Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Global economic evaluations of rotavirus vaccines: A systematic review

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ARTICLE INFO

Article history:
Received 3 July 2016
Received in revised form 17 April 2017
Accepted 19 April 2017
Available online xxxx

Keywords:
Rotavirus
Vaccine
Economic evaluations
Systematic review

ABSTRACT

Introduction: World Health Organization (WHO) recommends Rotavirus vaccines to prevent and control rotavirus infections. Economic evaluations (EE) have been considered to support decision making of national policy. Summarizing global experience of the economic value of rotavirus vaccines is crucial in order to encourage global WHO recommendations for vaccine uptake. Therefore, a systematic review of economic evaluations of rotavirus vaccine was conducted.

Methods: We searched Medline, Embase, NHS EED, EconLit, CEA Registry, SciELO, LILACS, CABI-Global Health Database, Popline, World Bank - e-Library, and WHOLIS. Full economic evaluations studies, published from inception to November 2015, evaluating Rotavirus vaccines preventing Rotavirus infections were included. The methods, assumptions, results and conclusions of the included studies were extracted and appraised using WHO guide for standardization of EE of immunization programs.

Results: 104 relevant studies were included. The majority of studies were conducted in high-income countries. Cost-utility analysis was mostly reported in many studies using incremental cost-effectiveness ratio per DALY averted or QALY gained. Incremental cost per QALY gained was used in many studies from high-income countries. Mass routine vaccination against rotavirus provided the ICERs ranging from cost-saving to highly cost-effective in comparison to no vaccination among low-income countries. Among middle-income countries, vaccination offered the ICERs ranging from cost-saving to cost-effective. Due to low- or no subsidized price of rotavirus vaccines from external funders, being not cost-effective was reported in some high-income settings.

Conclusion: Mass vaccination against rotavirus was generally found to be cost-effective, particularly in low- and middle-income settings according to the external subsidization of vaccine price. On the other hand, it may not be a cost-effective intervention at market price in some high-income settings. This systematic review provides supporting information to health policy-makers and health professionals when considering rotavirus vaccination as a national program.

Contents

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http://dx.doi.org/10.1016/j.vaccine.2017.04.051
0264-410X/

1. Introduction

Infection by rotaviruses (RVs) is globally the leading cause of severe diarrhea and dehydration in young children aged under 5 years old [1]. These highly contagious viruses have commonly infected most children before their fifth year of life. Each year rotaviruses cause approximately 111 million episodes of rotavirus gastroenteritis (RVGE) in young children [2]. Severe RVGE episodes mostly occur in low-income countries (LICs) and affect infants under 1 year of age [1,3]. As of April 2016, the World Health Organization estimated that globally 215,000 (197, 000–233,000) child deaths occurred during 2013 due to rotavirus infection [4]. The epidemiology of rotavirus infection episodes can be transmitted and observed year-round in most LICs in Asia and Africa, while a distinct winter seasonality is typically observed in high-income countries (HICs) [3].

RVs spread rapidly, presumably through person-to-person contact, airborne droplets, or possibly contact with contaminated toys [3]. They belong to the *Reoviridae* family and their outermost layer contains the proteins VP7 and VP4. At least 12 different VP7 antigens (G-types) and 15 different VP4 antigens (P-types) of human RVs have been identified. Currently, 5 G-P combinations (G1P [8], G2P [5], G3P [8], G4P [8]), and G9P [8]) account for approximately 90% of all human infections [3]. The enterocyte lining of the small intestinal villi is damaged by RV infection, resulting in reduction of absorptive capacity and diarrhea. The wide clinical spectrum ranges from transient loose stools to severe diarrhea and vomiting causing dehydration, electrolyte disturbances, shock and, in untreated cases, death. The cornerstones of treatment of severe RVGE are fluid replacement and zinc supplementation. An etiological diagnosis of RVGE requires laboratory confirmation [2,3].

To prevent and control RVGE, vaccination against rotavirus was recommended to be included in all national immunization programs (NIPs), particularly a priority in high RVGE-associated fatality rates, by WHO since 2009 [1,4]. Two effective vaccines based on live, oral, attenuated rotavirus strains of human and/or animal origin that replicate in the human gut, Rotarix (GSK Biologicals, Belgium)-a monovalent (RV1) originating from a human strain and RotaTeq (Merck & Co, US)-a pentavalent (RV5) containing 5 reassortants developed from rotaviruses of human and bovine origin, have been approved and licensed for internationally use since 2006 [3,5]. In addition, both vaccines have been prequalified in 2008 and 2009 by WHO [6]. The full course of RV1 is 2 doses, while 3 doses for RV5. Furthermore, 2 newer brands, ROTAVAC (Bharat Biotech International Limited, India) and Lanzhou lamb rotavirus (LLR) vaccine (Lanzhou Institute of Biomedical Products, China) have also been produced with a cheaper price [7,8]. Meta-analysis study of randomized, controlled trials has shown that both RV1 and RV5 are approximately 80–90% and 40–60% efficacious for the prevention of severe RVGE in countries with low-mortality and high-mortality rates, respectively [8]. In most cases, these are likely to provide protection against severe RVGE for at least 2 years [9,10]. Breastfeeding and prematurity (<37 weeks' gestation) do not significantly impair the response to the rotavirus vaccines [3]. In addition, no differences in terms of serious adverse events were observed between vaccine and placebo groups in large clinical trials [1,3,8–10]. Post-marketing surveillance in some settings has detected a small increased risk of intussusception (bowel obstruction which occurs when one segment of bowel becomes enfolded within another segment caused by rotavirus vaccine) which is about 1–2 per 100,000 infants vaccinated shortly after the first dose. However, the benefits through prevention of RVGE and RV-associated mortality may far exceed the risk of vaccine-induced intussusception [3]. To maximize vaccine impact, recipients have to be given the vaccine before RVGE occurs and before a sizeable proportion of the targeted population acquires natural infection. As of 16 December 2016, 87 out of 194 member states of WHO (44.8%) have been introduced rotavirus vaccine into their NIPs [11].

Prior to the implementation of preventive vaccination of RV infection, policy makers and public health stakeholders need among other information on health economic evaluation assessing the costs and benefits of adopting the new intervention [12]. Despite the fact that previous systematic review had been conducted [13], it was not specific to rotavirus vaccines and did not go in depth to critically appraise the quality and reporting of economic value from all available studies. Economic evaluations (EE) have been considered an important evidence supporting informed national decision making in many states. As there is an increasing in number of EE studies, summarizing global experience of economic value of rotavirus vaccines is crucial to strengthen global WHO policy recommendation. The evidence can be used by WHO to encourage member states for vaccine uptake or facilitate a conduct of study with sound methodology to help clinicians and policy makers make the evidence-informed decision for national immunization program. Therefore, this update and comprehensive systematic review of economic evaluations of rotavirus vaccines was conducted.

2. Methods

2.1. Data sources and searches

A systematic search for relevant articles published worldwide in each database from inception to November 2015 was electronically performed. Eleven databases including Medline, Embase, NHS EED (National Health Service Economic Evaluation Database), EconLit, CEA Registry, SciELO (Scientific Electronic Library Online), LILACS (Index of scientific and technical literature of Latin America and the Caribbean); CABI-Global Health Database, Popline, World Bank - e-Library, and WHOLIS (WHO Library & Information Networks For Knowledge Database) under GIFT (Global Information Full Text) of WHO web portal were accessed for systematic searching.

The search strategies used controlled vocabulary terms under thesaurus of each databases, whenever available, and relevant free-text terms, including 'rotavirus', 'vaccine', 'vaccination

Please cite this article in press as: Kotirum S et al. Global economic evaluations of rotavirus vaccines: A systematic review. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.04.051