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Review

Impact of vaccination on the molecular epidemiology and evolution of group A rotaviruses in Latin America and factors affecting vaccine efficacy

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ABSTRACT

Despite high rotavirus (RV) vaccine coverage (~83%) and good effectiveness (~77%) against RV-diarrhea hospitalization, RV is still contributing to the burden of diarrhea that persists in hospital settings in several Latin American countries, where RV vaccination is being implemented. Due to the extensive genomic and antigenic diversity, among co-circulating human RV, a major concern has been that the introduction of RV vaccination could exert selection pressure leading to higher prevalence of strains not included in the vaccines and/or emergence of new strains, thus, reducing the efficacy of vaccination. Here we review the molecular epidemiology of RV in Latin America and explore issues of RV evolution and selection in light of vaccination. We further explore etiologies behind the large burden of diarrhea remaining after vaccination in some countries and discuss plausible reasons for vaccine failures.

Contents

1. Introduction

Rotavirus (RV) is the most important pathogen of severe diarrhea in infants and young children globally; and the foremost cause of diarrheal deaths (Tate et al., 2012). The high medical and economic burden combined with high morbidity in industrialized countries and high mortality in less developed countries have led to the recommendation of inclusion of RV vaccine in all national immunization programs worldwide (Parashar et al., 2003; Rheingans et al., 2009; Tate et al., 2012; WHO, 2009, 2013). RV vaccination programs have subsequently been established in several Latin American countries using one of the two licensed live-attenuated vaccines, either Rotarix (RV1), a human-attenuated G1P[8] RV vaccine (GlaxoSmithKline) and/or RotaTeq (RV5), a human-bovine RV reassortant vaccine (Merck)

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Table 1
Latin American countries with RV vaccination and reported RV surveillance including genotype characterization.

Country, year of introduction[a]	RV vaccine coverage (%)[b]	RV vaccine effectiveness against hospitalization (%)[c]	RV in the hospital setting (%)[d]	Most common RV genotypes after vaccine introduction		References
				Genotype	Years	
Mexico, 2006	84	ND[e]	ND	G9P[4] G9P[8]	2010	Esparza-Aguilar et al. (2014) and Quaye et al. (2013)
Nicaragua, 2006	96	46	17–27	G2P[4] G1P[8] G12P[8]	2006–2013	Bucardo et al. (2015), Khawaja et al. (2014) and Patel et al. (2009)
El Salvador, 2006	84	76	20–43	G1P[8]	2007–2009	de Palma et al. (2010)
Brazil, 2006	84	85	12–26	G2P[4]	2006–2010	Carvalho-Costa et al. (2009), Gurgel et al. (2014), Gurgel et al. (2007), Lanzieri et al. (2010), Linhares and Justino (2014) and Safadi et al. (2010)
Venezuela, 2006	62	ND	8–30	ND	ND	
Bolivia, 2008	88	69	19–33	G9P[8] G2P[4] G9P[6]	2010–2011	Patel et al. (2013)
Honduras, 2009	89	ND	21–24	G1P[8] G9P[4]	2012–2013	De Oliveira et al. (2013) and Quaye et al. (2013)
Colombia, 2009	81	84	7–18	G2P[4] G9P[8] G9P[6]	2011–2013	Cotes-Cantillo et al. (2014) and De la Hoz et al. (2010)
Guatemala, 2010	78	ND	33–47	G9P[4]	2009–2010	Quaye et al. (2013)
All countries	83	77	7–47	G2P[4] G9P[8] G1P[8] G9P[4] G9P[6] G12P[8]	2006–2013	

[a] All countries introduced RV1 vaccine except Nicaragua that introduced RV5.
[b] Average of the yearly coverage, source: WHO vaccine-preventable diseases: monitoring system 2014 global summary. Data from year of introduction not included.
[c] Due to RV diarrhea.
[d] PAHO, RV surveillance and other scientific reports, most of them not including year of vaccine introduction.
[e] ND: no data found in PUBMED.

(Table 1) (Ruiz-Palacios et al., 2006; Vesikari et al., 2006). A high reduction of RV-induced diarrhea has been observed in the majority of countries that have introduced RV vaccination (Yen et al., 2011b). However, although the efficacy of both vaccines is high (>85%) in developed countries, it has been shown to be remarkably lower in developing countries, especially in sub-Saharan Africa, and Asia (Armah et al., 2010; Glass et al., 2014; Lopman et al., 2012; Madhi et al., 2010; Soares-Weiser et al., 2012; Zaman et al., 2010). Furthermore, in countries such as Nicaragua, where the vaccine efficacy has been moderately good, a large burden of diarrhea persists after vaccination (Becker-Dreps et al., 2014a, 2011; Bucardo et al., 2014; Patel et al., 2009). The reasons for the vaccine failures are not known and are probably multifactorial; plausible reasons include general health status, malnourishment, avitaminoses, RV strain diversity, concomitant infections, and host genetic factors (Chattha et al., 2013; Kandasamy et al., 2014; Vlasova et al., 2013). As a general rule, the RV diversity is higher in developing countries; whether this has an effect of vaccine efficacy is debated. A further concern is that introduction of universal mass vaccination will select for strains not included in the vaccines; or drive evolution of new antigenically different strains, which will reduce the efficacy of vaccination (vaccine escape mutants). Here we will explore these issues by reviewing the molecular epidemiology of rotavirus disease in Latin America in the context of rotavirus vaccination.

2. Rotavirus structure, classification, diversity and evolution

Rotaviruses belong to the family *Reoviridae* and have a naked icosahedral triple-layered capsid containing 11 segments (genes) of double-stranded (ds) RNA, of which six encode 6 structural (VP) and 5–6 non-structural proteins (NS) (Estes and Kapikian, 2007; Trask et al., 2012). The middle protein layer VP6 elicits group specific antibodies and eight groups (A to H; also termed species) of RV have been described; with group A being by far the most commonly found in humans (Estes and Kapikian, 2007; Matthijnssens et al., 2012).

The outer capsid glycoprotein VP7 and protease-activated spike protein VP4 elicit neutralizing antibodies, and their antigenic and genetic properties have historically been used to define RV G and P serotypes or genotypes, respectively (Gentsch et al., 2005; Gouvea et al., 1990; Hoshino and Kapikian, 1996). Currently, at least 27 G (G1–G27) and 37 P (P[1]–P[37]) genotypes have been described for group A RV, of which 12 G in combination with 15 P types have been found to infect humans (Matthijnssens et al., 2011; Trojnar et al., 2013). Further analysis of VP7 or VP4 genes from strains of the same genotype have shown presence of genetic subsets of groups (clades or lineages) which are evolutionally shaped by time and/or place (da Silva et al., 2013; Matthijnssens et al., 2010a).

Systematic reviews of regional and temporal trends of global RV strain diversity have shown that five G genotypes (G1–G4, and G9), mainly in conjunction with P[8] or P[4] genotypes accounted for 88% of all RVs strains circulating globally during the pre-RV vaccine era (Banyai et al., 2012; Santos and Hoshino, 2005). However, large variation of genotypes exists, often depending on geographic setting. For example, the globally most common genotype, G1P[8], generally accounted for over 70% of RV infections in North America, Europe and Australia, but only about 30–40% of the infections in Latin America and Africa (Castello et al., 2004; Espinoza et al., 2006; Santos and Hoshino, 2005).

The genetic and antigenic diversity of RV is driven by several evolutionary mechanism, including: (1) accumulation of point mutations (genetic drift) that can lead to antigenic changes; (2) genome reassortment (genetic shift) between human strains or human and animal strains which can give rise to viruses with novel