ADIS SPOTLIGHT

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Pharmacoeconomic Spotlight on Rotavirus Vaccine RIX4414 (Rotarix™) in Developed Countries†

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Contents

Abstract

The most common cause of severe diarrhea in infants and young children is rotavirus gastroenteritis (RVGE), which is associated with significant morbidity, healthcare resource use, and direct and indirect costs in industrialized nations. The monovalent rotavirus vaccine RIX4414 (Rotarix™) is administered as a two-dose oral series in infants and has demonstrated protective efficacy against RVGE in clinical trials conducted in developed countries. In addition, various naturalistic studies have demonstrated 'real-world' effectiveness after the introduction of widespread rotavirus vaccination programs in the community setting.

Numerous cost-effectiveness analyses have been conducted in developed countries in which a universal rotavirus vaccination program using RIX4414 was compared with no universal rotavirus vaccination program. There was a high degree of variability in base-case results across studies even when the studies were conducted in the same country, often reflecting differences in the selection of data sources or assumptions used to populate the models. In addition, results were sensitive to plausible changes in a number of key input parameters. As such, it is not possible to definitively state whether a universal rotavirus vaccination program with RIX4414 is cost effective in developed countries, although results of some analyses in some countries suggest this is the case. In addition, international guidelines advocate universal vaccination of infants and children against rotavirus. It is also difficult to draw conclusions regarding the cost effectiveness of rotavirus vaccine RIX4414 relative to that of the pentavalent rotavirus vaccine, which is administered as a three-dose oral series. Although indirect comparisons in cost-effectiveness analyses indicate that RIX4414 provided more favorable incremental cost-effectiveness ratios

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when each vaccine was compared with no universal rotavirus vaccination program, results were generally sensitive to vaccine costs. Actual tender prices of a full vaccination course for each vaccine were not known at the time of the analyses and therefore had to be estimated.

1. Introduction

Rotavirus gastroenteritis (RVGE) is the most common cause of severe diarrhea among infants and young children aged <5 years in developed and developing countries.[2-4] Symptoms can range from mild watery diarrhea to severe diarrhea with forceful vomiting, abdominal distress, and fever, which can lead to serious complications including dehydration, electrolyte imbalance, seizures, and death.[3,5-7] Although most of the estimated 600 000 childhood deaths associated with RVGE each year occur in developing countries,[8] RVGE is also responsible for significant morbidity among infants and young children in developed countries, as well as a substantial economic and societal burden on their parents, caregivers, and healthcare providers.[9]

Infants and young children who are infected with rotavirus develop partial immunity to subsequent infections and protection against subsequent severe RVGE, as demonstrated in longitudinal studies.[10-12] These beneficial effects increase with each natural infection,[10-12] and antibody responses to natural infection appear to provide protection against multiple serotypes of rotavirus,[13] the most common being G1, G2, G3, and G4 in conjunction with P[8] or P[4].[14] These serotypes (G1–G4) are responsible for >90% of episodes of RVGE in Europe and North America,[14] with regional and seasonal variations in the most prevalent types.[15,16] Data from a large European study conducted in 2004–5 indicate that serotypes G1, G2, G3, G4, and G9 accounted for >98% of cases of RVGE.[15]

These data highlight the importance of rotavirus vaccines that mimic natural rotavirus infection and protect against the most common serotypes of rotavirus, as reflected in international guidelines advocating universal vaccination of infants and children against rotavirus.[4,17-20] Despite these guidelines, which recommend either of the orally administered rotavirus vaccines currently available (a two-dose series of the monovalent vaccine RIX4414 [Rotarix™] or a three-dose series of the pentavalent rotavirus vaccine [RotaTeq®]), vaccination of infants and children against rotavirus is a much-debated topic often entangled in issues of cost effectiveness and health economics. This article focuses on the rotavirus vaccine RIX4414, which is composed of a monovalent, live, attenuated, human rotavirus strain of G1P[8] type.[21-23]

2. Clinical Profile of Rotavirus Vaccine RIX4414

Data on the protective efficacy of rotavirus vaccine RIX4414 against RVGE in developed countries are available primarily from a large, randomized, double-blind, phase III trial conducted in six European countries (Czech Republic, Finland, France, Germany, Italy, and Spain),[24] although supporting data from other relevant studies are also available.[25,26]

The large European study evaluated the efficacy of the vaccine in terms of its effects on the incidence of RVGE (including severe RVGE) and on healthcare resource use, such as hospitalization due to RVGE, among infants during their first 2 years of life.[24] A total of 3994 healthy infants aged 6–14 weeks were randomized to receive two oral doses of rotavirus vaccine RIX4414 (n = 2646) or placebo (n = 1348), which were administered at the same time as the first two doses of other, routine childhood vaccinations. The primary endpoint was vaccine efficacy against RVGE of any severity during a follow-up period from 2 weeks after administration of the second dose to the end of the first rotavirus season (2004–5), and all efficacy analyses were conducted in the per-protocol population. Vaccine efficacy was calculated using the following formula: 1 – incidence of RVGE in the vaccine group/incidence of RVGE in the placebo group.

For the primary endpoint, the protective efficacy of rotavirus vaccine RIX4414 against RVGE of any severity was 87.1% (95% CI 79.6, 92.1; $p < 0.0001$) during the first follow-up period.[24] Similar results were also demonstrated in the second follow-up period (2005–6) and when both follow-up periods were combined. For all follow-up periods, vaccine efficacy was also significant ($p < 0.0001$) against severe RVGE (defined as a score of ≥11 on the 20-point Vesikari scale), RVGE requiring hospitalization, and RVGE requiring medical attention. In addition, vaccine efficacy against any and severe RVGE caused by each of the rotavirus G types identified (G1, G2, G3, G4, and G9) was significant ($p \leq 0.02$) in the combined efficacy follow-up period.[24]

Various naturalistic studies conducted in developed countries have demonstrated the 'real-world' effectiveness of rotavirus vaccination after introduction of the vaccine for routine use in the community setting. Typically, these studies compared various outcomes, such as the numbers of RVGE cases, RVGE-related hospitalizations, and/or emergency department visits, that occurred during the pre-vaccination period with those that occurred during a specific period after widespread or universal introduction of a rotavirus vaccination program. Studies conducted in the Australian state of Queensland[27] and in European countries[28-30] involved rotavirus vaccination programs with either the monovalent or pentavalent rotavirus vaccine, whereas studies conducted in the US generally focused only on the pentavalent vaccine (reviewed elsewhere[31,32]).

Rotavirus vaccine RIX4414 was generally well tolerated in clinical trials, with an overall tolerability profile similar to that of placebo.[21,23] There was no increased risk of intussusception with rotavirus vaccine RIX4414 in a large ($n = 63\,225$), placebo-controlled, pre-licensure safety study conducted in Latin America and Finland.[21,25] However, interim results from a postmarketing active surveillance study conducted in Mexico, along with worldwide passive surveillance data, suggest that there may be an increased risk of intussusception during the first 7 days after administration.[21] Both the US prescribing information[21] and the EU summary of product characteristics[23] state that rotavirus vaccine RIX4414 should not be administered to infants with a previous history of intussusception or to those with uncorrected congenital malformation of the gastrointestinal tract (e.g. Meckel's diverticulum) that would predispose them to intussusception.

3. Pharmacoeconomic Analyses of Monovalent Rotavirus Vaccine RIX4414

Most of the published cost-effectiveness analyses of rotavirus vaccine RIX4414 were conducted in European countries and used decision-tree or Markov models that incorporated data from various sources, including protective efficacy results from large phase III trials with rotavirus vaccines and local cost data, to evaluate the cost effectiveness of introducing a universal rotavirus vaccination program compared with no universal vaccination program against rotavirus. In several analyses, both the healthcare payer and societal perspectives were used,[33-40] whereas other studies were conducted from either a societal[41,42] or a healthcare payer perspective.[43] Two studies adopted a 'limited societal' perspective, which excluded indirect costs but included out-of-pocket medical expenses along with other direct medical costs.[44,45] Some studies focused only on RIX4414,[36,37,42-44] while others also included indirect comparisons with the pentavalent rotavirus vaccine[34,35,38,39,41,45] or, in some cases, the universal rotavirus vaccination program being evaluated allowed for the use of either RIX4414 or the pentavalent rotavirus vaccine.[33,40,45]

A wide range of results was reported across the cost-effectiveness analyses, which appears to be related, at least in part, to the substantial heterogeneity among the models used in the studies. The analyses typically showed that the cost of a universal rotavirus vaccination program was partly offset by reductions in RVGE-related healthcare resource use and that the program was associated with quality-adjusted life-year (QALY) gains. However, the universal rotavirus vaccination program was deemed to be cost effective from the perspective of the healthcare payer only in some studies,[36,37,42,43] but not in others,[33-35,38-40,43] when applying commonly reported cost-effectiveness

thresholds, such as €20 000–50 000, $US50 000, or £20 000–30 000 per QALY gained.[46-49]

A consistent finding across studies that were conducted from both a healthcare payer and a societal (or 'limited societal') perspective was that incremental cost-effectiveness ratios (ICERs) were more favorable from a societal perspective,[33-40,43] as might be expected because additional costs associated with RVGE (e.g. out-of-pocket medical expenses and/or lost productivity of parents of children who develop RVGE) were included. Another consistent finding of the studies was that, compared with no universal vaccination program, ICER values for a two-dose oral series of rotavirus vaccine RIX4414 were more favorable than those for a three-dose oral series of pentavalent rotavirus vaccine when cost effectiveness of the two vaccines was evaluated separately in the same study.[34,35,38,39,41,45] However, modelled analyses directly comparing the two vaccines would require head-to-head clinical trial data, which are currently lacking. In addition, there are inherent uncertainties in comparing ICER values of the available rotavirus vaccines because of the tender process that would be used to establish the vaccine price in a universal program.

Although results of the cost-effectiveness analyses were sensitive to a number of parameters, which often varied between studies, there were also some common findings in the sensitivity analyses. Variations in the cost of vaccine, QALY losses for a caregiver, and the number of caregivers affected, as well as annual discount rates (particularly for outcomes), were among the most frequently reported parameters having the greatest impact on ICER values.

Economic models such as those used in the cost-effectiveness analyses with rotavirus vaccine RIX4414 have, out of necessity, the inherent limitations of using data from a variety of sources and extrapolating shorter-term clinical trial data to project longer-term costs and outcomes. Moreover, data or assumptions used to populate the models (e.g. waning of vaccine protection, rate of vaccine uptake, protective efficacy of partial vaccination, time period over which infections could be acquired, incidence of RVGE, probability of RVGE hospitalization) often varied between studies, which, together with results of sensitivity analyses, highlights some of the uncertainties in results from these modelled analyses.

Along with differences in the selection of data sources used in the analyses, other factors contributing to the wide variability in results include differences in the study perspective, year of costing, and discount rates, as well as country- or region-specific differences in estimates of healthcare resource use and associated costs. The type of model used in vaccine cost-effectiveness analyses can also affect results; for example, whether the main features of the model change over time (dynamic model) or not (static model).[50-54] The effects of herd immunity, whereby vaccination of part of a population confers partial indirect protection for the remainder,[50,52,54] are not captured in static models (e.g. decision-tree, Markov), which results in an underestimation of the cost effectiveness of a vaccination program.[52,54] Two analyses of rotavirus vaccine RIX4414 included the effects of herd immunity, using data from dynamic transmission models in the sensitivity analyses, and in both cases the inclusion of herd immunity effects markedly improved ICER values.[35,43]

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