Molecular epidemiology of rotavirus in the era of vaccination

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Rotavirus is the principal aetiological agent of severe acute gastroenteritis in young children worldwide[1]. Two vaccines, Rotarix [GlaxoSmithKline] and RotaTeq [Merck], have been developed to address the large burden of disease experienced worldwide. Both vaccines have been successful in decreasing morbidity and mortality associated with rotavirus gastroenteritis. Minor fluctuations in rotavirus epidemiology have been observed since vaccine introduction. However, it is unclear whether these observations are due to selection pressures specific to vaccine introduction or due to natural genotype fluctuations.

In children under five years of age, rotavirus causes 114 million episodes of diarrhoea, resulting in 24 million clinic visits and 2.4 million hospitalisations annually[1]. Worldwide, rotavirus infection results in approximately 453,000 deaths, equating to approximately 37% of deaths attributable to diarrhoeal disease and 5% of all deaths in children less than five years of age[2]. Rotavirus belongs to the *Reoviridae* virus family and the virion is comprised of three concentric protein layers. The outer capsid consists of two proteins, VP7 and VP4, that are used to classify rotavirus strains into G (glycoprotein) and P (protease sensitive) genotypes respectively[3]. Of the 12 G and 15 P genotypes known to infect humans, genotypes G1P[8], G2P[4], G3P[8], G4P[8]

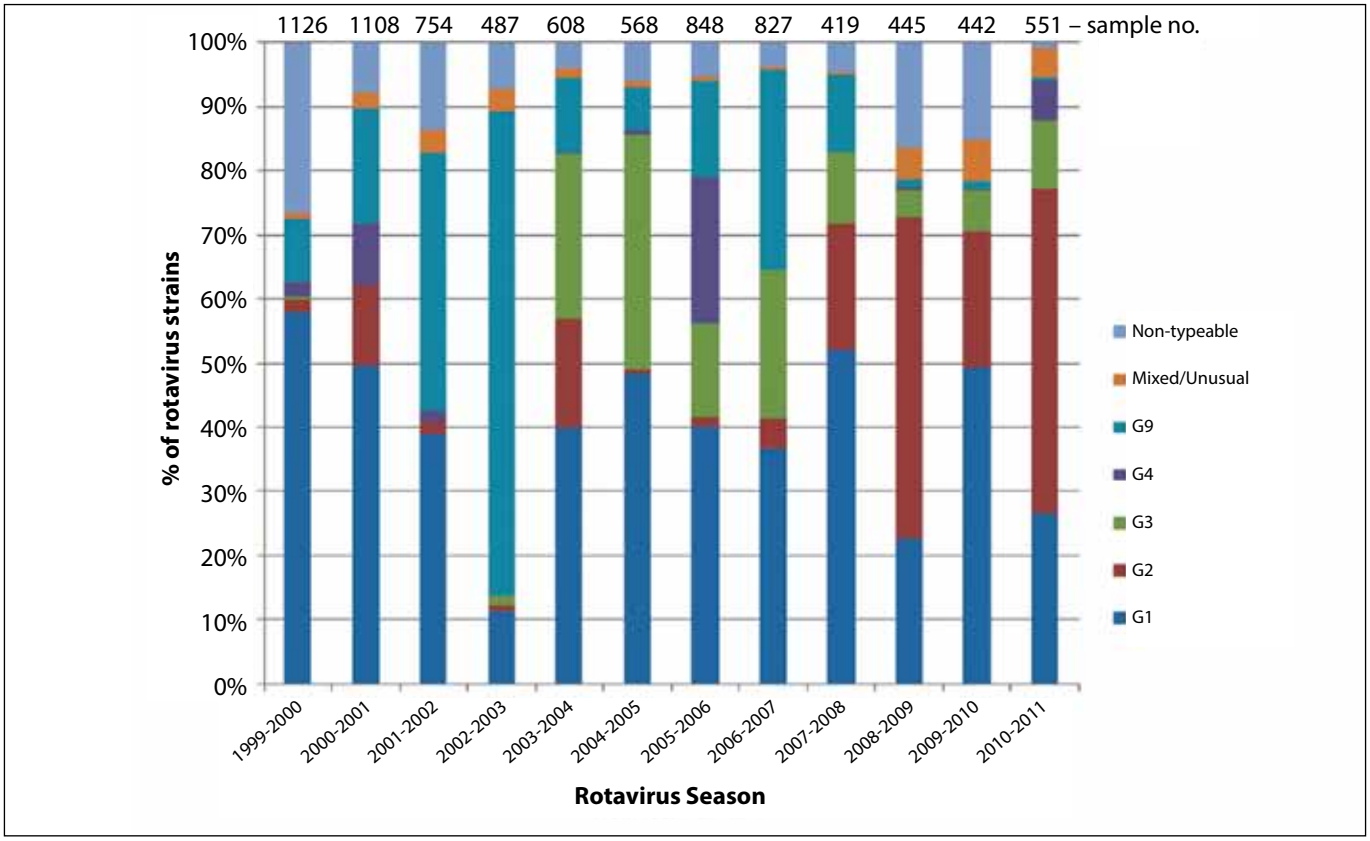

Figure 1. Genotype distribution on the basis of G genotype according to rotavirus reporting period (defined as July to the following June). Yearly genotype breakdown, reporting period 1999–2000 to 2006–2007 is pre-vaccine introduction and 2007–2008 to 2010–2011 is post-vaccine introduction. The number of samples collected each reporting period is stated.

and G9P[8] cause over 90% of rotavirus disease worldwide[4,5]. To reduce the significant global disease burden, rotavirus vaccines have been developed. Rotarix and RotaTeq are included in routine childhood vaccination programs in numerous countries including the USA, Brazil, Belgium and Australia[6]. RotaTeq is a live-attenuated pentavalent vaccine that contains five human-bovine reassortant virus strains. Each reassortant strain contains a human gene encoding one of the outer capsid proteins within a backbone of a bovine rotavirus strain (G6P[5]). Four reassortant strains have a VP7 gene encoding G1, G2, G3 or G4 and one reassortant strain carries the VP4 gene encoding P[8][7]. RotaTeq is administered using a three-dose schedule at two, four and six months of age. Rotarix is a live-attenuated, monovalent vaccine possessing a human-derived G1P[8] strain and is administered at two and four months of age[8].

Rotavirus vaccines were introduced into the Australian National Childhood Immunisation Program in July 2007[9]. Each state and territory health department independently selected which vaccine to implement. Victoria, Queensland and South Australia use RotaTeq; the remaining states and territories use Rotarix. Western Australia changed from Rotarix to RotaTeq in May 2009[10]. Importantly, both vaccines have been shown to be highly effective at preventing severe rotavirus disease. In Victoria, the introduction of RotaTeq has been associated with decreases in hospitalisation due to rotavirus infection of 53–68% (2007–2009), and with a reduction in rotavirus notification by 53% and 65% in 2007 and 2008 in Queensland[10-12]. Long-term evaluation of the effectiveness of the rotavirus vaccination program and the ability of each vaccine to sustain protection, requires an understanding of rotavirus epidemiology before and after vaccine introduction. The ongoing success of a rotavirus vaccination program will depend on understanding the long-term impact of immunisation on strain evolution.

Prior to vaccine introduction, G1P[8] was the dominant genotype isolated Australia-wide in six of the eight years reported by the Australian Rotavirus Surveillance Program (Figure 1). G9P[8] was the dominant genotype in two consecutive seasons (2001–2002 and 2002–2003). This was due to an outbreak in Alice Springs in May 2001, and subsequent spread of the strain around the country. G9P[8] was the dominant genotype isolated from every collection site during the 2002–2003 season. In addition to annual temporal genotype fluctuations, geographical fluctuations in genotype prevalence have also been observed in any given year. For example, during the 2006–2007 season, G3P[8] strains were dominant in Victoria, G9P[8] strains were dominant in the Northern Territory and G1P[8] strains were dominant in Western Australia[13].

Since rotavirus vaccine introduction, the genotype distribution has continued to fluctuate annually and geographically. Prior

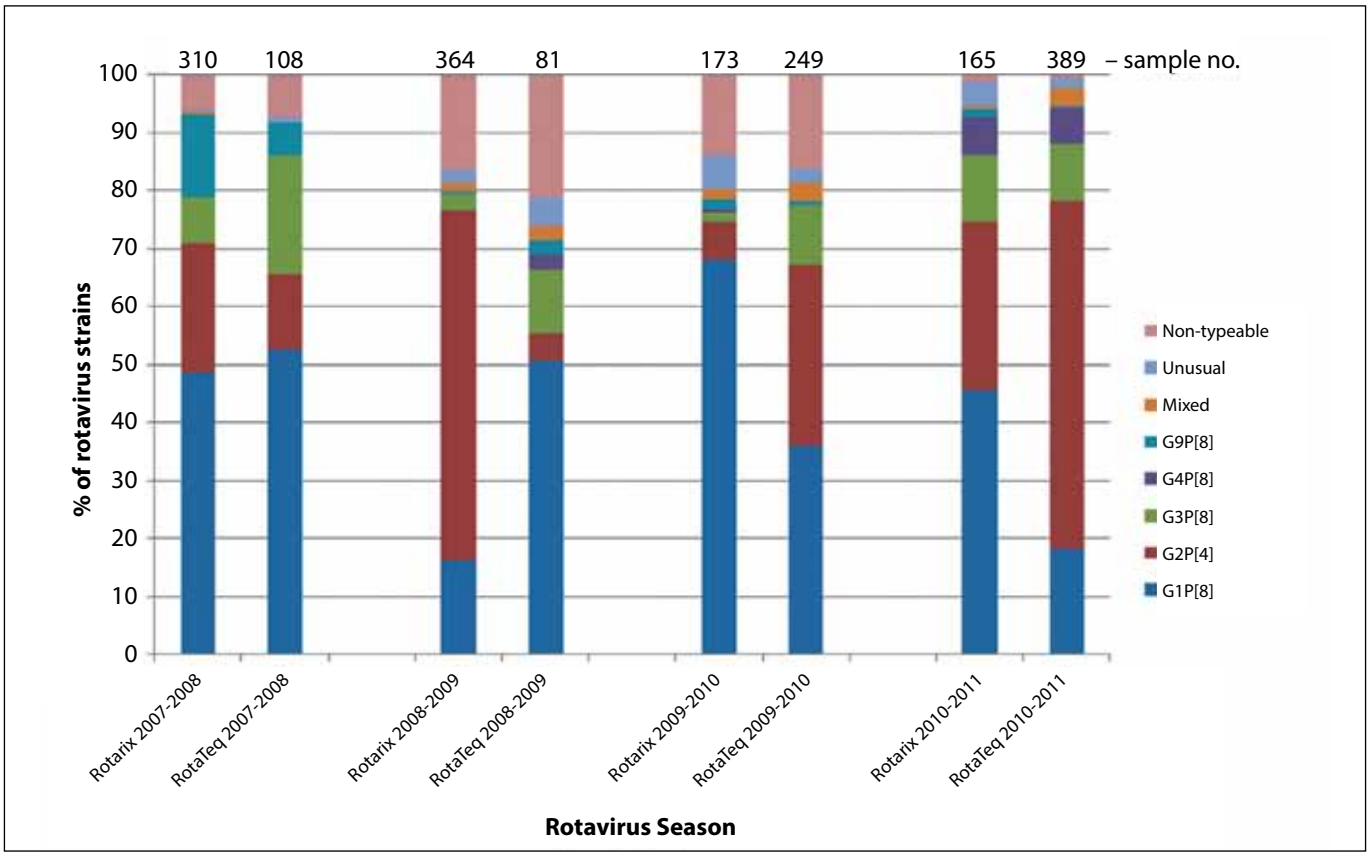

Figure 2. Genotype distribution during the vaccine era on the basis of G and P genotype according to rotavirus reporting period (defined as July to the following June) and vaccine usage. The number of samples collected each reporting period is stated.

to vaccine introduction G2P[4] strains represented a minor genotype accounting for 2-17% of strains isolated Australia-wide. Since vaccine introduction the prevalence of G2P[4] strains has increased to represent 50% of strains isolated across Australia (2008–2009 and 2010–2011 seasons). In the pre-vaccine era the high prevalence of G2P[4] strains was twice associated with a single location: Western Sydney (2000–2001) and an outbreak in the Northern Territory (May, 2004). However, in the vaccine era, G2P[4] strains were associated with an outbreak in Alice Springs in 2009, and were observed in high numbers in five states concurrently. Since vaccine introduction, G2P[4] and G1P[8] strains have alternated in dominance in each season Australia-wide.

At this stage, there does not appear to be any evidence of a correlation between vaccine use and genotype dominance (Figure 2). In the first two vaccine era reporting periods in Australia, G2P[4] strains were more common in Rotarix jurisdictions than in RotaTeq. However, in the 2009–2010 and 2010–2011 seasons G2P[4] strains were more common in RotaTeq jurisdictions than Rotarix. Elsewhere, G2P[4] strains increased at the time of vaccine introduction in Brazil (Rotarix) and Nicaragua (RotaTeq)[14,15]. In Belgium (Rotarix), an increase in G2P[4] strains has also been observed[16]. However, neighbouring countries that had not introduced either vaccine also detected an increase of G2P[4] strains.

In the first three vaccine era years in Australia, G3P[8] strains were more prevalent in RotaTeq jurisdictions, but during the 2010–2011 season G3P[8] strains were more prevalent in Rotarix jurisdictions. In the USA (RotaTeq) G3P[8] strains have been dominant since vaccine introduction[17]. However, increases in the prevalence of G3P[8] strains have been also observed in vaccine-naive populations in Vietnam and China[18,19]. Thus, fluctuations in genotype distribution post-vaccine introduction is not confined to Australia, nor to countries with rotavirus vaccination programs.

In conclusion, minor fluctuations in rotavirus epidemiology in the vaccine era have been observed. The alterations in prevalence of G1P[8] and G2P[4] strains are the most striking changes identified. However, it is unclear whether these observations are due to selection pressures specific to vaccine introduction or due to natural genotype fluctuations. Continued surveillance is required to monitor changes in genotype dominance to ensure the vaccination program remains effective in decreasing the burden of rotavirus disease in Australia.

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Biography

Celeste Donato is a PhD student based at the Murdoch Children's Research Institute. Her research focuses on the impact of rotavirus vaccine introduction on circulating wild-type rotavirus strains.