Rotavirus, Vaccine and Unanswered Questions: A Perspective from a Least Developed Country

Sher Bahadur Pun,[1]

[1]Clinical Research Unit, Sukraraj Tropical and Infectious Disease Hospital, Kathmandu, Nepal

ABSTRACT

Two rotavirus vaccines, RotaTeq (Merck) and Rotarix (GlaxoSmithKline) have been developed to neutralize the most common rotavirus serotypes, and are now available in the global market. These vaccines are primarily aimed at reducing rotavirus gastroenteritis in children in the least developed countries, where rotavirus mortality rate is believed to be greatest. Thus, the World Health Organization (WHO) has recommended rotavirus vaccination be included in all national immunization programs, while the least developed countries have so far not come up with clear vision and long term strategy on vaccine implementation, and several questions, in addition to this, remain unanswered.

Keywords: *least developed country; rotavirus; vaccines.*

INTRODUCTION

Rotavirus infection is considered as a leading cause of acute gastroenteritis in infants and young children worldwide.[1] Vaccines against rotavirus gastroenteritis have been developed and are being introduced into childhood immunization programs worldwide. Most clinical trials of Rotavirus vaccines have shown to be highly efficacious, particularly in middle and high income countries. So far, very few clinical trials have been conducted in the least developed countries, but with unsatisfactory results. Researchers and donors, however, have suggested include rotavirus vaccines in their national immunization programs. There still remain other differences in views between developed and poor developing countries about rotavirus infection, and have rarely been debated among researchers in the past, which are negligible but highly questionable in the least developed countries. The present article, therefore, attempts to raise these issues from the view point of least developed countries.

ROTAVIRUS VACCINE AND UNDERESTIMATED CHALLENGES

Currently, G1-4, G9 and G12 are known to be the most common and clinically important serotypes in humans worldwide, while detection of unusual strains, unusual combinations of G and P types and mixed infections (more than one serotypes) have been increasingly reported in humans in recent years. The relatively high frequency of unusual rotavirus strains have been reported from poor developing countries and have the potential to become common serotypes in coming years. Researchers have therefore long been raising grave concern about unusual rotavirus strains and their impact on the currently available vaccines in the long run, while enough attention have not been paid to untypeable strains, and their potential role on vaccine efficacy. These unexpected but increasing trends of untypeable strains are being the leading cause of severe gastroenteritis in children in poor developing countries.

Correspondence: Dr. Sher Bahadur Pun, Clinical Research Unit, Sukraraj Tropical and Infectious Disease Hospital, Teku, Kathmandu, Nepal G.P.O.Box: 8975 E.P.C.No:1196, Email: drsherbdr@yahoo.com, Phone: +977-9849246140.

Despite this growing concern, there have not been enough studies available showing significant protective efficacy against unusual and untypeable strains. Recent studies of rotavirus vaccine efficacy rates in countries in sub-Saharan Africa have shown to be unsatisfactory.[2] A significantly higher proportion of unusual and untypeable (probably new strains) rotavirus strains circulating during clinical trials in this region might have resulted in lower efficacy of the vaccine.[3] It is believed that malnutrition, multiple infections, immune compromised diseases and high titers antibody of breast milk are other possible explanations for poor immunogenicity of rotavirus vaccine, and these phenomena are common in poor developing countries. Several studies have shown that there are variations in vaccine efficacy even within developing countries. For example, efficacy of rotavirus vaccine against severe gastroenteritis in Bangladesh and Vietnam were found to be 42.7% and 63.9%,[4] while Kenya, Ghana and Mali showed 63.9%, 55.5% and 17.6%,[2] indicating that besides the point mentioned above, cultural backgrounds could be another major factor that may influence the efficacy of the vaccine, though it has not yet been widely discussed. Vaccine effectiveness rate thus cannot be predicted based on developed and developing countries (resource-based) or by region. Moreover, within the same country different results from individual studies have created confusion over whether rotavirus should be given higher priority than any other vaccine-preventable disease in their immunization programs. Almost all studies conclude rotavirus vaccine be included in immunization programs in poor developing countries regardless of large variation in efficacy rate and its unknown specific causes. It may, therefore, be early to recommend rotavirus vaccine for use in the least developed countries, unless it ensures that it can provide an adequate level of protection against severe rotavirus gastroenteritis in children.

ARE WE ESTIMATING ROTAVIRUS DISEASE MORBIDITY/MORTALITY ACCURATELY?

An accurate estimate of the disease burden is crucial to assess need and evaluate the impact of a new vaccine. It is estimated that more than 80% diarrhea-related childhood deaths attributable to rotavirus infection occur in resource poor countries.[5] Due to poor hygiene practices and inadequate sanitation infrastructure, patients with diarrhea are infected with more than one infectious agent; have been increasingly documented in recent years.[6,7] However, researchers have been estimating disease burden based on detection rate for a single pathogen according to their field of interest. Rotavirus researchers, for example, detect only rotavirus pathogen in hospitalized patients, and estimate morbidity accordingly. It is, however, not clear whether rotavirus infection is solely responsible for hospitalization, because researchers rarely look for other enteric pathogens simultaneously owing to resource limitations. For instance, our unpublished data (study from Bangladesh) shows that approximately 27% of rotavirus infection in children under age 5 years were co-infected with other viral, bacterial or protozoan pathogens. In another words, rotavirus researchers may estimate 27% of hospitalization children as a result of rotavirus infection, though this does not necessarily mean that rotaviruses are solely responsible for hospitalization in these children (Figure1).

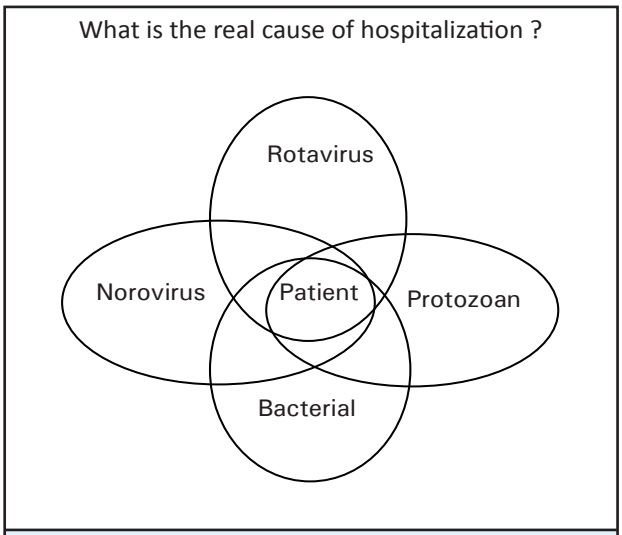

Figure 1. Cause of Hospitalisation

The most recently published data from Bangladesh showed that 76.4% of children with acute diarrhea presented to hospitals were infected with multiple viruses.[8] Rotavirus, probably, is one of the most common infectious agents found and stable at high or low relative humidities in the environmental surfaces[9] and is easily transmissible between species compared to other organisms, and thus making children more susceptible to rotavirus infection because they are more physically active; and spend more time outdoors such as kindergartens, schools, nurseries or community playgrounds. This may explain why rotavirus detection rate in young children is comparatively more common than in adults. A recent study has shown that although detection rate of rotavirus was high in children < 5 years old hospitalized with diarrhea, higher mortality rate was associated with bacterial infections.[10] Rotavirus infection may cause mild to moderate diarrhea, whilst non-viral enteric infections are equally known to cause severe diarrhea in young children in developing countries.[11] High incidence of co-infection of enteric agents in children with rotavirus gastroenteritis may be more common than previously known, particularly in poor developing countries. Obtaining such comprehensive data perhaps may give new insights into

the role of other associate enteric pathogens, and their clinical importance. Current method to estimate disease burden, therefore need to bring into a logical debate to get more accurate data on mortality of gastroenteritis attributable to rotavirus infection globally.

DOES NEONATAL ROTAVIRUS INFECTION DECREASE THE SEVERITY OF SUBSEQUENT INFECTION?

Substantial progress has been made in understanding rotavirus infection, since bishop and colleagues first described rotavirus as a cause of severe diarrhea in infants and young children,[12] and two licensed rotavirus vaccines are currently available in the global market. The first dose of either vaccine is recommended to be administered no earlier than age six weeks. Primary rotavirus infection in the neonatal period has long been broadly recognized, particularly in resource poor settings. In India, for example, rotavirus infection was detected up to 78% among hospitalized neonates.[13] It can be, thus, postulated that majority of infants might have been infected with multiple rotavirus strains before they get their first vaccination. Until recently, the overwhelming majority of studies have suggested that asymptomatic neonatal rotavirus infection confers protection against severe gastroenteritis during re-infection. Based on these outcomes, several neonatal based rotavirus vaccines are under development and evaluation in preclinical studies. On the other hand, this conclusion appears to be contrary to other studies, which is rarely debated among researchers. For example, neonatal rotavirus infection has been more commonly reported in developing countries compared to developed countries, meaning that rotavirus disease burden in poor developing countries must have been lower than developed countries, if neonatal rotaviruses confer protection against severe rotavirus gastroenteritis in later life (Conceptual Figure 2).

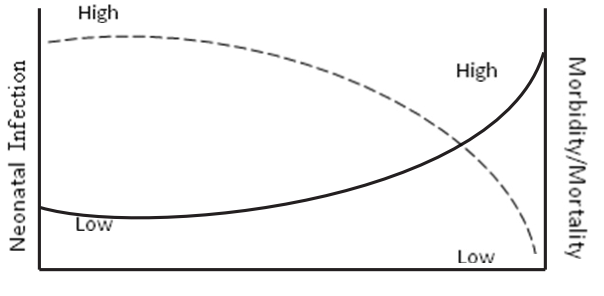

Figure 2. Neonatal Infection and morbidity and mortality

---------- **Developing Countries**
_____ **Developed Countries**

In addition to this, breastfeeding provides protection against rotavirus gastroenteritis in infants has been documented previously, [14] and south Asia has the highest rates of breastfeeding among infants in the world.[15] In contrast to this presumption, disease burden attributable to rotavirus infection have been shown to be comparatively higher in poor developing countries than developed countries. Thus, the role of neonatal rotavirus infection in humans remains controversial and inconclusive, and no unanimous consensus has been reached among researchers so far. Although most epidemiological studies have shown to have higher rotavirus infection in patients aged between 12 and 23 months,[16,17] a 2-month age interval study showed equally high rates of rotavirus infection in the first 2 months of life.[18] One possible explanation for the limited efficacy of the currently available vaccines in poor developing countries may be due to high prevalence of rotavirus infection during neonatal period. Detection of symptomatic and asymptomatic rotavirus infection has been shown an almost equal-ratio in infants.[19] Asymptomatic neonatal infection may have an equivalent role to attenuated vaccine, though comparable studies of asymptomatic and symptomatic neonatal infection and their impact during re-infection in later life have not been well studied. Further studies are required to better describe the role of neonatal infection in humans which may have implications for the design of more effective rotavirus vaccine.

CONCLUSIONS

Many least developed countries are eligible to receive financial assistance from the global alliance for vaccines and immunization (GAVI alliance), and hence are encouraged to include rotavirus vaccine in their routine immunization programs, while long term financial sustainability remains uncertain. Although rotavirus vaccine is being introduced into childhood immunization programs worldwide, no least developed country has so far come up with specific plan to give continuity to rotavirus vaccination program after the withdrawal of financial support from the alliance. There are several examples in the least developed countries that established budget line items do not fund them and most of the countries with financial plans do not use them to the degree expected.[20] A lack of political commitment and will to implement, public awareness and poor knowledge about rotavirus gastroenteritis in policy makers are major obstacles to implement long term rotavirus vaccination program in the least developed countries. The reasons for lower immunogenicity in the least developed countries, differences in vaccine efficacy within resource poor settings, obscure methods to estimate disease burden, and the role of neonatal rotavirus infections are still unanswered questions but critically important from the view point of least developed countries.

REFERENCES

1. Pun SB. Rotavirus infection: An unrecognised disease in Nepal. Kathmandu Univ Med J (KUMJ). 2010; 8(29):135-40.
2. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, et al. Efficacy of Pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Sub-Sahara Africa: a randomized, double-blind, placebo-controlled trial. Lancet. 2010; 376:606-14.
3. Mwenda JM, Ntoto KM, Abebe A, Enweronu-Laryea C, Amina I, Mchomvu J, et al. Burden and epidemiology of rotavirus diarrhea in selected African countries: preliminary results from the African Rotavirus Surveillance Network. J Infect Dis 2010; 202 Suppl:S5-S11. doi: 10.1086/653557.
4. Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, et al. Efficacy of Pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomized, double-blind, placebo-controlled trial. Lancet. 2010; 376:615-23.
5. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis. 2006; 12:304-6.
6. Enzensberger R, Besier S, Baumgärtner N, Brad V. Mixed diarrhoeal infection caused by Vibrio cholerae and several other enteric pathogens in a 4-year-old child returning to Germany from Pakistan. Scand J Infect Dis. 2005; 37:73-5.
7. Masoumi JP, Anwar MS, Bokhari SR. Clinical features of infantile diarrhea associated with single or multiple enteric pathogens. J Pak Med Assoc. 1995; 45:266-69.
8. Mitui MT, Bozdayi G, Ahmed S, Matsumoto T, Nishizono A, Ahmed K. Detection and molecular characterization of diarrhea causing viruses in single and mixed infections in children: A comparative study between Bangladesh and Turkey. J Med Virol. 2013 published online Sep 16. http:// doi: 10.1002/jmv.23744.
9. Moe K, Shirley JA. The effects of relative humidity and temperature on the survival of human rotavirus in faeces. Arch Virol. 1982; 72:179-86.
10. O'Reilly CE, Jaron P, Ochieng B, Nyaguara A, Tate JE, Parsons MB, et al. Risk factors for death among children less than 5 years old hospitalized with diarrhea in rural western Kenya, 2005-2007: a cohort study. PLoS Med. 2012; 9(7):e1001256. doi: 10.1371/journal.pmed.1001256.
11. Jafari A, Aslani MM, Bouzari S. Escherichia coli: a brief review of diarrheagenic pathotypes and their role in diarrheal diseases in Iran. Iran J Microbiol. 2012;4(3):102–7.
12. Bishop RF, Davidson GP, Holmes IH, Ruck B. Virus particles in epithelial cells of duodenal mucosa from children with acute non-bacterial gastroenteritis. Lancet. 1973; 8:1281-3.
13. Cicirello HG, Das BK, Gupta A, Bhan MK, Gentsch JR, Kumar R, et al. High prevalence of rotavirus infection among neonates born at hospitals in Delhi, India: predisposition of newborns for infection with unusual rotavirus. Pediatr Infect Dis J. 1994; 13:720-4.
14. Prameela KK, Vijaya LR . The importance of breastfeeding in rotaviral diarrhoeas. Malays J Nutr. 2012; 18:103-1.
15. UNICEF .Overview of breastfeeding patterns [online] 2009. [cited 2013 Oct 8]. Available from http://www.childinfo.org/breastfeeding_overview.html.
16. Pandey BD, Pun SB. Trends of rotavirus in Nepal. Kathmandu Univ Med J (KUMJ). 2011; 9:32-5.
17. Sherchand JB, Nakagomi O, Dove W, Nakagomi T, Yokoo M, Pandey BD, et al. 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 Suppl 1:S182-7.
18. Clark HF, Marcello AE, Lawley D, Reilly M, DiNubile MJ. et al. Unexpectedly high burden of rotavirus gastroenteritis in very young infants. BMC Pediatr 2010; 11;10:40. doi:10.1186/1471-2431-10-40
19. Ramani S, Sowmyanarayanan TV, Gladstone BP, Bhowmick K, Asirvatham JR, Jana AK, et al. Rotavirus infection in the neonatal nurseries of a tertiary care hospital in India. Pediatr Infect Dis J. 2008;27:719-23.
20. Arevshatian L , Clements CJ , Lwanga SK , Misor AO, Ndumbe P. Seward JF, et al. An evaluation of infant immunization in Africa: is a transformation in progress? [cited 2013 Oct 3]. Available from http://www.who.int/bulletin/volumes/85/6/06-031526/en.