/5–1/8 of the market prices (In Turkey 2012, the market prices were US$157.8 per course for monovalent and US$190 per course for pentavalent vaccines). We calculated the estimated maximum price (1/5 of the market price) that would be in a national vaccination schedule for the RV vaccine. According to these data we assumed the cost of monovalent and pentavalent RV vaccine course were US$31.5 and US$38, respectively.

Economic modeling methods outlined in the WHO generic protocol to estimate health care costs of RV-specific diarrhea and cost-effectiveness of RV vaccination were used.[18]

A model was used that incorporates information on disease burden, vaccine coverage, and vaccine effectiveness to obtain the cost effectiveness of a routine vaccination program. Vaccination costs included the cost of administration, the price of the vaccine, and expected losses from unused vaccines. The estimated cost of vaccine administration was US$1 per vaccine course. A national RV immunization program would cost:

[(1.25 million children × coverage %) × US$ (1–40) + (1.25 million children × coverage %) × administration cost)]. (1)

Demographic data on the Turkish population was based on the national statistics data from 2012. The national gross domestic product (GDP) per capita in Turkey in 2012 was 18,957 TL (US$10,504).[19]

Results

Of 4126 patients included in the study, 1782 (43.2%) are girls and 2344 (56.8%) are boys. Rotavirus was positive in 1261 patients (30.6%). Mean age of RV positive patients was 31.1 ± 22.6 months. Two hundred and eighteen RV positive patients were followed up in the hospital, the others were outpatients and mean duration of hospital stay was 3.9 ± 2.4 days.

Economic burden of rotavirus diarrhea

Economical data was combined with RV-positive patients having acute diarrhea. Patient hospital expenditures were computed using the official hospital invoices. All patients admitted to the university hospital were assumed to be admitted to a public and a private hospital (Table 2). Total direct medical costs of the university hospital were 1.4 times higher than the public hospital and private hospital costs were two times higher than the university hospital. The average direct medical costs (hospitalization,

Table 2 Estimated mean (standard deviation) values for direct medical costs[a] associated with rotavirus diarrhea among children treated[b] in university, public, and private hospitals.

	Hospital			Average
	University	Public	Private	
Hospitalization costs (US$)	173.06 ± 106.49	123.89 ± 76.24	383.99 ± 236.30	226.98 ± 139.68
Outpatient costs (US$)[c]	27	21.6	30 ± 15[d]	26.2 ± 5

[a] Costs expressed in 2012 US$ (US$1 = 1.8 TL).
[b] Mean duration of hospital stay was calculated as 3.9 ± 2.4 days.
[c] Outpatient costs ($) in university and public hospitals were calculated based on fiscal control formal health institution package price tariff (only 1 price).
[d] Outpatient cost in a private hospital was the calculated package price tariff (only 1 price) + the mean cost of extra charge.
TL = Turkish Liras; US = United States.

US$226.98 ± 139.68; outpatient, US$26.2 ± 5) of the three facilities (university, public, and private hospital) were simulated to the model described by Parashar et al[2] to obtain the economic burden of RV specific diarrhea in Turkey. The RV associated economic burden was found to be US$17,909 million per year (US$14.33 per birth annually) in direct medical costs by using the national level of RV diarrhea disease burden estimates (Table 3).

Table 3 Economic burden of rotavirus-specific diarrhea in Turkey.

	Total mean cost[a] in 1000s (95% confidence interval)			Annual average total cost per child[b]
	Hospitalization	Outpatient visits	Total cost	
Medical direct cost ($)	11,406 (4387–18,425)	6503 (5262–7746)	17,909 (9649–26,171)	14.33 (7.72–20.94)

[a] Costs expressed in 2012 US$ (US$1 = 1.8 TL).
[b] Based on a 1-year birth cohort (1.25 million).
TL = Turkish Liras; US = United States.

Table 4 Percentage reduction due to a national monovalent and pentavalent rotavirus vaccination program.

	Reduction due to vaccination (%)	Prevented by vaccination (*n*)	RV with vaccination (*n*)
Hospitalization			
Monovalent	84	42,212	8041
Pentavalent	90	45,211	5042
Mean coverage (estimated)	85	42,715	7538
Outpatient visit			
Monovalent	70	173,760	74,469
Pentavalent	85	211,054	37,174
Mean coverage (estimated)	85	210,994	37,235

Economic benefit of vaccination

Introduction of monovalent RV vaccines into the Turkish National Immunization program could prevent ~42,212 hospitalizations and 173,760 outpatient visits and 45,211 hospitalizations and 211,054 outpatient visits for the pentavalent vaccine. If the mean coverage rate of both vaccines was estimated to be 85%, prevention was ~42,715 hospitalizations and 210,994 outpatient visit (Table 4). Multiplying our cost estimates by the number of healthcare visits averted, introduction of monovalent RV vaccines into the Turkish National Immunization program could save US$14,133 million per year (US$11.30 per birth annually), US$15,790 million per year (US$12,632 per birth annually) for the pentavalent vaccine and US$15,223 million per year (US$12.17 per birth annually) for estimated mean coverage rate (85%) of both vaccines (Table 5).

Cost of RV vaccination program

At a cost per child (US$1–40 per vaccine course), with a vaccine administration cost of US$1 per child and a vaccine coverage rate of 85%, we assumed the cost of the monovalent and pentavalent RV vaccine course were US$31.5 and US$38, respectively. The cost of a national RV immunization program for monovalent and pentavalent vaccine:

[(1.25 million children × coverage 85%) × US$ (31.5/38) + (1.25 million children × coverage 85%) × US$1)] = for monovalent vaccine = US$34,531,250 and for pentavalent vaccine = US$41,437,500 (2)

Incremental cost and cost-effectiveness ratio

The incremental costs for monovalent and pentavalent vaccines were estimated at US$3776 and US$2119 million, retrospectively. The cost-effectiveness ratio for the monovalent vaccine was ICER = US$3667/LYG and for pentavalent vaccine ICER = US$4615/LYG. Both of them were lower than the national GDP per capita in Turkey (US$10,504 per capita in 2012; Table 6). Therefore, the national vaccination program can be considered as cost-effective if the cost of a vaccination course would be 1/5

Table 5 Economic benefits of rotavirus-specific diarrhea prevented by vaccination in Turkey.

Medical direct cost (US$)	Total mean cost[a] in 1000s (95% confidence interval)			Annual average total cost per child[b]
	Hospitalization	Outpatient	Total cost	
Monovalent	9581 (3685–15,477)	4552 (3683–5421)	14,133 (7368–20,898)	11.30 (5.89–16.72)
Pentavalent	10,261 (3946–16,577)	5529 (4474–6584)	15,790 (8420–23,161)	12.632 (6.74–18.53)
Mean coverage estimated (85%)	9695 (3728–15,661)	5528 (4472–6584)	15,223 (8200–22,245)	12.17 (656–1779)

[a] Costs expressed in 2012 US$ (US$1 = 1.8 TL).
[b] Based on a 1-year birth cohort (1.25 million).
TL = Turkish Liras; US = United States.

Table 6 Base case results of cost effectiveness analysis of vaccination (the mean coverage rate of both vaccines is 85%) (TUIK 2012: GDP per capita = US$10,504).

Number of life year gained (LYG)	
For monovalent vaccine	4.356 (4.214–4.498)
For pentavalent vaccine	4.778 (4.257–5.319)
Vaccination costs[a]	
For monovalent vaccine (US$31.5 per course)	34,531,250
For pentavalent vaccine (US$38 per course)	41,437,500
Cost effectiveness analysis[b]	
ICER (US$/LYG)	
For monovalent vaccine	US$3667/LYG (1887–5447)
For pentavalent vaccine	US$4615/LYG (2342–6888)

[a] Based on a 1-year birth cohort (1.25 million).
[b] ICER = (total cost of vaccination for birth cohort - total cost of no vaccination)/LYG.
GDP = gross domestic product; ICER = incremental cost-effectiveness ratio; TUIK = Turkish Statistical Institute; TL Turkish Liras; US = United States.

of the marketing prices for monovalent (US$31.5) and pentavalent (US$38) vaccines.

Discussion

This economic evaluation provides information for decision making for the introduction of the RV vaccine into the Turkish National Immunization Program. Although the results of the costs of RV disease that were avoided by vaccination were less than the cost of a vaccination program, both RV vaccination strategies were cost effective and cost saving because ICER's for both vaccines were lower than the national GDP per capita in Turkey (US$10,504 per capita in 2012).[19]

This study was estimated to cover three types of hospital (university, public, and private) costs available in Turkey and represented an average cost of gastroenteritis due to RV. All patients admitted to the university hospital were assumed to be admitted to a public and a private hospital. The average total direct cost for the three facilities (university, public, and private hospital) was US$226.98 $\pm$ 139.68. Expenditures of diagnosis and treatment accounted for $\sim$67% of total direct costs. Total direct medical cost per patient was US$151, another study performed in the training and research hospital found that 65% of this cost was related to treatment and diagnosis expenditures.[20] The differences arise as the study was performed only at a public hospital. In a study conducted in Mexico, the total direct medical cost per patient was US$211 and diagnostic procedures and medications consisted of 92% of this cost.[21]

In our study, vaccination can effectively reduce the burden and healthcare costs of RV. Total direct medical costs were US$17,909 million (US$14.33 per birth annually) and US$15,223 million (US$12.17 per birth annually) could be prevented if the RV vaccine is included in the vaccination program. In comparison with RV AGE costs in several studies, the costs of illness in our study have turned out to be less. With regards to the rules and regulations in effect in Turkey, the public payer is responsible for a large amount of population-based health costs, and the public payer cost is usually cheaper than private hospitals in Turkey. If the costs of RV infection are retrieved from a university hospital, costs are expected to be higher than in a public hospital due to relatively higher prices, the availability of a greater number of procedures, and more advanced technology. The costs from a private hospital are expected to be higher than in a university and public hospital because of the extra charges. It is known that RV cases are seen less and hospitalizations are less in developed countries however, the economic burden of the disease is greater than in Turkey due to the high expenditure of health services.[22] In a study from the United States of America, the mean direct cost was US$4565.[23] The results in a study investigating the effectiveness of RV vaccine in Canada were similar to ours. In public health perspective, cost of vaccination was found to be greater than not vaccinating (US$69) both for RotaTeq (Merck Sharp&Dohme Corp., Whitehouse Station NJ, USA) (US$207 for one course) and Rotarix (GlaxoSmithKline, Rixenrant, Belgium) (US$199 for one course). However, the 5-year economic burden of RV infections is much more than US$125 million.[24]

In our study the cost effectiveness ratio was US$3667/LYG for monovalent vaccine and US$4615/LYG for pentavalent vaccine, which is largely lower than the national GDP per capita in Turkey (US$10,504 per capita in 2012) and therefore cost-effective. A national vaccination program can be considered as cost-effective if the costs of the vaccination course would be $\leq$ 1/5 of the marketing prices for monovalent (US$31.5) and pentavalent (US$38) vaccines. This is a desired result but not appropriate for Turkey yet. The results of our analyses are similar with other analyses performed on RV monovalent or pentavalent vaccines, which demonstrated that an RV vaccination is likely to be cost effective.[16,25] RV vaccinations were previously reported to be cost-effective across various European countries.[16] A cost-effectiveness analysis for RV vaccination in England and Wales showed that routine vaccination of all children appeared to be cost effective.[1] In the study performed in Thailand, generalization of the RV vaccine was reported to be beneficial both for the disease and economy however the price of the vaccine should be less than US$10.[26]

At present, Turkey has not undertaken universal immunization of infants with RV, although it is considering the implementation of such a program. The future effect of an RV vaccination program in Turkey will depend on the vaccine coverage rate and serotype and their clinical importance.

In our study, considerable healthcare and societal costs result from the estimated 50,253 hospitalizations and 248,229 outpatient visits to hospital facilities per year in children younger than 5 years attributable to RV. In a study from Vietnam, RV vaccines reduce outpatient clinic admissions, hospitalizations, and deaths by $>$ 67% and the vaccine was found to be effective in terms of public health.[27] Similar results have been found in a study from Bolivia. Rotavirus vaccination was seen

to reduce hospitalizations, outpatient clinic admissions, and total direct expenses by 60%. The price of the vaccine was reported to be US$9 for each dose in order to be cost-effective.[28]

A limitation of our analysis is that it was assumed that there was no loss of labor and there was the same vaccine efficacy for all ages, including the first 2 months when full immunization would not yet have been achieved. The indirect medical and nonmedical costs for the RV AGEs were not included in this study. They may even exceed the direct medical costs of RV AGE and may add extra benefits to cost effectiveness of the RV vaccination.

In recent studies, the RV vaccine was shown to protect not only vaccinated babies but also nonvaccinated babies and older children, in other words provide "herd immunity".[29] These studies support the recommendation of WHO that the RV vaccine should be added to the national vaccination program in all countries worldwide.

Rotavirus disease among Turkish children causes significant morbidity and mortality and important costs to the Turkish healthcare system. Vaccination can effectively decrease this burden and healthcare costs. If the available prices are approximately $\leq$ US$31.5 for monovalent and $\leq$ US$38 for pentavalent per course; the cost per LYG for both vaccines are estimated to be lower than one GDP per capita in Turkey. Vaccination of children with RV is not publicly funded in Turkey. As a result, the RV vaccine coverage rate in Turkey has been minimal and its' increase should improve public health. More cost-effectiveness studies are needed in order to include RV vaccines into routine vaccination programs. Informing families and increasing vaccination rates, reducing high prices will play an important role in the prevention of RV infections until the vaccine is included in the national vaccination program. Considering all costs (direct medical, indirect medical, and nonmedical), a RV vaccination program in Turkey will be cost saving and cost-effective.

Conflicts of interest

None declared.

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