Clinical Microbiology and Infection 22 (2016) S128–S135

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Potential safety issues and other factors that may affect the introduction and uptake of rotavirus vaccines

N. Aliabadi*, J.E. Tate, U.D. Parashar

Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA

ARTICLE INFO

Article history:
Received 13 October 2015
Received in revised form
22 February 2016
Accepted 13 March 2016
Available online 26 April 2016

Editor: I. Gyssens

Keywords:
Diarrheal disease
Immunization safety
Rotavirus vaccine
Vaccine implementation
Vaccine preventable diseases

ABSTRACT

Rotavirus vaccines have demonstrated significant impact in reducing the burden of morbidity and mortality from childhood diarrhoea in countries that have implemented routine vaccination to date. Despite this success, in many countries, rotavirus vaccine coverage remains lower than that of other routine childhood vaccines. Several issues may potentially affect vaccine uptake, namely safety concerns related to intussusception with consequent age restrictions on rotavirus vaccination, contamination with porcine circovirus, vaccine-derived reassortant strains and hospitalization in newborn nurseries at time of administration of live oral rotavirus vaccine. In addition to these safety concerns, other factors may also affect uptake, including lower vaccine efficacy in the developing world, potential emergence of strains escaping from vaccine protection resulting in lower overall impact of a vaccination programme and sustainable vaccine financing. Although further work is needed to address some of these concerns, global policy bodies have reaffirmed that the benefits of rotavirus vaccination outweigh the risks, and vaccine use is recommended globally. **N. Aliabadi, CMI 2016;22:S128**
Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases.

Introduction

Rotavirus infection is a major contributor to severe childhood diarrhoea, causing significant morbidity and mortality, with nearly 200 000 deaths among children younger than 5 years of age attributable to rotavirus in 2011 [1–4]. The majority of rotavirus deaths occur in the developing world, with several countries in sub-Saharan Africa reporting rotavirus-specific death rates of over 100 per 100 000 children [4]. While mortality from rotavirus is uncommon in developed settings, the burden of severe morbidity is substantial. In the United States, before vaccine introduction, an estimated 55 000–70 000 hospital admissions for severe rotavirus gastroenteritis occurred each year in children under 5 years of age, with 20 to 60 deaths [5].

In 2006, two live, attenuated rotavirus (RV) vaccines, a pentavalent (RV5; RotaTeq; Merck and Co.) and a monovalent (RV1 Rotarix; GSK Biologicals) formulation, demonstrated 85–98% efficacy against severe rotavirus gastroenteritis in large clinical trials conducted in the Americas and Europe [6,7]. These vaccines were subsequently recommended and licensed for routine use in the United States [5] and worldwide, with an emphasis on countries where mortality from diarrhoeal deaths was ≥10% among children under 5 years of age [8]. As of January 2016, these vaccines are being used in the national immunization programs of 80 countries [9] (http://sites.path.org/rotavirusvaccine/files/2015/12/PATH-Worldwide-Rotavirus-Vaccine-Introduction-Map-EN-2016.01.01_WHO.jpg) (Fig. 1).

The burden of rotavirus has significantly decreased in many countries that have adopted routine rotavirus vaccination. Notably, reductions in diarrhoea deaths have been reported after rotavirus vaccine introduction in Brazil, Panama and Mexico [9]. In Brazil, rotavirus vaccine coverage reached 90% for the first dose of RV1 and 77% for the second dose among infants by 2008. That same year, the gastroenteritis mortality rate among children less than 1 year of age decreased from 57 per 100 000 in 2004–2005 to 35 per 100 000, representing a relative reduction of 39% (95% confidence interval (CI), 29–49) [10]. In Mexico vaccine coverage reached 74% for the first dose of RV1 and 51% for the second dose among infants before the 2008 rotavirus season; during 2008, diarrhoea-associated mortality among infants 11 months of age or younger declined by 41% (95% CI, 36–47) to 36 per 100 000 compared to 62 per 100 000 during the prevaccine years from 2003 to 2006 [11]; this reduction was sustained for 4 years [12,13]. Similarly, in Panama, where

* Corresponding author. N. Aliabadi, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE MS A-34, Atlanta, GA 30329, USA.
E-mail address: ydh6@cdc.gov (N. Aliabadi).

http://dx.doi.org/10.1016/j.cmi.2016.03.007
1198-743X/Published by Elsevier Ltd on behalf of European Society of Clinical Microbiology and Infectious Diseases.

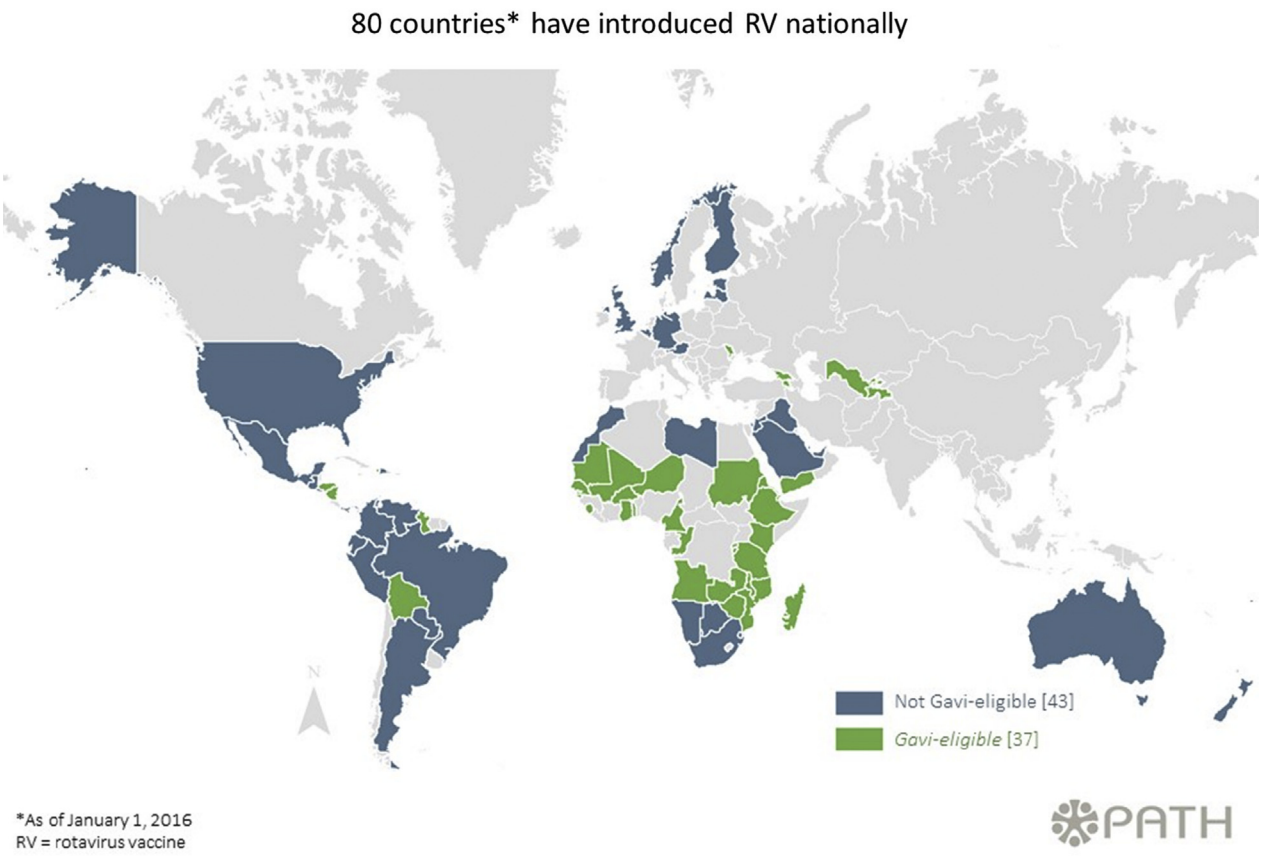

Fig. 1. Rotavirus introduction worldwide, PATH, as of January 2016.

vaccine coverage reached 71% in 2008, gastroenteritis-related mortality rate for children under 1 year of age decreased from 73 deaths per 100 000 in the 2000–2005 prevaccine period to 40 per 100 000 in 2008, representing a 45% decrease [14]. In addition to these remarkable mortality benefits, reductions of 17–55% in hospitalizations for all-cause diarrhoea and of 49–92% in hospitalizations for rotavirus-specific diarrhoea have been reported in the United States, Europe, Australia, Latin America and Africa [9,15–17]. Since vaccine introduction in the United States in 2006, rotavirus seasons have been delayed in onset, of shorter duration and of diminished magnitude (Fig. 2) [18,19].

Despite the remarkable overall impact of rotavirus vaccination, vaccines have not been universally adopted around the world; notably, no country in Asia has adopted a routine nationwide rotavirus vaccination programme to date. In addition, in many countries that have adopted vaccination, coverage of rotavirus vaccines remains lower than that of other established childhood vaccines (http://www.who.int/mediacentre/factsheets/fs378/en/) [20]. Here we discuss some of the potential barriers that might be affecting uptake and use of rotavirus vaccines.

Safety Concerns

Intussusception

Intussusception is a condition where one part of the intestine telescopes into an adjacent section, creating blockage and decreased circulation. If not corrected, it can lead to necrosis and perforation of the bowel and death. Mortality among young children hospitalized for intussusception is primarily related to suboptimal or delayed access to health care, and it ranges from as little as 0.1% in developed settings such as the United States and Europe to as high as 10–35% in some countries of Africa [21].

The first commercially available rotavirus vaccine, the rhesus rotavirus reassortant tetravalent vaccine (RRV-TV; Rotashield; Wyeth Vaccines), was introduced in 1998 in the US market and was recommended by the US Advisory Committee on Immunization Practices (ACIP) to be provided to all US infants as a three-dose schedule given at 2, 4 and 6 months of age. Shortly after vaccine introduction, an increase in reports of intussusception among infants given RRV-TV was noted through the national Vaccine Adverse Event Reporting System [22]. This led to a temporary suspension of vaccine administration, and formal studies were launched to examine the association between RRV-TV and intussusception. Data from these studies confirmed an increased risk of intussusception with RRV-TV, with an almost 30-fold elevated risk of developing intussusception during the first 3 to 7 days after the first dose of RRV-TV [23]. An expert group estimated that the population attributable risk of intussusception was ~1 excess case per 10 000 recipients of RRV-TV [24]. This level of risk was deemed unacceptable for further vaccine use; the ACIP withdrew its recommendation [25], and the manufacturer withdrew RRV-TV from the US market in 1999.

Both RV5 and RV1 have undergone close scrutiny for intussusception risk as a result of the RRV-TV experience. In large prelicensure clinical trials which included over 60 000 participants each, neither vaccine demonstrated an increased risk of intussusception [6,7]. The RV5 trial reported a relative risk of intussusception within 42 days after any of the three vaccine doses of 1.6 (95% CI, 0.4–6.4) [6] while the RV1 trial reported a relative risk of 0.85