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Interventions for the control of diarrhoeal diseases among young children: chemoprophylaxis*

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A number of situations place young children at increased risk of diarrhoea. Among these, the best documented in developing countries is contact with a diarrhoea case in a family or household. The most common application of chemoprophylaxis in developing countries is to prevent cholera or shigellosis among household contacts of known cases. There is little evidence that chemoprophylaxis is effective in reducing diarrhoea morbidity and mortality, except perhaps in travellers. Theoretical calculations in this paper (based on optimistic assumptions) suggest that chemoprophylaxis of household contacts of known cholera cases in Bangladesh might reduce overall diarrhoea incidence rates in children under 5 years of age by 0.02–0.06% and diarrhoea mortality rates by 0.4–1.2%. Chemoprophylaxis of household contacts of known shigellosis cases might reduce overall diarrhoea incidence rates by 0.15–0.35% and diarrhoea mortality rates by 0.3–0.7% in the same age group. The correct identification of index cases of cholera and shigellosis, followed by the rapid distribution of drugs to their household contacts, requires skills and resources that are scarce in the developing countries. Chemoprophylaxis can contribute to the widespread emergence and dissemination of antimicrobial resistance. The available evidence suggests that chemoprophylaxis is not feasible in many settings and that, even if successfully implemented, it is not a cost-effective intervention for national diarrhoeal diseases control programmes.

The main application of drugs in the control of diarrhoeal diseases is in the treatment of selected cases in order to reduce the duration and severity of illness and prevent death. Additionally, because the duration of excretion of the infectious agent may sometimes be reduced, mass chemotherapy, or the widespread administration of drugs to cases and to infected asymptomatic persons, has been recommended (*90*) for the purpose of reducing the pool of excreters and thereby the potential for transmission. Drugs may also be used to protect uninfected individuals from infection or illness. In this way, antimicrobials have been given prophylactically to individuals at high risk, such as close contacts of known cases or travellers to endemic areas. In practice, mass chemotherapy and individual chemoprophylaxis repeated on a large scale merge into each other because the presence of infection is not always ascertained or recognized.

In this review, we define chemoprophylaxis of diarrhoea as the administration of drugs to persons exposed to a recognized risk, whether infected or not, to prevent diarrhoea in these persons and to reduce the sources of infection. We consider here the role of chemoprophylaxis in national programmes to reduce diarrhoea morbidity and mortality among children under 5 years of age. This paper is the sixth in a series of reviews of potential anti-diarrhoea interventions published in the *Bulletin of the World Health Organization* (*3, 38–42*).

EFFECTIVENESS

For chemoprophylaxis to be an effective intervention to control diarrhoeal diseases it must be true that:

either

a considerable proportion of diarrhoea morbidity or mortality in young children occurs in children who are exposed to a recognized risk, such as contact with a known case	*hypothesis 1*

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Table 1. Additional cases and infections among household contacts of index cases having diarrhoea of known etiology

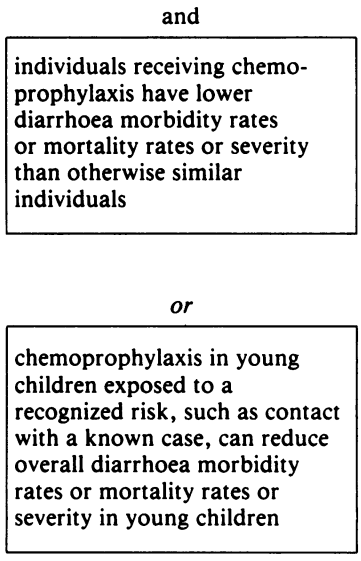
Etiology of index case	Country	Age group of contacts (years)	Case rate (%)	Infection rate (%)	Reference
Enterotoxigenic *Escherichia coli*					
ST/LT strains	Bangladesh	0-1	21	29	*10*
		2-4	10	23	
		All ages	4	11	
ST strains		0-1	22	22	
		2-4	10	15	
		All ages	4	10	
All strains	Thailand	0-4	8	42	*34*
		All ages	1	9	
Giardia lamblia	Canada	All ages	2-5	7-13	*70*
	USA	All ages	17	ND[a]	*119*
Norwalk agent	USA	All ages	30-32	ND[a]	*1*
	USA	0-4	40	ND[a]	*5*
		All ages	19	ND[a]	
Rotavirus	Canada	All ages	21	46	*147*
	New Zealand	0-12	66	75	*55*
		All ages	38	46	
	Norway	0-14	62	62	*59*
		All ages	36	44	
	Sweden	0-12	15	22	*151*
		All ages	13	24	
	USA	Adults	8	35	*66*
	USA	Adults	8	55	*78*
	USA	Adults	71	ND[a]	*121*
	USA	All ages	15	ND[a]	*119*
Salmonella spp.	United Kingdom	0-14	24	ND[a]	*149*
		All ages	18	ND[a]	
	USA	0-4	30	48	*124*
		All ages	19	35	
Shigella dysenteriae type 1	Bangladesh	0-4	31	31	*76*
		All ages	13	20	
	Bangladesh	0-4	11	11	*77*
		All ages	4	7	
Shigella flexneri	Bangladesh	0-4	0	11	*75*
		All ages	4	21	
	Bangladesh	0-4	33	50	*77*
		All ages	13	32	
	Marshall Islands	All ages	6	ND[a]	*144*
Shigella flexneri & sonnei	USA	0-4	68	ND[a]	*103*
		All ages	56	ND[a]	
	USA	0-14	50	40	*111*
		All ages	36	31	

Table 1 (*continued*)

Etiology of index case	Country	Age group of contracts (years)	Case rate (%)	Infection rate (%)	Reference
Shigella sonnei	United Kingdom	0-7	34	45	*23*
		All ages	16	33	
	USA	0-4	81	ND[a]	*86*
		All ages	51	ND[a]	
	USA	0-5	45-54	ND[a]	*157*
		All ages	27-36	ND[a]	
	USA	All ages	46	ND[a]	*146*
Shigella spp.	Bangladesh	0-4	24	ND[a]	*73*
		All ages	14	ND[a]	
	Bangladesh	All ages	14	32	*71*
	USA	All ages	26	ND[a]	*119*
Vibrio cholerae					
Classical	Bangladesh[b]	All ages	4-16	11-24	*37*
El Tor	Six countries[b]	All ages	2-25	4-32	

[a] No data.

[b] Feachem (*37*) reviewed 20 studies of cholera attack rates in households of index cases in Bangladesh, India, Hong Kong, Israel, Philippines and China (Province of Taiwan).



The potential effectiveness of chemoprophylaxis would be suggested by a demonstration either of the correctness of hypotheses 1 and 2 or of the correctness of hypothesis 3. We examine below the evidence for and against the three hypotheses and we consider the magnitude of reductions in diarrhoea morbidity and mortality in young children that may be achieved by chemoprophylactic measures.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children occurs in children who are exposed to a recognized risk, such as contact with a known case.*

Several recognized situations place young children at increased risk of diarrhoea. We describe here these high-risk situations and consider their significance with regard to overall diarrhoea morbidity and mortality in young children.

Contact with a known case in the family or household. Numerous studies have been conducted on the transmission of diarrhoeal diseases within households. Data on additional cases and infections among household contacts of a known index case are set out in Table 1 (in this context, the index case is the first recognized case in the household). These studies used different methods. Most were prospective, with observation periods ranging from 1 to 65 days. All index cases had diarrhoea of known etiology and, in some studies, only cases and infections caused by the same organism as the index case were included in the analysis. In other studies microbiological surveillance of contacts was not carried out and all additional cases of diarrhoea were included.

All additional cases and infections among household contacts following the identification of an index case were recorded and therefore both co-primaries and secondaries are included. We are concerned here with the risk of disease among contacts after identification of an index case and it is of no

importance whether the additional cases and infections resulted from a common-source exposure or secondary spread. The terms additional case and additional infection, rather than secondary case and secondary infection, are used throughout this paper.

Additional case rates among household contacts ranged from 1% to 71% and additional infection rates ranged from 4% to 55%. Both rates tended to be higher in the younger age groups. When infected, young children were also more likely to have symptoms than older children and adults. Not only were young children at greater risk of contracting diarrhoea after introduction of the disease into the household, but they also played a major role in the introduction and spread of the disease in the household (*10, 52, 74, 77, 95, 149, 157*).

Household contacts, therefore, are at considerable risk of contracting diarrhoea after identification of an index case. This risk is highest immediately after onset of diarrhoea in the index case, and wanes rapidly thereafter. Among household contacts of known cholera cases, 12–43% of additional cases were identified on the first of 10 days of observation and 85–88% by the sixth day (*8, 95, 116, 139*).

In the above studies, the household was the unit of investigation and it was usually assumed that all household contacts were members of a single family. Increased risk of cholera, enterotoxigenic *Escherichia coli* (ETEC) diarrhoea, and shigellosis has also been reported among persons in the same cluster of houses or neighbourhood as an index case (*18, 34, 61*).

Attendance at day-care centres and schools. A number of studies from industrial countries have examined the role of day-care centres and schools in the spread of diarrhoeal diseases. It has been shown that children attending these centres have a higher risk of contracting diarrhoea than children who remain at home (*9, 25, 28*). Black et al. (*11*) found that children were at increased risk of diarrhoea two to four weeks after enrolment in a day-care centre, which suggests that illness follows contact with other infected or ill children. Investigations within day-care centres have shown a pattern of repeated outbreaks caused by a variety of pathogens and sometimes having high attack rates (Table 2). Studies from the United Kingdom and North America provide evidence that young children in close contact with other children in day-care centres or schools play a major role in introducing diarrhoea into their households and spreading it to other young children (*9, 23, 25, 70, 119, 146, 157, 158*).

No prospective studies of this kind from developing countries have been located. Outbreaks of diarrhoeal disease in day-care centres and schools have been described in countries such as Brazil (*145*) and China (*136*), and it is probable that day-care centres, schools and informal neighbourhood play groups where many children congregate constitute high-risk situations for children everywhere.

Table 2. Attack rates during diarrhoea outbreaks recorded in day-care centres

Etiology	Country	Attack rate (%)	Reference
Astrovirus	Japan	52	*80*
Campylobacter jejuni	Belgium	20-50	*83*
Clostridium difficile	USA	20-58	*79*
Giardia lamblia	Canada	20-39	*70*
	USA	27-35	*9*
	USA	17	*119*
Rotavirus	Belgium	58-78	*43*
	USA	100	*121*
	USA	71	*119*
Shigella spp.	United Kingdom	51	*150*
	USA	73	*48*
	USA	38-51	*158*
	USA	33	*119*
	USA	36-50	*146*
Multiple etiologies	USA	51-57	*119*
	USA	14-92	*35*

Contact with a known case in institutions and hospitals. Institutions such as residential homes for children and institutions for the mentally retarded are associated with a high risk of diarrhoeal disease in industrial countries, where diarrhoea incidence rates are low in the community. Despite the prophylactic and therapeutic use of drugs and the application of isolation techniques, diarrhoeal diseases (particularly shigellosis, giardiasis and amoebiasis) continue to be a significant health problem among institutionalized children in these countries. Children are at highest risk of infection and illness shortly after admission (*19, 29*).

Hospital-acquired diarrhoeal diseases are well documented in industrial countries and may well represent a significant problem in developing countries. In a recent review of publications on nosocomial infections originating from developing countries (*159*), most reported diarrhoea outbreaks in nurseries for premature babies and paediatric wards. Hospital outbreaks may be serious (*115*) and may lead to considerable disruption of patient services (*81*). In industrial countries at least, a considerable

proportion of the diarrhoeal diseases treated in hospital may be nosocomially acquired (*100, 113, 127, 140*). The etiological agent implicated is often rotavirus (*127*), reflecting its importance as a cause for hospitalization among young children.

Importance of these high-risk situations with regard to overall diarrhoea morbidity and mortality. We have described various situations associated with a high risk for diarrhoea, but it is not clear, from the evidence presented so far, what proportion of all diarrhoea morbidity and mortality occurs in these situations. There are limited data on the importance of these high-risk situations in the epidemiology of cholera and shigellosis. We here summarize some of these reports:

—*Cholera.* Detailed studies from Hong Kong, China (Province of Taiwan), and the Philippines suggest that cholera did not spread easily, if at all, within households or among households in a community (*44, 90, 104, 118, 148, 154, 164*). Reported cases were in general sporadic, dispersed throughout the community, and contact-tracing identified few additional cases or infections. In Bangladesh, on the other hand, active transmission within households and from household to household within neighbourhoods has been reported and most cases tended to appear in short family or community outbreaks in urban (*95*) and rural areas (*106, 138*). A recent report from Tanzania (*99*) has documented the role of a hospital in the spread of cholera in an urban centre.

—*Shigellosis.* Data from industrial countries suggest that young children attending day-care centres and schools may play a major role in the spread of shigellosis to the community at large by spreading infection in their own households and from household to household (*103, 126, 146, 150, 157, 158*). Institutions, on the other hand, have not been demonstrated to be a source of infection for the community at large. Shigellosis in institutions may, nonetheless, represent a substantial proportion of all cases (*20, 123*). Data from developing countries on the mode of spread of shigellosis through communities are limited to epidemic situations in which whole communities are suddenly at high risk of diarrhoeal disease. High attack rates and death rates have been recorded (*94, 120*) but clustering by household or neighbourhood does not appear to be prominent (*47, 144*).

Conclusions on hypothesis 1. We have described several situations that place young children at increased risk of diarrhoea. Among these, the best documented in developing countries is contact with a known case in a family or household. The most common application for chemoprophylaxis in

Table 3. Detectable index and additional cholera cases for various values of hospitalization rate, household size and additional case rate

Hospitalization rate (%)	Household size (persons)	Additional case rate[a] (%)	No. of detectable index cases per 100 cases[b]	No. of detectable additional cases per 100 cases[c]	No. of detectable index plus additional cases per 100 cases
30	6	5	24	6	30
30	6	15	17	13	30
30	6	25	13	17	30
30	10	5	21	9	30
30	10	15	13	17	30
30	10	25	9	21	30
50	6	5	40	10	50
50	6	15	29	21	50
50	6	25	22	28	50
50	10	5	34	16	50
50	10	15	21	29	50
50	10	25	15	35	50

[a] See Table 1.

[b] A detectable index case is an index case who is hospitalized.

[c] A detectable additional case is one occurring in the household of a detectable index case in the 10 days following the reporting of the index case.

Table 4. Detectable index and additional shigellosis cases for various values of hospitalization rate, household size and additional case rate

Hospitalization rate (%)	Household size (persons)	Additional case rate[a] (%)	No. of detectable index cases per 100 cases[b]	No. of detectable additional cases per 100 cases[c]	No. of detectable index plus additional cases per 100 cases
5	6	20	2.5	2.5	5.0
5	6	30	2.0	3.0	5.0
5	6	40	1.7	3.3	5.0
5	10	20	1.8	3.2	5.0
5	10	30	1.4	3.6	5.0
5	10	40	1.1	3.9	5.0
10	6	20	5.0	5.0	10.0
10	6	30	4.0	6.0	10.0
10	6	40	3.3	6.7	10.0
10	10	20	3.6	6.4	10.0
10	10	30	2.7	7.3	10.0
10	10	40	2.2	7.8	10.0

[a] See Table 1.

[b] A detectable index case is an index case who is hospitalized.

[c] A detectable additional case is one occurring in the household of a detectable index case in the 10 days following the reporting of the index case.

developing countries is to prevent cholera or shigellosis among household contacts of known cases. We here estimate on a theoretical basis the proportion of all cholera and shigellosis cases that occurs among household contacts of known cases, and is thus potentially preventable by chemoprophylaxis.

In most circumstances, a case of cholera or shigellosis will only be identified if he or she is hospitalized. The calculations for cholera are set out in Table 3.[a] Data from Bangladesh and the Philippines indicate that hospitalization rates for cholera vary between 23% and 74% (*4, 6, 72, 74, 92, 105, 116, 160, 161*). Hospitalization rates of 30% and 50% are adopted in Table 3. Two household sizes, comprising 6 and 10 persons, are used. Six is approximately the mean family size in many developing countries while ten represents the larger extended families, or households comprising, on average, just under two families. Three additional cholera case rates (5%, 15% and 25%) are adopted on the basis of data summarized in Table 1. The proportions of all cholera cases that are detectable additional cholera cases are 6–21% for a hospitalization rate of 30% and 10–35% for a hospitalization rate of 50%.

[a] The formula used to make these calculations is available on request from R.G.F.

Similar calculations for shigellosis are presented in Table 4.[a] A hospitalization rate for shigellosis of 8% has been reported from rural Bangladesh (*13, 14*) and rates of 5% and 10% are used in Table 4. Three additional shigellosis case rates (20%, 30% and 40%) are adopted on the basis of data summarized in Table 1. The proportions of all shigellosis cases that are detectable additional shigellosis cases are 2.5–3.9% for a hospitalization rate of 5%, and 5.0–7.8% for a hospitalization rate of 10%.

The proportions of all cases that are detectable additional cases, and thus potentially preventable by chemoprophylaxis, are 6–35% for cholera and 2.5–7.8% for shigellosis. These proportions are correlated both with the additional case rate and with the hospitalization rate. Thus for shigellosis, despite the fact that additional case rates are high (20–40%), the proportion of detectable additional cases is low because the hospitalization rates are low (5–10%). Hospitalization rates depend on the severity of the symptoms and on the hospital facilities available in the area. The hospitalization rates adopted in Tables 3 and 4 are mainly derived from studies in the Matlab area of Bangladesh. The longstanding presence of a hospital specializing in acute diarrhoeal diseases, and the availability of ambulance services in this area, may lead to higher hospitalization rates than in most other rural areas of developing countries.

Table 5. Summary of trials of chemoprophylaxis among household contacts of cholera cases

Country (place)	Period of follow-up	Drug	Dosage	Results		Reference
				Proportion of household contacts who excreted *V. cholerae* (%)	Proportion of samples from household contacts which were positive for *V. cholerae* (%)	
Bangladesh (Dhaka)	10 days	Tetracycline	4 doses daily × 5 days	0	–	*91*
			Single dose daily × 5 days	1	–	
			Single dose	8	–	
		Placebo		13	–	
India[a] (Calcutta)	10 days	Tetracycline	2 doses daily × 3 days	–	1.5	*62*
		Placebo		–	3	
India (Calcutta)	15 days	Sulfadoxine	Single dose	19[b]	3	*24*
		Tetracycline	2 doses daily × 3 days	21[b]	3	
		Placebo		42[b]	7	
India (Calcutta)	10 days	Doxycycline	Single dose	15[c]	2	*134*
		Placebo		23[c]	4	

[a] *V. cholerae* was isolated from only 60% of index cases.
[b] Excluding contacts infected only on day 1 but including contacts infected on day 1 and on subsequent days.
[c] Excluding contacts infected on day 1.

Hypothesis 2. *Individuals receiving chemoprophylaxis have lower diarrhoea morbidity rates or mortality rates or severity than otherwise similar individuals.*

Chemoprophylaxis of diarrhoea has been recommended and used in numerous situations: to limit the spread of cholera epidemics (*22, 46, 90, 98*), to control shigellosis in institutions, such as institutions for the mentally retarded in the USA (*7, 49, 50, 84, 163*), and to prevent travellers' diarrhoea (*141*). Yet, despite such widespread use, few controlled trials have been conducted to assess the effectiveness of chemoprophylaxis in limiting transmission and reducing diarrhoea morbidity and mortality. The evidence is mainly from three sources:

—studies of chemoprophylaxis among household contacts of cholera cases;
—studies of the prolonged use of antimicrobials to prevent infections in young children;
—studies of chemoprophylaxis of travellers' diarrhoea.

These three types of studies are considered in turn.

Chemoprophylaxis among household contacts of cholera cases. Four studies, one from Bangladesh and three from India, have assessed the impact of chemoprophylaxis on infection among household contacts of a cholera index case (*24, 62, 91, 134*). Different methods were used to analyse the data but the study design was similar in all cases. Families of hospitalized cholera cases were assigned to one of various drug groups or to a control group. Household contacts were followed bacteriologically over a period of 10–15 days. Clinical information was reported in only one study (*62*) where it is stated that all *Vibrio cholerae* excreters were healthy. These studies therefore assessed the effect of chemoprophylaxis on the duration of excretion of *V. cholerae* among infected contacts and on transmission of infection within the household. They did not assess the protective effect of chemoprophylaxis on diarrhoeal illness. The drugs tested were effective in reducing the prevalence of infection on successive days and the proportion of infected household contacts (Table 5). This effect, however, was of short duration and after a period of 5–6 days the infection rates were similar in the treatment and control groups. The only study (*24*) that analysed the data by age groups reported that the maximum impact of chemoprophylaxis was observed in children under 5 years of age and in adults.

Only one study (*72*) has been located that tested the value of chemoprophylaxis in the prevention of diarrhoea among close contacts of cholera cases. In this trial from Bangladesh, two doses of tetracycline were administered to household contacts of hospitalized cholera cases. A similar control group was visited but did not receive any medication. All families were revisited after 10–12 days to check on any new cases of diarrhoea and hospitalization. The attack rate of diarrhoea among household contacts was similar in the treatment (13%) and control groups (14%). The occurrence of cases requiring hospitalization was, however, significantly lower in the treatment group (4%) than in the control group (8%). The presence of *V. cholerae* in the stools of contacts was not assessed.

Results from these studies suggest that chemoprophylaxis is effective in reducing the prevalence of infection among household contacts of cholera cases. This effect appears to be greatest shortly after initiation of the course and wanes rapidly so that after 5 to 6 days the infection rates are similar in the treatment and control groups. Maximum effectiveness is observed, nonetheless, during the period of greatest risk of infection. Presumably the observed effect is due to a shortening of the duration of excretion among contacts already infected and to a reduction in transmission of infection to other contacts. Khan (*72*), in contrast, found no impact of chemoprophylaxis on the attack rates of diarrhoeal illness among household contacts of cholera cases. The observed reduction in hospitalization rates for diarrhoea in the treatment group is ascribed to a possible effect on the severity of the illness. No placebo was given in Khan's study and the increased tendency to report to the hospital with diarrhoea may have been associated with the absence of medication in the control group. If the difference is real, a concomitant decrease in the attack rates of milder diarrhoea would be expected. Only a study that combines bacteriological surveillance with regular clinical assessment can clarify this issue.

Prolonged use of antimicrobials in young children. Low-dose antibiotic feeding is common practice in livestock and poultry husbandry. The addition to feed of small daily doses of broad-spectrum antibiotics has been shown to stimulate growth and to prevent infections, especially in weak animals reared in insanitary conditions or fed deficient diets (*88, 110*). The prolonged use of antimicrobials in children has been studied in a number of circumstances, such as during surveillance of recurrent attacks of rheumatic fever (*93*) or in the management of dietary deficiencies (*65*). These studies yield conflicting results, but suggest that the prolonged use of antimicrobials may occasionally be associated with improved growth and decreased morbidity and mortality, especially in malnourished children or in children suffering from a chronic disease (*122*).

Table 6. Effect of long-term chemoprophylaxis on diarrhoea morbidity in young children

Country	Study population	Age group	No. of children receiving the drug	Drug	Duration of study	Results	Reference
India	Hospitalized malnourished children	6 months to 7 years	10	Chlortetracycline or oxytetracycline	2 months	Faster recovery, reduced incidence of diarrhoea, reduced mortality.	*87*
Kenya	Hospitalized malnourished children	2 years (average)	38	Chlortetracycline	2-7 weeks	Faster weight gain, reduced incidence of intercurrent infection, reduced frequency of weight faltering or weight loss during infection, reduced duration of diarrhoea.	*89*
Honduras	Village children	6 months to 6 years	54	Iodoxychloroquinoline or metronidazole	Four 16-week periods	Reduced incidence of diarrhoea in children $\geqslant$ 2 years old.	*155*
USA	Children in an Apache community	1-42 months	81	Colistin sulfate	13 weeks	Children < 7 months old, increased prevalence of diarrhoea; 7-30 months old, reduced prevalence; 31-42 months old, no effect.	*60*

Table 7. Controlled trials of the chemoprophylaxis of travellers' diarrhoea

Country	Study population	Duration of trial	Drug groups	Diarrhoea attack rates (%)	Percentage reduction	Reference
Egypt and Far East	Danish tourists	25 days	Mecillinam	13	75	*15*
			Placebo	53	–	
Honduras	Peace Corps volunteers	3 weeks	Doxycycline	33	NS[a]	*132*
			Placebo	45	–	
Honduras	Peace Corps volunteers	3 weeks	Doxycycline	32	68	*131*
			Placebo	100	–	
Kenya	Peace Corps volunteers	3 weeks	Doxycycline	6	86	*129*
			Placebo	43	–	
Mexico	US students	2 weeks	Clioquinol	39	NS[a]	*67*
			Neomycin (with kaolin and pectin)	20	39	
			Placebo	34	–	
Mexico	US students	2 weeks	Neomycin	16	NS[a]	*68*
			Phthalylsulfathiazole	12	50	
			Placebo	24	–	
Mexico	US students	3 weeks	Bismuth subsalicylate	23	62	*30*
			Placebo	61	–	
Mexico	US travellers	For duration of voyage (4–13 days)	Erythromycin	0	100	*2*
			Placebo	29	–	
Mexico	US students	3 weeks	Trimethoprim-sulfamethoxazole	16	71	*31*
			Placebo	55	–	
Mexico	US students	2 weeks	Trimethoprim-sulfamethoxazole	2	94	*32*
			Trimethoprim	14	58	
			Placebo	33	–	
Mexico	US Navy personnel	For duration of exposure (0.5–2.5 days)	Doxycycline	4	81	*45*
			Placebo	21	–	
Morocco	Peace Corps volunteers	3 weeks	Doxycycline	8	83	*130*
			Placebo	46	–	
Sri Lanka[b] and Kenya	Swiss tourists	2 weeks (duration of voyage: 2–4 weeks)	Streptotriad[c]	16	58	*141*
			Placebo	38	–	
Various destinations[b]	British airline personnel and their families	3 weeks (duration of voyage: 2 days to over 6 weeks)	Streptotriad[c]	12	25	*152, 153*
			Neomycin-sulfonamides[d]	19	NS[a]	
			Placebo	16	–	

[a] No significant difference in diarrhoea attack rates compared with the control group.
[b] Poorly controlled and supervised trial.
[c] Streptomycin + sulfadimidine + sulfadiazine + sulfathiazole.
[d] Neomycin + sulfadimidine + sulfadiazine + sulfathiazole.

Four controlled trials have been located that document the effect of the prolonged administration of antimicrobials on diarrhoea morbidity in young children. They are summarized in Table 6. The first two studies, conducted in India and Kenya, report the effect of chemoprophylaxis on the recovery of children hospitalized for malnutrition (*87, 89*). Both document faster recovery and reduced incidence of diarrhoea in children receiving antibiotics. The study from Kenya also noted a decreased duration of diarrhoea. Two further studies, from Honduras (*155*) and the USA (*60*), investigated the protective effect of prolonged administration of antimicrobials on diarrhoea morbidity among children in the community. The results suggest that the prolonged administration of antimicrobials to young children in endemic areas may have an impact on diarrhoea incidence or duration in certain age groups. Detailed etiological investigations were not conducted. Also, the children were randomized within age groups to the different treatment cells and we cannot therefore assess the effect of chemoprophylaxis on the transmission of diarrhoea within households.

Chemoprophylaxis of travellers' diarrhoea. Travellers' diarrhoea may affect from 10% to 60% (*30, 125*) of travellers from low-risk to high-risk areas during their first few weeks of travel. The condition is primarily infectious, with ETEC as the most common pathogen, isolated from 30% to 70% of cases (*30, 51, 56, 97, 125, 128, 131, 135*). Fourteen controlled trials that investigated the effectiveness of chemoprophylaxis of travellers' diarrhoea are summarized in Table 7. Early studies with poorly absorbed antimicrobials, such as neomycin and phthalylsulfathiazole (*67, 68, 152, 153*), showed a modest effect. With improved understanding of the etiology of travellers' diarrhoea, doxycycline was tested in a number of trials. Sack et al. (*129, 130*) showed that a single daily dose of doxycycline was highly effective in preventing diarrhoea in Peace Corps volunteers travelling to Kenya and Morocco. Protection from ETEC and other diarrhoeas was observed during the treatment period and for the first week after cessation of doxycycline. In the Moroccan study, however, the volunteers were followed over a longer period of time and a significant increase in the attack rate was later observed in the treatment group compared with the control group. In a study in Honduras (*132*), biweekly prophylaxis with doxycycline was only marginally effective, an outcome that may be due to the decreased dosage or to the increased prevalence of resistant *Escherichia coli* found in Honduras. In a subsequent study in Honduras (*131*), a daily dose of doxycycline was found to be effective in reducing diarrhoea attack rates, although it did not prevent diarrhoea caused by doxycycline-resistant ETEC. Doxycycline also significantly reduced the severity of the illness in those who had diarrhoea. Freeman et al. (*45*) demonstrated the effectiveness of daily doxycycline in US Navy personnel making a short port call to Mexico. No rebound disease in acute diarrhoea was noted in the treatment group after departure from the high-risk area. Other antibiotics found to be effective in controlled trials are erythromycin (*2*), mecillinam (*15*), trimethoprim-sulfamethoxazole, and trimethoprim alone (*31, 32*). In the latter two studies among US students who remained in Mexico on completion of the trial, rebound diarrhoea was noted in the first week following cessation of the treatment. Finally, a non-specific drug, bismuth subsalicylate, has been found to have some protective effect when ingested in doses too large to be taken routinely (*30*).

In all of these studies, the drug was administered only for the first few weeks of residence in the high-risk area, and both effectiveness and the development of resistance during longer periods of chemoprophylaxis were not evaluated. Most studies were conducted in small groups of similar individuals, such as US students and Peace Corps volunteers, visiting a single high-risk area. These individuals were often in close contact with each other, sometimes eating together or sharing the same accommodation. Transmission of diarrhoea within the study groups may have been facilitated under such conditions. There is some evidence of this in one study (*68*). On the other hand, it is possible that the potential for transmission was reduced within the study group owing to the administration of drugs to some members of the group. No well controlled trials of chemoprophylaxis in large groups of travellers to multiple destinations have yet been carried out.

Conclusions on hypothesis 2. Numerous studies have been conducted but there is little evidence that chemoprophylaxis can reduce diarrhoea morbidity, except perhaps in travellers. No studies have been located that consider the effect on diarrhoea mortality. Chemoprophylaxis among household contacts of cholera cases has been shown to reduce the prevalence of infection during the period of most active transmission, but no impact on diarrhoea attack rates has been documented. There is some indication, however, that the severity of diarrhoea may be reduced in the treated household contacts. Broad-spectrum antibiotics administered to malnourished children have been shown to prevent nosocomial diarrhoea, but the impact of prolonged chemoprophylaxis among young children in the community remains unclear. Studies on travellers' diarrhoea indicate that chemoprophylaxis may be highly effective in reducing the incidence of diarrhoea among adult travellers making short visits to high-risk

Table 8. Reduction in cholera incidence following chemoprophylaxis of household contacts of known cholera cases

Household size (persons)	Additional case rate[a] (%)	Proportion of all cholera cases that occur as detectable index and additional cases[b] (%)	Reduction in additional case rate due to chemoprophylaxis (%)	Reduction in cholera incidence rate due to chemoprophylaxis (%)
6	5	30	20	1.2
6	5	30	40	2.4
6	5	30	60	3.6
6	5	50	20	2.0
6	5	50	40	4.0
6	5	50	60	6.0
6	15	30	20	2.6
6	15	30	40	5.1
6	15	30	60	7.7
6	15	50	20	4.3
6	15	50	40	8.6
6	15	50	60	12.8
6	25	30	20	3.3
6	25	30	40	6.7
6	25	30	60	10.0
6	25	50	20	5.6
6	25	50	40	11.1
6	25	50	60	16.7
10	5	30	20	1.9
10	5	30	40	3.7
10	5	30	60	5.6
10	5	50	20	3.1
10	5	50	40	6.2
10	5	50	60	9.3
10	15	30	20	3.4
10	15	30	40	6.9
10	15	30	60	10.3
10	15	50	20	5.7
10	15	50	40	11.4
10	15	50	60	17.2
10	25	30	20	4.2
10	25	30	40	8.3
10	25	30	60	12.5
10	25	50	20	6.9
10	25	50	40	13.8
10	25	50	60	20.8

[a] See Table 1.
[b] See Table 3.

Table 9. Reduction in shigellosis incidence following chemoprophylaxis of household contacts of known shigellosis cases

Household size (persons)	Additional case rate[a] (%)	Proportion of all shigellosis cases that occur as detectable index and additional cases[b] (%)	Reduction in additional case rate due to chemoprophylaxis (%)	Reduction in shigellosis incidence rate due to chemoprophylaxis (%)
6	20	5	20	0.5
6	20	5	40	1.0
6	20	5	60	1.5
6	20	10	20	1.0
6	20	10	40	2.0
6	20	10	60	3.0
6	30	5	20	0.6
6	30	5	40	1.2
6	30	5	60	1.8
6	30	10	20	1.2
6	30	10	40	2.4
6	30	10	60	3.6
6	40	5	20	0.7
6	40	5	40	1.3
6	40	5	60	2.0
6	40	10	20	1.3
6	40	10	40	2.7
6	40	10	60	4.0
10	20	5	20	0.6
10	20	5	40	1.3
10	20	5	60	1.9
10	20	10	20	1.3
10	20	10	40	2.6
10	20	10	60	3.9
10	30	5	20	0.7
10	30	5	40	1.5
10	30	5	60	2.2
10	30	10	20	1.5
10	30	10	40	2.9
10	30	10	60	4.4
10	40	5	20	0.8
10	40	5	40	1.6
10	40	5	60	2.3
10	40	10	20	1.6
10	40	10	40	3.1
10	40	10	60	4.7

[a] See Table 1.
[b] See Table 4.

areas if the appropriate drug is used in the correct dosage, and if the causative enteric pathogens (particularly ETEC) are susceptible. The severity of illness may also be reduced. Of concern, however, is the rebound increase in diarrhoea incidence that has been documented when travellers remain in the high-risk area after discontinuation of the drug.

Hypothesis 3. *Chemoprophylaxis in young children exposed to a recognized risk, such as contact with a known case, can reduce overall diarrhoea morbidity rates or mortality rates or severity in young children.*

The test of this hypothesis would come from a study in which chemoprophylaxis was given to young children exposed to one of the high-risk situations described in hypothesis 1, and where the impact on overall diarrhoea rates among young children was monitored. No study of this kind has been located. The two studies described in hypothesis 2, which considered the effect on diarrhoea morbidity of the prolonged administration of drugs to children in the community, cannot be used to test hypothesis 3 because the children in the treatment groups were not selected on the basis of their exposure to high-risk situations.

Hypothesis 3 must be examined, therefore, by theoretical calculations of the reductions in diarrhoea rates that may result from chemoprophylaxis of young children exposed to a recognized risk. Let us consider the most common of the identified high-risk situations: contact in the household with a known case of cholera or shigellosis, and calculate the potential impact of chemoprophylaxis on the incidence of specific diarrhoeas.[b]

The calculations for cholera are set out in Table 8. Two household sizes (6 and 10) and three additional case rates (5%, 15% and 25%) are used as before. For the purposes of this discussion, optimistic assumptions are made on the reduction in additional case rates due to chemoprophylaxis and three values (20%, 40% and 60%) are adopted on the basis of the data summarized in Table 5. The expected reduction in cholera incidence rates due to chemoprophylaxis, computed on the basis of these assumptions, ranges from 1.2% to 16.7% for a household size of 6 and from 1.9% to 20.8% for a household size of 10.

Similar calculations for shigellosis are presented in Table 9. The expected reduction in shigellosis incidence rates due to chemoprophylaxis ranges from 0.5% to 4.0% for a household size of 6 and 0.6% to 4.7% for a household size of 10.

The impact of chemoprophylaxis on overall diarrhoea incidence rates depends on the prominence of cholera and shigellosis as a cause of diarrhoea and this varies greatly from country to country. For cholera, we may take the extreme example of Bangladesh, where cholera is endemic and accounts for approximately 0.4% of all diarrhoea cases in children under 5 years (*12, 14, 92, 102, 106*). If we take values of 5–15% from Table 8 as estimates of the expected reduction in cholera incidence rates due to chemoprophylaxis of household contacts of known cholera cases, the intervention might reduce overall diarrhoea incidence rates in children under 5 years by 0.02–0.06%. In developing countries shigellosis accounts for approximately 10% of all diarrhoea cases in children under 5 years (*12, 14, 57, 64, 102*). Chemoprophylaxis of household contacts of known shigellosis cases might reduce shigellosis incidence rates by an estimated 1.5–3.5% (Table 9), and therefore might reduce overall diarrhoea incidence rates in children under 5 years by 0.15–0.35%.

In the absence of other information, it may be assumed that the reductions in cholera and shigellosis mortality rates caused by chemoprophylaxis of household contacts of known cases are the same as the reductions in incidence rates shown in Tables 8 and 9. We have calculated elsewhere (*27*) that, in Bangladesh, cholera may account for 8% of diarrhoea deaths in children under 5 years of age. If chemoprophylaxis of household contacts of known cholera cases reduces the cholera mortality rates in children under 5 years by 5–15%, then this intervention might, in Bangladesh, reduce the overall diarrhoea mortality rate in the same age group by 0.4–1.2%. Where shigellosis is responsible for 20% of diarrhoea deaths in children under 5 years (a speculative but reasonable assumption), if chemoprophylaxis of household contacts of known shigellosis cases reduces the shigellosis mortality rate in children under 5 years by 1.5–3.5%, then this intervention might reduce the overall diarrhoea mortality rate in the same age group by 0.3–0.7%.

FEASIBILITY

The likely effectiveness of chemoprophylaxis in the control of diarrhoeal diseases should not be considered in isolation from the unwanted effects of the drugs used and obstacles to the widespread implementation of the intervention.

The use of prophylactic drugs. No prophylactic drug has yet been identified which is universally safe and effective. A number of drugs, such as neomycin (*63, 69*) and the halogenated hydroxyquinolines (*109, 114, 133*), previously in common use, are now out of

[b] The formula used to make these calculations is available on request from R.G.F.

favour because of their potential adverse reactions. Antimicrobials are popular, but they have selective action against certain bacteria and protozoa only. A number of other agents, such as phage preparations (*82, 107, 112*), lactobacilli preparations (*21, 26*), and bismuth subsalicylate (*30, 53*) have been considered for the chemoprophylaxis of diarrhoea but are probably of limited value.

Antimicrobials are all associated with adverse reactions, some of them severe, and their use may be contraindicated in certain persons; for example, the administration of tetracyclines to children and to pregnant or lactating women is discouraged because of their dental staining effect (*156*). Antimicrobials may also increase host susceptibility to some enteric pathogens (*16, 96*), and alter the activity of pancreatic enzymes (*17*) and the metabolism of bile acids (*58*). Of greatest concern, however, is that the use of antimicrobials provides an advantage to resistant strains and imposes selective pressure to assist in their spread (*36, 85, 101, 108, 142, 162*). There is also the sinister possibility that the emergence of resistance is associated with increased virulence or communicability of certain strains (*33, 117, 137, 143, 165*). Finally, antimicrobials may mask other bacterial infections and complicate their therapy. Their extensive use cannot be recommended in the absence of monitoring for adverse reactions.

Implementation. The application of chemoprophylaxis among family contacts of known cholera and shigellosis cases requires the correct identification of the index cases followed by the administration of drugs to their family contacts. Under normal circumstances, only hospitalized diarrhoea cases are likely to be investigated and correctly diagnosed. As discussed earlier, hospitalization rates vary widely from area to area and will often be lower than those adopted in our calculations. Outbreaks of diarrhoeal disease that need intensified control measures should be detected as soon as possible, but reporting systems based on routine data collected from health facilities are not very sensitive (*54*) and the laboratory services needed to make an accurate diagnosis of etiology and to test for antimicrobial sensitivity may not always be available (*47, 94*). Once the index case of cholera or shigellosis is recognized, the at-risk family members must be located for the distribution of drugs. Time is at a premium here, as the additional case rate among household contacts is highest on the first day of observation in the studies reported in Table 1 and falls rapidly thereafter. The distribution of drugs may be a complex task, especially in rural areas and when a multiple-dose drug regimen is used.

In short, the detection of cases and the rapid follow-up of their contacts and distribution of drugs require skills and resources that are scarce in developing countries. The workload may be especially heavy in epidemic situations when the number of contacts to be reached will be very high. Chemoprophylaxis might then direct attention from other, more effective, control measures.

COST

The costs of chemoprophylaxis have not been documented. The costs involved fall into four main categories:

— The cost of the drugs. Drug bills place a considerable burden on the health budget of most governments. There are large cost variations between drugs and even for the same drug, depending on the price per unit for that particular drug, the quantity required, the preparation chosen, and the purchasing and distribution systems used.

— The cost of surveillance (including laboratory surveillance). This cost is difficult to determine as few reporting systems for health expenditure list these items separately. This cost would be shared with other interventions.

— The cost of the distribution of the drugs, including manpower and logistics.

— The cost of unwanted effects. These include the cost of treatment of adverse reactions due to the drugs used in chemoprophylaxis and the increased cost of new drugs used in therapy to replace old ones that become inadequate because of the emergence of antimicrobial resistance.

CONCLUSIONS

There is little evidence that chemoprophylaxis is effective in reducing diarrhoea morbidity and mortality. The most common application of chemoprophylaxis in developing countries is to prevent cholera or shigellosis among selected high-risk groups, such as household contacts of known cases. A theoretical case has been made out, based on optimistic assumptions, that chemoprophylaxis of household contacts of known cholera cases in Bangladesh might reduce overall diarrhoea incidence rates in children under 5 years of age by 0.02–0.06% and diarrhoea mortality rates by 0.4–1.2%. Chemoprophylaxis of household contacts of known shigellosis cases might reduce diarrhoea incidence rates by 0.15–0.35% and diarrhoea mortality rates by 0.3–0.7% in the same age group.

The correct identification of index cases of cholera and shigellosis, followed by the rapid distribution of drugs to their household contacts, requires skills and resources that are scarce in the developing countries.

All the drugs currently used have side-effects that should be carefully monitored. Chemoprophylaxis can contribute to the widespread emergence and dissemination of antimicrobial resistance. The costs of chemoprophylaxis have not been documented but are likely to be high and no long-term benefits may be derived. The available evidence suggests, therefore, that chemoprophylaxis is not feasible in many settings and that, even if successfully implemented, it is not a cost-effective intervention for national diarrhoeal disease control programmes.

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RÉSUMÉ

INTERVENTIONS DESTINÉES À LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS: CHIMIOPROPHYLAXIE

Cet article est le sixième d'une série passant en revue les interventions possibles en vue de réduire la morbidité et la mortalité par diarrhée parmi les enfants de moins de 5 ans dans les pays en développement. Un certain nombre de situations font courir aux jeunes enfants un risque accru de diarrhée. Parmi celles-ci la mieux étudiée dans les pays en développement est le contact avec un cas connu dans la famille ou le ménage. L'application la plus fréquente de la chimioprophylaxie dans ces pays vise à prévenir le choléra ou les shigelloses parmi les contacts de cas connus dans les ménages. Il ne semble pas que la chimioprophylaxie puisse réduire efficacement la morbidité et la mortalité par diarrhée, sauf peut-être chez les voyageurs. D'après les calculs théoriques du présent article (fondés sur des hypothèses optimistes), la chimioprophylaxie appliquée à des contacts dans les ménages comptant des cas connus, au Bangladesh, pourrait réduire de 0,02–0,06% les taux d'incidence globaux de la diarrhée et de 0,4–1,2% les taux de mortalité par diarrhée chez les enfants de moins de 5 ans. En ce qui concerne les shigelloses, la chimioprophylaxie administrée à des contacts de cas connus dans des ménages pourrait réduire de 0,15–0,35% les taux d'incidence globaux de la diarrhée et de 0,3–0,7% les taux de mortalité par diarrhée dans le même groupe d'âge.

Le dépistage correct des cas initiaux de choléra et de shigellose suivi d'une distribution rapide de médicaments à leurs contacts dans les ménages demande des compétences et des ressources qui sont rares dans les pays en développement. Tous les médicaments actuellement en usage présentent des effets secondaires qui doivent être minutieusement surveillés. En outre, point capital, la chimioprophylaxie peut contribuer à l'apparition et à la dissémination de la résistance aux antimicrobiens sur une grande échelle. On ne connaît pas les coûts de la chimioprophylaxie, mais ils sont probablement élevés et l'on ne peut en attendre d'avantages à long terme. D'après les données existantes, la chimioprophylaxie est donc irréalisable dans de nombreuses circonstances et, même si elle est appliquée avec succès, ce n'est pas une intervention rentable pour les programmes nationaux de lutte contre les maladies diarrhéiques.

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