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Rotavirus vaccines: current perspectives

Vaccination against rotavirus has been considered as one of the best cost effective method for prevention of morbidity and mortality due to rotavirus diarrhoea. This is primarily due to the fact that improvements in hygiene as well as provision of safe potable water are not as effective in the prevention of rotavirus diarrhoea as bacterial enteritis. Therefore, an accelerated development and introduction plan has been established since 2003 with the involvement of the WHO, CDC-USA and PATH with a view to reducing child mortality and morbidity from rotavirus diarrhoeal diseases by accelerating the availability of rotavirus vaccines appropriate for use in developing countries.

An ideal rotavirus vaccine should protect against moderate to severe disease, preventing deaths, hospitalisation, reducing all direct and indirect costs associated with the disease and attenuating the severity as well as the duration of the breakthrough disease. Monovalent, live attenuated, human rotavirus strain vaccines and rotavirus reassortant vaccines (combined human and animal strains) are the current, leading rotavirus vaccine candidates in the world. The SAGE of the WHO recommends that the regional and phased introduction of the rotavirus vaccine is appropriate on the basis of successful phase III study results. Lessons of introduction and post marketing surveillance in early introducing regions will be valuable to the others. However, communication strategies are equally important to prevent misconceptions about the efficacy of rotavirus vaccine against all cause diarrhoeal morbidity and mortality. WHO emphasises the need of efficacy data in Africa and Asia for global recommendation of rotavirus vaccines. Currently, large scale phase III trials are underway in South Africa, Malawi, Mali, Ghana Bangladesh and Vietnam. Results are expected to be released from 2008 to 2010.

Globally, almost all children are exposed to rotavirus and acquire antibodies by the age 3-5 years with the most severe symptomatic disease occurring at 3-24 months. If a vaccine is introduced, logically, children in the age group of 3-24 months should be targeted for maximum results. The strategy of reducing morbidity and mortality due to rotavirus diarrhoea through vaccination is based on the fact that the initial, wild type rotavirus infection protects against subsequent rotavirus diarrhoeal episodes. Primary infection induces homotypic immunity. This immunity appears to be serotype specific. Generated serum neutralising antibodies (SNA) are homologus to the infecting serotype. Degree of protection increases with the number of previous infections. Subsequent infections provide heterotypic protection against multiple rotavirus strains. The greatest protection is conferred to moderate and severe cases of rotavirus infections, less protection to mild infections and the least protection against asymptomatic infections. Proponents of the monovalent, live attenuated, human rotavirus vaccine argue that human strain vaccines provide better protection than reassortants because it is closely related to the naturally occurring human strains.

RIX 4414, monovalent, live attenuated Rotavirus vaccine:

This vaccine has been developed from the 89-12 rota virus strain, an isolate from an infected infant in Cincinnati by cloning and further attenuating it by passing it in Vero cells.

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This contained G1P 1A serotype and P8 genotype.

Selection of the human vaccine candidate was based on evidence that natural infection provides excellent heterotypic protection against subsequent severe illness regardless of infecting serotypes. RIX 4414, monovalent, live attenuated rotavirus vaccine is a lyophilised, oral vaccine administered as two doses within the first six month of life. The first dose may be administered from the age of 6 weeks (between 6-14 weeks). The second dose should be given by 24 weeks (between 14-24 weeks) . There should be an interval of at least 4 weeks between doses. The vaccine should be stored at a temperature of 2-8 ^{0} C.

Efficacy : Vaccination with two doses was associated with 85% reduction in overall severe rotavirus gastroenteritis and a 91% reduction in rotavirus diarrhoea due to homologous G1 strains. Vaccine efficacy has been reported to be up to 100% against the most severe gastroenteritis. Furthermore, its ability to elicit cross protection has also been reported.

Immunogenicity : The vaccine was found to be highly immunogenic in a two dose regimen. It has been demonstrated that the vaccine was more immunogenic when the first dose was given at 10-14 weeks, although it was still immunogenic when given at 6-10 weeks of age. Monovalent, live attenuated rota virus vaccine is no way reported to have interfered with the immune response to concomitantly administered EPI vaccines including Oral Polio Vaccine.

Safety : In safety studies, the vaccine has been well tolerated. The reactogenicity profile of the vaccine in terms of solicited symptoms (diarrhoea, fever, vomiting, irritability and loss of appetite) was similar to the placebo groups in studies.

The withdrawal of the first licensed rhesus human reassortment vaccine earlier due to reported association with intussusception has raised concerns regarding the safety of subsequent vaccine candidates. There is no evidence to the effect that natural rotavirus infections cause intussusception. Therefore, it is theoretically impossible for the monovalent, live attenuated rotavirus vaccine to cause intussusception.

<u>Pentavalent human-bovine reassortant rotavirus vaccine (HBRV)</u>

Pentavalent HBRV is a live, oral vaccine given in a three dose regimen. The development of this vaccine is based on the fact that vaccination at a young age with a multivalent vaccine directed against most prevalent serotypes is likely to provide the most comprehensive protection against rotavirus diarrhoea. Thus, HBRV is directed against most prevalent serotypes in the world namely G1, G2, G3, G4 and P1.

HBRV has been developed by reassortment of bovine rota virus strain, Wister calf 3 (WC3) with human rota virus. Though viable efficacy was demonstrated, WC 3 vaccine did not induce cross reacting Serum Neutralising Antibodies (SNA) against the outer surface G proteins of the common human rotavirus serotypes. Therefore, the reassortment ensured the combination of acceptable safety and immunogenicity of the WC 3 vaccine with the antigenic specificity of the prevalent human rotavirus serotypes. The vaccine formulation includes a buffer to protect vaccine degradation from gastric acid and a stabiliser to allow for a 24 month shelf life and for storage at refrigerator temperature.

Efficacy : It has been demonstrated that vaccine prevented 100% of episodes of severe rotavirus gastroenteritis, 75% of any rotavirus gastroenteritis regardless of the severity during rotavirus season after vaccination. The efficacy of the 3 doses of the high, middle and low potencies of the pentavalent HBRV was 69%, 77% and 59% respectively against any rotavirus gastroenteritis regardless of the severity.

Immunogenicity : Immunogenicity of the vaccine was measured in terms of SNA response to human outer protein (G1 G2 G3 G4 P1) and bovine outer protein (G6, P7) and serum anti rota virus Ig A. HBRV induces a significant serum anti rota virus Ig A response in 88%-99% of recipients. A significant faecal anti rota virus Ig A has also been reported.

Safety : In safety studies, HBRV has been well tolerated. Though fever, vomiting, diarrhoea, behavioural changes have been reported as adverse events, these were not reported to be greater among recipients than among placebo groups. Shedding of the vaccine strains in the faeces of vaccine recipients was uncommon.

Schedule: Clinical trials have evaluated 2, 4, 6 months and 2, 3, 4 month schedules for the vaccine.

In addition to these two leading vaccine candidates, currently, research is underway to produce a hexavalent, human rotavirus bovine reassortent vaccine to be used in developing countries. The Indian researchers are also involved in developing a vaccine with the use of Indian strains. Rotavirus vaccines have already been introduced in the public sector in some Latin American countries: Brazil, Panama, Venezuela, Mexico, El Salvador, Ecuador and Nicaragua. The experiences of these countries will be important for the rest of the developing countries in their pursuit for reducing morbidity and mortality due to rotavirus diarrhoea through vaccination. However, the challenge of creating context for rotavirus vaccines for developing countries is to affirm that rota virus vaccine is only a part of a comprehensive package of strategies directed at enhancing diarrhoeal disease control in their respective countries.

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Proceedings of the 6th workshop of the members of the Asian Rotavirus Surveillance Network held in Bangkok, Thailand on 3 -4, December, 2007

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This article was compiled by Dr Ranjan Wijesinghe, Consultant Epidemiologist and the coordinator of rotavirus surveillance in Sri Lanka under the ARSN.

Table 1: Vaccine-preventable Diseases & AFP

19th - 25th Jan 2008 (4th Week)

Disease	No. of Cases by Province									Number of cases during current week in 2008	Number of cases during same week in 2007	Total number of cases to date in 2008	Total number of cases to date in 2007	Difference between the number of cases to date between 2008 & 2007
	W	C	S	N	E	NW	NC	U	Sab					
Acute Flaccid Paralysis	01 CO=1	00	00	00	00	00	00	00	00	01	02	07	08	-12.5%
Diphtheria	00	00	00	00	00	00	00	00	00	00	00	00	00	00.0%
Measles	00	00	00	00	00	00	00	00	00	00	00	04	00	+400.0%
Tetanus	00	00	00	00	00	00	00	00	00	00	00	03	02	+50.0%
Whooping Cough	00	00	00	00	00	00	00	00	00	00	01	01	02	-50.0%
Tuberculo-sis	85	02	09	17	05	10	04	00	06	138	237	912	763	+19.5`%

19th - 25th Jan 2008 (4th Week)

Table 2: Newly Introduced Notifiable Diseases

Disease	No. of Cases by Province									Number of cases during current week in 2008	Number of cases during same week in 2007	Total number of cases to date in 2008	Total number of cases to date in 2007	Difference between the number of cases to date between 2008 & 2007
	W	C	S	N	E	NW	NC	U	Sab					
Chicken-pox	30	04	16	00	01	12	06	18	07	94	54	327	142	+130.3%
Meningitis	05 GM=3 CO=2	01 KD=1	07 GL=6 MT=1	00	00	06 KR=6	01 PO=1	02 BD=2	04 RP=2 KG=2	26	01	143	35	+308.6%
Mumps	04	02	04	00	12	05	09	03	07	46	13	184	43	+327.9%

Key to Table 1 & 2

Provinces: W=Western, C=Central, S=Southern, N=North, E= East, NC=North Central, NW=North Western, U=Uva, Sab=Sabaragamuwa.

DPDHS Divisions: CB=Colombo, GM=Gampaha, KL=Kalutara, KD=Kandy, ML=Matale, NE=Nuwara Eliya, GL=Galle, HB=Hambantota, MT=Matara, JF=Jaffna, KN=Killinochchi, MN=Mannar, VA=Vavuniya, MU=Mullaitivu, BT=Batticaloa, AM=Ampara, TR=Trincomalee, KM=Kalmunai, KR=Kurunegala, PU=Puttalam, AP=Anuradhapura, PO=Polonnaruwa, BD=Badulla, MO=Moneragala, RP=Ratnapura, KG=Kegalle.

Table 3: Laboratory Surveillance of Dengue Fever

19th - 25th Jan 2008 (4th Week)

Samples	Number tested	Number positive *	Serotypes				
			D_1	D_2	D_3	D_4	Negative
Number for current week	04	00	00	00	00	00	00
Total number to date in 2008	16	00	00	00	00	00	00

Source: Genetech Molecular Diagnostics & School of Gene Technology, Colombo. * Not all positives are subjected to serotyping.

NA= Not Available.

Data Sources:

Weekly Return of Communicable Diseases: Diphtheria, Measles, Tetanus, Whooping Cough, Human Rabies, Dengue Haemorrhagic Fever, Japanese Encephali - tis, Chickenpox, Meningitis, Mumps.

Special Surveillance: Acute Flaccid Paralysis.

National Control Program for Tuberculosis and Chest Diseases: Tuberculosis.

Table 4: Selected notifiable diseases reported by Medical Officers of Health

19th - 25th Jan 2008 (4th Week)

DPDHS Division	Dengue Fever / DHF*		Dysentery		Encephal-itis		Enteric Fever		Food Poisoning		Leptos-pirosis		Typhus Fever		Viral Hepatitis		Human-Rabies		Returns Re-ceived Timely**
	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	%
Colombo	38	154	01	14	01	03	03	13	00	44	00	09	00	00	00	10	00	00	**85**
Gampaha	15	125	01	07	00	02	01	04	00	00	01	15	00	00	01	16	00	00	**93**
Kalutara	18	48	19	35	00	00	00	04	00	00	01	13	00	01	00	04	00	00	**100**
Kandy	04	18	02	20	01	01	00	02	01	04	04	22	02	04	10	21	00	00	**83**
Matale	02	09	05	21	00	00	01	05	00	00	09	66	00	01	00	01	00	00	**75**
Nuwara Eliya	00	00	01	02	00	00	00	03	00	00	00	01	01	05	01	08	00	00	**67**
Galle	05	20	05	18	00	00	00	03	00	00	01	33	01	02	00	01	00	00	**88**
Hambantota	08	14	01	13	00	01	01	02	00	00	02	13	01	06	00	00	00	00	**91**
Matara	05	28	02	13	00	00	01	11	00	00	03	15	07	23	00	01	00	01	**94**
Jaffna	00	16	02	08	00	00	07	24	00	02	00	00	03	41	00	07	00	00	**50**
Kilinochchi	00	00	00	00	00	00	00	00	00	00	00	00	00	00	00	01	00	00	**25**
Mannar	00	00	00	00	00	00	03	19	00	00	00	00	00	00	00	01	00	00	**75**
Vavuniya	02	07	02	06	01	01	00	00	00	00	00	00	00	00	00	01	00	00	**100**
Mullaitivu	00	00	00	01	00	00	01	02	00	00	00	00	00	00	00	02	00	00	**60**
Batticaloa	08	09	02	07	00	00	00	01	00	00	00	00	00	00	06	13	00	00	**73**
Ampara	00	00	04	22	00	00	00	00	00	00	00	01	00	00	00	00	00	00	**43**
Trincomalee	14	20	03	08	00	00	00	00	00	01	00	00	00	00	00	02	00	00	**89**
Kurunegala	12	74	06	48	00	02	02	07	00	00	00	02	01	03	03	06	00	00	**89**
Puttalam	12	50	03	15	00	00	03	13	00	01	00	02	00	02	02	04	00	00	**100**
Anuradhapur	03	33	01	12	00	02	00	01	00	02	02	07	00	03	01	01	00	00	**84**
Polonnaruwa	03	14	04	14	01	01	01	02	01	01	02	03	00	00	01	03	00	00	**86**
Badulla	01	08	10	37	00	00	00	06	00	01	00	03	01	07	05	18	00	00	**93**
Monaragala	01	02	04	20	00	00	01	03	00	03	00	09	02	08	01	02	00	00	**90**
Ratnapura	02	19	03	15	00	02	00	05	00	41	01	06	00	03	00	02	00	00	**50**
Kegalle	02	30	09	46	03	08	01	02	00	00	01	10	05	06	01	14	00	00	**73**
Kalmunai	00	00	06	11	00	00	00	00	00	00	00	00	00	00	01	04	00	00	**77**
SRI LANKA	**155**	**698**	**96**	**413**	**07**	**23**	**26**	**132**	**02**	**100**	**27**	**230**	**24**	**115**	**33**	**143**	**00**	**01**	**81**

Source: Weekly Returns of Communicable Diseases (WRCD).
***Dengue Fever / DHF** refers to Dengue Fever / Dengue Haemorrhagic Fever.
****Timely** refers to returns received on or before 2 February . 2008 Total number of reporting units =290. Number of reporting units data provided for the current week: 238

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