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

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The effects of measles immunization on diarrhoea morbidity and mortality are reviewed using data from field studies and theoretical calculations. Two types of measles-associated diarrhoea are distinguished: with-measles diarrhoea, which starts between 1 week pre-rash-onset and 4 weeks post-rash-onset, and post-measles diarrhoea, which starts 4–26 weeks post-rash-onset. The etiology of these measles-associated diarrhoeas is unknown, but some evidence points towards a frequently severe and dysenteric form of disease, with Shigella *playing a major role. Theoretical calculations indicate that measles immunization, at the age of 9–11 months, with coverage of between 45% and 90% can avert 44–64% of measles cases, 0.6–3.8% of diarrhoea episodes, and 6–26% of diarrhoea deaths among children under 5 years of age. The cost of measles immunization is in the range of US$ 2–15 (1982 prices) per child vaccinated. The impact of measles immunization on diarrhoea mortality may be partly additional to the impact of oral rehydration because it averts deaths that are not prevented by oral rehydration. Community research is urgently needed to confirm or reject these theoretical suppositions, to clarify the etiology of measles-associated diarrhoea, and to determine the cost-effectiveness of measles immunization as an intervention to reduce diarrhoea mortality.*

Measles immunization is now an integral part of the Expanded Programme on Immunization (EPI) which many developing countries are implementing with the support of the World Health Organization. In some developed countries, e.g., Czechoslovakia and the USA, the elimination of measles may soon be achieved (*12*). There is a marked association between measles and diarrhoea in developing countries today, as there was in developed countries in earlier times (*20*). Since cases of measles complicated by diarrhoea have a high fatality rate, measles immunization is a potential intervention for diarrhoea control. This review of the role of measles immunization in diarrhoeal disease control is the first in a series of reviews of potential anti-diarrhoea interventions which will be published in the *Bulletin of the World Health Organization* (*9*).

EFFECTIVENESS

For measles immunization to be an effective diarrhoea control intervention, the following hypotheses have to be tested and proved:

either

a considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is associated with measles — *hypothesis 1*

and

measles immunization can reduce the incidence of measles — *hypothesis 2*

or

measles immunization can reduce diarrhoea morbidity or mortality rates in young children — *hypothesis 3*

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If hypotheses 1 and 2 are true, it could be appropriate to field test hypothesis 3; whereas if hypothesis 3 is known to be true, measles immunization could be recommended as an operational component of national diarrhoeal diseases control programmes. The evidence for and against these hypotheses is examined below.

Hypothesis 1. *A considerable proportion of diarrhoea morbidity or mortality in young children in developing countries is associated with measles*

Definitions

Two kinds of measles-associated diarrhoea are distinguished in this review; with-measles diarrhoea and post-measles diarrhoea. With-measles diarrhoea is diarrhoea occurring in close association with an attack of measles and is defined, arbitrarily, by the period of time separating the appearance of the measles rash and the onset of diarrhoea. Authors differ in their definition of this time period. Scrimshaw et al. (*25*) reported diarrhoea episodes in 127 measles-infected Guatemalan children, under 5 years of age, which occurred from 2 weeks pre-rash-onset to 2 weeks post-rash-onset and found that the great majority of diarrhoea episodes started between 8 days pre-rash-onset and 5 days post-rash-onset. These authors subsequently defined the time limits of with-measles diarrhoea as that starting between 7 days pre-rash-onset and 7 days post-rash-onset. In a study in Nigeria of 142 children suffering from measles and diarrhoea (*20*), it was found that the diarrhoea started 14–7 days pre-rash-onset in 5% of cases, 6–1 days pre-rash-onset in 19% of cases, 0–6 days post-rash-onset in 25% of cases, 7–14 days post-rash-onset in 11% of cases, and more than 14 days post-rash-onset in 40% of cases. This high (40%) proportion of diarrhoea occurring more than 2 weeks after the rash-onset may be related to the phenomenon of post-measles diarrhoea discussed below. Koster et al. (*14*), after studying 119 village children in Bangladesh who had measles and diarrhoea over a 6-month period, reported a marked increase in diarrhoea starting between 1 week pre-rash-onset and 4 weeks post-rash-onset. With-measles diarrhoea is defined, in the present review, as that starting between 1 week pre-rash-onset and 4 weeks post-rash-onset, although it must be cautioned that most studies do not report the exact time frame but imply that with-measles diarrhoea occurs shortly before or during the exanthem.

A second type of measles-associated diarrhoea, called here post-measles diarrhoea, was hinted at by some earlier writers and has recently been investigated in Bangladesh. Morley et al. (*20*), for example, reported from Nigeria that children "were susceptible to diarrhoea for a long period after the measles itself had subsided" and that "the diarrhoea may continue or reappear over a period of many weeks". More recently, in Bangladesh, a substantial predisposition to dysentery, though not to watery diarrhoea, was found in children for a period of five months following an attack of measles.[a] There is thus some evidence for a phenomenon of post-measles diarrhoea, which is defined here, arbitrarily, as diarrhoea occurring in the period 4–26 weeks post-rash-onset, over and above that which could occur in that age group at any time.

In summary, the total of measles-associated diarrhoea cases is defined here as the sum of with-measles diarrhoea cases (starting between 1 week pre-rash-onset and 4 weeks post-rash-onset) and post-measles diarrhoea cases (starting 4–26 weeks post-rash-onset). There is, as yet, very little information on the magnitude or nature of post-measles diarrhoea.

Measles-associated diarrhoea morbidity

The proportion of diarrhoea episodes that are measles-associated can be derived theoretically and from the results of field studies.

Among children aged 0–59 months in developing countries, there are on average 2.2 episodes of diarrhoea per year per child (*26*). If we assume that every child also has measles before 5 years of age and that every measles case has one associated diarrhoea episode, then in the first five years of life an average child will have 11 episodes of diarrhoea, of which 1 is measles-associated diarrhoea. Therefore a theoretical upper proportion of measles-associated diarrhoea to all diarrhoea in the first five years of life is 9%.[b] A review of 10 community-based studies in 5 countries[c] shows that only 15–63% of measles cases in children have accompanying diarrhoea. Using these extreme figures, the proportion of diarrhoea in the first 5 years of life that is with-measles diarrhoea is 1.0–4.0%, assuming that 70% of children have measles before they are 60 months old (70% is the median figure from 18 studies in 10 countries[c]). In addition, data on post-measles diarrhoea from Bangladesh suggest that 18% of children who have measles will experience an episode of diarrhoea in the following 6 months, which they would not otherwise have had.[d] By the addition of these post-measles diarrhoea episodes, it is calculated that 2.1–5.2% of diarrhoeal episodes in the first 5 years of life are measles-associated, assuming that 70% of children contract measles before the age of 60

[a] SHAHID, N. S. ET AL. *Long-term complication in measles in rural Bangladesh.* International Centre for Diarrhoeal Disease Research, Bangladesh, 1982 (unpublished report).

[b] This is not the theoretical maximum proportion since it is possible that each measles attack is associated with more than 1 diarrhoea episode.

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

[d] See footnote *a*, above.

months. This calculation is sensitive to the assumptions made about the proportion of measles cases that have with-measles or post-measles diarrhoea and to the assumption that 70% of children have measles before they are 60 months old. Table 1 presents the proportions of diarrhoeas in the first 5 years of life that may be measles-associated, based on different values of these parameters. The range of proportions is 1.4–6.6%, and is subject to the cautions given in the footnote to Table 1.

Data from community studies support this theoretical range. In Imesi, Nigeria, 259 children under 5 years old averaged 2.3 episodes of diarrhoea per year per child over a 3-year period, of which 0.14 (or 6%) were measles-associated (*20*). In Santa Cruz Balanya, Guatemala, each child under 5 years of age was found to suffer an average of 1.65 episodes of diarrhoea in the year commencing April 1963 (*10*). During a 4-month period of that year, there was a measles epidemic in the village and, during that time, a child suffered on average 0.6 episodes of diarrhoea of which 0.098 were with-measles diarrhoea. Therefore, computed over the year and assuming that no measles occurred outside the period of the epidemic, the proportion of diarrhoea episodes that were measles-associated was 6%. The proportion over the period of the epidemic only was 16%, thus illustrating the manner in which measles-associated diarrhoea becomes more prominent during a measles epidemic and especially when, as commonly occurs, measles epi-

Table 1. The proportion of diarrhoea episodes in the first five years of life that is measles-associated, based on various assumptions

Proportion of measles cases having with-measles diarrhoea (%)	Proportion of measles cases having post-measles diarrhoea (that they would not otherwise have had) (%)	Proportion of children contracting measles before age 60 months (%)	Measles-associated diarrhoea incidence per 100 children aged 0–59 months per year	Proportion of all diarrhoea episodes among children aged 0–59 months that is measles-associated (%)[a]
20	10	90	5.4	2.6
20	10	70	4.2	1.9
20	10	50	3.0	1.4
20	20	90	7.2	3.3
20	20	70	5.6	2.6
20	20	50	4.0	1.8
40	10	90	9.0	4.1
40	10	70	7.0	3.2
40	10	50	5.0	2.3
40	20	90	10.8	4.9
40	20	70	8.4	3.8
40	20	50	6.0	2.7
60	10	90	12.6	5.7
60	10	70	9.8	4.5
60	10	50	7.0	3.2
60	20	90	14.4	6.6
60	20	70	11.2	5.1
60	20	50	8.0	3.6

[a] These calculations assume that, on average, a child has 2.2 episodes of diarrhoea per year in the first five years of life (*26*). In areas where children have more frequent diarrhoea, the proportion that is measles-associated will be lower, while where diarrhoea is less frequent, the proportion that is measles-associated will be higher. It is further assumed that measles-associated diarrhoea is recorded as diarrhoea in surveillance data and thus forms a part of the 2.2 episodes of diarrhoea per child per year. In the case of post-measles diarrhoea this is almost certainly a correct assumption, but with-measles diarrhoea may be recorded as a complication of measles rather than a case of diarrhoea.

demics occur in the cool, dry season when diarrhoea incidence is at its lowest.

In summary, theoretical considerations indicate that 1–7% of diarrhoea episodes in under-5-year-old children may be measles-associated (Table 1), while studies in Nigeria and Guatemala both report a figure of 6%.

Measles-associated diarrhoea mortality

As with measles-associated diarrhoea morbidity, the proportion of diarrhoea deaths that are measles-associated may be derived theoretically and from field data.

Theoretically computed measles-associated diarrhoea incidence rates are presented in Table 1. They range from 3 to 14 cases per year per 100 children aged 0–59 months. By the application of case-fatality rates to these incidences, mortality rates for measles-associated diarrhoea may be derived. The case-fatality rates for measles-associated diarrhoea are high. A review of 13 studies from 11 countries[e] shows that in hospitals, which tend to see more severe cases, 5–29% of young children with measles and diarrhoea die, whereas fatality rates reported from community studies are between 2% and 9%. In Table 2, three possible case-fatality rates (3%, 6% and 9%) are applied to three possible measles-associated diarrhoea incidence rates (4, 8 and 12 per 100 children aged 0–59 months) to obtain a range of measles-associated diarrhoea mortality rates. These mortality rates are then compared with an overall diarrhoea mortality rate of 1.4 per 100 under-5-year-old children per year (*26*) to obtain the proportions of diarrhoea deaths that are measles-associated. The range of proportions is considerable (9–77%), and is subject to the important cautions given in the footnote to Table 2.

Table 2. The proportion of diarrhoea deaths in the first five years of life that is measles-associated, based on various assumptions

Measles-associated diarrhoea incidence per 100 children aged 0–59 months per year	Case-fatality rate for measles-associated diarrhoea (%)	Measles-associated diarrhoea mortality per 100 children aged 0–59 months per year	Proportion of all diarrhoea deaths among children aged 0–59 months that are measles-associated (%)[a]
4	3	0.12	8.6
4	6	0.24	17.1
4	9	0.36	25.7
8	3	0.24	17.1
8	6	0.48	34.3
8	9	0.72	51.4
12	3	0.36	25.7
12	6	0.72	51.4
12	9	1.08	77.1

[a] These calculations assume that the annual mortality rate from diarrhoea in the first five years of life is 1.4 per 100 children (*26*). In areas where children die more frequently from diarrhoea than this, the proportion of deaths that are measles-associated will be lower, while in areas where the diarrhoea death rate is lower, the proportion will be higher. It is further assumed that measles-associated diarrhoea deaths are recorded as diarrhoea deaths. In the case of post-measles diarrhoea deaths this is a reasonable assumption, but many with-measles diarrhoea deaths will be recorded as deaths from measles rather than deaths from diarrhoea. If all with-measles diarrhoea deaths were recorded as measles deaths, the proportions given in the final column should be reduced by 50–86% (see Table 1). These calculations also assume that the case fatality rates for with-measles diarrhoea and post-measles diarrhoea are the same; there is no evidence on which to judge the correctness of this assumption.

Only one field report giving the proportion of diarrhoea deaths that are measles-associated has been located (*14*). It describes a one-year surveillance of 5775 rural Bangladeshi children under 10 years old, 29 of whom died of diarrhoea alone and 15 of diarrhoea with measles (death within one month of rash-onset). Thus, 34% of these diarrhoea deaths were measles-associated. In this same study, a further 8 children died with measles complicated by a combination of diarrhoea and respiratory symptoms or by various other complications. If 2 of these 8 deaths are included as deaths from measles-associated diarrhoea, the proportion of diarrhoea deaths that were measles-associated rises from 34% to 37%. These data relate to 0–9-year-old children, not 0–4 years as in Table 2. The effect of considering this older age group may be to increase the proportion of diarrhoea deaths that are measles-associated because the mortality rate from all diarrhoeas declines more rapidly after 5 years of age than does the mortality rate for measles. Expressing the mortality rate among 6–9-year olds as a percentage of the rate among 4–5-year olds, the same researchers (*14*) found that it was 6% for diarrhoea and 23% for measles. This effect may be partly counteracted by the exclusion from these data of deaths due to post-measles diarrhoea.

In summary, theoretical considerations indicate that perhaps 9–77% of diarrhoea deaths in the first 5 years of life are measles-associated, while the one field study providing data on this suggests a figure of 37% (for 0–9-year-old children).

Etiology of measles-associated diarrhoea

The etiology of measles-associated diarrhoea remains largely unknown. The high case-fatality rates, however, suggest a severe form of the disease.

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

Indications that with-measles diarrhoea may be primarily dysenteric in nature are based on reports from several studies. Thus, blood was commonly present in the stools of Gambian village children suffering from with-measles diarrhoea (*16*). Hospital data from East and West African countries found 62% (*21*) and 65% (*22*), respectively, of with-measles diarrhoea to be mucoid or mucoid and bloody, or to be associated with anal prolapse. In the above reports, bloody and mucoid diarrhoeas with measles were more fatal than those described as mucoid only (11% vs 6% in East Africa; 18% vs 11% in West Africa), although the mucoid diarrhoeas were the majority of the dysenteric diarrhoeas (68% and 72% respectively). Bacteriological examination detected *Shigella* species in "approximately 50%" of faecal samples from children having with-measles diarrhoea in Bangladesh (*14*). Although this observation was uncontrolled, it may be contrasted with the typical 4–10% isolation rates of *Shigella* from paediatric diarrhoea cases in the same area of Bangladesh (*2*). In Bangladesh it was also observed (*14*) that the with-measles diarrhoea cases were of significantly longer average duration (51% of episodes lasting more than 6 days) than other diarrhoeas (only 25% of episodes lasting more than 6 days). Immunological factors that may account for the association between measles and diarrhoea have been reviewed by Greenwood & Whittle (*11*).

With regard to post-measles diarrhoea, recent evidence from Bangladesh suggests the predominance of dysentery.[f] In a comparison of children in the five months after measles with matched controls, it was found that the attack rates for watery diarrhoeas were 47% in the post-measles cases and 56% in the controls (not significant), whereas the attack rates for mucoid diarrhoeas were 42% among the cases and 19% among the controls ($P < 0.01$) and the attack rates for bloody diarrhoeas were 21% among cases and 9% among controls ($P < 0.05$).

In contrast to these findings, a hospital study in Kenya (*23*) reported that, of 200 rectal swabs taken from children having with-measles diarrhoea, only 3 were positive for *Shigella* and 1 for *Salmonella*; the stools of these patients were described as bloody and mucoid. The case-fatality rate in this Kenyan series was, however, high at 29%. A study of 54 children hospitalized with measles and diarrhoea in Rwanda found *Shigella* in the stool of only 1 child, whereas *Salmonella* was found in 16 (*7*). A retrospective study in Thailand found diarrhoea to be a common complication of hospitalized measles (26%), but the diarrhoea was reported to be rarely severe and almost always responded to oral rehydration.[g] Interestingly, measles in general was not considered to be especially life-threatening in Thailand, and the hospital case-fatality rate for all measles cases was only 2.3%.

The etiology of measles-associated diarrhoea, and in particular the role of *Shigella* and other agents of dysentery, requires urgent investigation. Such studies are under way, with WHO support, in Rwanda and should be conducted in other sociocultural and environmental settings as well.

Hypothesis 2. *Measles immunization can reduce the incidence of measles*

The experience of some developed countries, such as Czechoslovakia and the USA which are close to measles elimination, clearly shows that measles immunization can reduce the incidence of measles very greatly (*12*). In developing countries, however, many factors intervene to reduce the overall impact of a measles immunization programme.

Consider, for example, a group of 1000 children born alive. By the age of immunization (usually 9–11 months), 150 will have died,[h] and a proportion of those surviving will have had measles. Data from 18 studies in 10 developing countries show that the proportion of children contracting measles before the age of immunization is 4–25% and that the figure is generally higher in urban than in rural areas;[i] the figure of 11% will be adopted here as it is the median figure from the data reviewed. Therefore, of the 850 children surviving to immunization age, 11% or 94 would have had measles and it will be assumed that a further 2%, or 3 of the 150 children who died earlier, had measles before they died. Therefore, out of the 1000 children born in month 0, there will be 97 measles cases by month 12.

During months 9–11, the 850 surviving children will be the subjects of a measles immunization programme; 756 (850 − 94) would not have had measles and a proportion of these will receive the vaccine. This proportion depends on the programme coverage. Theoretically, this coverage can be 100% but in practice it is lower. As many countries do not have an effective measles immunization programme, the coverage figures for a whole region are generally less than 10%. The coverage figures for individual selected countries can be higher (Table 3), although some of the figures reported are very optimistic estimates. In subsequent tabulations (Tables 5 and 6), four possible coverage figures have been adopted for comparative purposes (45%, 60%, 75% and 90%). For the present example, we shall assume a coverage

[f] See footnote *a*, page 642.

[g] WARD, N. A. *Survey to determine mortality and morbidity patterns in measles, Thailand.* Unpublished WHO document SEA/EPI/5, 1979.

[h] The infant mortality rate varies greatly among countries. A figure of 150 is adopted for the purposes of this illustrative example. No allowance is made for mortality after 1 year of age.

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

Table 3. Reported coverage rates for measles immunization in some developing countries reporting > 50% coverage as at 1982

WHO Region	Country or area	Reported coverage (%)[a]
Africa	Botswana	63
	Gambia	61
	United Republic of Tanzania	82
Americas	Argentina	60
	Brazil	58
	Chile	88
	Costa Rica	68
	Ecuador	67
South-East Asia	Maldives	98
	Mongolia	98
Europe	Turkey	52
Eastern Mediterranean	Bahrain	63
	Egypt	63
	Islamic Republic of Iran	81
	Israel	69
	Kuwait	71
	Libyan Arab Jamahiriya	65
	Tunisia	65
Western Pacific	American Samoa	86
	Brunei	73*
	Hong Kong	74*
	Niue	77*
	Singapore	86
	Trust Territory of the Pacific Islands	53*

[a] Coverage rates refer to the proportion of children vaccinated by 12 months, except in cases marked * where they describe immunization coverage by 60 months. For most countries the figures refer not to the whole country but to selected regions where measles immunization has been initiated on a pilot basis.

(Source: Data reported to WHO)

figure of 75%, bearing in mind that the relevant coverage figure is not what is now being achieved in countries with only limited immunization programmes, but what might be reasonably expected in countries committed to measles immunization and with a national programme built up over several years.

Thus, of the 756 children requiring measles vaccine, 567 (75%) will be vaccinated. The remaining 189 will not be vaccinated and an estimated 66%,[j] or 125 of these, will go on to contract measles before month 60.

Of the 567 vaccinated children, a proportion would have been immunized successfully. The not successfully immunized ones will be those who were susceptible but failed to seroconvert, plus those who were not susceptible because of persisting maternal antibodies. The seroconversion rate at 9–11 months, based on reports from developing countries, is generally > 90% although lower figures have also been reported (Table 4). High seroconversion rates are reported from carefully organized research studies in which the vaccine's potency is well maintained. Seroconversion rates in on-going immunization programmes are probably lower because of operational factors. In addition, a small proportion of children (probably 1–5%) at ages 9–11 months are not susceptible owing to persisting maternal antibodies. Taking these considerations into account, it may be assumed for the present example that 90% of children without a history of measles who are vaccinated at ages 9–11 months will seroconvert and be immune to measles. In Table 5, two seroconversion rates have been adopted for comparison (80% and 90%). Thus, of the 567 vaccinated children, 510 (90%) would have been effectively immunized and 57 would not; 38 (66%) of these 57 would then go on to contract measles before month 60.[j]

In summary, out of 1000 children born alive, the following will get measles between months 0 and 60: 3 will have measles and then die before 9–11 months, 94 will have measles and recover before 9–11 months, 125 will not be vaccinated and will go on to get measles before month 60, and 38 will be vaccinated but will nevertheless get measles before month 60. This makes a total of 260 measles cases.

The number of measles cases in the absence of an immunization programme may be computed in a similar manner. Of 1000 children born alive, 150 will die before 12 months and 3 of these will have measles before they die. Of the remaining 850, approximately 70% (or 595) will have measles before the age of 60 months. This makes a total of 598 measles cases in the first five years of life. Therefore, in the first five years of life, the number of measles cases averted per 1000 live births by a measles immunization programme will be 338 (598–260), or 57%.

This calculation is presented in Table 5, using four levels of programme coverage (45%, 60%, 75% and 90%), and two rates of successful seroconversion after measles immunization at 9–11 months of age (80% and 90%). A correction using infant mortality

[j] If 11% have measles before 12 months, and 70% before 60 months, the proportion of those who have not had measles at 12 months but who will have it by 60 months is 66%.

Table 4. Age-specific seroconversion rates following measles immunization

Country	Seroconversion rate (%) at:							Reference
	6	7	8	9 months	10	11	12	
Africa								
Kenya	52	72	86	95	98			*29*
Nigeria							94[a]	*13*
South Africa	23	45	57	86	71	86	80	*8*
United Republic of Tanzania		44		63		74		*28*
Upper Volta	76	90	97					*17*
Zimbabwe	59			97				*4*
North America								
USA							80–85	*15*
South America								
Chile	57	59		99				*3*
3 countries:[b]								*5*
well nourished[c]	59	69	84	87	93	94	97	
undernourished[d]	81	91	93	94	90	96	86	

[a] Children aged 12–23 months
[b] Brazil, Chile and Ecuador
[c] > 85% weight-for-age
[d] 60–85% weight-for-age

rates is not shown in Table 5 because these rates affect equally the communities both with and without a measles immunization programme and they do not change the computed proportions of measles cases averted. The proportion of measles cases in children aged 0–59 months averted by measles immunization (Table 5) is between 30% and 68%, depending on the programme coverage and, to a lesser extent, on the assumed seroconversion rate. The reader who is interested in a particular locality and knows that the programme coverage, seroconversion rate and age at immunization are different from those assumed above may use his figures and make a calculation to obtain the percentage of measles cases averted.

These calculations reflect the situation of a community having no measles immunization and the same community immediately after the implementation of a measles immunization programme with a specified level of coverage. As this programme continues, the age distribution of measles cases will shift upwards, reducing the proportion of children who acquire measles before the age for immunization and increasing the proportion of unimmunized children who acquire measles after their fifth birthday. Both these changes will cause an increase in the pro-

Table 5. Proportion of measles cases averted in the first five years of life by measles immunization, based on various assumptions on coverage and the proportion of children successfully immunized[a]

Measles immunization coverage (%)	Proportion of children successfully immunized[b] (%)	Proportion of cases averted among 0–4-year-old children (%)
45	80	30
45	90	34
60	80	41
60	90	46
75	80	51
75	90	57
90	80	61
90	90	68

[a] The logic and assumptions underlying these computations are set out in an illustrative example in the text.
[b] The proportion of children not having had measles who, when vaccinated at 9–11 months of age, are subsequently immune to measles.

portion of measles cases averted in under 5-year-old children, as a result of the measles immunization programme.

Hypothesis 3. *Measles immunization can reduce diarrhoea morbidity or mortality rates in young children*

Field reports on the effect of measles immunization on diarrhoeal disease rates have been looked for without success, although studies of this type are under way in Bangladesh and possibly elsewhere.

The only approach, at present, to assessing hypothesis 3 is, therefore, a theoretical one using information computed during the assessment of hypotheses 1 and 2. If, among under-5-year-old children, 4% of diarrhoea morbidity (Table 1) and 30% of diarrhoea mortality (Table 2) were measles-associated, and if 54% of the measles cases could be averted by measles immunization with a coverage of 75% (Table 5), then measles immunization might reduce diarrhoea morbidity by 2.2% and diarrhoea mortality by 16% in children in this age group. Table 6 presents the results of these computations for various values of measles-associated diarrhoea morbidity (2%, 4% and 6%), measles-associated diarrhoea mortality (20%, 30% and 40%), and immunization programme coverage (45%, 60%, 75% and 90%). It is concluded that measles immunization among children aged 0–59 months may reduce diarrhoea morbidity by 0.6–3.8% and diarrhoea mortality by 6–26%. These calculations all depend on the assumption that, if a case of measles is averted by immunization, the diarrhoea (both with-measles and post-measles) associated with that case of measles will also be averted. This is only true if measles-associated diarrhoea is actually "caused" by measles (not necessarily in the sense that the measles virus causes the diarrhoea but in the more general sense that measles infection leads to diarrhoea by still unknown immunological or pathological mechanisms) and not because the susceptibilities to measles and diarrhoea are both dependent on some other factor.

The proportions of diarrhoea morbidity and mortality averted in children under 5 years of age are likely to increase as the immunization programme continues and herd immunity rises, with a consequent decrease in the proportion of children acquiring measles before the age of immunization and an in-

Table 6. Reduction of diarrhoea morbidity and mortality in the first five years of life by measles immunization at various levels of coverage

Coverage of measles immunization (%)	Proportion of measles cases averted by measles immunization (see Table 5) (%)	Proportion of diarrhoea episodes that are measles-associated (see Table 1) (%)	Proportion of of diarrhoea episodes averted by measles immunization[a] (%)	Proportion of diarrhoea deaths that are measles-associated (see Table 2) (%)	Proportion of diarrhoea deaths averted by measles immunization[a] (%)
45	32	2	0.6	20	6.4
45	32	4	1.3	30	9.6
45	32	6	1.9	40	12.8
60	44	2	0.9	20	8.8
60	44	4	1.8	30	13.2
60	44	6	2.6	40	17.6
75	54	2	1.1	20	10.8
75	54	4	2.2	30	16.2
75	54	6	3.2	40	21.6
90	64	2	1.3	20	12.8
90	64	4	2.6	30	19.2
90	64	6	3.8	40	25.6

[a] These calculations assume that measles-associated diarrhoea occurs with equal frequency among measles cases that are and are not averted by measles immunization. If failure to be immunized and measles-associated diarrhoea are both associated with an independent factor (say, low socioeconomic status), then this assumption does not hold and the impact on diarrhoea of measles immunization will be lower than predicted here.

crease in the proportion of unimmunized children acquiring measles after their fifth birthday.

As the estimated mortality reduction is considerable, there is a need for field studies to assess the role of measles immunization in reducing diarrhoea mortality. If a considerable proportion of measles-associated diarrhoea is dysenteric in nature, it may respond poorly to oral rehydration therapy in the home or at a peripheral health centre. Thus the mortality averted by measles immunization (6–26%) may be, in part, additional to that averted by oral rehydration. This would make measles immunization an especially attractive intervention, since certain other interventions might only reduce the mortality that is largely averted by oral rehydration.

Possibility that diarrhoea is caused by measles immunization. It is necessary to consider whether the above computations require modification because diarrhoea in some children may be caused by measles immunization. Only one controlled study on post-immunization diarrhoea using the further-attenuated vaccine strains (Schwarz and Moraten) has been located. This study, which was carried out in Israel (*27*) among children aged 9–47 months, showed that the period prevalence of diarrhoea during days 6–14 after immunization was 12–14% among children receiving measles vaccines (Schwartz and Moraten) and 12% among children receiving a placebo (sterile saline). A survey of 10 035 children aged between 10 and 18 months, who had been immunized against measles in England, showed that only one child (with a congenital oesophageal atresia) was admitted to hospital with diarrhoea and vomiting one week after the immunization (*18*). A recent review of experience with 131 million cases of measles immunization in the USA did not mention diarrhoea as an adverse reaction (*19*). This limited evidence suggests that diarrhoea is not an adverse reaction to the measles vaccines in current use.

The effect of undernutrition. The role of poor nutritional status in the synergism between diarrhoea and measles has not so far been mentioned in this review. There is evidence that poor nutritional status predisposes to death from both diarrhoea and measles and so it is likely that the death rate from measles-associated diarrhoea is higher among children who are nutritionally deprived. The calculations in this paper are based on data from Africa, Asia and Latin America and reflect the situation in communities with widely differing levels of undernutrition. The calculations are thus generalized across individual countries and environments. In some communities the key variables may approximate the median figures used in this paper, in which case the impact of measles immunization on diarrhoea may be as calculated here. In other communities the key variables may differ considerably from the values used here, in which case the impact of measles immunization on diarrhoea may be considerably greater or less than our calculations. It is likely that in communities where the prevalence of undernutrition is exceptionally high, the impact of measles immunization on diarrhoea mortality will be greater than estimated in this review.

FEASIBILITY

Measles immunization is well established and highly successful in some developed countries (*12*). Some developing countries have initiated measles immunization programmes that are achieving reasonable coverage in selected regions. The main operational difficulties are maintaining vaccine potency and achieving high coverage of children within the target age range (typically 9–11 months). It is expected that, as experience in measles immunization in developing countries grows, and as its benefits to child health become more widely appreciated, these operational difficulties will be overcome.

COSTS

Few developing countries as yet have national measles immunization programmes and there is little reliable information on the cost of such programmes. Table 7 provides cost data for five countries, of which the comparative costings of the EPI programmes in Indonesia, Philippines and Thailand are probably the

Table 7. Costs of immunization

Country	Immunizations	Cost per child vaccinated[a] (1982 US$)	Reference
Indonesia	DPT, BCG	4	*6*
Ivory Coast	measles	15	*30*
Philippines	DPT, BCG	6	*6*
Thailand	DPT, BCG	14	*6*
Zambia:			*24*
rural	measles	8–14	
urban	measles	2–5	

[a] Costs converted to 1982 US$ using exchange rates and GNP deflators computed from data in *International Financial Statistics*.

most reliable. Unfortunately these costs refer to BCG and DPT (rather than measles) immunization. Measles immunization may be cheaper than BCG plus DPT, since it is a single-dose vaccine. As only 10–20% of the cost of an immunization programme is due to the vaccines (*6*), the additional cost of adding measles immunization to an existing EPI programme may be low. A reason for the apparently high cost figure from Ivory Coast (Table 7) is that the reverse approach was taken, 75% of all shared EPI costs being allocated to measles immunization. This has the effect of making measles immunization appear expensive, while other immunizations appear relatively cheap.

Future research will generate improved data on the cost and impact of measles immunization and will permit cost-effectiveness comparisons of measles immunization with other diarrhoea control interventions. Care is required in the allocation of costs and benefits between diarrhoeal disease control programmes (CDD) and EPI programmes and it must be recognized that many with-measles diarrhoea deaths are recorded as measles deaths (see footnote to Table 2). On the other hand, measles immunization may avert a considerable number of post-measles diarrhoea deaths that are not currently accounted for in evaluations of the impact of measles immunization programmes (*1*).

CONCLUSIONS

A theoretical case has been made out that measles immunization can substantially reduce diarrhoea mortality among children under five years of age. Immunization with a coverage of 60% may reduce diarrhoea mortality in children aged 0–59 months by 9–18%, coverage of 75% may reduce diarrhoea mortality by 11–22%, and coverage of 90% may reduce diarrhoea mortality by 13–26% (see Table 6). The impact of measles immunization on diarrhoea mortality is likely to increase as the measles immunization programme continues and the age distribution of measles cases shifts upwards. The impact of measles immunization on diarrhoea mortality may be partly additional to the impact of oral rehydration because it averts deaths that are not prevented by oral rehydration. Community research is urgently needed to confirm or reject these theoretical suppositions and to clarify the etiology of measles-associated diarrhoea.

If community studies confirm that measles immunization can reduce diarrhoea mortality, over and above the reduction achieved by oral rehydration, detailed cost-effectiveness analyses are required to compare measles immunization with other possible interventions for averting the same diarrhoea deaths.

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RÉSUMÉ

STRATÉGIES POUR LA LUTTE CONTRE LES MALADIES DIARRHÉIQUES CHEZ LES JEUNES ENFANTS: VACCINATION ANTIROUGEOLEUSE

Cette étude est la première d'une série consacrée aux stratégies susceptibles d'abaisser la morbidité et la mortalité dues aux maladies diarrhéiques chez les enfants de moins de cinq ans dans les pays en développement. On constate actuellement dans ces pays, comme jadis dans les pays aujourd'hui développés, une nette association entre la rougeole et la diarrhée; la vaccination antirougeoleuse représente donc une arme possible dans la lutte antidiarrhéique. Sur la base de données provenant d'enquêtes sur le terrain et de calculs théoriques, les auteurs de l'étude passent en revue les effets de la vaccination antirougeoleuse sur la morbidité et la mortalité dues aux maladies diarrhéiques. De 1% à 7% des épisodes diarrhéiques et de 9% à 77% des décès par maladie diarrhéique chez les enfants de moins de cinq ans pourraient être liés à la rougeole. Une distinction est faite entre deux types de maladies diarrhéiques associées à la rougeole: la diarrhée concomitante, dont le début se situe entre la semaine précédant l'apparition de l'éruption et les quatre semaines consécutives à celle-ci, et la diarrhée post-rougeoleuse qui commence de 4 à 26 semaines après l'apparition de l'éruption. L'étiologie de ces diarrhées liées à la rougeole est inconnue, mais certains indices laissent penser qu'il pourrait s'agir d'une forme fréquemment sévère et dysentérique de la maladie, dans laquelle *Shigella* jouerait un rôle primordial. Selon des calculs théoriques, la vaccination antirougeoleuse pratiquée entre 9 et 11 mois, avec une couverture vaccinale comprise entre 45% et 90%, serait à même d'empêcher de 44% à 64% des cas de rougeole, de

0,6% à 3,8% des épisodes diarrhéiques, et de 6% à 26% des décès dus à des maladies diarrhéiques chez les enfants de moins de cinq ans. Une couverture vaccinale de 75% permettrait d'éviter 2% des épisodes diarrhéiques et 16% des décès dus à des maladies diarrhéiques. Il n'existe pas de données fiables sur le coût de la vaccination antirougeoleuse, mais d'après des statistiques émanant de cinq pays il pourrait se situer entre 2 et 15 dollars (prix de 1982) par enfant vacciné.

L'impact de la vaccination antirougeoleuse sur la mortalité d'origine diarrhéique devrait augmenter à mesure que se développera le programme de vaccination et que diminuera la proportion des cas de rougeole concernant des enfants. Cet impact viendrait s'ajouter à celui de la réhydratation par voie orale puisque la vaccination tend à prévenir des décès que n'éviterait pas le traitement. Il est urgent de procéder à des enquêtes et études de population pour confirmer ou infirmer ces suppositions théoriques, clarifier l'étiologie de la diarrhée liée à la rougeole et déterminer l'efficacité, par rapport au coût, de la vaccination antirougeoleuse en tant que stratégie visant à réduire la mortalité due aux maladies diarrhéiques.

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