Lankinen KS, Bergström S, Mäkelä PH and Peltomaa M, eds.
Health and disease in developing countries. London:The Macmillan Press Limited, 1994:163–176.

17 MEASLES AND ITS CONTROL: dogmas and new perspectives

Peter Aaby, M.Sc. (Anthropology)
Statens Seruminstitut, Epidemiology Research Unit
Artillerivej 5, DK–2300 Copenhagen S, Denmark

Badara Samb, M.D.
ORSTOM
BP 1386, Dakar,
Senegal

INTRODUCTION

The WHO estimated in 1987 that measles kills two million children annually, making it the major killer among vaccine preventable diseases. The estimate has declined in recent years to 0.9 million (1991) due to the improved immunisation coverage in developing countries (DCs). Though the accuracy of these estimates can be discussed (see below), it is clear that measles poses a major public health problem in DCs. Since the long-term effects of measles have not been included in the above estimates, measles is likely to present a larger problem than usually understood.

Measles has often been considered 'the simplest of all infectious diseases' (Maxcy). It is probably the most 'visible' infection due to a consistent clinical picture and the fact that virtually everyone contracted it before vaccination was introduced in the early 1960s. However, 'simple' does not imply that measles is well-understood. Several recent studies have succeeded in disproving common beliefs about measles.

Measles in DCs had hardly been studied before the 1960s.[1] There are few community studies of this important infection. This chapter presents some divergent interpretations of existing data on measles. In order to improve control of measles, much further research is needed.

SEVERE MEASLES

Clinical and immunological features

The following account focuses on measles mortality, which in epidemiological studies means any death occurring within one month of the rash. The common complication leading to death is pneumonia. In one South African study of 21 children who died of pneumonia, one-quarter had active measles virus pneumonia, half had adenovirus or *Herpes simplex* pneumonia and one quarter had bacterial bronchopneumonia due to *Klebsiella*, *Staphylococcus*, or *Pseudomonas*.[2] In some areas, diarrhea has been found to be a major complication of measles. *Salmonella* has been associated with particularly severe diarrhea following measles.

Giant cell pneumonia without a rash has been reported in children with kwashiorkor dying of measles, similar to what happens in leukemic children. Malnourished children with severe measles excrete giant cells for up to 4 weeks. This would suggest that they excrete more virus and are infectious for a longer period than children with measles in industrialised countries.[1]

Immunological studies indicate that severe measles measured in terms of death or pneumonia is associated with a low lymphocyte count (≤ 2.000 cells/ml), raised complement

Table 17.1. Measles case fatality rates (CFR) in prospective community studies.[9]

Country	Immunization*	CFR (number of measles cases)	
		0–4 years	All ages
Africa – Rural			
Guinea-Bissau	NI	34% (101)	24% (162)
Gambia	NI	22% (259)	
Senegal	NI	20% (44)	13% (68)
Senegal	NI	18% (537)	
Kenya	I (20%)	8% (331)	6% (424)
Nigeria	NI	7% (222)	
Africa – Urban			
Guinea-Bissau	NI	21% (356)	17% (459)
Guinea-Bissau	I	15% (124)	14% (161)
Zaire	I	6% (1069)	
Other areas – Rural			
Guatemala	NI	5% (292)	4% (449)
Guatemala	NI	4% (231)	3% (276)
India	NI	3% (72)	1% (181)
Bangladesh	NI	4% (510)	4% (896)
Bangladesh	NI	2% (3458)	
Other areas – Urban			
India	NI	0% (318)	

* NI=no immunization; I=immunization programme (% coverage)

component C3, low antibody response and depletion of T-helper and T-suppressor cells.[3]

Though emphasis is on mortality as the expression of severe measles, measles virus may have many other severe consequences. In one study from Nigeria, 25 per cent of the children lost 10 per cent or more of their weight during measles.[1] Measles often precipitates kwashiorkor. It may lead to *cancrum oris* (Chapters 28 and 54) and is one of the major causes of deafness (Chapter 37). Most important is the fact that measles often precipitates blindness (Chapter 36).[4] Several studies from Africa have shown that more than 50 per cent of childhood blindness is related to measles infection. The mechanisms are still under discussion, but one study from Tanzania found that measles-precipitated blindness was associated with vitamin A deficiency (50 per cent), herpes simplex infection (21 per cent) or use of traditional eye medicine (17 per cent).[4] It is not clear whether vitamin A deficiency was a preexisting condition or a result of the acute infection.

Popular beliefs

In most cultures measles has a specific name and is often a feared disease. In studies from West Africa, a good correspondence has been found between parental diagnosis and clinical or immunological findings. There may be some underdiagnosis of measles cases. However, a positive parental diagnosis is nearly always correct.

The popular understanding of measles is usually centred around the rash. In some societies, the rash is believed to be the menstrual blood retained during pregnancy which comes out.[1] It is a common belief in all continents that if the rash stays inside the body and does not come out the disease will be more severe. In a sense this is a correct observation since the prodromal period is prolonged in severe cases and in very severe epidemics, a large proportion of the deaths have occurred before the appearance of the rash.[5,6] Given this emphasis on the rash, therapeutic practices are often geared to get the rash out, e.g. by

rubbing the skin with palm oil or kerosene. In West Africa, attempts are made to maintain the temperature since it is believed that cooling will keep the rash inside the body. Thus, the child may be bedded in hot sand, covered with blankets and not washed or given cold water to drink since this could cool the body, all practices that are likely to aggravate dehydration.

Though some believe that measles can be caught several times, there is often a close correspondence with Western medical understanding; everybody has to get measles but only once in a lifetime and it is more severe if caught as an adult. However, in contrast to the scientific understanding that measles infection in vaccinated children is due to vaccine failure, African mothers often believe that vaccinated children get milder measles infection.[7]

ESTIMATING MEASLES MORTALITY

The WHO estimate (1987) of two million measles deaths annually was based on the assumption that of the 83.3 million children in DCs surviving annually to the age of one year, only 24 per cent were protected by vaccination. The remaining children all get measles and the case fatality rate (CFR) of these children is 3.2 per cent on the average. The CFR has been assessed to be 3–4 per cent throughout Africa and Asia, and 2 per cent in the major countries of South America.[8] It is very difficult to assess the CFR in many of these areas due to lack of reliable registration. The available data of CFRs in longitudinal community studies are summarised in Table 17.1.[9] With few exceptions, the CFRs in these studies exceed the WHO estimate. For West and Central Africa, mortality in the community may well be two to three times higher than the estimated 3 per cent. During recent years, immunisation coverage has increased, and by 1991 the estimated number of deaths from measles had decreased to 0.9 million children.

INTERPRETATIONS OF SEVERE MEASLES

An adequate understanding of the epidemiology of measles should be able to account for the major variations in measles mortality as outlined in Table 17.2.[9–20] Measles virus is considered to be stable, and differences in its virulence are therefore unlikely to play a major role in the pathogenesis of severe measles.[1]

Table 17.2. Relative contrasts in measles case fatality rates (CFR).

High CFR	Low CFR
Africa	Asia, Latin America
West Africa	East Africa
Rural areas	Urban areas
Virgin soil epidemics	Endemic situation
Europe 1900	Europe 1940
Extended/polygynous families	Monogamous families
High birth rate/many siblings	Low birth rate/few siblings
Short spacing	Long spacing
Twins	Singletons
Multi-family dwellings	Single family housing
Small apartments (few rooms)	Many rooms
Institutions (refugee camps, military camps, orphanages)	
Genetic (HLA-Aw32)	
Chronic conditions: TB, leukemia, kwashiorkor	
Infants, adults	Children
Males	Females
Female closed societies	
Females	Males
Unimmunised	Immunised
	Immunoglobulin prophylaxis
	Treated with Vitamin A

Table 17.3. State of nutrition and severity of measles in community studies (w/h = weight-for-height; w/a = weight-for-age; muac = mid upper-arm circumference).

Country	Age (years)	Index	Nutritional status (% standard) Fatal cases *(N)*	Controls *(N)*	Type of control
Bangladesh	0–9	w/h	86% (33)	88 % (33)	No measles
	0–2	w/h	93% (4)	86 % (148)	Measles survivors
	3–9	w/h	85% (5)	88 % (170)	Measles survivors
Guinea-Bissau	0–4	w/a	87% (17)	90 % (27)	Measles survivors
	0–5	w/a	92% (60)	92 % (1188)	All children
		h/a	97% (60)	97 % (1172)	All children
		w/h	97% (60)	98 % (1167)	All children
	0–1	w/a	88% (10)	89 % (36)	Measles survivors
Kenya		muac	84% (31)	86 % (36)	Measles survivors
Zaire	0–4	w/a	12% (6/51)	<3rd; 53%	<50th centile
		w/h	6% (3/50)	<3rd; 56%	<50th centile
		muac/a	12% (6/51)	<3rd; 55%	<50th centile
Gambia		w/a	29% (2/7) of fatal cases were malnourished. More than 29% malnourished among controls		
Gambia	0–2	w/a	State of nutrition did not affect severity		
Nigeria		w/a	No relation between malnutrition and severe measles		
India	0–2	w/a	Among malnourished children, 29% had severe measles and 29% lost weight; among children of normal nutrition 33% had severe disease and 56% lost weight		
India	0–4	w/a	Severely malnourished children (<60% of w/a) had the same rate of complications and the same immunological responses		
Philippines			Well-nourished and undernourished had similar course and outcome of their illnes		

Instead, most explanations have emphasised host and care factors, particularly malnutrition, age at infection, type of complications and availability of medical care.[1,17]

Host and care factors

Malnutrition. Only one community study, from Bangladesh, has documented higher mortality among malnourished children. In this study, 2019 children aged 12–23 months were followed for 2 years. During this period, children with a weight-for-age (w/a) of less than 65 per cent of standard had a mortality risk of 1.5 per cent compared with 0.6 per cent for the children with a w/a of more than 65 per cent.[18] However, this comparison may be partly confounded because it is based on deaths in relation to the total population rather than in relation to the number of children catching infection. Since children from large families have lower w/a and a higher risk of contracting measles, part of the reason for the higher risk of dying of measles among children under the w/a percentage of 65 may be a higher incidence of measles. Furthermore, in this community, females had lower w/a and a higher CFR in measles. overrepresentation of females in the < 65 per cent group could also partly explain the higher mortality.

Table 17.4. Case fatality rate (CFR) in measles infection by age and type of exposure. Bandim, Guinea-Bissau, 1979.

Age (months)	CFR (%) (deaths/no. ill)		
		Houses with multiple cases	
	Isolated cases	Index cases	Secondary cases
0–5	0% (0/1)		24% (4/17)
6–11	14% (1/7)	0% (0/15)	42% (11/26)
12–23	11% (2/19)	21% (3/14)	33% (14/43)
24–35	0% (0/10)	14% (2/14)	38% (14/37)
36–59	0% (0/10)	5% (2/38)	13% (5/39)
60+	33% (1/3)	6% (2/36)	0% (0/50)
Total	8% (4/50)	8% (9/117)	23% (48/212)

Hence, there seems to be no evidence (Table 17.3) that malnutrition is a major determinant of measles mortality. Even though future studies may find some association between nutritional state and measles mortality, it could explain only a small part of the variation in mortality. For example, children in West Africa have a better nutritional status than children in Bangladesh or India but the mortality is much higher in West Africa (Table 17.1). In Guinea-Bissau, weight-for-height (w/h) of children under 3 years of age was 98 per cent of standard and the CFR was 25 per cent. In Bangladesh, w/h was only 87 per cent, but the CFR was no more than 3 per cent.[9]

Vitamin A deficiency has been suggested as a major determinant, but no community study has examined whether the pre-morbid vitamin A status had an effect on the outcome. This is possible, but West Africa, where CFR is highest, is not known to be the most deficient area in vitamin A. The observation that survival was increased among patients who received vitamin A treatment may reflect the fact that severe measles had depleted vitamin A stores rather than indicating that vitamin A deficiency was the cause of the severe disease.[16]

Age at infection. Since the CFR is usually highest among the youngest children, it has been suggested that measles mortality should be particularly high where many children contract measles at an early age.[10,17] From this perspective, it has been predicted that measles mortality would be lower in rural areas, where age at infection is higher, than in urban areas. However, there is good evidence that the CFR is higher in rural than in urban areas.[9]

It has also been suggested that the decline in measles mortality in the industrialised world at the beginning of this century is related to an increase in the age at infection. There is, however, no data to show that the age at infection did in fact go up when fertility rates decreased, although children in small families supposedly get infected at a later age.[10] On the contrary, it is known that the age at infection fell from 5.5 to 4.4 years between 1944 and 1968.

In Guinea-Bissau, CFR fell as the nutritional state deteriorated and the mean age at infection decreased.[19] Differences in age of infection explain only a small part of the variation in mortality across different societies. The major differences are due to different age-specific CFRs.[1]

Type and severity of complications. Differences in the incidence of potential complicating infections and pre-existing diseases (tuberculosis, kwashiorkor etc.) may account for some of the variation in severity of measles. For example, intercurrent malaria has been suggested to be the major cause of the high mortality in Africa. Furthermore, also the severity of the underlying measles infection could influence the risk of complications. For example, in Guinea-Bissau, secondary cases had more pneumonia and diarrhea.

Availability of medical care. It is usually assumed that mortality is lower where medical assistance is available.[17] Reconvalescence serum and later immunoglobulin (Ig) undoubtedly helped reduce measles mortality in the industrialised countries, because it provided protection for the most important risk group: young children exposed at home to a sibling with measles. In virgin-soil outbreaks, mortality has also been lower among individuals who received Ig. However, Ig has only rarely, if ever, been used in measles control in DCs. For the usual symptomatic treatment there are no

Table 17.5. Case fatality rate (CFR) in houses with two cases of measles. According to sex constellation.

Age group	CFR in houses with two cases(deaths/cases)	
	MF pairs	MM or FF pairs
Guinea-Bissau		
6–35 months	13% (5/39)	38% (14/37)
36–59 months	6% (1/17)	8% (2/24)
Total	11% (6/56)	26% (16/61)
Senegal		
4-41 months	8% (7/84)	12% (17/137)
42-65 months	0% (0/54)	4% (2/45)
Total	5% (7/138)	10% (19/182)

good community studies which have analysed whether the type of medical care available has an impact on mortality or not.

Transmission factors

In contrast to the emphasis on host factors in the pathogenesis of severe measles, recent studies from Africa have emphasised that variation in transmission may influence the severity of infection.[9] Children contracting infection from someone outside the home, the so-called index cases, have a much lower CFR, comparable with the mortality of children in houses with only a single case (Table 17.4). These tendencies have been found in several studies from Senegal, The Gambia, Guinea-Bissau, Kenya, Bangladesh, England, Germany and Denmark.[9]

Intensive exposure and dose of infection. Confounding factors cannot explain why secondary cases have higher mortality than index cases.[9] Since secondary cases are more intensively exposed within the house than index cases, it may be the intensity of exposure which determines severity of infection. Secondary cases presumably absorb a higher dose of measles virus and may also be more likely to contract complicating infection than the index case. The possibility that dose of measles virus is important for outcome of infection has rarely been considered, although, in experimental animal studies, it is well known that a high dose leads to a short period of incubation and a high CFR. Human studies seem to indicate an association between short period of incubation, long prodromes and more severe course of infection..[5,6]

Cross-sex transmission. Surprisingly, studies from Guinea-Bissau and Senegal have found that secondary cases have a higher mortality when infected by someone of the opposite sex instead of their own sex.[20] As a consequence, mortality was higher in houses where a boy and a girl had measles together compared with houses with two boys or two girls (Table 17.5). There is no apparent sociological reason why cross-sex transmission should lead to more severe infection.

Variation in exposure and mortality

If exposure is a major determinant of mortality, it is expected that the proportion of secondary cases is high where CFR is high. That is indeed what has been found so far (Table 17.6). For example, there is an enormous difference in the risk of intensive exposure between the two countries which we compared before; in Guinea-Bissau 61 per cent of the children under 3 years of age were secondary cases and the CFR was 25 per cent, in Bangladesh 14 per cent of the children of the same age group were secondary cases and the CFR was only 3 per cent.

The emphasis on exposure as a risk factor in severe measles suggests that socioeconomic and cultural conditions leading to the concentration of many susceptible children are major determinants of the risk of high mortality. Hence, institutions like polygyny, extended families, high birth rate and multifamily dwellings would increase the risk of intensive exposure and mortality.[9]

Geographical variation. There is no doubt that West Africa has the world's highest CFR in measles. This is related to the fact that West Africa has the highest proportion of polygynous families and the largest compounds and households.[9]

Table 17.6. Frequency of secondary cases and case fatality rate (CFR) in measles community studies.

Country	Age (years)	Rate of secondary cases *(N)*	CFR *(N)*
Guinea-Bissau	0–2	61% (203)	25 % (203)
Senegal	0–2	56% (171)	20 % (171)
England (1885)	0–2	46% (90)	14 % (100)
Guinea-Bissau	0–2	45% (77)	14 % (77)
Guatemala	0–4	38% (260)	5 % (292)
Kenya	0–2	22% (999)	6 % (592)
Bangladesh	0–4	20% (3181)	2 % (3458)
USA	0–4	14% (71)	10 % (30)
Bangladesh	0–2	14% (156)	3 % (156)
Gambia	0–2	8% (13)	0 % (13)

The rural–urban difference in mortality is also influenced by the pattern of measles transmission. In urban areas, where measles is endemic, siblings in a household will tend to be infected at a young age and not in the same year. Therefore, the risk of becoming a secondary case is relatively small. Conversely, in rural areas, where there is a long interval between epidemics, siblings are likely to become infected at the same time. The mean age at infection will be higher than in urban areas. Thus, children in rural areas have a higher risk of becoming exposed at home as a secondary case. This should increase the mortality of rural children relative to urban ones. This pattern has been documented in Guinea-Bissau, where the same ethnic group has been studied both in an urban and a rural environment.[19]

Age. Other aspects of the epidemiology of severe measles may also be related to the risk of intensive exposure. Virtually all studies have shown that measles is most severe for the youngest children under one year of age. Usually, severity increases again for teenagers and young adults, supporting the popular belief that childhood infections are more severe for adults. This U-shaped curve (Table 17.7) corresponds not to a biological model but to a social reality. Infections are transmitted between families in the age group with a high concentration of susceptible individuals. This age may vary according to social patterns of contact, e.g. age at schooling or the frequency of kindergartens. Most children infected at the age of inter-family transmission will be index cases infected outside the house. Children infected before or after that age have a much higher risk of being infected by a sibling who has brought the disease home. Since the secondary cases are more severe, part of the explanation for the higher CFR among the youngest children and young adults lies in their higher risk of having been intensively exposed.

Sex. Sex-related difference in severity could likewise be the result of variation in the risk of intensive exposure. Several studies from

Table 17.7. Case fatality rate (CFR) by age group.

England (1963)* Age (years)	CFR *(N)*	Guinea-Bissau (1979–83)† Age (years)	CFR *(N)*
0	1.11% (21 570)	0	46.7% (15)
1	0.54% (62 942)	1	52.4% (21)
2–4	0.13% (266 984)	2	26.9% (26)
		3	40.0% (20)
		4	5.3% (19)
5–9	0.07% (294 555)	5–9	4.5% (44)
10–14	0.44% (18 059)	10–	11.8% (17)
15–	1.75% (6 272)		

* Notifications

† Community study in rural area.

Table 17.8. Mortality during nine months of follow-up for measles patients and community controls in the Gambia.[21]

Age at infection	Mortality of measles cases		Mortality of controls
	Acute	1–9 months later	0–9 months later
3–11 months	18% (2/11)	56% (5/9)	3% (3/94)
1–2 years	9% (3/35)	13% (4/32)	2% (3/190)
3–4 years	6% (2/31)	7% (2/29)	1% (1/182)
5–6 years	0% (0/36)	6% (2/36)	1% (2/188)

developed countries have indicated that girls contract infection at a younger age than boys. Apparently, they contract infection more easily outside the home. Therefore, boys should have a greater risk of being exposed at home, and this may explain some of their excess mortality in industrialised countries. However, in cultures where girls are more confined to the home and boys attend school more frequently, girls may have a higher risk of being infected as a secondary case at home. In the one study from Senegal where this hypothesis has been examined, excess mortality among girls could indeed be explained on this basis.[20]

Decline in mortality. At the turn of the century, when measles mortality was high, the proportion of secondary cases in industrialised countries was very high (Table 17.6). The risk of intensive exposure within the family has been greatly reduced due to diminished family size, urbanisation and public child care. In Guinea-Bissau, measles mortality fell simultaneously with a fall in the frequency of secondary cases.[19] However, this cannot explain the whole change in mortality, because there are still secondary cases in the industrialised world and there is virtually no mortality any longer. Though *improved medical treatment* may have played some role, it is likely that positive feed-back in disease transmission has been important. Studies from Denmark and Kenya have shown that the severity of secondary cases depends on the severity of the index case. When the proportion of secondary cases is reduced in a community, more and more of the index cases will be mild due to infection from mild index cases rather than severe secondary cases. The implication is that secondary cases also become milder and that the general severity of measles in the community is gradually reduced.

Delayed impact of measles

Acute measles mortality is counted as death within one month of a measles rash. Though it is well recognised that measles may give rise to prolonged complications, such as diarrhea and respiratory problems, until recently there have been no studies of the long-term impact of measles infection. Within the last years, however, it has become clear that measles may have a profound effect on morbidity and mortality, also after the acute infection.[8,21]

Delayed mortality after measles infection. The five studies available from West Africa all suggest that delayed mortality is at least two to three times higher among previous measles cases than among controls.[8] One of these studies from Gambia is summarised in Table 17.8.[21] After acute infection and during the 9 months of follow-up, mortality among the previous measles cases was nine times higher than among community controls. These results could be confounded by background factors distinguishing cases from controls. However, the difference in mortality seems so large that confounding is unlikely to be the whole explanation.

Studies to date suggest that the risk is particularly high for children who have had measles before one year of age. Most studies have emphasised the period of 1–6 months after infection as the critical one. Intensity of exposure has also been found to be important for the long-term consequences. Hence, index

cases have lower post-measles mortality than do secondary cases.

There is some indication in studies from Guinea-Bissau and Senegal that excess mortality may not be very high if comparison is made with non-immunised controls rather than immunised controls. Hence, part of the excess mortality after measles infection may in fact be due to a non-specific beneficial effect of measles immunisation among the controls selected for comparison.

Early exposure to measles. Several studies from Guinea-Bissau have shown that children who live in houses where measles occurred during the first 6 months of their life had a mortality three to four times higher than community controls between 3 months and 5 years of age.[22] The difference in mortality could not be explained as a result of confounding factors. Diarrhea deaths were particularly common among the exposed children. Excess mortality was found among both the 20 per cent who had a history of measles and among those who did not. It is, however, possible that some of the children without a history of measles had, in fact, subclinical measles and that this infection could explain some excess mortality.

The delayed, fatal form of measles known as subacute sclerosing panencephalitis (SSPE) occurs mostly among children who have had measles early in life.

Exposure during pregnancy. Measles during pregnancy has been a rare event in the industrialised countries in the last decades. However, at the turn of the century it was a dreaded condition for both the mother and the fetus. Studies from virgin-soil epidemics have shown that pregnant women with measles have a higher mortality than non-pregnant women. In Greenland, mortality was 4.8 per cent (4/83) among pregnant but only 0.6 per cent (4/641) among other women aged 15–34 years.[6] Studies from Guinea-Bissau suggest that exposure during pregnancy may be dangerous even when the mother does not develop clinical measles. Children of a mother who lived in a house with a case of measles had four times the risk of being stillborn or dying within the first week of life (Table 17.9).

Conclusion. So far there are very few studies of the delayed impact of measles. There may therefore be doubts about the magnitude of the problem, and there are no explanations for the mechanisms leading to delayed mortality. However, this area of study is potentially very important because it may ultimately demonstrate that measles virus has a much higher impact than commonly assumed.

Immunity

Measles immunity is usually considered an either–or phenomenon. However, observations from DCs suggest that in some situations, immunity is only relative.

Maternal immunity. Children of immune mothers are usually assumed to be protected by maternal antibodies, at least to the age of 6 months. However, in DCs cases of measles are seen in children down to the age of 2–3 months without the mother necessarily having measles concurrently. When children younger than 6 months have measles, it almost always follows intensive exposure at home (or at a hospital). Antibody studies also indicate that many children under 6 months develop subclinical infection when exposed to a sibling with measles.

Vaccine-induced immunity. It has been commonly assumed that measles vaccine would produce a protective and lifelong immunity similar to natural infection. The large number of cases of measles in vaccinated children

Table 17.9. Perinatal mortality among children of mothers exposed to measles during pregnancy, Bandim, Guinea-Bissau, 1979. OR = Odds ratio (95 % confidence interval).

Type of mortality	Perinatal mortality risk (deaths/at risk)		
	Exposed	Controls	OR (95% CI)
Stillbirths	6.5% (7/107)	1.4% (5/346)	4.8 (1.7–13.8)
Died 1st week	9.0% (9/100)	2.6% (9/341)	3.6 (2.3–5.6)
Perinatal	15.0% (16/107)	4.0% (14/346)	4.2 (2.1–8.5)

observed in DCs have therefore been explained as vaccine failures, i.e. children who did not seroconvert due to improper storage or handling of the vaccine or because of interference from maternal antibodies. This explanation contrasts with popular perceptions in many parts of Africa that vaccinated children have a milder form of infection. Epidemiological studies have shown that mothers are correct. Vaccinated children who develop measles have lower mortality.[7] Vaccinated children are more likely to be secondary cases, which suggests that they contracted measles only because of the intensity of exposure. This would indicate that some of the children have indeed had partial immunity from vaccination. There are also a few reports of children who seroconverted after vaccination and subsequently developed clinical measles.

The relative importance of different causes of vaccine failure are likely to vary in different regions. It is important to detect these causes in measles control programmes. In most regions, vaccine failure may be due to breakdown of the cold chain and interference from maternal antibodies. However, it is important to recognise that partial immunity exists, since this has implications for the current vaccination strategy (see below).

Immunisation strategies

Measles vaccination and mortality. Since measles is believed to kill mostly malnourished children, it has sometimes been suggested that measles immunisation may have a limited impact on survival. It is thought that children saved from dying of measles will die of other infections instead. By this reasoning, nutrition and nutritional education is considered more important than immunisation. Since intensity of exposure is the major determinant of severe measles, it may not be the particularly weak children who die. Neither would they be more likely to die of other infections if surviving measles. Immunisation against measles should therefore have strong impact on mortality.

A study from Zaire is often quoted as having shown that immunisation had little impact on mortality.[23] In fact, the study found that in the critical period for child mortality, between 7 and 35 months of age, vaccinated children had a mortality of 3.8 per cent, i.e. 45–60 per cent lower than the three unvaccinated control groups (7.0–9.5 per cent). In spite of large variations in social settings and organisations, other studies of the impact of measles immunisation have found very similar trends. The available studies from West Africa, Zaire, Bangladesh and Haiti suggest a reduction in child mortality after the age of vaccination of at least 30 per cent, and eight of the 12 studies found a reduction of 45–50 per cent or more. The beneficial impact of measles vaccination has been found both in urban and rural areas and in countries with both high and low overall child mortality.

All studies suggest that the reduction in mortality is larger than would be expected from a reduction in the number of acute measles deaths. One possible explanation is in the delayed excess mortality of children with measles. This effect is likely to be preventable by vaccination as well. Thus, there is no support for the view that measles infection functions as a mechanism of natural selection, merely taking the weakest children likely to die anyway. However, the impact of measles immunisation on mortality seems larger than can explained by the prevention of the acute and long-term consequences of measles.[8]

Herd immunity effect of vaccination. Apart from the direct effect of vaccination in protecting some children from catching measles, vaccination also has an indirect effect. When some individuals are vaccinated in a community, there are fewer families where several children get measles simultaneously. As a consequence, the risk of intensive exposure is reduced. The implication is that vaccination also reduces mortality among unvaccinated children who catch measles.[19]

Measles immunisation policy in developing countries

The EPI (Expanded Programme on Immunization) of WHO recommends immunization with a *single dose of Schwarz attenuated live measles vaccine at the age of 9 months in DCs.* Due to maternal antibodies, not more than 80–90 per cent may seroconvert at this age. In the industrialised countries, measles vaccination is delayed to the age of 15 months or later in order to prevent interference from maternal antibodies. However, if immunisation was delayed that long in DCs, an unacceptably large proportion of the children would already have contracted measles before the age of vaccination. The 9-month age limit is a compromise between the need to protect children early and the lower seroconversion rate at lower ages.

Studies from Kenya on measles incidence and seroconversion rate in different age groups predicted that vaccination at 8 or 9 months would yield the same number of prevented cases, whereas postponement of vaccination to 10 months would imply that too many children had already had measles. The age of 9 months was then selected because vaccination at 8 months would mean more vaccine failures, presumably leading to popular lack of confidence in the vaccine. However, this line of reasoning is debatable. Very often mothers view mild measles as an advantage of the vaccine and not as a reason to lack confidence. If vaccinated children indeed have milder measles and early cases have strong delayed mortality, it might save more lives to vaccinate at 7 or 8 months instead of waiting to 9 months of age.[7]

Alternative immunisation strategies. With vaccination at 9 months, as many as 10–20 per cent may not seroconvert, and as many as 5–10 per cent of the children may get measles before this age. To find a strategy which could overcome these problems, experiments have been made with high-dose measles vaccine. The Edmonston–Zagreb (EZ) high-titre vaccine induces a good serological response and provides clinical protection even when given as early as 4–5 months. In 1989, WHO therefore recommended the use of EZ high-titre vaccine from the age of 6 months in areas with a high incidence before 9 months. However, subsequent follow-up to the age of 3 years in studies in Guinea-Bissau, Senegal and Haiti has documented that girls who have received high-titre vaccines had significantly higher mortality than girls who had received the standard low dose Schwarz measles vaccine. There was no difference for the boys.[24] Hence, WHO has been obliged to change the recommendation back to one dose at 9 months of age.[25]

It is worth emphasising that there is no simple explanation of the higher mortality among female recipients of high-titre vaccines. The difference in mortality had nothing to do with differences in protection against measles.[24] Since the high-titre vaccine was not associated with higher mortality in areas with low mortality or compared with control children who had not received the standard measles vaccine, it seems unlikely that the vaccine is dangerous in itself. Hence, the main problem may be that it does not entail the non-specific beneficial effect associated with standard Schwarz measles vaccine.

Given the failure of high-titre vaccination, researchers are looking for a new vaccine. At the present time (1993), it seems likely that this may be a genetically engineered vaccine based on the canarypox virus as carrier. However, if the failure of the high-titre strategy is really due to the standard vaccine having non-specific beneficial effect, a new vaccine may also end up showing increased mortality compared with the standard vaccine. It may therefore be advisable to consider the benefit of a *two-dose schedule* with Schwarz measles vaccine; the first probably at six months and the second at 9 or 12 months of age. Non-randomised studies from both Guinea-Bissau and Senegal have shown much better survival for children who received standard Schwarz measles vaccine at 4–8 months of age than for children immunised at 9–11 months. *Without a vaccine which can be used at 5–6 months of age, it will be impossible to stop the transmission of measles.*

Transmission patterns and control of measles

Measles transmission depends on contact between infectious cases and susceptible individuals. *There are no infectious carriers or non-human reservoirs.* Measles is extremely infectious; when susceptible individuals are exposed at home, they nearly all catch the infection. In studies in DCs, the secondary attack rate, i.e. the proportion who develop infection after exposure at home, has been very high.

Endemic–epidemic tendencies. Theoretical studies have suggested that a population of 300 000 is needed for continuous transmission of measles. Hence, the infection is endemic only in larger cities. However, even in cities there are seasonal fluctuations and cycles in the incidence pattern, with more cases every second or third year. One important consequence of the endemic pattern is that children in urban areas are much more likely to contract infection early in life. However, since their older siblings have usually already had measles there is less risk that measles cases will occur in groups of two or more.

In smaller towns and rural areas, the pattern will be epidemic with introductions from the outside. Most of the susceptibles will be infected at the same time, after which the disease disappears again. The interval between epidemics depends on both the size of the community and its degree of isolation. In

small isolated communities there may be long intervals, up to 10–15 years. Housing traditions may also be important for the way epidemics proceed in rural areas. Where compounds are close together, the epidemic will sweep through the village, attacking most susceptibles. In dispersed villages, an introduction of measles may attack only a few compounds.

Age and institutions of transmission. Interfamily transmission of measles occurs mainly in the age group where there is a high concentration of susceptible children. Individuals outside this age range will have a higher risk of being secondary cases infected at home.

The role of health care institutions needs to be particularly emphasised. Several community studies have shown that health centres and hospitals without isolation wards play a major role in the transmission of measles. In one urban community in Guinea-Bissau having a high vaccination coverage (> 80 per cent), half of the new introductions from outside the district were due to transmission at the hospital. It is also worth noting that children who catch measles at the hospital have much higher mortality compared with those hospitalised with measles.

Control measures

Improved vaccination coverage. Improving participation in vaccination programmes must have priority in measles control programmes. Lowering the age at vaccination is likely to increase the coverage. Most studies have shown that coverage for vaccines received before 4–5 months of age (DPT and polio) is much higher than for those given at 9 months. Acceptance of the rule of vaccinating all children attending health centres, even when sick would help improve coverage significantly.

Prevention of intensive exposure. Since secondary cases are a particular high risk group, intensive exposure at home should be prevented. Control of intensive exposure has not been attempted in DCs and the cost of immunoglobulin will be prohibitive in most places. However, if the index case is detected in the early phase of the rash, the effect of vaccinating susceptible contacts should be studied. Since the vaccine has a shorter period of incubation than the natural infection, it might be possible to prevent or attenuate some of the secondary cases.

Priorities in measles control. It seems likely that the source of outbreaks in rural areas is often introduced from the cities. Transmission in the rural areas would not be continued unless constant reintroduction from the cities took place. Therefore, a priority to high coverage in urban areas may be indicated. There also seem to be good reasons to attempt containment of outbreaks in rural areas. In outbreak campaigns, the age limit for vaccination has often been set at 2 or 5 years of age. However, experience from many rural areas suggests that a large proportion of the cases occur among children who are more than 5 years old.

Countrywide control or eradication of measles. Measles is reported to have been absent from The Gambia in a 2-year period in the 1960s, shortly after major campaigns were carried out simultaneously with the smallpox eradication programme. No other DC has attempted countrywide eradication of measles. A high degree of control requires at least the following:

1) A new vaccination strategy which provides effective immunisation at the age of 5–6 months. A two-dose schedule is probably necessary to prevent accumulation of susceptible non-seroconverters.
2) Systematic vaccination at all health institutions, including pediatric departments.
3) Some initiating vaccination campaigns to prevent outbreaks among susceptible older children who have accumulated due to isolation or previous vaccination activities.
4) Annual campaigns just before the local measles season.
5) Improved surveillance and containment vaccination when measles is introduced in a community.

CONCLUSION

Severe measles has usually been understood as a mechanism of natural selection which takes the weakest children. However, available data now suggest a quite different interpretation. Not only does measles kill many normal children in the acute phase of the infection, it may also weaken many children so that they become susceptible to delayed morbidity. It seems likely that future studies of the effects of measles will show that it kills considerably more than two million children annually.

The importance of transmission factors suggests that disease specific interventions may be very important, in addition to improvements

in nutrition and hygiene.[23] It is likely that measles control is one of the most important public health interventions in terms of reducing child mortality.[1,8]

Future research

Much more research is needed to improve understanding and control of measles. Some of the major research questions include:
1) What are the pathogenic mechanisms of severe measles?
2) Why is measles infection connected with delayed morbidity and mortality?
3) How can intensive exposure be prevented?
4) Why does standard measles vaccine have non-specific beneficial effects?
5) Why was high-titre vaccine associated with higher mortality?
6) What is the basis of the sex specific effects of the disease and of the vaccines?
7) What is the best vaccine and vaccination strategy?
8) What happens to immunity when there is little re-exposure to measles? Will immunity wane and make revaccination necessary?

References

1. Morley D. Pediatric priorities in the developing world. London: Butterworth, 1973.
2. Kaschula ROC, Druker J, Kipps A. Late morphologic consequences of measles: a lethal and debilitating lung disease among the poor. Rev Infect Dis 1983;5:395–404.
3. Kiepiela P, Coovadia HM, Coward P. T Helper cell defect related to severity in measles. Scand J Dis 1987;19:185–92.
4. Foster A, Sommer A. Corneal ulceration, measles, and childhood blindness in Tanzania. Br J Ophthalmol 1987;71:331–43.
5. Aaby P, Bukh J, Lisse IM, Smits AJ. Severe measles in Sunderland, 1885: a European-African comparison of causes of severe infection. Int J Epidemiol 1986;15:101–7.
6. Christensen PE, Schmidt H, Bang HO, Andersen V, Jordal B, Jensen O. An epidemic of measles in southern Greenland, 1951. Acta Med Scand 1953;144:313–22,430–54.
7. Aaby P, Bukh J, Leerhøy J, Lisse IM, Mordhorst CH, Pedersen IR. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. J Infect Dis 1986;154:858–63.
8. Aaby P, Clements J, Cohen N. Key issues in measles immunization research: a review of the literature. Geneva: WHO, 1987. (EPI/GAG/1987).
9. Aaby P. Malnutrition and overcrowding-exposure in severe measles infection. A review of community studies. Rev Infect Dis 1988;10:478–491
10. Reves R. Declining fertility in England and Wales as a major cause of the twentieth century decline in mortality. The role of changing family size and age structure in infectious disease mortality in infancy. Am J Epidemiol 1985;122:112–26.
11. Picken RMF. The epidemiology of measles in rural and residential area. Lancet 1921;i:1349–53.
12. Babbott FL, Gordon JE. Modern measles. Am J Med Sci 1954;228:334–61.
13. Bhuiya A, Wojtyniak B, D'Souza S, Nahar L, Shaikh K. Measles case fatality among under-fives: a multivariate analysis of risk factors in a rural area of Bangladesh. Soc Sci Med 1987;24:439–43.
14. Koster FT, Curlin GC, Aziz KMA, Haque A. Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. Bull WHO 1981;59:901–08.
15. Bhaskaram P, Madhusudhan J, Radhakrishna RV, Reddy V. Immune responses in malnourished children with measles. J Trop Pediatr 1986;32:123–6.
16. Barclay AJG, Foster A, Sommer A. Vitamin A supplements and mortality related to measles: a randomised clinical trial. Br Med J 1987;294: 294–6.
17. Foster SO. Immunizable and respiratory diseases and child mortality. Popul Dev Rev 1984;10(Suppl):119–40.
18. Chen LC, Chowdhury AKMA, Huffman SL. Anthropometric assessment of energy-protein malnutrition and subsequent risk of mortality among pre-school aged children. Am J Clin Nutr 1980:33:1836–45.
19. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality decline: Nutrition, age at infection or exposure? Br Med J 1988;296:1225–1228
20. Aaby P. Influence of cross-sex transmission on measles mortality in rural Senegal. Lancet 1992;340:388–391.
21. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. Lancet 1983;i:972–975.
22. Aaby P, Bukh J, Kronborg D, Lisse IM, da Silva MC. Delayed excess mortality after exposure to measles during the first six months of life. Am J Epidemiol 1990;132:211–19.
23. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7–35-month-old children in Kasongo, Zaire. Lancet 1981;i:764–767.

24. Aaby P, Knudsen K, Whittle H, *et al.* Long-term survival after Edmonston–Zagreb measles vaccination: Increased female mortality. J Pediatr 1993;122:904-8.
25. EPI. Safety of high titre measles vaccines. Weekly Epidemiological Record 1992;67:357–361.

About the authors

Peter Aaby *is a social anthropologist by training and currently the research coordinator of a long-term community study of the impact of infectious diseases in Guinea-Bissau. He has studied measles mortality and measles control for 15 years. His other research interests include the epidemiology of diarrhea and HIV-2, and – medical thinking.*

Badara Samb *has worked as a physician for 5 years on the impact of measles and high-titre measles vaccination in a rural community in Niakhar, Senegal. He is currently writing a thesis on the short- and long-term consequences of measles infection and measles immunizations.*

HEALTH AND DISEASE IN DEVELOPING COUNTRIES

Kari S. Lankinen
Staffan Bergström
P. Helena Mäkelä
Miikka Peltomaa

MACMILLAN