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REVIEW ARTICLE

Rotavirus vaccine – What are the concerns of the developing countries?

Nitin K Shah

Abstract:
It is estimated that 0.6 million children die annually due to rotavirus diarrhea under the age of 5 years world over. 90% of these deaths occur in developing countries. Western data suggests that current rotavirus vaccines have 85-95% efficacy against severe rotavirus gastroenteritis (RVGE). There are concerns while using the same in developing countries. Data from African trial has shown 76% efficacy against severe RVGE. Efficacy in malnourished children has been found to be 73% as against 74% in well nourished children. Co-administration of oral polio vaccine has shown no interference with rotavirus vaccine in study done in Bangladesh. European study showed efficacy of 86% with current rotavirus vaccines in breast-fed babies which is similar to 91% efficacy in top fed babies. Last concern is affordability of rotavirus vaccine in developing countries which is partially addressed by support from GAVI, which has pledged to support 3 life saving vaccines like rotavirus vaccine for 75 GAVI eligible countries by providing vaccine at US$ 0.15-0.30 per dose till 2015 and even beyond. By including current rotavirus vaccines in the national immunization program of these developing countries there is a potential to save 0.3 million children from dying due to severe RVGE every year.

Keywords: *Rotavirus, rotavirus gastroenteritis, rotavirus vaccine*
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Introduction

The four main concerns for the developing countries as far as rotavirus disease and its prevention using rotavirus vaccines is concerned are A) Why do developing countries need rotavirus vaccines? B) Will the currently available rotavirus vaccines work in developing countries? C) What will be the impact of including rotavirus vaccine in the National Immunization Program (NIP)? D) How will the developing countries afford these rotavirus vaccines?

A) Why do developing countries need rotavirus vaccine?

Child mortality and diarrhea: On an average each child suffers from 3-4 episodes of diarrhea per year in the initial years of life. It is estimated that world over 1.4 billion episodes of diarrhea occur every year in children < 5 years of age [1]. As per the state of world's children 2008 report, 9.73 million children under the age of 5 years die annually world over [2]. After pneumonia, diarrhea is the close second cause of child mortality contributing 17% of all under-five deaths world over [1,2]. It means that 1.6 million children under the age of five years die of diarrhea annually world over of which 0.37 million are contributed by India alone [1,2]. What is more important is that there is no equity in child health as 90% of these deaths occur in developing countries of Asia and Africa and 50% of them occur in just 6

countries i.e. India, Nigeria, China, Ethiopia, DR Congo and Pakistan.

Rotavirus disease burden: It is estimated that nearly 130 million episodes of rotavirus diarrhea occur annually world over in children < 5 years of age, of which 25 million need outdoor visit, 2.5 million need hospitalization and nearly 0.6 million die meaning a death due to rotavirus diarrhea almost every minute! It is estimated that a child has 1:1 chance of developing rotavirus diarrhea by 5 years of age, 1:5 chances that it will need outdoor treatment, 1: 50 chances that he will be hospitalized for the same and 1:205 chances that it will lead to death in that child. 53% of these deaths occur in Asia and 42% in Africa [2,3]. Rotavirus is not controlled by hygiene or safe water as is evident by the fact that incidence of rotavirus diarrhea is just the same world over including in developed countries as is in developing countries. What differs is the outcome, chances of death following severe rotavirus diarrhea is 1: 50,000 in USA as compared to 1:210 in developing countries due to lack of timely medical help in developing countries [2,3].

With better standards of sanitation and hygiene, rotavirus as a cause of severe hospitalized cases of diarrhea is on increase as other bacterial causes are on decline. Estimates in 2000-2004 in low income countries show that rotavirus contributes 39% (28-45%) of severe hospitalized cases of diarrhea as compared to 20% (16-27%) in 1986-1999; and in low middle income countries 40% (32-43%) in 2000-2004 as compared to 25% (20-33%) in 1986-1999 [3]. Applying this to 1.6 million childhood deaths due to diarrhea that occur in the world, it gives an estimate of 611,000 (450,000 – 700,000) deaths due to rotavirus diarrhea annually in the world [3]. Even the confounding factors that protect against severe diarrhea are unfavorable in developing countries. State of world's children 2008 report suggest that in developing countries, only 38% of children are exclusively breast-fed till 6 months of age, 56% are given proper breast-feeds and complimentary feeding till 6-9 months of age, 26% are underweight, 32% are stunted, 80% people use improved drinking water, 50% use adequate sanitation facilities and most important only 38% of children with diarrhea are prescribed ORS (plus appropriate feeding) [2]. Besides, a child with rotavirus diarrhea often has severe vomiting and high fever at the onset of illness making oral rehydration more difficult. Lack of proper medical help again increases chances of mortality due to any diarrhea, more so for rotavirus diarrhea where unscheduled IV fluids are required more often.

B) Will the current rotavirus vaccine work in developing countries?

Rotavirus vaccines have shown great efficacy in the Western world in the trials conducted with both the current rotavirus vaccines. *Rotarix*^{R} *(GSK)* in Latin American study showed 85% efficacy against severe rotavirus gastroenteritis (RVGE) in 1st year which was maintained at 81% in combined 2 years follow up [4,5]. Efficacy against all cause diarrhea hospitalization was 40% in 1st year and 39% in the 2nd year. In European study efficacy against severe RVGE was 96% in 1st year and 90% in 2nd year, against all cause diarrhea hospitalization was 75% in 1st year and 72% in 2nd year, and against any severity RVGE was 79% [6]. *Rotateq*^{R} *(Merck)* in its REST trial showed that efficacy against emergency care visit or hospitalization for severe RVGE was 94.5% during the 1st season of rotavirus disease, against hospitalization due to any cause of diarrhea was 58.9% and in the intention to treat analysis efficacy of 88% after the 1st dose against severe RVGE [7].

However there are concerns whether these vaccines will work as well in situations typical of developing countries like malnourished children, EPI schedule, co-administration with OPV, effect of breast-feeding and most important being live oral viral vaccines interference by prevalent multiple GI infections known to interfere with live oral viral vaccines. Oral polio vaccine (OPV) is one such example of another oral live viral vaccine which did not work as well in developing countries as in the Western world. In fact the per dose effectiveness of tOPV in areas like Uttar Pradesh in India which is the hot seat of wild polio is 9% against both type 1 and type 3 wild polio virus (WPV) [8]. Similar low efficacy with tOPV was also found in Nigeria. This is the reason why WHO insisted on efficacy data with rotavirus vaccines from at least one developing country from Asia and Africa before these vaccines are recommended in NIP of all the countries, including Asia and Africa. Subsequently both the vaccines have been tried in developing countries for efficacy [9]. *Rotarix*^{R} has been tried in South Africa and Malawi; and *Rotateq*^{R}

in Bangladesh, Ghana, Kenya, Mali, and Vietnam [10]. Data from some of these trials is now available.

Efficacy of Rotarix^R in developing countries: Rota O37 efficacy study was conducted simultaneously in South Africa and Malawi, where rotavirus disease burden is high, chances of a child dying of rotavirus diarrhea is 1 in 205, where 5-6% of birth cohort is HIV infected, and only 37% children with diarrhea are prescribed ORS. *Rotarix^R* was given in 2 (10, 14 weeks) or 3 (6, 10, 14 weeks) doses schedule to healthy infants (N=2115) and compared to placebo (N=1052) and subjects were followed up for 1 year for development of rotavirus gastroenteritis (RVGE). There was not much deference in efficacy between 2 or 3 doses. The pooled vaccine efficacy using 2 or 3 doses against severe RVGE was 61.2% (44-73.2%) overall, 76.9% (56-88.4%) in South Africa and 49.5% (19.2-68.3%) in Malawi (11). Efficacy against all cause severe GE was 30.2% (15.0-42.6%) overall (11). Though the efficacy was not as high as seen in Latin America or European study it was significant and reassuring as overall 5 epsidoes/100 infnats/yr were prevented by vaccine in this trial as compared to estimated 1 episode/100 infants/yr in most of thw western trials. This is due to higher burden of disease in community in developing countries as compared to developed world. Though the efficacy was inferior in Malawi than in South Africa, the vaccine saved more lives in Malawi than in South Africa as rotavirus disease burden in Malawi was 1.5 times higher than in South Africa. These results have shown that rotavirus vaccines are efficacious in developing countries and even when using EPI schedule of 6, 10 weeks.

Efficacy of Rotateq^R in developoing countries: *Rotateq^R* has been tried in 3 trials involving developing countries. Study done in Bangladesh and Vietnam used 3 doses of vaccine in 6-10-14 weeks schedule given to healthy infants (N=1018) compared to placebo (N=1018). HIV infected children were no excluded and simultaneous administration of OPV and breast-feeding were allowed [12]. The subjects were followed for 2 years. Overall combined efficacy against severe RVGE at 2 years was 48.3% (22.3-66.1%). In Bangladesh the efficacy was 42·7% (10·4 to 63·9%) and in Vietnam 63·9% (7·6 to 90·9%). The vaccine prevented 3 episodes/100 infant years. Similar study done in African countries (Ghana, Kenya and Mali) of using 3 doses of vaccine at 6-10-14 weeks schedule in healthy infants (N=2733) compared to placebo (N=2735) showed overall efficacy of 39·3% (19·1 to 54·7) at mean 21 months follow up leading to a rate reduction of 2 episodes/100 infants years by vaccine [13]. The effcicacy and disease rate reduction in this study was lesser than Asian study using *Rotateq^R* and African study usinf *RotarixR*. Lastly *Rotateq^R* was given through manufacturer sponsored program in Nicaragua for 3 years where the vaccine was introduced in NIP in October 2006. Case controlled study was conducted in next season of RVGE in 2007-08 [14]. *Rotateq^R* showed effectiveness of 46% (18-64%) against RVGE hospitalization and or need for IV fluids; 58% (30-74%) for severe RVGE and 77% (35-90%) for very severe RVGE. This was when 88% of circulating rotavirus strains was G2P4 strain.

These results with both the vaccines in developing countries have been reassuring and led WHO to now recommend rotavirus vaccine in the NIP of all the countries.

Immunogenicity study in India: A multi-centric immunogenecity trial was done in India, results of which are published recently [15]. 363 8 weeks old healthy infants were enrolled in the study. They were randomized equally to receive either 2 doses of *RotarixR* or placebo in 0-1 mo schedule orally and serum anti-rotavirus IgA antibody were estimated pre-dose 1 and 1 month post-dose 2 for seroconversion and GMCs. All other routine vaccines like OPV, DTP-HB, Hib were given 2 weeks apart (at 6, 10, 14 weeks). Seroconversion rates were 58.3% (95% CI 48.7-67.4) in vaccinees and 6.3% (95% CI 2.5-12.5) in placebo. GMC were 153.9 U/ml (95% CI 113.3-209.0) in vaccinees and 81.6 U/ml (95% CI 27.4-242.8) in placebo. Seroconversion rates in the vaccinees were similar to that seen in Latin America study vaccinees which had shown 86% efficacy of the vaccine.

Efficacy in malnourished children: A subset analysis was done in malnourished children in a study using 3 different formulations of *Rotarix^R* differing in contents of virus particles per dose [16]. Overall 17% of the subjects were malnourished, all mildly malnourished. These malnourished children had double the incidence and 1.5 times more severe rotavirus disease as compared to well nourished group. Pooled analysis of all 3 formulations showed

that the vaccine efficacy was 73% (11.2-92.3) in malnourished children as compared to 74.1% (52.2-86.2) in well nourished children and the formulation nearest to the current commercial preparation in its antigen content showed vaccine efficacy of 100% (39.8-100) in malnourished children as compared to 81.4% (50.7-94.4%) in well nourished children. This data shows that the current rotavirus vaccines are as efficacious in malnourished children as compared to well nourished children.

Immunogenicity when co-administered with OPV: Tow live oral vaccines can interfere with one another's efficacy and accordingly there is concern while administering OPV simultaneously with rotavirus vaccine. This is one reason why some trials on rotavirus vaccines staggered use of OPV for 2 weeks before or after rotavirus vaccine. In Bangladesh *Rotarix*^{R} was co-administered with or after 15 days of OPV at 12 and 16 weeks. The anti-rota IgA seroconversions were 56.5% (44.0-68.4%) when co-administered with OPV and 66.7% (54.0-77.8%), when *Rotarix*^{R} was administered after 15 days and GMCs were 46.6 (30.3-71.7) and 75.3 (47.5-119.4) respectively showing no statistically significant difference [17]. Similarly there was no effect on the seroconversion or GMCs for either polio vaccine virus by the rotavirus vaccine when co-administered with OPV. Both these data reassure us that the immunogenicity of the current rotavirus vaccines is not different when co-administered with OPV.

Effect of breast-feeding: Breast-feeding is a norm at least in the early age in developing countries. We know that breast milk does not interfere with other live viral vaccines like OPV. In European study using *Rotarix*^{R} breast-feeding was allowed by the mothers of the subjects. Subset analysis showed that efficacy against severe RVGE in breast-feeding population was 95.7% (88.2-98.9) and in formula fed population was 96.2% (74.1-99.9) and that against any RVGE was 86% (76.9-91.9) in breast-fed subjects and 90.8% (72.5-97.7) in formula fed subjects, again showing that breast-feeding did not interfere with the efficacy of the vaccine [6,18].

C) What will be the impact if including rotavirus vaccine in the National Immunization Program (NIP)?

Post marketing surveillance: *Rotateq*^{R} was recommended for routine use in infants in USA in February 2006. Studies in subsequent years have shown vaccine effectiveness of 85-95% against severe RVGE (10). CDC data shows that rotavirus diarrhea season was delayed by 2-4 months to February instead of mid-November as for the previous 15 rotavirus seasons. Proportion of all diarrhea tests that were positive for rotavirus fell from 41% in previous 15 seasons to 11-17% during 2007-2008, which was lower than the lowest ever seen in previous 15 years. Similarly, the total number of tests performed for rotavirus fell by 37% and % positive for rotavirus fell by 78.5% in 2007-2008 compared with previous 7 seasons. Mean coverage with 3 doses of rotavirus vaccine among children aged 13 months at the sentinel sites was 3.4% (range: 0--11.0%) in May 2007 and 33.7% (range: 1.1%--53.0%) in March 2008 [19]. It is obvious that the reduction in cases of rotavirus disease was far more than can be explained by the direct benefits to vaccinees alone, suggesting possibility of herd effects of vaccine in a population with significant coverage [10,19]. Similarly in Nicaragua the effectiveness of *Rotateq*^{R} was 52-63% against severe RVGE and 73-86% against very severe RVGE (14). In neighboring El Salvador effectiveness of *Rotarix*^{R} was found to be 74% against severe RVGE and 88% against very severe RVGE [10].

Potential impact of rotavirus vaccine on public health in developing countries: World over nearly 1.6 million under-five children die of diarrhea annually of which 0.6 million are due to rotavirus. As nearly 80% of these cases of severe rotavirus diarrhea are preventable by the current rotavirus vaccines, it has the potential to save 0.5 million under-five children world over if all the children of world receive rotavirus vaccine. Like the oral polio vaccine, rotavirus vaccine is given by oral route and can be given at 6 and 10 weeks of age. Hence one can achieve similar rate of coverage as that of OPV3 which stands at 58% as per the state of world's children 2008 report [2]. Hence at least 60% of the 0.5 million deaths due to rotavirus diarrhea i.e. 0.3 million, are immediately preventable by inclusion of rotavirus vaccine in the national immunization program by developing countries.

Extension of time limit for age of vaccination: The actual ages of vaccination in pivotal studies were 6 to

12 weeks for *Rotateq*^{R} and 6 to 14 weeks (Latin America) or 6 to 15 weeks (Europe) for *Rotarix*^{R}. The maximum age for last dose was 32 weeks for *Rotateq*^{R} and 24 weeks 6 days for *Rotarix*^{R}. However for various reasons children in developing countries may miss their rotavirus vaccine withing this tight time frame and hence may not benefit from the vaccine. SAGE in 2009 observed that by extending the maximum age of vaccination for the first dose to 15 weeks and last dose to 32 weeks will potentially increase the coverage from 57% to 70% for the first dose and from 36% to 42% for the second dose which will save that many more lives without jeopardizing the safety [10]. Some experts have gone beyond and looked at the potential impact of a policy of free vaccination with rotavirus vaccine till 1 year instead of restricted limit of 12 weeks In developing countries, assuming vaccine efficacy of 50% and 75% for doses 1 and 2, respectively, and a hypothetical six-fold and threefold increased relative risk of intussusception within 7 days of doses 1 and 2, respectively, initiating rotavirus immunization before 12 weeks of age would prevent 194,564 of the 517,959 annual rotavirus-associated deaths among children <5 years, while potentially resulting in 1106 fatal intussusception events. Administration of the first dose to infants up to 1 year of age would prevent an additional 54,087 rotavirus-associated deaths (total = 248,651) while potentially resulting in an additional 1226 intussusception deaths (total = 2332). Hence in developing countries, the additional lives saved by broadening the age restrictions for initiation of rotavirus vaccination would far outnumber the hypothetical excess intussusception deaths that would accompany such an approach [20].

D) How will the developing countries afford these rotavirus vaccines?

Based on the efficacy data available from African and Malawi, in the recent meeting of The Strategic Advisory Group of Experts (SAGE) in immunization, World Health Organization, it was recommended to include rotavirus vaccine in the NIP of each and every country, especially (10). In countries where diarrheal deaths account for ≥10% of mortality among children aged <5 years, the introduction of the vaccine is strongly recommended by WHO [10]. The problem in including the rotavirus vaccine (like many other life saving newer vaccines) in the NIP in developing countries is funding. At the current commercial price of US$ 25-35 per dose for rotavirus vaccine, it will cost fortune for any developing country to include this vaccine in the NIP. For example in India the current commercial price of one dose of *Rotarix*^{R} (the only vaccine available till time) is US$ 20. At this rate it will cost US$ 1.1 billion annually for 28 million birth cohort in India. Even if the coverage is 60% (as that of OPV3), it will cost US$ 0.66 billion, which is beyond the public health budget of India, especially as there are other public health priorities. That is where the role of international funding agencies comes in picture.

GAVI support: GAVI-Alliance has proposed to support inclusion of life saving childhood vaccines in NIP in 75 GAVI eligible countries [21]. Based on the current policy of GAVI-Alliance depending upon the affordability, the countries seeking such support from GAVI-Alliance have to co-finance the vaccine at a cost of US$ 0.10 (fragile states) to 0.30 (least poor countries) per dose for the first vaccine and US$ 0.15 for the subsequent two vaccines with incremental cost of US$ 0.15 per dose (for the least poor countries only) [21]. GAVI-Alliance has pledged US$ 4 billion for supporting such vaccination program for the poor countries till 2015 and has shown intention continue to help these countries even beyond 2015.

Rotavirus vaccine is one such vaccine that developing countries can avail support from GAVI–Alliance (in partnership with PATH) as it has potential to save nearly 0.6 million under-five deaths annually. In fact Rota Virus Program (RVP) final draft of PATH estimates that such subsidized rotavirus vaccine program can reach 716 million infants and save 2.4 million lives in next 20 years [22]. Accelerated Development and Introduction Plan for rotavirus vaccine (Rota-ADIP) has helped inclusion of rotavirus vaccine in the NIP of developing countries just within 2 years of its use in NIP by the Western world. As of January 2009, four countries, namely Bolivia, Guyana, Honduras, and Nicaragua, were approved for GAVI funding for rotavirus vaccine inclusion in the NIP [23]. It is now for the public health authorities of the other eligible developing countries to consider the prospects of including rotavirus vaccine in their NIP with support from GAVI-Alliance.

Indigenous rotavirus vaccines: One way out for the developing countries is to develop their own indigenous rotavirus vaccine which will make it cost effective for these countries to include rotavirus vaccine in their national immunization program (NIP). India is trying to develop its own rotavirus vaccine using two neonatal rotavirus strains i.e. 116E: G9P8(11) Human-bovine serotype from Delhi which is commonly found in neonatal nurseries in India and I321: G10P8(11) bovine-human type from Bangalore. One study compared 116E, I321 and placebo given a single oral dose to 8 weeks old infants. Results showed that serum IgA seroconversion rates were 73%, 39% and 20% in the 116E, I321 and placebo groups, respectively. Vaccine virus was shed on days 3, 7 or 28 in 11/30 infants of the 116E and none in the other two groups. Authors concluded that the 116E strain is attenuated, clinically safe and highly immunogenic with a single dose [24]. This vaccine is set for further trials using higher dose. Success of this or similar Indian vaccines will help us bring down the cost of vaccine and make us self sufficient for the huge demand it will pose if we include this vaccine in the NIP.

REFERENCES:

1. Parashar UD, Hummelman EG, Bresse JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Em Infect Dis, 2003;9:565-571.
2. UNICEF. 2008 State of the World's Children Report. http:// www. unicef. org/ sowc08/ fullreport /full_report.php. Accessed on 25th December 2009.
3. Parashar UD, Gibson CJ. Bresee JS, Glass RI. Rotavirus and Severe Childhood Diarrhea. Em Infect Dis, 2006;12:304-306.
4. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Clemens SC et al. Safety and Efficacy of an Attenuated Vaccine against Severe Rotavirus GastroenteritisN Engl J Med 2006;354:11-22.
5. Linhares AC, Velazquez FR, Pérez-Schael I, Llorens XS, Abate H, Espinoza S et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomized, double blind, placebo-controlled phase III study. Lancet, 2008; 371:1181-1189.
6. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 2007; 370: 1757–63.
7. Vesikari T, Matson D, Dennehy P, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006; 354: 23–33.
8. Grassly NC, Fraser C, Wenger J, Deshpande JM, Sutter RW, Heymann DL, et al. New strategies for the elimination of polio from India. Science 2006; 314: 1150–53.
9. Meeting of the immunization Strategic Advisory Group of Experts, November 2007 – conclusions and recommendations. Wkly Epidemiol Rev 2008;83:1-16.
10. Meeting of the immunization Strategic Advisory Group of Experts, November 2009 – conclusions and recommendations. Wkly Epidemiol Rev 2009;84:213-236.
11. Madhi, S, Nigel AC, Steele D, Witte D, Kirsten M, Louw C et al. Effect of Human Rotavirus Vaccine on Severe Diarrhea in African Infants. N Engl J Med 2010;362:289-98.
12. Zaman AK, Anh DD, Victor JC, Shin S, Yunus M, Dallas MJ. Effi cacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. Lancet 2010; 376: 615–23
13. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. Lancet 2010; 376: 606–14.
14. Patel M, Pidreira C, Oliveria LH, Tate J, Orozco M, Mercado J et al. Association Between Pentavalent Rotavirus Vaccine and Severe Rotavirus Diarrhea Among Children in Nicaragua. JAMA. 2009;301:2243-2251
15. Bose A, Narang A, Dutta P, Pandit A, Kang G, Bhattacharya SK et al. Safety And Immunogenicity of RIX 4414 (Rotarix TM) Live-Attenuated Human rotavirus Vaccine In Indian Infants Proc 5th World Congr Pediatr Infect Dis (WSPID) 2007.
16. Peres-Sachel I, Salinas B, Tomat M, Linhares AC, Guerrero ML, Ruiz-Palacios GM et al. Efficacy of Human Rotavirus Vaccine RIX4414

in malnourished children. J Infect Dis 2007;196:537-40.
17. Zaman K, Sack DA, Yunus M, Arifeen SE, Bouckenooghe A, Delem A et al.Immunogenicity of an oral polio vaccine is unaffected when co-administered with a human rotavirus vaccine in Bangladeshi children. Proc 5th World Congr Pediatr Infect Dis (WSPID) 2007.
18. Schuster V, Vesikari T, Karvonen A, Prymula R, Tejedor JC, Cohen R et al. Breastfeeding does not influence the efficacy of Rotarix™. Paper presented at 25th International Congress of Pediatrics (ICP) 2007, Athens, Greece PP0990.
19. Delayed Onset and Diminished Magnitude of rotavirus Activity --- United States, November 2007--May 2008. MMWR, June 25, 2008 / 57 (Early Release);1-4.
20. Patel MM, Clark AD, Glass RI, Greenberg H, Tate J, Santosham M et al. Broadening the age restriction for initiating rotavirus vaccination in regions with high rotavirus mortality: Benefits of mortality reduction versus risk of fatal intussusception. Vaccine 2009;27:2916–2922.
21. Policy brief GAVI Alliance new vaccine co-financing policy http://www.gavialliance.org/resources/GAVI_co_financing_policy_brief_Aug2008.doc accessed on 25th December 2009.
22. The PATH Rotavirus vaccine program Summary Report http:// rotavirus. org/ files/ RVP _ SummaryReport_Final.pdf Accessed on 25th December 2009.
23. Rotavirus vaccine – Countries approved for support http:// www. gavialliance. Org / performance / commitments/rotavirus/index.php accessed on 25th December 2009.
24. Bhandari N, Sharma P, Glass RI, Ray P, Greenberg H, Taneja S et al. Safety and immunogenicity of two live attenuated human rotavirus vaccine candidates, 116E and I321, in infants: Results of a randomised controlled trial. Vaccine. 2006;24:5817–5823.