UNIT NO. 6

PREVENTION OF CHILDHOOD DIARRHOEA AND THE ROTAVIRUS VACCINE

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ABSTRACT

The main enteric pathogens associated with childhood diarrhoea are viruses, with rotavirus being the most common. Salmonella, Campylobacter, Escherichia coli and Shigella are the causes of bacterial diarrhoea. As faecal-oral route is the most important method of transmission, good hygiene is essential for preventing the infection and for limiting the spread of the illness. Good hygiene practices include meticulous hand washing; thorough cooking of eggs, poultry and meat of animal origin; and separating raw meat from cooked food or fruits. Incidence of rotavirus infection has not shown a decline despite improved sanitation, clean water supply and increased affluence of the society. Vaccination against the rotavirus is the only effective method of reducing severe rotavirus diarrhoea. Effective and safe rotavirus vaccines will become available in the market in the next few years.

INTRODUCTION

Diarrhoeal disease remains a leading cause of morbidity and mortality in Children worldwide. In Singapore, approximately 10% of all paediatric hospitalizations are the result of diarrhoea.

AETIOLOGICAL AGENTS IN DIARRHOEA

A wide array of enteric pathogens is responsible for diarrhoea. Viruses are the most common agents and include rotaviruses, noroviruses, astroviruses and enteric adenoviruses. Locally, the commonest bacterial cause is salmonella. This is followed by campylobacter with shigella as the distant third. Escherichia coli is also a common cause. However, the incidence of E coli diarrhoea is not known as E coli is not routinely looked for. It is difficult for laboratories to differentiate diarrhoea-associated E coli strains from those of stool-flora E coli, the exception being E coli O157:H7. Diarrhoea arising from other bacteria is rare and that resulting from parasites is even rarer.

PREVENTIVE MEASURES IN CHILDHOOD DIARRHOEA

Diarrhoeal disease is transmitted mainly through the faecal-oral route. Salmonellosis can be acquired through contaminated poultry, under-cooked eggs and meat, and pets. Improperly cooked poultry, meat, unpasteurized milk in conjunction with field visits to dairy farms, untreated water and pets, have been the main vehicles of transmission of campylobacter. As humans are the natural host of shigella, transmission includes person-to-person contact, contact with contaminated fomites and ingestion of contaminated food or water. Houseflies also may be vectors through physical transport of infected faeces. Transmission of E coli is from food or water contaminated with human or cattle faeces. Good hygiene is, therefore, the most important factor for decreasing transmission of diarrhoea in children.

Good hygienic practices include:

1. Hand washing before preparing food and after handling raw poultry and meat, after using the bathroom, changing diapers or handling pets.
2. Wash cutting boards, dishes and utensils with soap and water after coming in contact with raw meat, poultry and seafood.
3. If possible, use one cutting board and knife for fresh produce and use a separate one for raw meat, poultry and seafood.
4. Avoid contact of fruits and vegetable with the juices of raw poultry or meat.
5. Through cooking of eggs, poultry and food of animal origin.
6. Avoid unpasteurized milk or untreated water.
7. Prevent transmission by fomites with cleaning of toys and contaminated surfaces.
8. Proper disposal of diapers and sanitary sewage.
9. Exclusion of infected people from handling food.
10. Exclusion of people with diarrhoea from using public recreational water.

ROLE OF ROTAVIRUS VACCINE

Rotavirus is recognized as the single most important agent associated with acute, severe diarrhoea illness in childhood worldwide. Parashar and colleagues estimated that, each year, rotavirus caused approximately 111 million episodes of gastroenteritis requiring only home care, 25 million clinic visits, 2 million hospitalizations and 440,000 deaths in children less than 5 years of age. Virtually all children are infected by the age of 5 years, regardless of nationality, level of hygiene, sanitation, access to clean water, and residency in developed or developing countries. In Singapore, since 1970's, rotavirus continues to account for approximately 30% of all children hospitalized for gastroenteritis.

As burden of rotavirus infection remains significant and life-saving intravenous treatment to rehydrate children with severe rotavirus diarrhoea is unavailable to many of the developing world's 575 million children under the age of 5 years, a vaccine will be the most cost effective way to protect against rotavirus gastroenteritis. World Health Organization has indeed, made development of rotavirus vaccine a public health priority.

There are many strains of rotavirus. The common serotypes seen are G1, G4, G3, G2 and G9. In naturally acquired

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rotavirus gastroenteritis, the younger is the child, the higher is the risk of severe disease and hospitalization. The first episode is the most severe and subsequent infections become progressively milder. This is in relation to the initial antibody response being serotype specific with limited production of cross-reactive antibodies. Subsequent infection increases antibodies that cross-react with multiple serotypes and therefore, mild disease after the second episode of rotavirus diarrhoea.

Repeated doses of rotavirus vaccine simulate naturally acquired infections in the development of immunity. As such, an effective rotavirus vaccine will not be able to eradicate rotavirus infection but is expected to protect against moderate and severe disease thereby decreasing the severity and duration of the illness, reducing morbidity and socioeconomic burden, and preventing against hospitalization and mortality. Besides effectiveness, the vaccine also needs to be safe and not to be linked with any serious events especially intussusception.

DEVELOPMENTS IN ROTAVIRUS VACCINE

Various approaches have been employed to develop rotavirus vaccine. On the basis of the contention that protection from rotavirus is achieved best by inducing local intestinal immune responses, vaccine efforts have been directed mostly at the development of live attenuated rotavirus vaccines. Most of these efforts have been concentrated on the use of animal rotavirus strains, labeled the Jennerian approach. The initial bovine rotavirus vaccine and rhesus monkey rotavirus vaccine gave variable results with disappointing efficacy in the less developed countries. The next approach labeled as modified Jennerian approach, was to introduce human rotavirus genes into the animal strains to create reassortant viruses. Attenuated human rotavirus strain and neonatal rotavirus strains have also been employed to produce vaccines and are in various phases of clinical study. Other approaches which are in the preclinical studies included the use of virus-like particles, DNA vaccine and subunit vaccines. Table I summarizes the development of various rotavirus vaccines. Four of the vaccines which are already licensed or in the late phase of development will be described.

Rotashield™

The first rotavirus vaccine to be licensed for use in the United States, in August 1998, was Rotashield (RRV-TV), a tetravalent rhesus-human reassortants G1, 2, 4 and G3. Prior to licensing, clinical trials in the United States, Finland and Venezuela had found it to be 80 to 100% effective at preventing serious rotavirus diarrhoea and researchers had detected no statistically significantly serious adverse effects. The vaccine was launched in November 1998. Nine months later, in July 1999, after the administration of approximately 1.5 million doses, the Centre for Disease Control and Prevention (CDC) reported 15 cases of intussusceptions in infants who had received this vaccine. Eleven of these intussusceptions occurred within 1 week of the first vaccine dose. CDC recommended suspending further vaccination while further investigation was carried out. In October 1999, the manufacturer of Rotashield decided to withdraw the vaccine from the market. Despite the temporal association between the intussusception and RRV-TV, debate about the real risk of intussusception continues. Recently, license to produce RRV-TV has been transferred to BIOVIRx Inc. of Minneapolis which hopes that it can convince the US Food and Drug Administration that the vaccine can be made safe simply by administering it at a younger age.

Table 1. Rotavirus Vaccines*

Involved in vaccine trials

NCDV-RIT $_{4237}$	Bovine Monovalent	1980s
WC_3	Bovine Monovalent	1980s
RRV	Monovalent rhesus	mid-1980s
M_{37}	Human attenuated	

Licensed

Product	Company	Concept	Status
RRV-TV (Rotashield)	Wyeth Averst, USA	Live oral rhesus strain with 3 monovalent RRV-human VP7 reassortants	Licensed 1998 Withdrawn 1999
(RRV-TV : license has been transferred to BIOVIRx Inc, USA)			
Lamb RV	Lanzhou Int. of Biol. Products	Live oral lamb strain G10P[12]	Licensed in China 2000

Phase III Trials

Product	Company	Concept
WC_3-QV (Rota Teq)	Merck	Live oral bovine strain with 2 human VP_7 reassortants + 1 VP_4 reassortant
RIX $_{4414}$ (Rotarix ™)	GSK	Live oral human monovalent GIPIA [8]

Phase II Trials

Product	Company	Concept
RV_3	University of Melbourne	Neonatal strain G_3P_{2A}[6]
UK-Reassortant Strain	US National Institute of Health	Tetravalent bovine human reassortants

Phase I Trials

Product	Company	Concept
Neonatal Strains: 116E and I-321	Bharat Bio Tech Ltd. India	Neonatal strains: 116E (g9, P8[11]) I321 (G10, P8[11])

* *Preclinical trials of parenteral vaccines :* Inactivated rotavirus vaccine, Virus-like particles, DNA vaccines, Expressed antigens

Lanzhou Lamb Rotavirus Vaccine

In China, Lanzhou lamb - derived monovalent rotavirus vaccine, G10P[12] was licensed in 2000 and had since been used in private market in China. Between year 2001 and

2004, more than 1 million doses had been administered. Vaccination involves 1 single dose of 3ml solution containing viruses of $>10^{5.5}$ ffu/ml given between 6 months to 3 years. This vaccine has been well tolerated with no serious adverse events.

Rotarix™

In Singapore, we have participated in clinical trials of RotarixTM, a live attenuated human monovalent G1P[8] strain RIX4414 rotavirus vaccine, developed by GlaxoSmithKline Biologicals. In a Phase II trial, 2464 healthy infants were randomized to receive two oral dose of human rotavirus vaccine at a concentration of $10^{4.7}$, $10^{5.2}$ or $10^{6.1}$ ffu or placebo at 3 and 4 months concomitantly with routine DTP_a-IPV-Hib vaccinations. This trial demonstrated that 2 doses of Rotarix were highly immunogenic, well tolerated and did not influence the response of concomitantly administered routine immunizations, DTPa-IPV-HiB and Hepatitis B. Phase III trial is now in progress.

Seven other Phase II trials were conducted in USA, Canada, Europe, Africa and Latin-American. A year ago, a large Phase III trial evaluating 63,000 infants had been recruited in 11 Latin-American countries and Finland. From these trials, the 2 doses of Rotarix had shown to be (1) highly immunogenic, (2) protective against rotavirus caused by G1 and non-G1 serotypes, 73% for any and 85-90% for severe rotavirus gastroenteritis, (3) of broad and early protection (4) of low reactogenicity and (5) safe with respect to intussusception.

GlaxoSmithKline Biologicals has submitted for licensure in more than 40 countries. In Mexico, licensure was obtained in July 2004 and vaccine became available commercially on 10 January 2005.

RotaTeq™

A pentavalent (G1, G2, G3, G4, P1) human-bovine reassortant rotavirus vaccine, RotaTeq™ by Merck & Co. has completed a large scale Phase III study, the Rotavirus Efficacy and Safety Trial or REST. More than 70,000 healthy infants took part. There was no increase in the risk of intussusception. The data supported that RotaTeq™ was generally well tolerated, highly efficacious against severe rotavirus gastroenteritis and associated hospitalizations, and efficacious against rotavirus gastroenteritis of any severity. Merck & Co. Inc. announced on 11 April 2005 that it has submitted a Biologic License Application to the US Food and Drug Administration.

Rotavirus was discovered by R Bishop from Melbourne, in 1973. After more than 30 years, safe and effective vaccines will eventually become available soon. It is now up to the individual country to decide what is its burden of rotavirus infection, what is the effect of rotavirus infection in terms of mortality and morbidity and come out with its own policy on rotavirus vaccination. It is known that countries who need the vaccine most are usually the ones who cannot afford to pay for the vaccine. It is important for international community to help in providing aids for the introduction of the effective vaccine for use in children in the developing countries to reduce and prevent the high death toll associated with rotavirus infection.

CONCLUSION

Diarrhoea remains a common cause of morbidity amongst Singapore children. Transmission is mainly through faecal-oral route. Good hygiene practice plays an important part in reducing the occurrence of diarrhoea. However, to prevent severe rotavirus diarrhoea, rotavirus vaccination is the only effective measure.

RECOMMENDED READING

1. Parashar UD, Hummelman EG, Bresse JS et al. Global illness and deaths caused by rotavirus disease in children. Emerg Inf Dis 2003; 9(5):565-72.
2. Glaso RI, Bresse JS, Parashar US et al. The future of rotavirus vaccines: a major setback leads to new opportunities. Lancet 2004;363:1547-50.

LEARNING POINTS

- **In Singapore, approximately 10% of all paediatric hospitalizations are the result of diarrhoea.**
- **The main enteric pathogens associated with childhood diarrhoea are viruses, with rotavirus being the most common.**
- **Good hygiene practices to prevent faecal-oral spread include meticulous hand washing; thorough cooking of eggs, poultry and meat of animal origin; and separating raw meat from cooked food or fruits.**
- **To prevent severe rotavirus diarrhea, rotavirus vaccination is the only effective measure.**
- **Various rotavirus vaccines have been developed and four of the vaccines are either already licensed or in the late phase of development.**