REVIEW ARTICLE

SURVEILLANCE STUDIES FOR ROTA VIRUS VACCINE IMPLICATION IN PAKISTAN

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ABSTRACT

Rotavirus is known to be one of the five top most pathogens causing gastroenteritis globally, mostly in children age group of less than 5 years. Almost every child during this age experiences at least one episode of rotavirus gastroenteritis. Amongst the various diseases in children, diarrhea accounts for 10.8% of under-five mortality in Pakistan, making it a leading cause of death in this age group. Furthermore, Pakistan is one of the six countries that accounts for 50% of all rotavirus-related deaths worldwide. About one third of children hospitalized with severe gastroenteritis in urban centers in Pakistan are reported to have rotavirus infections. Although rotavirus diarrhea is endemic throughout the year in this region, however, seasonal peaks are also observed in August and December. There are potentially very effective new vaccines available to control rotavirus infections. Nevertheless, it is utmost important to determine the true burden of disease and the viral type strains prevailing in community before administering the vaccine. This information provides the basis of strategic judgments about the use of rotavirus vaccines.

KEYWORDS: Rota Virus, Rotavirus Gastroenteritis, Diarrhea, Meningitis, Pneumonia.

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INTRODUCTION

Rotavirus is known to be the most common causative agent of childhood diarrhea and gastroenteritis[1]. Every child encountered rotavirus infection once at least during first five years of their life[2]. It is a democratic virus and is the problem for both developing & developed countries[3]. As per global estimates of 2011, more than 700,000 annual deaths were recorded that were due to diarrhea, out of which more than 28% deaths were related to rotavirus [4,5,6].

As of 2003 report, more than 10 million children died were the victims of preventable diseases, unfortunately belong to poor countries. Global statistics tells that half of these global mortalities of children under five years of age are mainly shared by only six countries, and Pakistan is one of them. However, the surveys and review about the causes of death show a significant difference of mortality among different countries. Pakistan accounted for 565,000 annual deaths among children of under the age of five years, mortality rated 43%[5]. This figure emphasized the need of very extensive surveillance program of child health care at national level

Researchers from all over the world are engaged in assessing the efficacy and efficiency of the available vaccines, especially the two multivalent rotavirus vaccines- Rotarix and Rota Teq [6-9].The rotavirus vaccine was licensed in the US market in year 1998 (10) and WHO also recommended the use of Rotavirus vaccine in 2003 [11, 12].

A few studies regarding rotavirus surveillance were also conducted in Pakistan [13-15]. However, it is always important to find the baseline burden of any disease and its etiology or the causative agent type strains before introducing any vaccine in a community setting. Such studies provide important information about the circulating viral type and emergence of new strains.

During 2005 to 2012, many surveillance studies were performed in Pakistan to investigate diarrheal etiology in children under five years of age [13-17]. A few of these regional surveillance studies provided information about rotavirus disease burden as well as prevalent rotavirus genotype in the investigating

region [13-15]. These studies were supported by different global health agencies such as Global Alliance for Vaccine and Immunization (GAVI) and World Health Organization (WHO) and GATES & Malinda Foundation [13, 16, 17].

Some surveillance data from Karachi City, south of the country conducted in 2009[13], and two other studies conducted by National Institute of Biotechnology and Genetic Engineering (NIBGE) and National Institute of Health Pakistan (NIH) from Faisalabad and Lahore - Punjab province, central region of country, in 2012 and 2013 respectively [14, 15]. All the above reports show discrete regional data related to diarrheal disease caused by rotavirus, however, the national data was missing till 2013. A national rotavirus surveillance investigation among Pakistani pediatric population was carried out with the help of World Health Organization (WHO) in 2006-2008 [17]. This study data of sentinel hospital based severe rotavirus infection was presented the national rotavirus disease burden as well as circulating genotype among Pakistani children. The study was conducted within main urban hospital setting of Pakistan, including Lahore, Rawalpindi, Peshawar and Karachi (Table 1).

TABLE 1. ROTAVIRUS SURVEILLANCE STUDIES IN PAKISTAN

STUDY TYPE	DURATION	STUDY SITE	NO OF SUBJECT	PREVALENT P	PREVALENT G	PREVALENT GENOTYPE
LOCAL (HOSPITAL BASED)	JAN 2008-DEC 2009	LAHORE	1306	-	-	$G2P^4$ (48%)
LOCAL (HOSPITAL BASED)	MAY-SEP 2010	FAISALABAD	300	P^8 (27%)	G1(60.3%)	$G1P^8$ (25.3%)
REGIONAL (COMMUNITY BASED)	JUN 2005-MAY 2007	KARACHI	717	P[8] (36%)	G1 (24%)	G9P[8] (15%) G1P[8] (13%)
NATIONAL (HOSPITAL BASED)	APR 2006-MAR 2008	KARACHI, LAHORE, RAWALPINDI, PESHAWAR	6679	P[6] (31%)	G1(28%)	G1P[8] (11.6%)
REF: [QAZI R ET AL 2009, TAYYABA IFTEKHAR ET AL 2012, ALAM MM ET AL, 2013, KAZI AM 2014]						

TABLE 2. PATHOGENS SIGNFICANTLY ASSOCIATED WITH MODERATE-TO-SEVERE DIARRHEA (MSD)

STUDY TYPE	DURATION	STUDY SITE	CASE	CONTROL	ROTA RELATED DISCOVERY
GLOBAL	2008- 2011	KARACHI-PAKISTAN MALI, MOZAMBIQUE, KENYA, GAMBIA, INDIA, BANGLADESH	9439	13129	2ND TOP MOST PATHOGEN (DIARRHEA CAUSING)
(THE GLOBAL ENTERIC MULTICENTER STUDY, GEMS): A PROSPECTIVE, CASE-CONTROL STUDY. LANCET 2014 382: 209–222.					

DISCUSSION

Rotavirus infection is declared as a vaccine preventable disease [18]. Nevertheless, the Rotavirus infection is still flagged as a major killer globally for children under five years of age. It is a viral infection of high mortality and morbidity irrespective of the economic state of any country [1]. National disease control program involved a big participation of Government to include available vaccine as a part of any national immunization program. Pakistan has its own national immunization program in which

nine vaccines against preventable disease coverage is provided including childhood tuberculosis, poliomyelitis, diphtheria, whooping cough (Pertussis), tetanus, measles, Hepatitis B, Meningitis and pneumonia [19].

Many studies on diarrheal disease burden have confirmed the fact that rotavirus is a main etiological agent among diarrhea causing pathogens[1, 16, 20-23]. Zoonotic transmission of this virus and existence of different viral type among animals was also proved[24]. Similarly, a few reports on native Rotavirus surveillance investigations were conducted in Pakistan which suggest to prepare a national strategy and plan of introduction of rotavirus vaccine in Pakistan[13, 16, 17]. Availability of effective rotavirus vaccine can help in reducing diarrheal disease morbidity and mortality as well as cost related to hospitalizations from rotavirus infection.

Five active surveillances studies were conducted regarding rotavirus infective gastroenteritis. Three of them were regional, one national and one global, for which Pakistan was one of the study site[17]. Three regional studies were from Lahore, Faisalabad and Karachi; among which Lahore and Faisalabad were hospital based; [14, 15] while the third study was from Karachi. It was a study from a community facilitated through Primary Health Care settings[13]. However, this is the data from small population of the country, and there is still a big gap felt to have a national estimate of rotavirus disease burden as well as type of existing virus.

A national data was collected from hospitalized children less than 5 years of age reported with diarrhea. It was an extensive two-year survey for the period between years 2006-2008. This study was conducted on 6500 subjects in five urban city hospitals of Pakistan. Seasonality of infection occurrences, susceptible age group, genotype/prevalent viral type was defined. Findings of this study were reported in year 2013[17].

Seasonal peaks of rotavirus diarrheal cases were mostly noted in August and December[13]. Similarly, the national studies reported the highest incidence of rotavirus infection in the month of December[17]. Generally, peak season for rotavirus appearance as gastroenteritis culprit is observed in winter. Closely matched peak prevalence of severe rotavirus disease in Iran was observed in September through January; and in China the infection reporting started from October and peak at November to January[25], India (December-February); Bangladesh (November to February)[26, 27].

Vulnerable age group for viral gastroenteritis caused by rotavirus was also the target search for Pakistani children. Generally, the most common age group was 2 years of age (13, 17): 12-17 months[15]; 0-11 months (64%)[13]; 0-11 months (60.9%)[17] ; and 7-12 months (35.4%) [14]. Similar results were reported from hospital based sentinel surveys: 85% Rota positive were reported during first two years of life from Iran and 94% of them were in age group between 6-23 months [25, 28]. Almost similar findings were reported in different countries including India, China and many other countries [25, 26].

The most widespread rotavirus genotype in Pakistan was found to be G1 [P8], 11.6%, n=593 [17] which was very much in line with first report of community setting and second Faisalabad hospital indicating G1[P8], 13%, n=85 and 25.3%, n=300 respectively [13, 14]. The data from Lahore hospital showed that G2[P4], 48%, n=1306, was second top most prevalent type as per national data set 10.4%, n=62/593 [15, 17]. These all three studies established the fact that G1[P8] is a leading genotype followed by G2[P4] in Pakistan, hence predicted the suitability of available rotavirus vaccine to be implemented in nationwide routine immunization program. Few cases with G12 were also reported first as 0.33% n=1/300 [14] and 0.5%, n=3/596 [17]. G12 cases were first reported in South Asia (Bangladesh in 2007) with the evolutionary history of G12 Rotavirus [29]. Although the data of genotypic marker is missing, but the Global Enteric Multicenter analysis showed that the rotavirus is a leading cause of diarrhea among Pakistani children [16].

According to the Pakistan's national data report, G4P[8] (30.9%) was found to be the most common type followed by G1[P8] (10.9%), G2[P4] (5.5%), however, many Rotavirus could not be typed [25]. While, G3P[8] was the most common type in China, however, G5P[8] and G5P[6], two new types with G5 combination were also reported [28]. During 2011-2013 high genetic diversity of Rotavirus was found in line with the greatest number of G2P[4] (39.6%) followed by G9 P[4] 27.5%, G1P[8] 13.5% and G9P[8] 11.9%. Newly emergent G12 was also found circulating (5.1%) with different P types from hospital setting of India[26]. From July 2012 to June 2015, seven hospital based data of Bangladesh was in consistent with the Pakistan, G1P [8] (31%) but widespread G12P[8] (29%) were present [27].

In 2014, as per global childhood vaccination access report statement Pakistan and its neighboring countries like Afghanistan and Bangladesh were GAVI planning for Rotavirus vaccine implication. Iran and India have had their own vaccination plan[30].

It is the high time to check the efficacy of the available vaccine in Pakistan. Furthermore, preferable dose and dose schedule of vaccine and the effect of breast feeding should also be studied. This has been done in countries where the rotavirus vaccine has already been introduced [31]. Other neighboring countries are far beyond for Rotavirus vaccine implementation. India and China are the producers of their own rotavirus vaccine and performing the

efficacy trials [32]. Vaccination coverage studies were also performed in few regions of China and got license for Lanzhou lamb rotavirus vaccine (LLRV)[33-35], while India reported successful Phase III clinical trials of its vaccine, ROTAVAC[36].

Earlier, the efficacy of the two available licensed vaccine RV-1 and RV-5 (Rotatrix and Rotateq) were found with low immunogenicity in Africa (South Africa, Malavi, Ghana, Kenya and Mali) and Asia (Bangladesh and Vietnam)[8, 9]. Some vaccine trial studies for improved immunogenic rotavirus vaccine on Pakistani pediatric population indicated that there is no significant immunogenicity difference due to change of schedule of Rotatrix RV1 vaccine administration and withholding of breast feeding [6, 7]. Similar results were reported from India for RV-1 vaccine trial, moreover, the immune response to Rotarix® was not boosted by withholding breastfeeding around the time of vaccination [37].

As a result of all above stated persuasive efforts of researchers related to rotavirus surveillance in country, Pakistan's Extended Program of Immunization (EPI) decided to incorporate Rotavirus vaccine as a part of EPI in Pakistan from Nov 2016. International vaccine access center report of January 2017 showed that 92 countries have introduced rotavirus vaccines. Moreover, Canada, Philippines, Sweden, and Thailand have introduced rotavirus vaccine on pilot scale, Pakistan is in the phase of introduction of rotavirus vaccine [38].

CONCLUSION

There is a dire need to determine the promising role of rotavirus vaccine in global communities Rotavirus disease burden and any change in the existing strain type during and post vaccination era are also point of consideration for further research.

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