Commentary

Anticipating rotavirus vaccine introduction in the national immunization programme in Nepal

Gauchan P, Nakagomi T, Nakagomi O.

Department of Hygiene and Molecular Epidemiology, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki, Japan

Correspondence to: Dr. Punita Gauchan Bhattachan

Department of Hygiene and Molecular Epidemiology, Graduate School of Biomedical Sciences, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan.

Email: punita-gauchan@nagasaki-u.ac.jp

Till date, diarrhoea remains one of the major causes of death in children under 5 years of age worldwide, claiming nearly 499,000 lives each year, and despite the availability of safe and effective rotavirus vaccines, an estimated 199,000, diarrhoeal deaths (95% Confidence Interval [CI]: 165,000-241,000) is attributed to rotavirus alone[1]. Rotavirus also results in a median of 39.4% (95% CI: 37.1 – 43.1%) of diarrhoeal hospitalisations[2]. As of March 2017, 92 countries have introduced rotavirus vaccines which includes 85 national, 2 ongoing phased, and 5 sub-national introductions. Nearly half of all rotavirus diarrhoeal deaths occur in Asia, yet less than 20% of Asian countries have introduced rotavirus vaccine nationally or sub-nationally (http://rotacouncil.org/vaccine-introduction/global-introduction-status/). In anticipation of imminent rotavirus vaccine introduction in Nepal, this commentary aims to highlight the burden of rotavirus diarrhoea and characteristics of circulating rotavirus strains in order to predict the public health impact the vaccine will have if and when it shall be introduced in the country's national immunization programme.

The key epidemiological features of rotavirus gastroenteritis in Nepali children under 5 years of age have previously been described. In brief, rotavirus causes one-third (33-37%) of hospitalisations and 23.9% (95% CI: 14.9 – 32.8%) of outpatient visits due to diarrhoea[3-5]; the incidence being the highest in children between 6 and 23 months of age[3,4,6]. The disease occurs year-round, but seasonality exists with greater case detection in cooler and dry months of the year[3,6,7]. Most recent estimates show rotavirus diarrhoea has an annual death toll of 308 (24.5%) out of a total of 1,257 diarrhoeal deaths reported[1]. Overall, a substantial burden of rotavirus disease exists evenly across the various categories of diarrhoeal disease severity. This huge burden of rotavirus diarrhoeal episodes in Nepal is expected to be alleviated using rotavirus vaccine. One issue in this regard is lower effectiveness of rotavirus vaccines in resource poor settings, and by extrapolating from the results obtained in low-income countries elsewhere in the world (Fig. 1)., rotavirus vaccine is expected to help avert nearly 50% of deaths due to rotavirus diarrhoea among Nepali children.

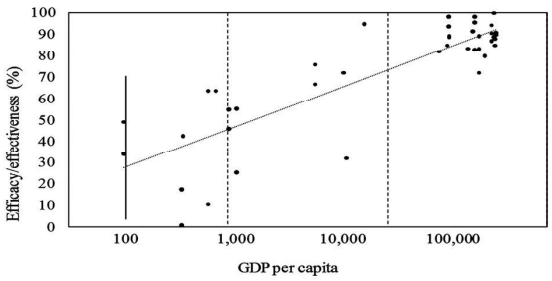

Figure 1: The efficacy/effectiveness of rotavirus vaccines and the wealth of nations measured by gross domestic product (GDP) per capita.

While a lower vaccine effectiveness and a slightly lower prevalence of rotavirus as the aetiology of diarrhoeal diseases resulting in hospitalisations/deaths are common with many other low-income countries, one unique feature of rotavirus molecular epidemiology in Nepal is the unusual genotype distribution carried by the circulating rotavirus strains. In stark contrast with the global trend where nearly three quarters of the six common genotypes, G1P[8], G2P[4], G3P[8], G4P[8], G9P[8] and G12P[8] (Figure 2a)[8], are carried by all human rotavirus strains, in Nepal G12P[6], which is

not among the six globally common genotypes, accounts for 33.4% and thus is the most prevalent genotype among rotaviruses detected in Nepali children (Figure 2b)[3-7,9-11]. On the other hand, the six globally common genotype combinations account for only 37.7% of the total rotavirus strains genotyped which mostly comprises 15% and 14% respectively of G1P[8] and G2P[4], and there appears to be a total absence of G4P[8] and G3P[8] (infrequent detection comprising only 0.2% of the genotypes)(Figure 2b). As for the predominance of G12P[6], what is noteworthy is the fact that this observation has been consistently made in all the studies published thus far[3-7,9-12], furthermore, in Nepal G12 is most frequently associated with P[6] (Fig. 2b) unlike elsewhere in the world where it is far more frequently associated with P[8].

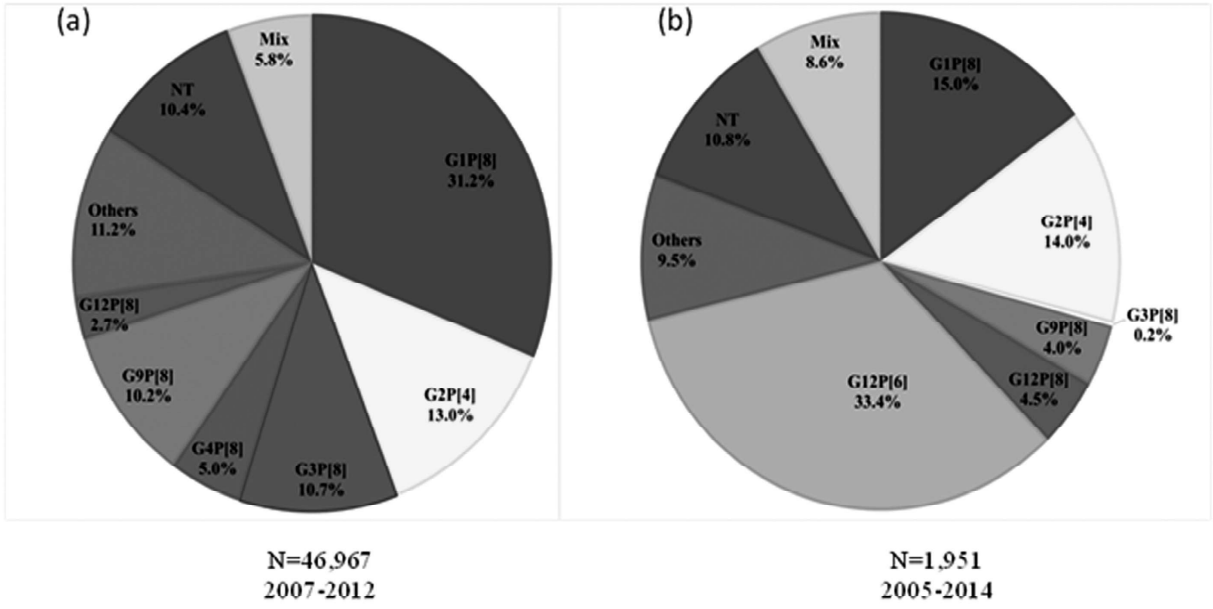

Figure 2: Relative frequencies of G and P genotype combinations of rotavirus strains detected from children with diarrhoea. (a) A global averaged relative frequencies reproduced based on the data reported by Doro, et al., 2014 (ref 8), and (b) An averaged relative frequencies calculated by including all published genotyping data from Nepal (2005-2012) based on refs 3-7, and 9-11,16.

From the perspective of protective immunity, G12P[6] is completely heterotypic to either of the two globally licensed rotavirus vaccines; Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck, and Co., Whitehouse Station, USA). While the efficacy of these vaccines against G12P[6] is not well documented, current vaccines are likely to confer protection against G12P[6][13] because it has been shown that Rotarix is protective against severe rotavirus gastroenteritis caused by fully heterotypic G2P[4][14]and G9P[4][15]strains.

Despite the potential challenges discussed above, the authors expect that rotavirus vaccine will help reduce rotavirus diarrhoeal deaths in children under 5 years of age in Nepal almost by half which roughly translates into 154 lives saved each year, not to mention many more hospitalisations. This underlines the importance and necessity for Nepal to introduce rotavirus vaccines into its national immunization programme, sooner than later.

Conflict of interest: None declared.

References

1. GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis, published online June 1, 2017: http://dx.doi.org/10.1016/S1473-3099 (17)30276-1.
2. Lanata CF, Fischer-Walker CL, Olascoaga AC, Torres CX, Aryee MJ, et al. (2013) Global causes of diarrheal

disease mortality in children ,5 years of age: A systematic review. PLoS ONE 8(9): e72788.

3. Sherchand JB, Nakagomi O, Dove W, Nakagomi T, Yokoo M, Pandey BD, Cuevas LE, Hart A and Cunliffe NA. Molecular epidemiology of rotavirus diarrhea among children aged <5 years in Nepal: Predominance of emergent G12 strains during 2 years. J Infect Dis. 2009; 200:4222-6.

4. Sherchand JB, Cunliffe NA, Tandukar S, Yokoo M, Pandey BD, Niraula P, Panta AR, NakagomiO. Rotavirus disease burden and molecular epidemiology in children with acute diarrhea ageless than 5 years in Nepal. J Nepal Pediatr Soc. 2011; 31(3): 215-18.

5. Cardemil, Cardemil CV, Sherchand JB, Shrestha L, Sharma A, Gary HE Jr, Estivariz CF,Diez-Valcarce M, Ward ML, Bowen MD, Vinjé J, Parashar U, Chu SY.Pathogen-specific burden of outpatient diarrhea in infants in Nepal: A multisite prospective case-control study. J Pediatr Infect Dis Soc. 2017 doi:10.1093/jpids/pix009.

6. Uchida R., Pandey BD, Sherchand JB, Ahmed K, Yokoo M, Nakagomi T Cuevas LE,Cunliffe NA, Hart CA, Nakagomi O. Molecular epidemiologyof rotavirus diarrhea among children and adults in Nepal: detection of G12 strains with [6] or P[8] and a G11P[25] strain. J Clin Microbiol. 2006; 44: 3499–505.

7. Pun SB, Nakagomi T, Sherchand JB, Pandey BD, Cuevas LE, Cunliffe NA, Hart CA, Nakagomi O. Detection of G 12 human rotavirus in Nepal. Emerg Infect Dis. 2007; 13: 482-83.

8. Dóró R, László B, Martella V, Leshem E, Gentsch J, Parashar U, Bányai K.Review of global rotavirus strain prevalence data from six years post vaccinelicensure surveillance: is there evidence of strain selection from vaccinepressure? Infect Genet Evol. 2014;28:446-61.

9. Sherchand JB, W William Schluter W, Sherchan JB, Tandukara S, Dhakwad JR, Choudhary GR, Mahaseth C. Prevalence of group A genotype human rotavirus among children with diarrhoea in Nepal, 2009–2011; WHO SE Asia J Public Health 2012;1(4):432-440.

10. Sherchand JB, Tandukar S, Sherchan JB, Dhakwa JR, Bichha RP, Mahaseth C. Molecular epidemiology of Rotavirus diarrhea among children in Nepal: Emergence of G12 and G9 strains. J Inst Med, 2013, 35: (2) 3-10.

11. Dhital S, Sherchand JB, Pokhrel BM, Parajuli K, Shah N, Mishra SK, Sharma S, Kattel HP, Khadka S, Khatiwada S, Parajuli N, Rijal B. Molecular epidemiology of Rotavirus causing diarrhea among children less than five years of age visiting national level children hospitals, Nepal. BMC Pediatr. 2017;17(1):101.

12. Gauchan P, Nakagomi T, Sherchand JB, Yokoo M, Pandey BD, Cunliffe NA, and Nakagomi O. Continued circulation of G12P[6] Rotaviruses over 28 Months in Nepal: Successive replacement of predominant strains. J Trop Med Health 2013; 41(1): 7–12.

13. Nakagomi T, Nakagomi O. A critical review on a globally-licensed, live, orally-administrable, monovalent human rotavirus vaccine: Rotarix. Expert Opin Biol Ther. 2009;9(8):1073-86

14. Correia JB, Patel MM, Nakagomi O, Montenegro FM, Germano EM, Correia NB,Cuevas LE, Parashar UD, Cunliffe NA, Nakagomi T. Effectiveness of mono valent rotavirus vaccine (Rotarix) against severe diarrhea caused by serotypically unrelated G2P[4] strains in Brazil. J Infect Dis. 2010; 201(3):363-9.

15. Yen C, Figueroa JR, Uribe ES, Carmen-Hernández LD,Tate JE, Parashar UD, Patel MM, López-Collado VR; Monovalent rotavirus vaccine provides protection against an emerging fully heterotypic G9P[4] rotavirus strain in Mexico. J Infect Dis 2011; 204 (5): 783-786.

16. Shrestha S, Upadhyay B, Limbu B, Pradhan R, Nakagomi T, Thorson S, Pollard AJ, Adhikari N. Rotavirus and its genotype distribution among children less than three years presenting with acute watery diarrhoea to a general hospital in urban Nepal. J Nepal Pediatr Soc. 2011; 31(2): 110-115.