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Viral vaccines

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DIARRHOEAL DISEASES CONTROL PROGRAMME

ROTAVIRUS VACCINES

Rotavirus diarrhoea. Rotaviruses are the major cause of severe dehydrating diarrhoea among young children in developed countries, where they are frequently responsible for 40-60% of the cases requiring hospitalization. Rotavirus diarrhoea is equally common in developing countries, but the proportion of all diarrhoea episodes caused by rotaviruses is smaller, owing to the higher incidence of bacterial and parasitic diarrhoeas. However, rotavirus diarrhoeas are of greater average severity than bacterial diarrhoeas; therefore rotaviruses account for a significant share, generally 20-40%, of severe diarrhoeas among young children in developing countries. Rotavirus diarrhoea is most common in children 6-24 months of age. It has been estimated that an effective rotavirus vaccine might reduce all diarrhoeal deaths by 30% in this age group (de Zoysa & Feachem, 1985). In other words, it might avert 500 000 - 1 000 000 deaths in children annually.

Rotaviruses. Rotavirus particles have two shells. The inner core of the rotavirus has one major protein (termed VP6) which is similar in human and animal rotaviruses. The outer shell has two proteins, termed VP7 and VP4. The VP7 protein is the major surface antigen involved in virus neutralization by antibodies, and serotypes of rotaviruses are determined by differences in this antigen. Currently there are four serotypes, designated 1 to 4 (WHO, 1984). All of them cause disease, but serotype 1 appears to be the most common cause of epidemic rotavirus gastroenteritis in countries with a temperate climate. Information on the distribution of rotaviruses according to serotype in developing countries is still limited.

Rotavirus candidate vaccines. Attempts to develop live attenuated, oral vaccines for human rotavirus gastroenteritis have used the following approaches:

1. Heterologous (animal) rotaviruses that are adapted to tissue culture. These include (a) bovine rotavirus - vaccines RIT 4237 and WC3, and (b) rhesus rotavirus - vaccine RRV-1.
2. Human-animal "reassortant" rotaviruses. In these, the VP7 surface protein of human rotaviruses, corresponding to serotypes 1-4, is incorporated into an animal host virus. They include (a) bovine-human vaccine viruses, and (b) rhesus-human vaccine viruses.
3. Naturally attenuated human rotaviruses ("nursery strains"). These differ from virulent rotaviruses by a modification in the VP4 surface protein.

Efficacy trials of rotavirus vaccines

Bovine rotavirus vaccines. The RIT 4237 strain of bovine rotavirus was tested in several clinical trials in developed and developing countries, but was later withdrawn by its manufacturer because it showed insufficient immunogenicity and efficacy. This vaccine, after 1 or 2 oral doses, induced 50-60% protection against all, and 80-90% protection against severe rotavirus diarrhoea in infants aged 6-12 months in Finland (Vesikari et al., 1984, 1985). In a WHO-supported trial in Peru, the vaccine given in 3 doses was 40% effective against all, and up to 75% effective (depending on the criteria) against severe rotavirus diarrhoea (Lanata et al., in press). However, in the Gambia, vaccine efficacy after 3 doses was only 33% (Hanlon et al., 1987), while in trials involving a single dose of vaccine in Rwanda (de Mol et al., 1986) and among Apache Indians in Arizona, USA, (Santosham et al., 1988) no efficacy was found.

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The WC3 vaccine strain is derived from a different bovine rotavirus and may be less attenuated than RIT 4237. The vaccine dose is 10^7 particles as compared with 10^8 for RIT 4237. In a trial in infants aged 3-11 months in Philadelphia, USA, this vaccine, after a single dose, evoked 76% protection against all, and 100% protection against severe rotavirus diarrhoea (Clark et al., 1988a). Further evaluations of the WC3 vaccine are under way in the Central African Republic and Israel, and other trials are planned.

Rhesus rotavirus vaccine. The RRV-1 vaccine has been tested in several efficacy trials in developed countries, with varying results. In the first of these, in Sweden, a vaccine dose of 10^5 particles conferred 48% protection against all, and up to 100% protection against severe rotavirus diarrhoea. This dose, however, caused fever in 79% of Swedish children (Gotheffors et al., in press). In other studies, a vaccine dose of 10^4 showed 38% protection in Finland (Vesikari et al., 1988), 29% in Baltimore, USA, (Rennels et al., 1988), 0% in Rochester, USA, (Christy et al., 1988a), and 0% in Apache Indians in Arizona, USA, (Santosham et al., 1987).

In a trial in Venezuela the RRV-1 vaccine induced much better protection: 64% against all, and 100% against severe rotavirus diarrhoea (Flores et al., 1987). In this trial rotavirus serotype 3 was the most common causative agent, and vaccine-induced protection against this serotype was 70%. The explanation for the better efficacy in this study as compared with the other trials might be the fact that RRV-1 is closely related to human rotavirus serotype 3 by its VP7 surface protein, and therefore induces neutralizing antibodies which may give enhanced protection against this rotavirus type. In the other trials, most diarrhoea episodes were caused by serotype 1, to which RRV-1 is not related by the VP7 antigen.

The finding of enhanced protection by vaccine against disease caused by the homologous rotavirus serotype encouraged the development of rhesus-human reassortant rotaviruses in which the VP7 antigens of serotypes 1, 2 and 4 of human rotaviruses are incorporated in the rhesus virus (Midthun et al., 1986).

Bovine-human reassortant rotavirus vaccine. A candidate vaccine in which the VP7 antigen of serotype 1 human rotavirus is incorporated in the WC3 bovine rotavirus, designated WI79-9, is being evaluated for efficacy in Philadelphia, USA. Preliminary results indicate that there is 100% protection against diarrhoea associated with the homologous virus, human rotavirus serotype 1 (Clark et al., 1988b).

Rhesus-human reassortant rotavirus vaccine. Candidate vaccines in which the VP7 antigens of serotype 1 and 2 human rotaviruses, respectively, are incorporated in rhesus rotavirus are being evaluated for efficacy in Finland, Peru and the USA. Preliminary results with the serotype 1 vaccine indicate that there is 88% protection against diarrhoea due to serotype 1 rotavirus in Finland (Vesikari et al., 1988) and 67% protection in Rochester, USA, (Christy et al., 1988b).

A combined rhesus-human reassortant rotavirus vaccine has been developed by mixing the rhesus-human viruses for serotypes 1, 2 and 4, and the rhesus rotavirus for serotype 3. A potential problem with the combined vaccine is that the components may interfere with each other, resulting in poorer neutralizing antibody responses to the individual serotypes than would be observed after vaccination with single serotype vaccines. The vaccine is being tested for efficacy in Peru and the USA.

Nursery strain vaccines. A naturally attenuated rotavirus, with an altered VP4 protein, has been developed as a candidate rotavirus vaccine in the USA (Flores et al., 1988). This strain, named M37, is an "intertypic" virus that cross-reacts with serotypes 1 to 4. The candidate vaccine is undergoing safety and immunogenicity trials in volunteers. The rationale for using a naturally attenuated human rotavirus as a vaccine is based on observations of neonatal rotavirus infections. Such "nursery strains"

frequently infect neonates in maternity wards without causing illness, and the infected infants are later protected, at least in part, against diarrhoea associated with fully virulent human rotaviruses (Bishop et al., 1983).

Research priorities of the WHO Diarrhoeal Diseases Control (CDD) Programme

WHO regards the development of an effective rotavirus vaccine as a high priority. Ideally, the vaccine should induce substantial, long-lasting protection against rotavirus diarrhoea in young infants, even neonates, following a single oral dose. Although the disease is most severe in infants aged 6-24 months, in developing countries cases occur in much younger infants; thus the vaccine should be administered at the age of 2-3 months. It is probable that, for any candidate rotavirus vaccine, multiple doses will be required for maximal efficacy. In this case, it would be important to be able to combine rotavirus and oral poliovirus vaccinations. The CDD Programme is currently supporting research in Thailand to determine whether the rhesus-human rotavirus vaccine and oral poliovirus vaccine can be given in combination or whether either one compromises the "take" of the other. Another important research question is whether breast-feeding interferes with the take of rotavirus vaccines.

The CDD Programme is continuing to support efficacy trials of several candidate rotavirus vaccines in developing countries; the most important candidate vaccines at present are the WC3 and the combined rhesus-human reassortant rotavirus vaccines. For the latter, however, it may be necessary to seek a new formulation with greater immunogenicity before embarking on further efficacy studies.

The CDD Programme has also provided support to research on other approaches to develop rotavirus vaccines, including genetically-engineered vaccines. At present, however, the conventional methods described above appear more likely to result in practical vaccines against rotavirus diarrhoea in the near future.

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