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Review

Effectiveness and impact of rotavirus vaccines in Europe, 2006–2014

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ABSTRACT

Prior to the introduction of rotavirus vaccines in 2006, rotavirus was the leading cause of severe gastroenteritis among European children <5 years of age. We conducted a systematic review of the published literature to examine the effectiveness and impact of rotavirus vaccines in Europe following the first eight years of routine use. Four publication databases were searched, yielding 276 unique citations from February 1st, 2006 to July 31st, 2014. Twenty four studies on effectiveness ($n = 9$) and impact ($n = 15$) met the inclusion criteria. Across Europe, vaccine effectiveness against rotavirus-related healthcare utilisation ranged from 68% to 98%, consistent with efficacy data from clinical trials. Reductions in rotavirus hospitalisations ranged from 65% to 84%, consistent with findings from post-marketing studies from the US and Latin America. We confirm the significant public health benefit of rotavirus vaccination in Europe and provide further evidence to support implementation of universal rotavirus vaccination in all European countries.

1. Introduction

Rotavirus is the leading cause of severe gastroenteritis in children under five years of age [1]. Prior to the introduction of rotavirus vaccines in Europe in 2006, it was estimated that 3.6 million episodes of rotavirus disease occurred annually among the 23.6 million children younger than 5 years of age [2]. Every year, rotavirus accounted for 231 deaths, over 87,000 hospitalisations and almost 700,000 outpatient visits in Europe [2].

In 2006, two rotavirus vaccines, Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck and Co, Sanofi Pasteur MSD, Lyon, France) were licensed for use in Europe. Both live attenuated rotavirus vaccines given orally have shown high efficacy and good safety profiles in large clinical trials [3,4]. Rotarix (RV1), which is administered as a two-dose schedule, is a monovalent human vaccine originating from a G1P [8] strain [3]. RotaTeq (RV5), which is administered as a three-dose schedule, is a pentavalent vaccine containing five human-bovine reassortant strains (G1, G2, G3, G4, and P1A [8]) [4]. In the US, RV1 is administered at 2 and 4 months of age, and RV5 is administered at 2, 4 and 6 months of age. However, the rotavirus vaccination schedules differ slightly across Europe to better align with the timing of administration of other routine immunisations. For examples, in the United Kingdom (UK) and Belgium RV1 is administered at 2 and 3 months of age, and in Finland RV5 is administered at 2, 3 and 5 months of age.

In April 2009 the World Health Organization Strategic Advisory Group of Experts (SAGE) recommended that all national immunisation programmes include rotavirus vaccination for infants [5]. Globally a number of countries have adopted this recommendation, however, only a limited number of European countries have done so [6]. By the beginning of 2014, rotavirus vaccination had been implemented nationally in Austria, Belgium, Luxembourg, Finland, Greece, Norway, and the UK; with vaccination coverage rates ranging from over 90% in the first four countries to 23.4% in Greece and less than 10% in Norway and the UK [6]. Many European countries are at various stages of issuing national or regional recommendations or integrating rotavirus vaccination into their national immunisation programmes.

Here, we summarise published data from the past eight years on the effectiveness and impact of RV1 and RV5 in European countries to generate a transparent base of evidence for policymakers across Europe.

2. Methods

2.1. Search strategy

We developed search terms to identify articles published between 1st February 2006 and July 31st 2014 reporting (1)

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Table 1
PubMed literature search terms.

Strategy: Citations are identified that contain text in the Title/Abstract/Keywords fields using the following strategy/search term group. Case Reports, Randomised Controlled Trials, Animal Studies, Reviews and Systematic Reviews were excluded where search engines allowed. (Search Group 1) AND (Search Group 2) AND (Search Group 3) AND (Search Group 4) Date range (1st February 2006–31st July 2014)
Search Group 1: Disease Terms "rotavirus"[MeSH] OR "rotavirus"[All Fields]
Search Group 2: Vaccine Terms "rotavirus vaccines"[MeSH] OR ("rotavirus"[All Fields] AND ("vaccine"[All Fields] OR ("vaccines"[All Fields])) OR "Rotarix"[MeSH] OR "RotaTeq"[MeSH] OR "RV1"[MeSH] OR "RV5"[MeSH]
Search Group 3: Outcome Terms "impact"[MeSH] OR "effect"[MeSH] OR "effectiveness"[MeSH] OR "trends"[MeSH] OR "diarrhoea"[All Fields] OR "gastroenteritis"[All Fields] OR "rotavirus disease"[All Fields] OR "hospitalisation"[All Fields] OR "hospital admission"[All Fields] OR "outpatient"[All Fields] OR "visit"[All Fields] OR "attendance"[All Fields] OR "consultation"[All Fields] OR "general practice"[All Fields] OR "primary care"[All Fields] OR "Accident and Emergency"[All Fields] OR "emergency department"[All Fields] OR "laboratory confirmed"[All Fields] OR "positive test"[All Fields] OR "microbiologically confirmed"[All Fields] OR "laboratory confirmed"[All Fields]
Search Group 4: Setting Terms (Countries in the WHO European Region) "European Union"[MeSH] OR "European countries"[MeSH] OR "European Union"[MeSH] OR "Europe"[MeSH] OR "Austria"[All Fields] OR "Belgium"[All Fields] OR "Finland"[All Fields] OR "Luxemburg"[All Fields] OR "United Kingdom"[All Fields] OR "England"[All Fields] OR "Wales"[All Fields] OR "Scotland"[All Fields] OR "Northern Ireland"[All Fields] OR "Germany"[All Fields] OR "Armenia"[All Fields] OR "Moldova"[All Fields] OR "Georgia"[All Fields] OR "Israel"[All Fields] OR "Albania"[All Fields] OR "Andorra"[All Fields] OR "Azerbaijan"[All Fields] OR "Belarus"[All Fields] OR "Bosnia and Herzegovina"[All Fields] OR "Bulgaria"[All Fields] OR "Croatia"[All Fields] OR "Cyprus"[All Fields] OR "Czech Republic"[All Fields] OR "Denmark"[All Fields] OR "Estonia"[All Fields] OR "France"[All Fields] OR "Greece"[All Fields] OR "Hungary"[All Fields] OR "Iceland"[All Fields] OR "Ireland"[All Fields] OR "Italy"[All Fields] OR "Kazakhstan"[All Fields] OR "Kyrgyzstan"[All Fields] OR "Latvia"[All Fields] OR "Lithuania"[All Fields] OR "Malta"[All Fields] OR "Monaco"[All Fields] OR "Montenegro"[All Fields] OR "Netherlands"[All Fields] OR "Norway"[All Fields] OR "Poland"[All Fields] OR "Portugal"[All Fields] OR "Romania"[All Fields] OR "Russian Federation"[All Fields] OR "Russia"[All Fields] OR "San Marino"[All Fields] OR "Serbia"[All Fields] OR "Slovakia"[All Fields] OR "Slovenia"[All Fields] OR "Spain"[All Fields] OR "Sweden"[All Fields] OR "Switzerland"[All Fields] OR "Tajikistan"[All Fields] OR "Macedonia"[All Fields] OR "Turkey"[All Fields] OR "Turkmenistan"[All Fields] OR "Ukraine"[All Fields] OR "Uzbekistan"[All Fields]

vaccine effectiveness (VE) of rotavirus vaccines in preventing rotavirus disease and/or healthcare utilisation due to rotavirus, and/or (2) impact of rotavirus vaccination on rotavirus disease trends and/or healthcare utilisation due to rotavirus (Table 1). Studies from any country in the WHO European Region [7] and published in any European language were identified (Table 1). Case Reports, Randomised Controlled Trials, Animal Studies, Reviews and Systematic Reviews were excluded. Databases searched included PubMed, Embase and Cochrane. We also searched Google Scholar and the System for Information on Grey Literature in Europe (SIGLE) for relevant citations.

2.2. Inclusion criteria

We reviewed the title and abstract of each article identified using the search strategy to determine whether the article was potentially relevant. The review was conducted by three reviewers independently and discrepancies resolved by consensus between reviewers. Potentially relevant articles were referred for a full abstraction. Cohort, observational studies (case-control and pre- vs. post-vaccine introduction time periods) and surveillance database analyses performed under conditions of post-licensure routine rotavirus vaccine use were included, as well as before/after studies if the impact data (percentage change in crude or adjusted rates) were provided or could be calculated. Studies reporting results in both vaccine-eligible (direct effects) and/or in non-vaccine-eligible age groups (indirect effects) were included. Health economic studies were excluded, along with time-series observational studies with only post-vaccine introduction data, and studies conducted among vulnerable populations not representative of the general population.

2.3. Abstraction process

We used EndNote X5 (Thomson Reuters) to organise and track the articles, adding databases sequentially beginning with PubMed, and performing automated and manual de-duplication following the addition of each subsequent database. We double-abstracted information about the study location, design, population characteristics and size, type of vaccine, and vaccine coverage directly into a customised Microsoft Excel spreadsheet. For outcomes of interest we abstracted information on number of events in the control (or pre-introduction) and intervention (or post-introduction) groups, and effect measures (e.g. risk ratios). All included studies were independently abstracted by three reviewers and harmonised by consensus.

2.4. Data analysis

We did not perform a meta-analysis because of the substantial heterogeneity across studies. For example, studies that examined time-trends used variable pre and post-vaccine year(s), with country specific differences in vaccine introduced, introduction date and vaccine coverage rates. Among case-control studies, case definitions of rotavirus disease were based upon laboratory testing, however, control groups varied between children with rotavirus negative gastroenteritis, those admitted to hospital or attending outpatient clinics for any reason other than gastroenteritis, as well as healthy children in the community. Thus, we summarised the data in descriptive analysis. For the analysis, the studies were grouped by design based on whether they were reporting on vaccine effectiveness or impact. The results reported within each study were then summarised by outcome and country.

3. Results

The systematic literature review yielded 276 unique citations from 1st February 2006 to July 31st 2014 (Fig. 1). Of these we reviewed 31 articles. Among these, 24 studies on the effectiveness ($n = 9$) and impact ($n = 15$) of rotavirus vaccines met the inclusion criteria (Fig. 1).

3.1. Vaccine effectiveness (VE)

Nine studies evaluating VE were identified: one from Austria [8], one from Belgium [9], one from Finland [10], one from Germany [11], two from Israel [12,13] and three from Spain [14–16] (Table 2). Seven studies looked at the combined VE of RV1 and RV5, one study looked specifically at RV1 [13] and one specifically at RV5 [10].

3.1.1. VE against RVGE hospitalisations

Eight studies examined VE against rotavirus gastroenteritis (RVGE) hospitalisations. The overall VE for at least one dose of rotavirus vaccine ranged from 89.4% (95% CI 51.9–97.6%) to 95.6% (95% CI 85.6–98.6%) (Table 3). The overall VE for fully vaccinated children ranged from 80% (95% CI 77–83%) to 98.3% (95% CI 87.4–99.8) (Table 3). One study from Spain examined VE separately for RV1 and RV5 and found no significant difference in effectiveness