the *in vitro* sensitivity of the isolated pathogen; bloody diarrhoea should be treated as shigellosis, using antibiotics to which most *Shigella* strains in the community are sensitive.

Management of infants with severe persistent diarrhoea. A small subgroup of children with severe persistent diarrhoea (purging rate greater than 5 ml/kg/h and marked weight loss) requires specialized treatment in hospital. These patients can be managed initially as described in the preceding sections. However, particular attention must be paid to maintaining both hydration and nutrition. If signs of carbohydrate intolerance (presence of reducing substances in the stool, low faecal pH, perianal inflammation) are present and improvement does not occur following the restriction of dietary lactose, then monosaccharide intolerance should be suspected. In such cases all carbohydrate should be removed from the diet, at least on a trial basis. Sensitivity to dietary protein should be considered in children who do not improve following the withdrawal of dietary carbohydrate and appropriate antibiotic therapy. Such patients can usually be managed by substitution of dietary protein: children who were initially receiving animal milk may be switched to soya or meat-based diets (for example, successful results have been described using finely ground chicken as a protein source).

Most children will respond to specific dietary and/or antimicrobial therapy (as discussed above). However, some with very severe food intolerance will be unable to take food orally and will have to receive intravenous alimentation for several days of weeks before progressive amounts of chemically defined, readily absorbable nutrients can be administered orally.

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Rotavirus Vaccines

The epidemiological features of rotavirus diarrhoea that are of greatest relevance to vaccine development are as follows:

- Rotavirus is the major cause of severe dehydrating diarrhoea in young children in both developed and developing countries.
- This organism is responsible for 40-60% of the diarrhoea cases requiring hospitalization in developed countries.
- It accounts for 20-40% of severe diarrhoeas among children in the developing world.
- Rotavirus diarrhoea is most common in children 6-24 months of age.

There are four serotypes of rotaviruses, designated 1 to 4. While they all cause disease, serotype 1 appears to be the most common cause of epidemic rotavirus

diarrhoea in countries with a temperate climate. Information on the distribution of rotavirus according to serotype in the developing countries is limited.

Potential rotavirus vaccines . It has been estimated that an effective rotavirus vaccine could : - reduce all diarrhoeal deaths by 30 percent in the age group 6-24 months, and - avert 500 000 - 1 000 000 deaths in children annually.

Efforts to develop live attenuated, oral vaccines for human rotavirus diarrhoea have resulted in five candidates: bovine, rhesus, bovine-human reassortant, rhesus-human reassortant, and nursery strain vaccines. The bovine vaccines (RIT 4237 and WC3) and rhesus vaccine (RRV-1) have been developed from animal rotaviruses that are adapted to tissue culture. Bovine-human and rhesus-human vaccines are genetically engineered, human-animal hybrid rotaviruses, in which a surface protein of a human rotavirus has been incorporated into an animal host virus. The nursery strain vaccine is a naturally attenuated human rotavirus.

Efficacy trials of rotavirus vaccines

Bovine rotavirus vaccines. The RIT 4237 strain of bovine rotavirus was found to lack significant immunogenicity and efficacy in several clinical trials in developed and developing countries; it has been withdrawn by the manufacturer. Evaluations of WC3 are under way in the Central African Republic and Israel, and other trials are planned.

Rhesus rotavirus vaccines. A trial in Sweden showed high efficacy; however, the vaccine caused fever in 79% of the children. High efficacy, but with fewer side effects, was also found in a study in Venezuela where there was a high prevalence of cases due to serotype 3, with which RRV-1 is closely related. In other studies in which serotype 1 was the most common cause of rotavirus diarrhoea, the vaccine was not as efficacious.

Bovine-human and rhesus-human reassortant rotavirus vaccines. According to the preliminary results of efficacy studies, a rhesus-human serotype 1 reassortant apparently confers a high degree of protection against serotype 1 disease. A combined rhesus-human reassortant rotavirus vaccine has been prepared by mixing together the rhesus-human viruses for serotypes 1, 2, and 4, and the rhesus rotavirus (for serotype 3). A potential problem with a combined vaccine is that the components may interfere with each other, resulting in poorer responses to the individual serotypes than would be observed after vaccination with single-serotype vaccines. Better immune responses may be achieved by giving multiple doses or by increasing the amount of virus in each dose. The vaccine is being tested for efficacy in Peru and the USA.

Nursery strain vaccines. The candidate vaccine M37 is currently being tested for safety and immunogenicity in volunteers. The rationale for using a naturally attenuated human rotavirus as a vaccine is based on observations that 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 caused by fully virulent rotaviruses.

Research priorities

The CDD Programme regards the development of an effective rotavirus vaccine as a high priority, and is continuing

to support efficacy trials of potential vaccines in developing countries. Ideally, the vaccine should :

- induce substantial, long-lasting protection against rotavirus diarrhoea in young children following a single oral dose, and
- be administered at the age of 2-3 months (although the disease is most severe in age group 6-24 months, some causes occur in much younger infants in the developing countries).

It is possible that, whatever the vaccine, multiple doses will be required for maximum efficacy. In such case, it would be important to be able to give rotavirus vaccine simultaneously with oral poliovirus vaccine (OPV) in national expanded programmes in immunization (EPI). The CDD Programme is currently supporting research in Thailand to investigate whether rhesus-human rotavirus and OPV can be given in combination without causing interference with the "take" of the OPV. Another important research question is whether breast-feeding interferes with the take of oral rotavirus vaccine.

The CDD Programme is also providing 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 in the near future.

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Vitamin A and Diarrhoea

Vitamin A deficiency results, primarily, from inadequate dietary intake of vitamin A. Its commonly known clinical manifestations are progressive eye signs and visual impairment, grouped under the term xerophthalmia, but recent studies have indicated that it may lead to an increased risk of morbidity, as well as mortality, from diarrhoeal and respiratory infections in infancy and childhood.

Incidence. Information on incidence and prevalence rates of vitamin A deficiency is scarce. It has been estimated, based on extrapolation from community surveys, that 10 million new cases of xerophthalmia occur per year worldwide, and that over 500 000 of these result in blindness (PATH, 1985). Prevalence rates for mild xerophthalmia in pre-school-age children rarely exceed 10% (Tielsch & Sommer, 1984), the rate for more severe cases being usually well below 0.5 per cent.

Biological role. Vitamin A status has been shown in animal studies to be a deter-