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Cost effectiveness evaluation of a rotavirus vaccination program in Argentina

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ABSTRACT

Background: Rotavirus diarrhea is one of the most important vaccine-preventable causes of severe diarrhea in children worldwide. There are two live-attenuated virus vaccines licensed, *Rotarix*® (RV1) a monovalent vaccine by GlaxoSmithKline and a pentavalent vaccine, *RotaTeq*® (RV5), by Merck & Co., with similar results. This study aim was to evaluate the cost-effectiveness of the utilization of RV1 compared with RV5 in Argentina.

Methods: A deterministic Markov model based on the lifetime follow up of a static cohort was used. Quality Adjusted Life Years (QALYs) as a measure of results, the perspective of the health care system and a 5% discount rate for health benefits and costs has been used. A review of the literature to obtain epidemiologic and resources utilization of rotavirus diarrhea was performed. The sources used to estimate epidemiologic parameters were the National Health Surveillance System, the national mortality statistics and national database of hospital discharges records. Costs were obtained from different health subsectors and are expressed in local currency.

Results: Both vaccination alternatives were less costly and more effective than the strategy without vaccination (total costs $ 69,700,645 and 2575 total QALYs lost). When comparing RV1 vs. RV5, RV1 was less expensive ($ 60,174,508 vs. $ 67,545,991 total costs) and more effective (1105 vs. 1213 total QALYs lost) than RV5, RV1 being therefore a dominating strategy. Probabilistic sensitivity analysis showed results to be robust with a 100% probability of being cost-effective at a WTP threshold of 1 GDP per capita when comparing the RV1 vs. no vaccination.

Conclusion: Both RV1 and RV5 schedules dominate the no vaccination strategy and RV5 was dominated by RV1. This information is a valuable input regarding the incorporation of this kind of vaccines into the national vaccination programs.

1. Introduction

Q4 Acute diarrhea is one of the 5 leading causes of death among children under 5 years in the Americas, it is estimated that over 500,000 children die each year in the region due to this disease [1]. Rotavirus diarrhea is one of the most important vaccine-preventable causes of severe diarrhea in children worldwide. The incidence is similar in all countries, but 80% of the deaths occur in developing countries [2].

A meta-analysis in Latin America and the Caribbean reported that the incidence rate of rotavirus cases between 1990 and 2009 was 170 per 1000 child-years (95% CI 130–210). The estimated annual mortality was 88.2 (95% CI 79.3–97.1) deaths per 100,000 children under 5 years [3]. Approximately, 1 out of 60 cases will require hospitalization [2].

In Argentina, according to 2009–10 rotavirus national surveillance data, out of 8637 acute diarrhea cases studied, rotavirus was detected in 2498 stool samples. The percentage of positivity was 22.4% in outpatient and 29.7% in hospitalized [4].

There are two live-attenuated virus vaccines licensed for use worldwide. *Rotarix*™ (RV1), a monovalent oral vaccine licensed by GlaxoSmithKline (GSK) in 2004 [5]. A second oral pentavalent live-attenuated virus vaccine, *RotaTeq*® (RV5), was introduced in the U.S. in 2006, licensed worldwide by Merck & Co., with similar results regarding disease reduction to those observed with RV1 [6]. RV1 is administered in a 2 dose schedule and RV5 in a 3 dose one.

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In 2009, WHO recommended the inclusion of rotavirus vaccines in all national immunization programs [7]. Additionally, the estimation of local burden of disease and the evaluation of its cost effectiveness was considered by WHO as an essential step before the introduction [8].

Till 2011, 14 countries in the region have adopted the rotavirus vaccine in their national immunization schedules; RV1 in Brazil, Ecuador, El Salvador, Panamá, Mexico, Venezuela, Honduras, Peru, Bolivia, Colombia, Paraguay and Guatemala; RV5 in Nicaragua, Caiman Islands and Guyana [9].

In Argentina, National Immunization Technical Advisory Groups (NITAG) is represented by the National Immunization Commission (CoNaIn), an organization created by the Ministry of Health in 2000. CoNaIn has provided advisory services and recommendations on immunization, which are reflected in the introduction of different vaccines into the immunization schedule. [58]

Since January 2015, rotavirus vaccine is included in the national immunization program in Argentina in a two dose schedule.

This study aims to evaluate the cost-effectiveness of the utilization of RV1 compared with RV5 in Argentina.

2. Methods

2.1. Model structure

A deterministic Markov model based on lifetime follow up of a birth cohort developed by GlaxoSmithKline Biologicals in Microsoft Excel was used to estimate the cost-effectiveness of rotavirus vaccines [10–12]. The model simulates the effectiveness of the vaccine at steady state post vaccine introduction.

The model includes four health states: birth, healthy, sick with community-acquired diarrhea and death. The Markov model has monthly cycles so that more precision about the occurrence of diarrhea events and the onset of vaccine benefit can be better modeled with different dosing schedules. Time horizon used is life expectancy at birth in Argentina to assess deaths and life years lost; 0–5 years of age to assess rotavirus associated events.

The model considers both direct and indirect cost associated with each health state, but it considers the perspective of the health care system in the base case. A 5% discount rate for health benefit and cost is used [13]. The value of 1 GDP (Gross Domestic Product) per capita for 2010, corresponding to AR$ 33,294 (USD 8261.54) [14,15], is considered as the willingness to pay threshold for the payer.

The utility measure used by the model is the Quality Adjusted Life Years (QALYs).

The model assesses the incremental cost and health effect of introducing the vaccine (2 or 3 dose schedules) compared against each other and with a no vaccination scenario.

2.2. Epidemiologic parameters

A review of the literature to obtain local data related to epidemiology and resource use of rotavirus diarrhea was performed (see Table 1). The birth cohort included comprised 746,460 subjects first year based on the Argentine population census of the year 2008 [16]. Life expectancy was of 75.24 years and the estimated child mortality was 12.5 per 1000 for the population under one year of age and 0.6 per 1000 for the children from one to four years [17].

The sources for the estimation of rotavirus disease burden (episodes of diarrhea, emergency room consultations, outpatients visits, hospitalizations and deaths) in children younger than five years of age were the National Health Surveillance (SNVS) [18], the national mortality statistics [19] and hospital discharges records from the National Health Information Unit DEIS [20]. Most of this information comes solely from the public health subsector; therefore adjustments in its coverage were made to estimate these parameters at national level, due to the existence of different health sectors (private, social security and public) in the country.

Ambulatory cases were estimated from cases of diarrhea reported to SNVS [18]. 16.8% of the cases were attributable to rotavirus as reported in the meta-analysis of Linhares et al. [3]. It was estimated that 10% of the diarrhea cases does not seek medical care when ill according to Permanent Household Survey [21].

For this purpose the following equation was used:

$$\text{No. rotavirus diarrhea calls} = \text{SNVS diarrhea cases} \times \%\,\text{rotavirus diarrhea/SNVS coverage adjustment}$$

Data from the 2007 national survey on breastfeeding [22] were incorporated to account for the protective effect of breastfeeding on the incidence of diarrhea in the first 12 months of life. Duration of the episode of rotavirus diarrhea used was 4 days, based on a Cochrane review [23].

Using the data sources described above, the estimation of rotavirus diarrhea cases in the birth cohort up to the age of 5 years was 418,811. To validate this critical input an alternative estimation was made using a different methodology based on a meta-analysis of rotavirus diarrhea incidence in Latin America performed by Linhares et al. [3] and a study about the global incidence of diarrhea of any cause under 5 years by Parashar et al. [2]. The result was similar to the one calculated above (422,870 rotavirus diarrhea cases among children under 5) proving the robustness of our estimation.

Rotavirus diarrhea hospitalizations were estimated from the average number of hospital discharges associated with diarrhea reported by DEIS between 2005 and 2007 (21,397 diarrhea hospitalizations per year) [20] and the rate of rotavirus-attributed diarrhea reported (29.7%) in the meta-analysis of Linhares et al. [3] adjusted by the hospitalization coverage. Deaths were estimated from the 2005–2008 average diarrhea deaths reported by DEIS (102 diarrhea deaths per year) [19] and the rate of rotavirus-attributed diarrheas estimated from Gomez et al. study (37.36%) [24]. Finally, hospital length of stay was obtained from DEIS hospitalization discharge database [20].

2.3. Vaccine efficacy

Vaccine efficacy was estimated using regional [25,26] and global studies [27,28]. For both vaccines completed schedules (two doses for RV1 and three doses for RV5), the efficacy was 70% reduction in outpatient rotavirus diarrheas, a 75% reduction in emergency room rotavirus diarrheas and an 85% reduction in hospitalized rotavirus diarrheas, the same for both vaccines. For incomplete schedules efficacy was taken from two studies, one conducted in Europe by Jit et al. [29] and the other in the USA by Weycker et al. [27]. Based on them, it was assumed that the efficacy of the 2nd dose of the 3 doses schedule vaccine was equivalent to the efficacy of the 1st dose of the 2 doses schedule vaccine [27]. Additionally, the efficacy of the 1st dose of the 3 doses schedule vaccine represents an 84.3% of full schedule [29].

Adverse effects were not taken into consideration because of its very low frequency [57].

The vaccine coverage rate at steady state for the first, second and third doses was estimated using data from the WHO-UNICEF [30–32] database on rotavirus vaccine coverage for the Latin American countries adjusted by the Sabin vaccine coverage for Argentina [31]. All vaccine efficacy and coverage data included in the model is shown in Table 1.

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