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Cost-effectiveness estimates of vaccination against rotavirus in Piedmont, Italy

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ABSTRACT

Background: Rotavirus-induced gastroenteritis (RVGE) represents the most frequent form of severe gastroenteritis in children. In such a scenario, the availability of an efficient anti-Rotavirus (anti-RV) vaccine represents an effective prevention tool able to prevent those complications mainly linked to the moderate-severe forms of this disease, which require hospital care. The aim of the present study is to estimate the cost effectiveness of universal routine infant RV vaccination program and its budget impact on the Regional Health Service (RHS) of Piedmont, Italy, in order to evaluate the opportunity of the implementation of a national anti-Rotavirus vaccination programme.

Methods: The researchers performed a cost-effectiveness analysis comparing costs and benefits of a Rotarix two-dose vaccination versus non vaccination and a budget impact analysis (BIA), complementary to the cost-effectiveness analysis.

Results: Our results show that the mass implementation of an anti-RV vaccination in Piedmont, in addition to the expected public health benefits, also allows the RHS to save a considerable amount of money within a short period of time, due to the remarkable reduction of direct health costs associated with RVGE management. In fact, as the analysis shows, a universal vaccination against RV results in money-saving for the RHS already from the 2nd year (with a vaccination coverage of 50%). During the five year period, the active and free offer of the anti-RV vaccination would determine a total saving for RHS of about € 503.000. The cost-effectiveness analysis results showed a cost-saving ICER (incremental cost-effectiveness ratio) relevant to the RHS and equal to – €12.197/QALY.

Conclusion: In conclusion the adoption of a universal preventive strategy for all the infants in the Piedmont Region may contribute significantly towards the control of RVGE incidence, thus allowing a noteworthy saving of economic and social resources for both the RHS and the general public.

Introduction

Globally, rotavirus-induced gastroenteritis (RVGE) represents the most frequent form of severe gastroenteritis in children, particularly for those under the age of two. It is estimated that every year the pathogen causes about 25 million medical examinations, 2 million hospital admissions and 215.000 deaths [1,2].

Within the European Union (EU), rotavirus gastroenteritis (RVGE) places a high demand on healthcare systems [3]. Surveillance studies showed that Rotavirus represents the greatest burden of disease consistently observed in children aged under 2, and, moreover, accounts for up to two thirds of admissions to hospital and emergency room visits and one third of primary care consultations for Acute Gastro-Enteritis (AGE) among children under 5 years. RVGE is estimated to occur at a rate of 1 symptomatic infection in every 7 children each year, accounting for 231 deaths, more than 87,000 hospitalizations and almost 700,000 outpatient visits [4–7].

In light of the above, it is clear that RVGE represents an important worldwide public health issue. Since 2006, two RV vaccines, Rotarix and RotaTeq, have been licensed and widely used in many countries around the world [8].

More than 10 years after the authorization of two vaccines of demonstrated efficacy and with a strongly positive benefit-risk

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Table 1
Epidemiological data.

Variable	Number		Sources
Total of 2014 cohort (Piedmont Region)	34637		Demo-Istat [17]
	Reference percentage	No vaccination	
RVGE cases/RV-specific diarrhoea	45.45%	15742	Soriano-Gabarró et al., Vitale et al. [3,29]
Medical consultations/paediatric examinations	22%	7606	Mattei et al., Gil et al. [18,19]
Emergency room visits	9.8%	3391	Giaquinto et al 2008 [20]
Hospital admissions	2.74%	951	Giaquinto et al. [20]
Admissions for nosocomial infection of RV-specific diarrhoea	1.51%	521	Health for All, Istat Ministero della Salute, numero ricoveri [21]
Deaths	0%	0	Marchetti et al. [11]

Table 2
Unit costs and sources.

Cost items	Values	Sources
Family pediatrician visits	€ 18	Estimate from Gross annual salary considering an average time of 10 min/visit
Emergency room visit cost	€ 241	Ministero della Salute, 2011 Progetto Mattoni [22]
Hospital admission cost	€ 1222.50	Ministero della salute – Decreto 18 ottobre 2012 – GU n. 23 del 28 gennaio 2013. Mean of DRG 422 (€1660) e DRG 184 (€785) [23]
Hospital admission cost for nosocomial infections	€ 2156	Ministero dell'Economia e delle Finanze, Gianino et al., Bierman et al. [24–26]
Rotarix vaccine cost (per dose)	€ 33.50	Cost consistent with Piedmont Region tender price
Administration cost	€ 0	Vaccine administration scheduled together with hexavalent and pneumococcal conjugate vaccinations

profile, uptake in Europe remains low: around 40% of countries currently have no existing national recommendations [9].

In such a scenario, the availability of an anti-Rotavirus (anti-RV) vaccine represents an effective prevention tool able to prevent those complications mainly linked to the moderate-severe forms of this disease, which require hospital care [3,10–12]. As a matter of fact, scientific literature has demonstrated how hygiene standards, such as hand washing and disinfection of surfaces, albeit effective, are still not adequate to halt the spreading and the manifestation of the viral disease [13].

The new "Piano Nazionale per la Prevenzione Vaccinale (PNPV) 2017–2019" [14], approved in Italy in January 2017 within the approval plan of the new "Livelli Essenziali di Assistenza", anticipates the introduction of the anti-Rotavirus vaccination for all children in their first year of life (Law n. 119, 31 July 2017).

In this context, the PNPV needs strong evidence to be scientifically supported by data and findings reported from the currently available literature.

In order to adequately assess the available vaccination technologies and their impact, in 2005 the World Health Organization (WHO) published a document that points out the criteria that must be followed to evaluate and decide on the introduction of new vaccines within the health systems. These criteria highlight the need to investigate the vaccine's efficacy profile, security and economic sustainability. The WHO also suggests considering the assessments on the feasibility of the vaccination programme, from both a technical and logistical point of view [15]. The most suitable approach to this evaluation framework appears to be that of the Health Technology Assessment (HTA), which consists in a multidisciplinary assessment that includes all the best available evidence on the impact of a new health technology upon its introduction in a health system.

In 2014 a complete economic analysis on the universal routine infant RV vaccination program with the Rotarix vaccine was published, within a HTA report on the anti-RV vaccination with the Rotarix vaccine [10]. This assessment was conducted on a national scale with the aim of evaluating the cost-effectiveness of a universal routine infant RV vaccination program and its budget impact on the National Health Service (NHS), in order to guide the decision-making processes in the light of the best existing evidence.

In this study, a similar approach [10] was applied to the Piedmont Region, in order to conduct an evaluation adapted to a regional context, with the aim of estimating the RVGE associated costs and the health and economic benefits of the universal vaccination with the Rotarix vaccine, in order to evaluate the opportunity of the implementation of a national anti-Rotavirus vaccination programme.

When the present analysis was performed in Italy there was a strong debate on mandatory vaccination programmes and the opportunity of the implementation of a national anti-Rotavirus vaccination programme also. Currently, the anti Rotaviurs vaccination has been introduced in the new "Piano Nazionale per la Prevenzione Vaccinale (PNPV) 2017–2019" [14] as recommended one.

Materials and methods

The vaccine

ROTARIX is a vaccine indicated for the prevention of rotavirus gastroenteritis caused by G1 and non-G1 types (G3, G4, and G9). ROTARIX is approved for oral use in infants 6 weeks to 24 weeks of age [16].

The analysis

The methodology used to conduct the present analysis is inspired by the one used for the national evaluation [10] but it considers the specific data of the Piedmont Region [17].

Starting from the number of deaths at the national level, as reported in the literature [11], these represent a percentage equal to 0.00038% (2 deaths) compared to the entire Italian population. By reporting this value to the only cohort considered in the Piedmont Region, in the "non-vaccination" scenario, this number translates into an absolute value of about 0.13 still equal to 0.00038% of the regional population.

National data were used for all other parameters as summarized in Tables 1, 2 and 4. The references of the sources included in the tables are the following: Refs. [3,17–26].

On this basis, two analyses were conducted:

- A cost-effectiveness analysis comparing costs and benefits of a Rotarix two-dose vaccination administered concomitantly with other early childhood vaccines during the third and fifth month

Table 3
Utility values (quality of life).

Event	QoL value (age dependent)	
	Children (>12 months)	Infants (0–12 months)
Diarrhoea	0.844	0.891
Severe diarrhoea	0.200	0.425
Paediatric examination	0.688	0.781
Emergency room visit	0.425	
Hospitalization for RV	0.200	0.425
Severe diarrhoea (nosocomial infection)	0.200	0.425

of age (hexavalent and pneumococcal conjugate) versus non vaccination.
- Budget impact analysis (BIA), complementary to the cost-effectiveness analysis, which estimates the potential financial consequences of the introduction of the anti-RV vaccination by considering the cost burden on the Regional Health Service (RHS) of Piedmont, Italy .

Cost-effectiveness analysis

The analysis was conducted using a Markov model which is a deterministic (not random) and static (not dynamic) characterization. This model simulates the epidemiological trend of RV infection and its possible consequences, the costs associated to the different kinds of management and treatment, and the vaccination benefits.

The model considers six health conditions or events that highlight the changes occurring in terms of costs and/or Quality Adjusted Life Years (QALYs) over time:

1. Healthy.
2. Diarrhoea.
3. Pediatric examination.
4. Emergency room access.
5. Hospital admission.
6. Death.

The analysis observes the vaccine effects over a five year time frame (higher infection risk period) in a birth-cohort of children born in 2014. More specifically, the model follows this birth-cohort and simulates the development of RV disease until the age of five, dividing it into "monthly" time cycles [27]. Every month, each individual present in the model may or may not experience a first episode of diarrhoea caused by RV infection. Thereafter, the episode of diarrhoea may or may not lead to a medical consultation and/or to an emergency room access and/or to a hospital admission. RVGE cases are classified as mild, moderate and severe, each involving different management procedures (home managed care, pediatric visits, emergency room visits, hospitalizations) and a relative impact on quality of life, employment of resources and death risk. The child's age (with a progressively decreasing probability of contracting the disease as the child reaches the fifth year of life) and the month of the year (periodicity of the disease) constitute the main parameters for the variation of the transition probability introduced in the model, which regulate the shift from one health condition to another. These probabilities also take into account the protective effect of breastfeeding and the differences between the first and the second RV infection. After a first event, the same individual might experience a second episode of RV infection, with or without diarrhoea, generally less severe and therefore presumed not to lead to hospitalization (Fig. 1).

The analysis model assumes an annual vaccination coverage of 100% and the cost values of the model refer to the current rates in use (vaccine cost: € 33.5/dose, entirely at the expense of the RHS).

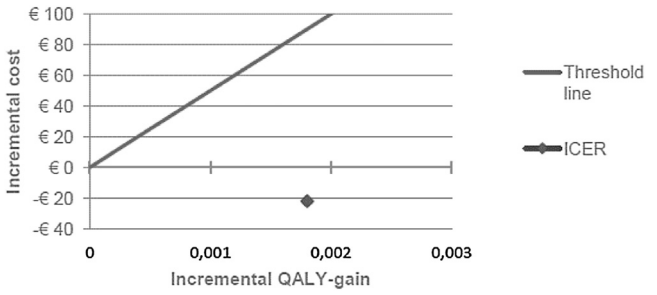

Fig. 1. ICER.

Since the anti-rotavirus vaccination is provided by the Vaccination Centres of the Local Health Unit, the cost of administration was not considered in the analysis as attributable to the ordinary management expenses of the Regional Health Services.

The analysis was conducted from a NHS perspective (by assuming a discount rate of 3% for both costs and benefits). The main outcomes considered, resulting from the anti-RV vaccination, are the incremental cost-effectiveness ratio (ICER) expressed as €/QALY and a reduction in episodes of diarrhoea, number of hospital admissions and nosocomial infections.

Table 1 includes RVGE epidemiological data estimated in the Piedmont Region.

The analysed cost items and their relative sources are presented in Table 2.

Because of a lack of data relative to the Italian scenario, the quality scores (QALY) used to measure the vaccination benefits (as shown in Table 3) are derived from a study conducted in Great Britain where EQ-5D questionnaires, concerning their RVGE-affected patients, were administered to paediatricians and general practitioners [28].

Budget impact analysis (BIA)

This analysis considered two different scenarios, one with the Rotarix anti-RV vaccination and one without, and used the same data entered in the cost-effectiveness model described in the previous paragraph. The acquisition cost of the vaccine (equal to € 33.50, for a total of € 67) was considered as being entirely at the expense of the RHS. As opposed to the cost-effectiveness model, the vaccination coverage was assumed as a variable from the first to the fifth year (with a gradual growth from the first to the fifth year from 40% to 95%, more specifically: 40%, 50%, 65%, 80% and 95%). Further reference on the methodological details and the cost values ascribed in the model can be found in the HTA report on the anti-RV vaccination with Rotarix [1].

Results

Cost-effectiveness analysis in the Piedmont Region

In a cohort of 34.637 individuals born in Piedmont in 2014, the number of hospitalizations caused by RV in absence of a vaccination was 951. Assuming that 100% of the infants receive two doses of the anti-RV vaccine, the vaccination would lead to an 84% reduction of RVGE cases, a 99% reduction of RVGE-related hospitalizations and an 89% reduction of nosocomial RV-infections, thus influencing the quality of life and death rate of the population analysed. (Table 4).

The introduction of the vaccine would bring a profit of 0.0216 QALMs (Quality Adjusted Life Months) resulting in 0.0018 QALYs per child compared to a scenario without vaccination.

The effect on health outcomes determines a strong economic impact due to the decrease of medical examinations, hospitaliza-

Table 4
RVGE-related epidemiological data, hospitalizations and deaths, estimated in the Piedmont Region before and after vaccination.

	Reference percentage	Number of cases (No vaccination)	Number of cases (vaccination)	Number of cases (difference vaccination vs no vaccination)	% Difference vaccination vs no vaccination
Total 2014 cohort (Piedmont Region)	34637		100% Coverage		
RVGE cases/RV-specific diarrhoea	45.45%	15742	2518	13224	−84%
Medical consultations/paediatric examinations	22%	7606	238	7368	−97%
Emergency room visits	9.8%	3391	104	3287	−97%
Hospital admissions	2.74%	951	10	941	−99%
Admissions for nosocomial infection of RV-specific diarrhoea	1.51%	521	55	466	−89%
Deaths	0%	0	0	0	0

Table 5
Costs per category, including total costs, with and without vaccination.

	No vaccination (€)	Vaccination (€)	Cost difference (€)
Vaccine cost	0	2,320,679	2,320,679
Medical consultations/paediatric visits	136,908	4284	132,624
Emergency room visits	817,231	25,064	792,167
Hospitalizations for RV	1,162,598	12,225	1,150,373
Admissions for nosocomial RV-diarrhoea	1,123,276	118,580	1,004,696
Total costs	3,240,013	2,480,832	759,181
Cost per individual	93.54	71.62	21.92

Table. 6
Budget impact analysis — economic impact.

Economic impact	No vaccination (€)	1st year (€)	2nd year (€)	3rd year (€)	4th year (€)	5th year (€)
Vaccine cost	–	1,040,455	1,271,667	1,502,879	1,849,698	2,196,516
Residual pathology cost	3,240,013	2,400,845	1,839,300	1,444,210	1,045,357	622,416
Total cost	3,240,013	3,441,300	3,110,967	2,947,089	2,895,055	2,818,932
Total Δ		297,942	−32,391	−196,269	−248,303	−324,426
Budget difference after 5 years (€)	−503,447					

tions and emergency room visits. The incremental cost resulting from the vaccine appears to be abundantly compensated by the reduction of the healthcare-related costs and this is mainly due to reduced hospital admissions and emergency visits costs. The annual cost of the RV pathology at the expense of the Piedmont Region is of € 3.242.936; the introduction of the vaccination plan would result in a cost reduction of € 761.291 (Table 5).

The cost-effectiveness analysis results showed a cost-saving ICER (incremental cost-effectiveness ratio) relevant to the RHS and equal to €12.197/QALY.

Hence, the introduction of the vaccine appears to be the best option, as it leads to an increase of QALYs (more effective) and to a reduction of costs for the RHS (less expensive).

Budget impact analysis (BIA) in the Piedmont Region

As shown in Table 6, having assumed an increasing vaccination coverage rate, the acquisition cost of the vaccine increases from the first to the fifth year. At the same time, with the gradual introduction of the anti-RV vaccination, a progressive cost reduction was observed. This is due to the rise in the vaccination's clinical benefits, which leads to a consequent reduction in the healthcare-related medical costs and to money-saving from the second year onwards.

The cost reduction related to the vaccination programme and the consequent savings from the second year on is clearly shown in Table 6; the total expected saving is about € 503.000.

Discussion

The present study evaluated, through a cost-effectiveness analysis and a budget impact analysis, the economic impact of the introduction of a universal anti-RV vaccination in the Piedmont Region, i.e. its economic sustainability for RHS.

Our results show that the mass implementation of an anti-RV vaccination in Piedmont, in addition to the expected public health benefits, also allows the RHS to save a considerable amount of money within a short period of time, due to the remarkable reduction of direct health costs associated with RVGE management. In fact, as the analysis shows, a universal vaccination against RV results in money-saving for the RHS already from the 2nd year (with a vaccination coverage of 50%). During the five year period, the active and free offer of the anti-RV vaccination would determine a total saving for the RHS of about € 503.000.

Therefore, these results appear to be in line with similar evaluations performed both on a national [29,30] and European scale, thus reporting a quite reassuring picture of the prevention perspective of the pathologies related to the pathogen examined. Other economic evaluations show a cost saving profile of the vaccines, as results [31,32].

In the current literature some studies have investigated the impact of RV vaccination. In particular, Austria was the first country in Europe implementing a universal mass vaccination program against RVGE for all infants. Published data show that incidence rates of children hospitalized with RVGE decreased in 2009 compared to the prevaccination period [33].

The same was observed in Belgium and England [34,35].

Moreover, from a strictly organizational point of view, the vaccination, being orally administered and co-administrable with other vaccines, would also add a number of other logistical/economic advantages, without further weighing down the vaccine organization system.

Interestingly, an increased risk of intussusception (~1–6 per 100,000 vaccinated infants) after RV vaccination has been documented in some contexts, but this is outweighed by the large benefits of vaccination [36].

In consequence of this, the role of the intussusception after the introduction of RV vaccination should be addressed: in Italy the

hospitalization rate for intussusception had a slight increase in trend from 2009 to 2014 (18%) but the role played by different risk factors, including acute gastroenteritis, have to be investigated [37], especially in order to fight the possible "fear" of intussusception among paediatricians and vaccination units physicians that could represent a problem for vaccination acceptance [38].

In conclusion, considering the well documented clinical effectiveness of the currently available anti-RV vaccines and their good safety and tolerability profiles, the adoption of a universal preventive strategy for all the infants in the Piedmont Region may contribute significantly towards the control of RVGE incidence, thus allowing a noteworthy saving of economic and social resources for both the RHS and the general public.

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Competing interests

None declared.

Ethical approval

Not required.

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