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Interventions for the control of diarrhoeal diseases among young children: rotavirus and cholera immunization*

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The potential effects of rotavirus and cholera immunization (with an improved vaccine) on diarrhoea morbidity and mortality among young children are reviewed using data from field studies and theoretical calculations. In developing countries rotavirus may be responsible for about 6% of all diarrhoea episodes and 20% of all diarrhoea deaths in children under 5 years of age. In industrial countries these proportions may be higher. Rotavirus immunization may reduce overall diarrhoea morbidity rates by 2–3% and diarrhoea mortality rates by 6–10% among children under 5 years of age in developing countries, depending on vaccine efficacy and programme coverage. The impact of improved cholera vaccines depends on the prominence of cholera as a cause of diarrhoea, and this varies greatly from country to country. Taking the extreme example of Bangladesh, where cholera is endemic and may account for about 0.4% of all diarrhoea episodes and 8% of all diarrhoea deaths in children under 5 years of age, cholera immunization might reduce overall diarrhoea morbidity rates by 0.06–0.13% and diarrhoea mortality rates by 1–2% among these children. The similar incidence rates in industrial and developing countries suggest that rotavirus diarrhoea may not be controlled by improvements in water supply, sanitation, or hygiene. Control may depend upon the widespread use of an effective vaccine.

Over recent years substantial resources have been invested into research to develop a vaccine against rotavirus diarrhoea and an improved vaccine against cholera. Rapid progress has been made and field trials of candidate vaccines against these diseases are under way. It is timely, therefore, to examine the potential role of rotavirus and cholera immunization in national programmes to reduce diarrhoea morbidity and mortality among children under 5 years of age. In this review we do not examine the potential benefits of rotavirus and cholera immunization that might extend to older children, adults, or especially susceptible or at-risk groups, nor do we consider the potential role of cholera immunization in epidemic control. Several recent reviews on the epidemiology and control of rotavirus diarrhoea (*41*, *83*) and cholera (*13*, *16*, *17*, *33*, *46*) provide a useful background to this more focused analysis. This paper is the seventh in a series of reviews of potential anti-diarrhoea interventions published in the *Bulletin of the World Health Organization* (*1*, *15*, *18–22*).

EFFECTIVENESS

For rotavirus or cholera immunization to be an effective intervention for the control of diarrhoeal diseases it must be true that:

either

a considerable proportion of diarrhoea morbidity or mortality in young children is caused by rotavirus or *Vibrio cholerae* O1	*hypothesis 1*

and

vaccines against rotavirus, *V. cholerae* O1, or their products have the potential to reduce morbidity rates or mortality rates or the severity of diarrhoea caused by these organisms	*hypothesis 2*

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or

rotavirus or cholera immunization (when effective vaccines are available) has the potential to reduce overall diarrhoea morbidity rates or mortality rates or the severity of diarrhoea in young children	*hypothesis 3*

The potential effectiveness of rotavirus or cholera immunization in the control of diarrhoeal diseases would be suggested by a demonstration either of the correctness of hypotheses 1 and 2, or of the correctness of hypothesis 3. The evidence for and against the three hypotheses is examined below.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children is caused by rotavirus or* V. cholerae *O1.*

Rotavirus

Rotavirus-associated morbidity. We have located in the literature only 7 prospective, community-based studies that have assessed the importance of rotavirus diarrhoea among children in the community (Table 1). Four studies (*6, 7, 31, 49*) report the incidence rates of rotavirus-associated diarrhoea and rotavirus isolation rates, and three others (*30, 53, 68*) give only the isolation rates. Multiple infections were common in all the studies: other enteric pathogens were detected in up to half of all episodes of rotavirus-associated diarrhoea. The data in Table 1, as far as possible, refer only to episodes where rotavirus was the sole recognized enteric pathogen. In some studies, stools were not examined for some common pathogens such as enterotoxigenic *Escherichia coli* (ETEC) (*49*) and *Campylobacter jejuni* (*6, 7, 31, 49, 68*).

Recorded incidence rates of rotavirus-associated diarrhoea ranged from 0.2 to 0.8 episodes per child per year. Incidence rates were low in children aged 0–5 months, reached a peak in children aged 6–11 months, remained high in children aged 12–23 months, and dropped to low levels thereafter. It is notable that the incidence rate of rotavirus-associated diarrhoea found in the study from Winnipeg, Canada (0.3 episodes per child per year among children aged 0–23 months) (*31*) was similar to the rate reported from Bangladesh in the same age group (0.4 episodes per child per year) (*6*). The incidence of all diarrhoeas, however, was lower in Canada and the proportion of diarrhoea episodes associated with rotavirus was accordingly higher.

We estimate that, in developing countries, rotavirus accounts for about 8% of all diarrhoea episodes in children aged 0–5 months, 10% in children aged 6–23 months, 1% in children aged 24–59 months, and 6% in children under 5 years. These figures are used in the computations below. In a particular country, where more reliable age-specific proportions are available, other figures may be substituted. It will be noted that the incidence rate of rotavirus-associated diarrhoea found in different studies (Table 1) did not vary as much as the incidence

Table 1. Community-based studies of rotavirus-associated diarrhoea

Country	Age (months)	Number of person-years	Number of episodes of:		Proportion of diarrhoea episodes associated only with rotavirus (%)	Reference
			Diarrhoea from all causes	Diarrhoea associated with rotavirus alone		
Bangladesh	0–23	112	377 (3.4)[a]	43 (0.4)	11	*6*
	24–59	112	243 (2.2)	0	0	
Bangladesh	2–23	77	497 (6.4)	32 (0.4)	6	*7*
	24–59	92	444 (4.8)	3 (0.03)	0.7	
Brazil	All ages	765	1097 (1.4)	– (0.15)[b]	11	*30*
Canada	0–23	139	165 (1.2)	40 (0.3)	24	*31*
El Salvador	0–35	–	–	–	7	*68*
Guatemala	0–35	132	1050 (7.9)	109 (0.8)	10	*49*
USA	0–23	–	–	–	10	*53*

[a] Figures in parentheses are the number of episodes per person-year.
[b] Estimated incidence rate.

rate of diarrhoea from all causes. The proportion of all diarrhoea episodes attributable to rotavirus is likely to be greater than our estimate in settings where the incidence rate of diarrhoea from all causes is low, and smaller where the incidence rate of diarrhoea from all causes is high.

To assess the impact of rotavirus diarrhoea on the health services, rotavirus isolation rates reported in 77 hospital-based studies from 37 countries have been reviewed.[a] Caution is necessary in the interpretation and comparison of these rates. Different diagnostic methods were used for the detection of rotavirus and the findings were reported in different age groups. Many studies did not span an entire year, and large seasonal fluctuations in rotavirus isolation rates are well documented. Bearing these factors in mind, we see that in nearly all the studies rotavirus was the single most common enteric pathogen identified in children attending hospital for the treatment of diarrhoea.

In studies of hospitalized children that lasted at least one year, the median isolation rate was 34% (range, 12–71%). The median rate was similar in studies from developing and industrial countries (respectively, 35% and 34%; with ranges, 16–71% and 12–65%). In general, the age-specific isolation rates were low in infants aged 0–5 months, reached a peak in infants aged 6–11 months, remained high in children aged 12–23 months, and dropped rapidly thereafter. Because a considerable proportion of all diarrhoea cases that are admitted to hospital occur in infants, most rotavirus-positive cases were found in this age group. Indeed, in a number of studies, large numbers of rotavirus-positive cases were found among hospitalized children aged 0–5 months, despite low isolation rates in this age group. Among the 19 studies that reported these data the proportion of all rotavirus-positive cases among hospitalized children aged 0–23 months that occurred in the first 6 months of life ranged from 4% (*62*) to 73% (*57*), with a median of 35%. We have located only 5 studies in which the data are examined in narrower age-bands. In these studies, the proportion of all rotavirus-positive cases among infants (0–11 months) admitted to hospital for diarrhoea that occurred in the first 3 months of life ranged from 11% to 37%, with a median of 26% (*2*, *36*, *57*, *58*, *74*).

Studies conducted among children treated for diarrhoea on an outpatient basis or in short-stay rehydration units reported lower rotavirus isolation rates. In studies that lasted at least one year the median rate found among these patients was 28% (range, 10–49%). Where outpatients and inpatients were examined concurrently the rates were found to be lower among outpatients. This finding is difficult to interpret because the two groups of patients were not strictly comparable in all studies (*8*).

Two studies have assessed population-based hospital case rates. In Washington, DC, USA (*66*), a population of about 29 000 children aged 0–14 years was defined whose primary health care was provided by a health maintenance organization. Over a period of 27 months, 38 children from the health maintenance organization were admitted to hospital for the treatment of diarrhoea. Rotavirus was recovered from 60% of cases. Yearly population-based hospitalization rates for rotavirus-associated diarrhoea were 3.7 per thousand in infants and 2.2 per thousand in children aged 12–23 months, and dropped to 0.2 per thousand in children aged 24–59 months. Hospitalization for rotavirus-associated diarrhoea was not observed after 5 years of age. In a district of Copenhagen County, Denmark (*32*), rotavirus was detected among 37% of children aged 0–14 years admitted to the district hospital because of diarrhoea over a 12-month period. Yearly population-based hospitalization rates for rotavirus-associated diarrhoea were 5.4 per thousand in infants, 4.1 per thousand in children aged 12–23 months, and 1.4 per thousand in children aged 24–47 months. No admissions for rotavirus-associated diarrhoea were observed in children over 4 years of age.

Thus, despite low isolation rates in the community, rotavirus is responsible for about one-third of diarrhoea episodes that require hospital admission among young children, suggesting that diarrhoea caused by rotavirus is of above-average severity. Prospective studies of diarrhoea episodes acquired in the community provide evidence that rotavirus-associated diarrhoea leads more frequently to dehydration and attendance at a health facility than all other diarrhoeas in the same age group (*6*, *7*, *49*, *81*). In these studies, although the incidence of rotavirus-associated diarrhoea was low, rotavirus was responsible for about half of all dehydrating episodes.

Rotavirus-associated mortality. Rotavirus-associated diarrhoea may therefore take on severe forms and is clearly responsible for a proportion of all deaths due to diarrhoea. Diarrhoea mortality rates are low in industrial countries, yet fatal episodes of diarrhoea associated with rotavirus have been described. Over a 5-year period, 21 deaths associated with rotavirus were recorded among young children in Toronto, Canada (*10*). The severe course of the diarrhoea was highlighted by the fact that all deaths occurred within 3 days of onset of symptoms and that the parents of 16 of the children had had some contact with a physician during the course of their child's illness. Similarly, in the course of an explosive

[a] Tabulated data and sources are available on request from R.G.F.

Table 2. The proportion of diarrhoea deaths in the first five years of life associated with rotavirus in developing countries, based on various assumptions

Age (months)	Distribution of 100 diarrhoea deaths[a]	Proportion that are acute watery diarrhoea deaths[b] (%)	Number of acute watery diarrhoea deaths	Proportion of acute watery diarrhoea deaths that are associated with rotavirus[c] (%)	Number of rotavirus-associated diarrhoea deaths
0–5	29	60	17	20	3.4
6–11	16	60	10	50	5.0
12–23	35	60	21	50	10.5
24–59	20	50	10	10	1.0
0–59	100		58		19.9

[a] These calculations assume that diarrhoea mortality rates are 20 per 1000 per year in the 0–11-month age group, 18 per 1000 per year in the 12–23-month age group, and 4 per 1000 per year in the 24–59-month age group (derived from ref. *67*). Overall mortality rates vary greatly from country to country. Values adopted here are: infant mortality rate 120 per 1000 live births, mortality rate 40 per 1000 per year in the 12–23-month age group, and 10 per 1000 per year in the 24–59-month age group. It is further assumed that 66% of infant diarrhoea deaths occur in the first 6 months of life (the median figure from 8 studies).

[b] Estimates based on data from Oberle et al. (*60*) and Chen et al. (*12*).

[c] Estimates based on data in the text on the proportion of hospitalized diarrhoea cases and the proportion of dehydrated diarrhoea cases seen in the community, which were associated with rotavirus.

outbreak of 3439 reported cases of rotavirus-associated diarrhoea in an isolated Pacific island group (*24*), 7 children died, all from dehydration due to diarrhoea and vomiting and all within the first 4 days of illness.

For developing countries, where mortality due to diarrhoea is considerable (*67*), we have theoretically derived the proportion of all diarrhoeal deaths that are associated with rotavirus. On the basis of the calculations set out in Table 2, rotavirus may, in developing countries, account for about 12% of all diarrhoea mortality in infants aged 0–5 months, 30% in children aged 6–23 months, 5% in children aged 24–59 months, and 20% in children under 5 years.

Cholera

The prominence of cholera varies greatly from country to country. In this review we consider the extreme case of Bangladesh, where cholera is endemic and has been studied intensively over a number of years.

Cholera morbidity in Bangladesh. Table 3 summarizes data from six studies from Dhaka and Matlab

Table 3. Community-based studies of cholera in Bangladesh

Place	Dates of study	Age groups	Cholera incidence rate (episodes per 1000 per year)	Proportion of diarrhoea episodes associated with *V. cholerae* 01 (%)	Reference
Dhaka	Sep. 75 to Dec. 76	All ages	3	0.7	*54*
Matlab	Nov. 63 to June 66	0–59 months All ages	10 3	– 0.7	*50*
Matlab	July 69 to June 70	0–11 months 12–59 months All ages	0 9 3	– – –	*56*
Matlab	Dec. 77 to Nov. 78	0–23 months 2–9 years	– –	< 2[a] < 3[a]	*6*
Matlab	March 78 to March 79	2–59 months	–	0.3	*7*

[a] This proportion refers to all infections with enteric pathogens other than ETEC, *Shigella* and rotavirus, and to mixed infections.

Table 4. *Vibrio cholerae* isolation rates among diarrhoea cases in hospitals in Bangladesh

Place	Dates of study	Type of patient	Age groups	*V. cholerae* 01 isolation rates (%)	Reference
Dhaka	July 64 to June 66	Inpatients	All ages	40	*48*
Dhaka	Dec. 79 to Nov. 80	Outpatients and inpatients	0–11 months 12–59 months All ages	1 6 6	*69*
Matlab	Nov. 63 to June 66	Inpatients	All ages	25	*50*
Matlab	July 69 to June 70	Outpatients and inpatients	All ages	27	*56*
Matlab	Jan. 75 to Dec. 75	Inpatients	0–11 months 12–59 months All ages	1 27 28	*60*
Matlab	Feb. 77 to Jan. 79	Outpatients and inpatients	0–23 months 2–9 years All ages	2 31 13	*5*

in which surveillance of cholera was conducted in the community. Three studies recorded cholera incidence rates, which were very low at 3 episodes per thousand per year. Rates were highest in children aged 12–59 months and lowest in infants. Overall, the proportion of all diarrhoea episodes associated with *V. cholerae* O1 was less than 1%. For the computations that follow it will be assumed that, in Bangladesh, cholera accounts for 0.2% of diarrhoea episodes in children under 2 years of age, 0.6% in children aged 24–59 months, and 0.4% in children under 5 years of age.

Table 4 lists the *V. cholerae* O1 isolation rates reported in hospital-based studies conducted in Dhaka and Matlab. The proportion of diarrhoea episodes associated with *V. cholerae* ranged from 6% to 40% according to the hospital and the year of study. We cannot tell from these data whether the *V. cholerae* isolation rates were lower in outpatients than inpatients, but there is evidence to suggest that patients presenting to hospital with cholera have a greater risk of moderate or severe dehydration requiring inpatient therapy than other patients (*5*, *69*). *V. cholerae* isolation rates were low in the first 2 years of life and reached a peak in children over 5 years of age.

Three studies have assessed population-based hospital case rates. Martin et al. (*48*) analysed the admissions to the Dhaka diarrhoeal diseases hospital between July 1964 and June 1966 and found a hospitalization rate for classical cholera of 0.4 admissions per thousand population per year with a peak rate of 0.7 per thousand per year in children below 5 years of age. The hospitalization rate for cholera (mainly eltor) in the same hospital was 1.7 admissions per thousand population in 1974 and 1.4 in 1975 (*44*), with the highest rates in children aged 2–9 years. Glass et al. (*25*) examined the attendance at Matlab hospital for the 15-year period between January 1966 and December 1980. In that period, *V. cholerae* O1 was isolated from 7141 of the more than 50 000 patients who presented to the hospital with diarrhoea. From 1966 to 1973, 97% of the *V. cholerae* isolates were of the classical biotype. The eltor biotype was first identified in the Matlab area in 1969 and was the only biotype present from 1973 to the end of the study. There was great year-to-year variation in the number of cases, particularly during the eltor period. The overall attendance rate for cholera in the classical period was 1.3 patients per thousand per year and in the eltor period 2.9 patients per thousand per year, with the highest rates in children aged 2–9 years.

Cholera, then, presents an extreme case of a diarrhoeal disease that is rare in the community but may nevertheless place a considerable burden on the health services. In a study conducted in Matlab (*50*), cholera accounted for only 0.7% of all diarrhoea episodes acquired in the community, yet 25% of all hospital admissions for treatment of diarrhoea during the same period were associated with *V. cholerae*. Other data from Bangladesh indicate that the proportion of cholera cases that require hospitalization varies between 23% and 74% and is higher for classical than for eltor cholera (*3*, *42–44*, *61*, *78*, *79*). These findings support the view that cholera is an unusually severe disease.

Cholera mortality in Bangladesh. There are no data on cholera mortality rates in Bangladesh. In the study areas, deaths due to acute diarrhoea are very rare in hospital and those that occur in the community have no etiological diagnosis. For the computations that follow it will be assumed that, in Bangladesh, cholera accounts for 5% of diarrhoea deaths in children under 2 years of age, 20% in children aged 24–59 months, and 8% in children under 5 years of age. These estimates are based on data summarized in Table 4 on the proportion of hospitalized diarrhoea cases that is associated with *V. cholerae* in different age groups in Bangladesh.

Hypothesis 2. *Vaccines against rotavirus,* V. cholerae *O1, or their products have the potential to reduce morbidity rates or mortality rates or the severity of diarrhoea caused by these organisms.*

Rotavirus vaccines. Mechanisms of immunity to rotavirus and advances in rotavirus vaccine development have recently been reviewed (*41*). To date, research has focused on the development of live attenuated human rotavirus vaccines, live rotavirus vaccines from animal hosts, and live attenuated reassortant vaccines, for delivery by the oral route. Each of the four recognized human rotavirus serotypes has now been successfully cultivated (*85*), and live attenuated human rotavirus vaccines can be prepared by conventional tissue-culture methods. A tissue-culture-adapted mutant of the Wa strain of human rotavirus (*82*) is under evaluation for immunogenicity and safety in susceptible volunteers (*39, 40*). Cold-adapted strains of human rotavirus are also under investigation as attenuated human rotavirus vaccines (Kono, personal communication, 1984). In addition, strains obtained from asymptomatically-infected neonates are under study as naturally attenuated strains (Bishop, personal communication, 1984). These strains are promising candidate vaccines in view of the evidence that immunity induced by neonatal infection prevents the development of clinically severe illness for at least the first 3 years of life (although it does not protect against infection) (*4*).

Another approach is to prepare vaccine material from animal rotavirus strains that are antigenically related to human rotavirus (*35, 38, 84*). Bovine rotaviruses grow well in tissue culture (*51*) and have been used to prepare candidate vaccines. The feasibility of this approach was demonstrated in experimental studies in animals (*80, 86, 88*). A rotavirus vaccine of bovine origin (strain RIT 4237) was shown to be immunogenic and safe in young children (*75*) and a field trial in a group of Finnish children aged 8–11 months using one dose of vaccine of high titre ($10^{8.1}$TCID$_{50}$) showed a protective efficacy of 50% for all rotavirus-associated diarrhoea and of 88% for rotavirus-associated diarrhoea lasting more than 24 hours (*76*). In a subsequent trial in which 2 doses of vaccine were given one month apart to Finnish children aged 6–12 months, vaccine efficacy was found to be 58% for all rotavirus-associated diarrhoea and 82% for rotavirus-associated diarrhoea that was clinically significant (Vesikari, personal communication, 1984). Infants who seroconverted appeared to have the highest level of protection, but protection was also observed in infants who did not seroconvert. Seroconversion rates may be improved by giving a milk feed (infant formula or diluted cow's milk) immediately before and after vaccination (*77*). Further field trials with this vaccine are under way in Peru and the Gambia. Another promising candidate vaccine is a rhesus rotavirus strain (*70, 84*) which has been tested for immunogenicity and safety in human volunteers and is now under field trial in the USA. Finally, reassortant viruses have been recovered from mixed tissue-culture infection (*27–29*), opening the way to the development of a live attenuated reassortant rotavirus vaccine.

In conclusion, good progress has been made in the development of candidate rotavirus vaccines using different approaches. Further candidate vaccines may be developed using recombinant DNA technology. Field trials of rotavirus vaccines of bovine and simian origin are under way. These vaccines appear to prevent or modify rotavirus-associated illness. Studies in progress will assess the duration of protection induced by these vaccines and their strain specificity. The optimal age of vaccination must be determined, bearing in mind the need to vaccinate infants in the first 6 months of life, and the possible interference of breast-feeding or of residual maternal antibodies on seroconversion rates. Information is also needed on the number of doses required in order to determine the most appropriate vaccination schedule, with regard to production and delivery costs and eventual combination with oral polio vaccine. Other issues to be addressed concern the stability of the rotavirus vaccine, its cold-chain requirements, and its possible interaction with oral polio vaccine.

Cholera vaccines. Advances in cholera vaccine development have recently been reviewed (*46*). The ideal antigenic composition of an effective oral cholera vaccine is not at present known (*13*) and work is under way to identify the major protective somatic and toxin-derived antigens. The only vaccines currently available for general use are killed whole-cell vaccines for parenteral administration. Field trials with these vaccines have established that induced protection is moderate (50–70%) and of short duration (3–6 months), depending on the age group, quality of the vaccines, and dosage schedule

(*23*). Current research efforts are centred on the development of a cholera vaccine for oral use, in order to stimulate local intestinal immunity and to avoid a possible suppressive effect of parenteral immunization on local antigenic stimulation (*64*, *87*). Whole-cell vaccines taken orally afford some (56%) degree of protection against experimental cholera and reduce the severity of diarrhoea in ill volunteers (*11*; Levine, personal communication, 1984). A whole-cell vaccine for oral use is currently under field trial in Bangladesh. Another killed oral vaccine has been prepared by ultrafiltration of the culture supernatant of two eltor strains of *V. cholerae* O1. Results from a field trial in Zaire suggest that this vaccine may have protective properties against natural disease.[b]

The immunogenicity and efficacy of toxin derivatives have also been evaluated. Field trials of parenterally administered toxoids, consisting of purified cholera toxin inactivated with either formaldehyde or glutaraldehyde, have demonstrated slight or no protection against cholera (*14*, *59*). In volunteers, large, multiple oral doses of purified toxoid are safe and immunogenic but have failed to provide protection against experimental challenge (*45*). Procholeragenoid, a heat-induced aggregate of cholera toxin (*46*) and the purified B subunit of cholera toxin (*26*, *72*) are safe and immunogenic in volunteers but their protective effects have not yet been reported.

Animal studies have shown that antibacterial and antitoxic intestinal antibodies are synergistically protective (*63*, *65*, *71*), suggesting that a vaccine prepared from a combination of somatic and toxin-derived antigens holds promise. One approach is to develop attenuated *V. cholerae* strains for use as oral vaccines. Studies have been carried out on Texas Star-SR, an attenuated strain derived by chemical mutagenesis from an eltor Ogawa organism (*34*). Texas Star-SR produces the B subunit of cholera toxin but no detectable A subunit. In US volunteers it was shown to provide a moderate (61%) degree of protection against experimental challenge with *V. cholerae* and to reduce the stool volume in ill vaccinees (*47*). Unfortunately, 24% of vaccinees had mild or moderate diarrhoea. Of further concern is the fact that the precise genetic lesion responsible for the inability of the strain to elaborate cholera toxin is unknown, and reversion is theoretically possible.

Recombinant DNA techniques have been applied to develop attenuated *V. cholerae* oral vaccine strains incapable of genetic reversion (*37*, *52*). Precise deletions of the genes encoding both the A and B subunits of cholera toxin have produced a strain (JBK-70) that protects volunteers from subsequent challenge to a degree (89%) similar to recovery from the disease (*46*). This strain, however, was also associated with diarrhoea in an unacceptable proportion of recipients. Research is under way to identify the factors responsible for the observed side-effects.

Another approach is to prepare an oral killed vaccine containing a combination of somatic and toxin-derived antigens. Studies in volunteers of vaccines prepared from killed whole-cell vibrio combined with procholeragenoid or glutaraldehyde-treated toxoid have demonstrated complete safety and protective efficacy rates of 27% (with procholeragenoid) and 67% (with toxoid) (*46*). A combined B subunit and killed whole-cell oral vaccine has been shown to be safe in volunteers in Bangladesh and Sweden, and capable of inducing in Bangladeshi volunteers a local immunological response comparable to that evoked by the disease (*73*). Subsequent challenge studies among US volunteers demonstrated a vaccine efficacy of 64% and complete protection against severe disease (*46*). Field trials of the combined B subunit/whole-cell vaccine and whole-cell vaccine alone are in progress in Bangladesh to determine the protective efficacy of the vaccines and the duration of protection in an endemic area. A number of issues remain unresolved, as with rotavirus vaccine, concerning especially the influence of age, breast-feeding practices, and residual maternal antibodies on protection.

Hypothesis 3. *Rotavirus or cholera immunization (when effective vaccines are available) has the potential to reduce overall diarrhoea morbidity rates or mortality rates or the severity of diarrhoea in young children.*

At present, the only approach to assessing hypothesis 3 is a theoretical one using information computed during the assessment of hypotheses 1 and 2.

Rotavirus immunization. The potential impact of rotavirus immunization on overall diarrhoea rates in children under 5 years will depend upon the age of immunization, vaccine efficacy, and programme coverage. The recommended vaccination schedule will be determined when data are obtained on dose requirements, the effect of breast-feeding and residual maternal antibodies, and the effect of interaction with antigens delivered in the context of the Expanded Programme on Immunization (EPI). The goal of rotavirus immunization programmes will be to vaccinate children as early as possible, but operational and immunological factors may prevent the achievement of full immunization before 6 months of age. Field trials of the RIT 4237 rotavirus vaccine in Finland have shown efficacies of 50–58%

[b] BWANGA, M. [First controlled trials of oral anticholera vaccine during a cholera epidemic in the zone of Matemba – Nkulu (Shaba-Zaire).] *Bulletin de la Société de Pathologie exotique*, 77: 13–16 (1984) (in French).

Table 5. Maximum impact of rotavirus immunization on diarrhoea morbidity and mortality rates among children under 5 years of age in developing countries, assuming 100% vaccine efficacy, 100% programme coverage, and an average age of full immunization of 6 months[a]

Age (months)	Proportion of diarrhoea episodes		Proportion of diarrhoea deaths	
	Caused by rotavirus[b] (%)	Averted by rotavirus immunization (%)	Caused by rotavirus[c] (%)	Averted by rotavirus immunization (%)
0-5	8	0[d]	12	0[d]
6-23	10	10	30	30
24-59	1	1	5	5
0-59	6	5[e]	20	16[f]

[a] The computed proportions of episodes and deaths averted are directly proportional to the vaccine efficacy and the programme coverage, and thus the effects of different values for these parameters may be readily computed.

[b] See text.

[c] See Table 2.

[d] Average age of full immunization assumed to be 6 months.

[e] These calculations assume that diarrhoea morbidity rates are 3 per child per year in the 0-5-month age group, 4 per child per year in the 6-11-month age group, 4 per child per year in the 12-17-month age group, 3 per child per year in the 18-23-month age group, and 2 per child per year in the 24-59-month age group (derived from ref. *67*).

[f] Based on age-specific diarrhoea mortality rates given in footnote *a* to Table 2.

against all rotavirus-associated diarrhoea and 82-88% against rotavirus-associated diarrhoea of clinical significance in children aged 6-12 months (*76*; Vesikari, personal communication, 1984). In an ongoing immunization programme aimed at younger children the efficacy rates may be lower. An efficacy of rotavirus vaccine of 80% is assumed here. The proportion of children who would receive the vaccine depends on programme coverage. Three coverage figures are adopted here (45%, 60% and 75%), bearing in mind that these figures are not now being achieved in countries with limited immunization programmes, but may be expected in countries committed to the EPI and with a national programme built up over several years.

The proportions of all diarrhoea cases and deaths averted by rotavirus immunization are directly proportional to both vaccine efficacy and programme coverage, but not to age of immunization. Table 5 presents computations of the maximum impact of rotavirus immunization at 6 months of age on overall diarrhoea morbidity and mortality rates in developing countries, assuming 100% efficacy and 100% programme coverage. Under these ideal conditions, rotavirus immunization might reduce diarrhoea morbidity rates by 5% and diarrhoea mortality rates by 16% among children under 5 years of age. With a vaccine having 80% efficacy and levels of coverage of 45%, 60% and 75%, rotavirus immunization might reduce diarrhoea morbidity rates, respectively, by 1.8%, 2.4% and 3.0% and diarrhoea mortality rates by 6%, 8% and 10%. If immunization against rotavirus is completed at a younger age, say 3 months, the potential reductions in diarrhoea morbidity and mortality rates may only be marginally greater: 1.9-3.3% for morbidity and 6-11% for mortality (assuming that half of the diarrhoea episodes and deaths that occur in the first 6 months of life occur in the first 3 months of life; calculations not shown). The proportional impact of rotavirus immunization on diarrhoea morbidity rates among young children in industrial countries is likely to be greater because the proportion of diarrhoea episodes attributable to rotavirus in those countries is higher. The difference may not be marked for reductions in mortality rates, however, judging from the similar isolation rates for rotavirus found among young children admitted to hospital for severe diarrhoea in developing and industrial countries.

Two major hospital-based studies have been examined to assess the potential reduction in hospital reporting rates for diarrhoea that might be achieved by a rotavirus immunization programme. Data from a one-year study of patients reporting to the diarrhoeal diseases hospital in Dhaka, Bangladesh (*69*) suggest that rotavirus immunization might have averted 7-12% of attendances for diarrhoea to the hospital among children under 5 years of age. Data from an 8-year study of inpatients in a children's hospital in Washington, DC, USA (*9*) suggest that

Table 6. Maximum impact of cholera immunization on diarrhoea morbidity and mortality rates among children under 5 years of age in Bangladesh, assuming 100% vaccine efficacy, 100% programme coverage, and an average age of full immunization of 2 years[a]

Age (months)	Proportion of diarrhoea episodes		Proportion of diarrhoea deaths	
	Caused by *V. cholerae* 01[b] (%)	Averted by cholera immunization (%)	Caused by *V. cholerae* 01[c] (%)	Averted by cholera immunization (%)
0–23	0.2	0[d]	5	0[d]
24–59	0.6	0.6	20	20
0–59	0.4	0.3[e]	8	4[f]

[a] The computed proportions of episodes and deaths averted are directly proportional to the vaccine efficacy and the programme coverage and thus the effects of different values for these parameters may be readily computed.

[b] See text.

[c] See text.

[d] Average age of full immunization assumed to be 2 years.

[e] Based on age-specific diarrhoea morbidity rates given in footnote *e* to Table 5.

[f] Based on age-specific diarrhoea mortality rates given in footnote *a* to Table 2.

rotavirus immunization might have averted 9–14% of admissions for diarrhoea over that period. These calculations assume a vaccine efficacy of 80%, coverage of 45–75%, and an average age of full immunization of 6 months.

Cholera immunization. In Bangladesh, cholera may account for about 0.4% of all diarrhoea morbidity and 8% of all diarrhoea mortality in children under 5 years of age. Again, values for the efficacy of a new cholera vaccine have to be assumed. A protective efficacy of 64% has been found in challenge studies among adult US volunteers receiving 3 oral doses of combined B subunit/whole-cell vaccine (*46*). A value for the efficacy of a new cholera vaccine of 70% is assumed here. The vaccination schedule for this vaccine is unknown at present. If a new vaccine does not give long-lasting protection, the optimal age of administration may be around 24 months, before the peak in age-specific cholera incidence rate. In this case it will not be delivered within the existing EPI and so coverage may be low. Three coverage figures are adopted here: 30%, 45% and 60%.

Table 6 presents computations of the maximum impact of cholera immunization at 2 years of age on overall diarrhoea morbidity and mortality rates in Bangladesh, assuming 100% vaccine efficacy and 100% programme coverage. Under these ideal conditions, cholera immunization might reduce overall diarrhoea morbidity rates by 0.3% and diarrhoea mortality rates by 4% among children under 5 years of age in Bangladesh. With a vaccine having 70% efficacy and levels of coverage of 30%, 45% and 60%, cholera immunization at 2 years of age might reduce diarrhoea morbidity rates by 0.06%, 0.09% and 0.13% and diarrhoea mortality rates by 0.8%, 1.3% and 1.7%. If immunization against cholera is achieved at a younger age, say 6 months, and accordingly better coverage figures are adopted (45%, 60% and 75%), the potential reductions would be 0.11–0.19% for diarrhoea morbidity rates and 2.1–3.4% for diarrhoea mortality rates (calculations not shown).

In this review, we do not examine the benefits of cholera immunization that might extend to older children and adults in endemic areas if immunity induced by an improved vaccine is long-lasting, nor do we consider the potential role of cholera immunization in epidemic control[c] and in the protection of especially susceptible or at-risk groups. Finally, there are insufficient data to assess the exciting possibility that a vaccine prepared from antigens derived from cholera toxin may induce cross-protection against ETEC (LT-only or LT-ST) diarrhoea.

Cholera immunization may not have a measurable impact on hospital attendance rates for diarrhoea among young children. Data from the hospital-based study in Dhaka cited above (*69*) suggest that cholera immunization might have averted only 0.6–1.2% of attendances for diarrhoea among children under 5 years of age. Among older patients these potential reductions in attendances are 2–4%, assuming repeated vaccinations or long-lasting immunity.

[c] The role of immunization in the prevention and control of cholera epidemics will be considered in another review (Blake and Feachem, under preparation).

These calculations assume a vaccine efficacy of 70%, coverage of 30–60%, and an average age of full immunization of 2 years.

FEASIBILITY

The delivery requirements of the candidate rotavirus and cholera vaccines are at present unknown. The simultaneous administration of rotavirus vaccine with another vaccine currently included in the EPI would facilitate its delivery. Three doses of oral polio vaccine are usually recommended in the first 6 months of life and it is hoped that rotavirus vaccine can be combined with one or all 3 doses of oral polio vaccine without interference with seroconversion to either virus. The cold-chain and handling requirements of rotavirus and oral polio vaccines are likely to be similar. In this optimal case, rotavirus immunization would require few additional inputs for its delivery.

The delivery requirements of cholera vaccine are more speculative. A killed cholera vaccine may prove to be relatively temperature-stable, whereas a live cholera vaccine may have stringent cold-chain requirements. Cholera immunization with an improved vaccine may be indicated in the second year of life and may involve multiple doses. Cholera vaccine would not, in this case, be delivered within the EPI, but would require additional immunization services. The main operational difficulty would be achieving high coverage of children in this older age group. If a new cholera vaccine can induce long-lasting protection, its delivery will be greatly simplified.

Finally, a major constraint on the successful delivery of oral vaccines against both rotavirus diarrhoea and cholera would be the need to protect the vaccine against gastric acidity, in order to assure its safe passage into the small intestine.

COSTS

Rotavirus and improved cholera vaccines are still under development, so the cost estimates must be derived from data on current immunization programmes. In a recent review, Creese (under preparation) has estimated the likely costs of delivering these new vaccines on the basis of data from 9 cost-appraisal studies of immunization programmes in developing countries. Costs depend heavily on the extent to which the new vaccines can be incorporated into an existing immunization programme. The actual vaccine costs for current EPI vaccines account for only a small proportion (around 10%) of total programme costs.

Assuming an optimal delivery strategy for rotavirus immunization, in which a single dose of rotavirus vaccine is administered within an existing EPI programme without increased frequency of contacts, the likely marginal cost is US$ 2 (1982 prices) per fully immunized child. If cholera immunization requires additional contacts because it is targetted at a different age group than the EPI, estimated costs are from US$ 5 (if a single dose is required) to US$ 15 (if three doses are required) per child fully immunized against cholera (1982 prices). It is here assumed that the cost per vaccinated child is independent of the number of children vaccinated, within likely limits.

These cost estimates can be brought together with the effectiveness data computed above in order to calculate the likely cost-effectiveness range of the proposed interventions in developing countries. Two indicators of cost-effectiveness are considered here: cost per case averted and cost per death averted.[d]

For rotavirus immunization at age 6 months with a vaccine having 80% efficacy and a marginal cost of US$ 2 per fully immunized child, the cost-effectiveness figures are:

— US$ 4 (1982 prices) per diarrhoea case averted in a child aged 0–59 months;
— US$ 312 (1982 prices) per diarrhoea death averted in a child aged 0–59 months.

For cholera immunization at age 2 years in Bangladesh with a vaccine having 70% efficacy and a cost of US$ 5–15 per fully immunized child, the cost-effectiveness figures are:

— US$ 183–549 (1982 prices) per diarrhoea case averted in a child aged 0–59 months;
— US$ 3571–10 714 (1982 prices) per diarrhoea death averted in a child aged 0–59 months.

If cholera immunization is achieved at 6 months of age at the marginal cost of US$ 2–6 per fully immunized child, the likely cost-effectiveness of the intervention is greatly improved (cost per case averted US$ 61–183 and cost per death averted US$ 872–2617).

CONCLUSIONS

In developing countries, rotavirus may be responsible for about 6% of all diarrhoea episodes and 20% of all diarrhoea deaths in children under 5 years of age. In industrial countries these proportions may be higher. A theoretical case has been made, based on various assumptions about vaccine efficacy and

[d] The formulae used to calculate these cost-effectiveness figures are available on request from R.G.F.

programme coverage, that rotavirus immunization might reduce overall diarrhoea morbidity by 2–3% and diarrhoea mortality by 6–10% among children under 5 years of age in developing countries.

The impact of improved cholera vaccines depends on the prominence of cholera as a cause of diarrhoea and this varies greatly from country to country. Taking the extreme example of Bangladesh, where cholera may account for about 0.4% of all diarrhoea episodes and 8% of all diarrhoea deaths in children under 5 years of age, cholera immunization might reduce overall diarrhoea morbidity by 0.06–0.13% and diarrhoea mortality by 1–2% among these children, based on various assumptions.

These vaccines are under development and vaccination schedules and delivery requirements are at present unknown. If an immunization programme can incorporate rotavirus vaccine at a marginal cost of US$ 2 (1982 prices) per fully immunized child, the likely cost-effectiveness values for the intervention are US$ 4 per diarrhoea case averted and US$ 312 per diarrhoea death averted in children under 5 years. For cholera immunization which may require additional immunization services at a cost of US$ 15 (1982 prices) per fully immunized child, the likely cost-effectiveness values are US$ 549 per diarrhoea case averted and US$ 10 714 per diarrhoea death averted in children under 5 years. These estimates are extremely tentative and are subject to revision as more is learnt about the epidemiology of rotavirus diarrhoea and cholera, and the features of immunization programmes against these diseases. In areas where more accurate epidemiological and economic data are available other estimates of cost-effectiveness can be computed.

The prominence of rotavirus diarrhoea in industrial countries, and the similar incidence rate in industrial and developing countries, suggest that rotavirus diarrhoea may not be controlled by improvements in water supply, sanitation, or hygiene. Control may depend upon the development, trial, and widespread use of an effective vaccine. It is hoped that rotavirus vaccine can be delivered within existing EPI programmes, and rotavirus immunization may prove to be a cost-effective intervention for national diarrhoeal diseases control programmes.

The cost-effectiveness of cholera immunization, as an intervention to reduce overall diarrhoea morbidity and mortality rates among young children, is more doubtful, even in Bangladesh, although it may have other applications. More data are required on vaccine efficacy and the duration of protection before firmer conclusions can be reached.

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RÉSUMÉ

INTERVENTIONS DANS LE CADRE DE LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES DU JEUNE ENFANT: VACCINATION ANTICHOLÉRIQUE ET VACCINATION CONTRE LES ROTAVIRUS

Cet article est le septième d'une série d'études concernant les interventions susceptibles de réduire la morbidité et la mortalité imputables aux maladies diarrhéiques chez les enfants de moins de cinq ans dans les pays en développement. Nous avons étudié les effets potentiels de la vaccination contre les rotavirus et de la vaccination anticholérique (à l'aide d'un vaccin amélioré) sur la morbidité et la mortalité diarrhéiques, en utilisant des données provenant d'enquêtes de terrain et de calculs théoriques. Dans les pays en développement, les rotavirus sont probablement responsables d'environ 6% de tous les épisodes morbides et de 20% de l'ensemble des décès d'origine diarrhéique chez les enfants de moins de cinq ans. Ces proportions sont peut être plus élevées dans les pays industriels. Les effets potentiels d'une immunisation à l'égard des rotavirus sur le taux général d'atteinte diarrhéique chez les enfants de moins de cinq ans dépendra de l'âge auquel se pratique la vaccination, de l'efficacité du vaccin utilisé et de la couverture assurée par le programme. Avec un vaccin efficace à 80% et un taux de couverture de l'ordre de 45 à 75%, une vaccination contre les rotavirus pratiquée à l'âge de six mois peut diminuer les taux de mortalité diarrhéique de 1,8 à 3,0% et les taux de mortalité de 6 à 10%. Si cette vaccination est pratiquée à un âge moins avancé, par exemple trois mois, le gain sur cette

baisse des taux peut n'avoir qu'une importance marginale: 1,9-3,3% pour la morbidité et 6-11% pour la mortalité.

Les effets d'une amélioration des vaccins anticholériques dépendent du rôle prépondérant du choléra en tant que cause des maladies diarrhéiques — rôle qui varie considérablement d'un pays à l'autre. Au Bangladesh, le choléra est probablement responsable d'environ 0,4% de l'ensemble de la morbidité diarrhéique et de 8% de la totalité des décès d'enfants de moins de cinq ans imputables à ces maladies. Dans le cas particulier, on a supposé que le nouveau vaccin anticholérique était efficace à 70%. Le schéma d'administration utilisé pour ce nouveau vaccin est actuellement inconnu. Lorsqu'un nouveau vaccin ne confère pas de protection durable, l'âge optimal pour son administration se situe aux alentours de 24 mois, c'est-à-dire avant l'apparition du pic d'incidence cholérique spécifique pour cette classe d'âge. En pareil cas, le vaccin ne sera pas administré dans le cadre du PEV existant et, de la sorte, la couverture sera peut-être faible. Avec un vaccin efficace à 70% et un taux de couverture de l'ordre de 30 à 60%, la vaccination anticholérique pratiquée à l'âge de deux ans au Bangladesh pourrait diminuer les taux de morbidité diarrhéique de 0,06 à 0,13% et les taux de mortalité de 0,8 à 1,7%. Si la vaccination anticholérique est pratiquée à un âge moins avancé, par exemple six mois, et si par conséquent une meilleure couverture peut être assurée (45-75%), la réduction potentielle serait de l'ordre de 0,11 à 0,19% pour la morbidité diarrhéique et de 2,1 à 3,4% pour la mortalité.

S'il est possible d'englober dans un programme de vaccination une immunisation à l'égard des rotavirus moyennant un coût marginal de US$2 (prix de 1982) pour la vaccination complète de chaque enfant, le rapport coût-efficacité de cette intervention sera de l'ordre de US$4 pour chaque cas de maladie diarrhéique qu'il a été ainsi possible de prévenir, et de US$312 par décès évité chez les enfants de moins de cinq ans. Pour une vaccination anticholérique qui peut exiger un renforcement des services de vaccination d'un coût s'élevant à US$15 (prix de 1982) pour la vaccination complète de chaque enfant, le rapport coût-efficacité au Bangladesh sera vraisemblablement de US$549 pour chaque cas de maladies diarrhéiques qu'il sera possible de prévenir et de US$10 714 pour chaque décès évité chez les enfants de moins de cinq ans.

L'importance des maladies diarrhéiques à rotavirus dans les pays industriels, et l'analogie de leur taux d'incidence entre pays industriels et pays en développement, suggèrent qu'une amélioration des approvisionnements en eau, de l'assainissement ou de l'hygiène ne suffit peut-être pas pour juguler les affections de ce type. Leur maîtrise dépend sans doute de l'élaboration, de l'essai et de l'utilisation généralisée d'un vaccin efficace. Il est permis de penser qu'un vaccin contre les rotavirus pourrait être administré dans le cadre du Programme élargi de Vaccination et que cette intervention se révélera intéressante, sur le plan du rapport coût-efficacité, pour les programmes nationaux de lutte contre les maladies diarrhéiques. La vaccination anticholérique, en revanche, peut exiger un renforcement des services de vaccination entraînant des coûts élevés pour un faible taux de couverture. Même au Bangladesh, le rapport coût-efficacité des interventions en faveur d'une diminution de la morbidité et de la mortalité diarrhéiques chez les jeunes enfants ne sera peut-être pas positif, bien que d'autres applications puissent être envisagées dans ce cadre.

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