Lessons for the past: Third World evidence and the reinterpretation of developed world mortality declines

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Abstract

Measles is the largest single killing infection of children in the world, and it is likely that its toll is heightened by the occurrence of a serious delayed effect of early infection. Variations in measles mortality, and in the seriousness of infection, have often been explained in terms of nutritional factors, but intercountry comparisons within the Third World fail to bear this out. In this paper an alternative interpretation is developed, based on the severity of the infective dose to which individuals are exposed. It is shown that this can account for a wide variety of observations which are inexplicable on the nutritional hypothesis, and can also explain the severity of virgin-soil epidemics without reference to the effects of genetic selection. The exposure hypothesis predicts that measles vaccination should have a marked effect on childhood mortality as a whole, and this prediction is born out in practice. The success of this interpretation has important implications for our understanding of historical mortality declines in the developed countries, particularly the decline in smallpox mortality.

Introduction

The interpretation we adopt of morbidity and mortality patterns in the past necessarily reflects our current understanding of the biological and social causes of severe infection and high mortality. Given the belief of the 'Second World War generation' in the importance of nutrition, hygiene and medical care, it is no surprise that declining mortality in the industrialized world should have been interpreted in such terms. The relative importance of these factors has been the subject of much discussion, and nutritional improvement (McKeown, Brown and Record 1972), sanitary reform and improved personal hygiene (Razzell 1974), and advances in treatment stemming from medical research, have all had their partisans. Other writers have argued, more modestly, that no good explanation yet exists for the dramatic fall in the severity of many infectious diseases in the industrialized world before the advent of antibiotics (Lancaster 1952).

Underlying these different interpretations is a rather limited set of factors which are, in principle, capable of explaining why infections that are nowadays relatively harmless should so often have proved fatal in the days of severe child mortality. These factors can be grouped under three headings: '**host factors**', aggravating the infection: malnutrition, young age at infection, genetic susceptibility; '**transmission factors**': greater exposure, more virulent strains of pathogen, synergism between infections; and **treatment and medical-care factors**: ineffective or aggravating treatment, non-use of effective treatment and preventive activities.

Most attempts to explain major historical or regional variations in child mortality patterns focus on one, or a few, of these factors, and it is usually the first group, the host factors, which are singled out (McKeown et al. 1972; Reves 1985). This choice has obvious implications for how we conceptualize the social production of health (Mosley and Chen 1984), and for our understanding of the historical process of health transition. Clearly, how we understand the mechanisms of severe and fatal infection

will affect the direction of sociocultural and historical investigations. If this understanding is not correct the latter are unlikely to generate information of any use in public-health planning or in development projects aiming at health improvements.

I shall argue, based on my work in Guinea-Bissau, that interpretations based exclusively on host factors are likely to be too limited in their scope; if not simply wrong. Research on the determinants of measles mortality suggests that a number of other factors are more capable of explaining the known regional and historical variations in its severity. These factors are probably implicated in other disease too, and they may be 'good to think with' when we try to understand the social production of health in general.

In the present paper the alternative mechanisms potentially responsible for severe forms of infection ('severe infection') will be briefly summarized. It would be interesting to apply the same principles to historical data on health, but my work in Guinea-Bissau has left me no time for primary research on such material. I shall therefore merely attempt to show the usefulness of this approach by reviewing current interpretations of some historical health issues: the causes of the decline in measles mortality in the industrialized world, sex differences in severity of infection, the causes of particularly high mortality in virgin-soil epidemics, and the role of smallpox control in the industrialized world's mortality decline. I hope that this will support my view that the mechanisms governing severe infection must be viewed more broadly if we are to understand the socioeconomic and cultural processes which produce health and disease.

Host or transmission factors?

Measles is the single largest killing infection in the world where children are concerned, with a death toll currently estimated at around 1.5 million each year (Aaby 1989, 1991a). Our understanding of this infection and variations in its severity thus has important health-policy implications. For measles, as probably for many other infections, the dominant approach has been to search for distinctive features among those individuals who die or suffer a severe infection, that is, the host factor approach (Aaby 1991a). It is assumed that there must be something wrong with these people since they die where most others survive the illness.

Those who die are seen as somehow weaker than other individuals, reconfirming our underlying cultural notion of 'survival of the fittest'. Thus, severe measles has been explained particularly with reference to malnutrition, the age at infection, genetic susceptibility and underlying diseases. There may be something to the emphasis on host factors in the developed countries since here very few individuals die, and these are mostly children previously affected by an underlying disease such as leukemia, AIDS or hereditary problems such as Down's Syndrome. But this perspective has little to offer where major regional and historical variations in case fatality rates (CFRs) are concerned.

Thus the nutritional hypothesis would lead us to expect much higher measles mortality in Bangladesh than in, for example, Guinea-Bissau as the state of nutrition is substantially better in the latter country. However, as Table 1 shows, the reverse is the case. The CFR is many times higher in Guinea-Bissau than it is in Bangladesh. Furthermore, there are no community studies to show unequivocally that nutritional state prior to infection has an effect on the latter's outcome, and there are several studies which have shown that it had no effect (Aaby 1988b).

Table 1
State of nutrition (weight/height) and measles case fatality ratio (CFR), children under three years of age only

	Weight/height	Measles CFR

	%	%
Bangladesh	87	3
Guinea-Bissau	97	24

CFRs are highest among the youngest children, and this has led some writers to argue that age at infection is a major determinant of the level of severity of measles in the community, and hence that changes in age at infection could explain changes in severity (Reves 1985). It has thus been predicted that measles mortality will be higher in urban areas than in the countryside as the age at infection is generally lower in the former (Davis 1982; Foster 1984). These propositions are not supported by data from developing countries. All community studies suggest that the CFR is higher in rural areas than in urban areas (Aaby 1988b). Within a region, CFR may in fact be higher where mean age at infection in the community is highest. Thus we have shown that mortality risks from measles in rural Senegal are highest in the smallest villages where the interval between epidemics is longest, and the age of infection is highest (Pison, Aaby and Knudsen 1992).

Transmission factors

Major host factors do not seem to contribute much to a better understanding of variations in measles mortality, and it may be better to look for factors intrinsic to the infection itself rather than to inter-individual differences in levels of resistance.

Intensity of exposure and dose of infection

A common feature found in most circumstances where measles has a high acute CFR is that many individuals have contracted the infection simultaneously. In several outbreaks in Guinea-Bissau we found that age-specific mortality was considerably higher in houses with multiple cases than in those with only a single case (isolated cases) as is shown in Table 2 . This association has been confirmed in all the other studies in which it has been tested (Aaby 1988b, 1989), and although in principle it might arise from underlying differences in the characteristics of households with different numbers of children, it has been possible to test empirically whether it reflects variations in the intensity of exposure to infection.

Table 2
Case fatality ratio in measles infection according to age, clustering and type of exposure, Bandim, Guinea-Bissau, 1979

	Case fatality ratio % (deaths/no. ill)			
		Houses with multiple cases		
Age (months)	Isolated cases %	Index cases %	Secondary cases %	
0–5	0 (0/1)	0	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)**

Source: Aaby (1989).

All of the isolated cases can be classified as 'index cases' infected from someone outside the home. Some of the multiple cases are secondary cases infected by an index case in the same house, and others are index cases who have contracted the infection elsewhere (Table 2). Where several cases occur in the same house the secondary cases will, presumably, have been more intensively exposed than was the index case. Difference in the severity of infection between index and secondary cases have now been examined in several studies from developing countries, as well as in reanalyses of historical data from Europe (Table 3). All these studies have found a significantly, or nearly significantly, higher mortality among secondary cases. Usually the latter's CFR is at least two to three times higher than that of the index cases.

In the studies from Guinea-Bissau, isolated cases display very similar mortality rates to those of index cases in multiple-case households (see Table 2) suggesting that the contrast between single and multiple cases is not due simply to differences in genetic constitution, sociocultural and therapeutic practices, or the risk of complications in families of different size. The difference between index and secondary cases could, however, be confounded by higher general mortality in the larger families which would also have a higher proportion of secondary cases. This possibility has been examined in studies from Kenya (Aaby and Leeuwenburg 1990) and Copenhagen (Aaby 1988a), and the relative risk (RR) between index and secondary cases was found to be the same regardless of family size.

Maternal fatigue could also be a confounding factor if mothers provided less care for secondary cases because they already had to care for an index case. However, an analysis of data from several epidemics in Guinea-Bissau showed that the mortality of secondary cases who had the same mother as the index case (25%, n=55) was no higher than that of other secondary cases (42% n=60) (Aaby et al. 1988c). Thus, differences in maternal care due to fatigue are unlikely to explain the excess mortality of secondary cases.

Table 3
Severity of measles infection according to type of exposure in different community studies

Country (reference)	Age	Case fatality ratio % (deaths/no.ill)		Relative risk (95% C.I.)
Urban studies				
Guinea-Bissau (Aaby 1989)	0–4	8 (10/128)	30 (48/162)	3.8 (2.1–6.7)
Guinea-Bissau (Aaby et al. 1988a)	0–4	3 (1/37)	38 (10/26)	14.2 (3.4–59.5)
Guinea-Bissau (Aaby et al. 1988a)	0–4	5 (3/66)	17 (14/81)	3.8 (1.3–11.4)
England (Aaby et al. 1986a)	0–2	8 (4/48)	22 (8/36)	2.7 (0.9–7.8)
Copenhagen (Aaby (1988a)	0–2	11 (28/252)	27 (49/183)	2.4 (1.6–3.6)
Rural studies				
Guinea-Bissau (Aaby 1989)	0–4	7 (1/15)	38 (33/86)	5.8 (1.4–24.5)
Senegal	0–4	4 (8/198)	14 (37/226)	3.4 (1.7–6.7)

(Garenne and Aaby 1990)							
Kenya	0–4	3	(11/381)	7	(21/287)	2.5	(1.3–4.9)
(Aaby and Leeuwenburg 1990)							
Bangladesh	0–2	1	(1/134)	18	(4/22)	24.4	(5.6–106.1)
(Koster 1988)							
Bangladesh	0–4	15	(38/2551)	3	(17/630)	1.8	(1.0–3.1)
(Bhuiya et al. 1987)							
Germany	0–14	2	(2/93)	11	(10/95)	3.7	(1.1–12.1)
(Pfeilsticker 1863)							
Ratio of severe cases							
Gambia	0–23	7	(3/41)	31	(4/13)	4.2	(1.2–15.3)
(Lamb 1988)							

Table 4
Case fatality ratio among secondary cases of measles according to the number of index cases, Copenhagen, 1915–1925 and Kenya 1974–1981

Country (reference)	Age (years)	1 Index case		>2 Index case		Relative risk[a]	
Denmark	0–4	18	(28/152)	35	(15/43)	1.8	(1.1–3.1)
Kenya	0–6	6	(18/303)	14	(5/73)	2.5	(0.9–6.6)

Source: Aaby and Leeuwenburg (1991)
[a]Mantel-Haenszel relative risk has been used to stratify for age.

If no confounding factor can be found to explain this excess (Aaby 1989), it is likely to be a biological phenomenon related to the difference in exposure. If so, a dose response effect should be expected. This was tested by examining whether the number of index cases affected the CFR of secondary cases in a study of hospital records from Copenhagen. Here children exposed to two or more index cases proved to have a significantly higher CFR than those exposed to a single case (RR=1.81; 95% CI:1.05 - 3.11, Aaby 1991a). A similar tendency was found in a reanalysis of data from the Machakos area in Kenya; secondary cases exposed to a single index case had a CFR of six per cent compared with 14 per cent for those exposed to more than one (RR=2.5; 95% CI: 0.9-6.6, Aaby and Leeuwenburg 1990).

Following the same line of reasoning we should expect severity to increase with the intensity of contact. We were able to test this expectation in a rural community study in Senegal (Garenne and Aaby 1990). In this area the Serer population live in large compounds divided into several households, and members of the same household may sleep in several different huts. In this setting we assume that the intensity of contact experienced by secondary cases increases gradually, from cases infected by a child from a different household in the same compound, through those infected by a household member sleeping in a different hut, to someone infected by another child sleeping in the same dwelling. As will be seen in Table 5, there was a corresponding increase in the CFR. Most studies have only analysed differences between index and secondary cases in the same house or household, but these results point to the importance of variations in the intensity of contact between infected children and the sources of infection.

Table 5
Measles case fatality ratio by age and intensity of exposure, Niakhar, 1983–1986

Age (months)	Case fatality ratio % (deaths/no.ill)			
	Secondary cases infected from			
	Same compound different household		Same Household Different hut	Same hut
0–5	0 (0/4)	0 (0/2)	0 (0/6)	13 (2/15)
6–41	7 (8/115)	11 (10/89)	12 (18/152)	18 (31/174)
42–65	0 (0/79)	2 (1/50)	6 (4/66)	5 (4/77)
66+	0 (0/122)	0 (0/62)	0 (0/86)	2 (2/129)
Total	**3 (8/320)**	**5 (11/203**	**7 (22/310)**	**10 (39/395)**
Odds ratio	**1.0**	**1.9**	**2.3**	**3.8**

Differences in the risk of becoming a secondary case apparently explain a very large part of observed variations in measles mortality, and mortality is correspondingly high where the proportion of secondary cases is large (Aaby 1988b). For example, the contrast in measles mortality between Guinea-Bissau and Bangladesh—incomprehensible from the nutritional point of view—is quite logical from the perspective of exposure. In Guinea-Bissau 61 per cent of the children under three years of age were secondary cases, and the CFR was 25 per cent whereas in Bangladesh the figures were only 14 per cent and three per cent respectively. Larger families and a high incidence of polygyny mean that children in West Africa have a much greater risk of becoming secondary cases (Aaby 1988b), and the level of measles mortality is particularly high. Consistent with the difference in CFRs, polygyny is found much more widely in West than in East Africa, married men having an average of 1.6–1.7 wives in the former compared with only 1.2 in the latter (Goody 1973).

The apparent contradiction between high mean age at infection and a high CFR may also be explained from the exposure perspective. In rural areas, epidemics occur infrequently, and the number of susceptible children per family thus increases. When an epidemic does arrive these are all likely to fall ill at once, and the risk of intensive exposure is therefore higher in such areas. A high mean age of infection indicates the relative isolation of the community and thus a larger mean number of susceptible children per family (Aaby et al. 1988a; Pison et al. 1992).

The simplest explanation of the higher CFR following intensive exposure would be that the absorbed dose of measles virus is greater (Aaby et al. 1985). In animal studies higher doses have been found to result in shorter periods of incubation. We have thus examined hospital records from Copenhagen in the period 1915–1925, so as to determine the interval between the occurrence of a rash in the index case and those in the secondary cases (Aaby 1992) which should serve as an approximation for the latter's incubation period. Fatal secondary cases displayed a much shorter interval than did survivors ($p<0.05$, Wilcoxon two sample test) indicating a correspondingly shorter period of incubation. In fact this difference may be understated because the prodromal period has been found to be prolonged in severe cases (Aaby et al. 1986a), and so our method will tend to exaggerate the length of their period of incubation.

These observations are thus all compatible with the hypothesis that the occurrence of severe infection is related to the absorption of a high dose of virus (Aaby et al. 1986a).

Amplification of severity or mildness in the community

Most studies on the severity and transmission of infection have restricted themselves to differences between index and secondary cases (Aaby 1988b). However, since severe cases excrete more measles

virus (Scheifele and Forbes 1972)—and presumably other pathogens as well—the severity of the secondary cases might depend on that of the index case. This possibility has been tested among children in the Copenhagen infectious diseases hospital, where both the index and secondary cases were hospitalized and their clinical severity assessed. Secondary cases infected by a severe index case (pneumonia or death) had significantly more pneumonia, and a significantly higher CFR, than those infected by milder index cases, and their relative risk of dying was 4.6 times greater (95% CI: 2.1 - 10.1, Aaby 1991a).

A similar observation was made in Kenya where secondary cases infected by an index case who died experienced significantly higher mortality than those where the index case survived (RR=4.7; 95% CI:1.6 - 13.4; Aaby and Leeuwenburg 1990). Although poor treatment of both the index case and the secondary case may contribute to this difference, the data do suggest that severe index cases generate secondary cases of greater severity. Depending on the pattern of transmission of measles in a community either positive or negative feedback processes may occur. Where most index cases are mild the cases to which they give rise will also be relatively mild, and the net result will be a lowered mortality. However, where the index cases themselves are severe they will transmit an even more severe infection to the new cases, further aggravating the overall level of mortality.

It is probably this mechanism which underlies the increasing severity sometimes observed in institutional outbreaks. For example, in a outbreak among soldiers of the Highland Regiment at Bedford in 1914–1915, the CFR was only two per cent (n=87) in the first month but rose to 14 per cent (n=442) in the two subsequent months (RR=6.2, 1.6 - 24.9, p=0.002; Kinnear 1923). Among children in a German refugee camp in 1915, during the First World War, the CFR increased from ten per cent (n=50) in the first two months of the epidemic, to 45 per cent (n=628) during the remaining four months (RR=4.6, 2.0-10.5, p<O.0001; Reder 1918).

A special instance of this 'amplification' phenomenon was found in our Senegal study where in the very large compounds outbreaks could take the form of a series of waves of infection, the CFR increasing exponentially with each new generation of cases (Table 6) (Garenne and Aaby 1990). This pattern of amplification presumably reflects increases in the infective dose, since severe cases apparently excrete more measles virus than do the milder ones. However, it is possible that severe cases are also more likely to transmit complications, and this too may contribute to the phenomenon.

Table 6
Measles case fatality ratio by age and generation of cases (wave), Niakhar, 1983–1986

Age (months)	Index cases %		Secondary cases according to generation of cases %							
			2nd wave		3rd wave		4th wave		5th wave	
0–5	0	(0/4)	0	(0/13)	22	(2/9)	0	(0/1)		
6–41	7	(8/115)	12	(36/290)	12	(11/90)	29	(7/24)	45	(5/11)
42–65	0	(0/79)	4	(5/142)	5	(2/38)	0	(0/9)	50	(2/4)
66+	0	(0/122)	1	(1/177)	1	(1/81)	0	(0/15)	0	(0/4)
Total	**3**	**(8/320)**	**7**	**(42/622)**	**7**	**(16/218)**	**14**	**(7/49)**	**37**	**(7/19)**
Odds ratio	**1.0**		**2.3**		**3.6**		**5.5**		**16.1**	

Cross-sex transmission

As an unexpected extension of the transmission perspective, we found in several studies in Guinea-Bissau that secondary cases infected by someone of the opposite sex had a higher CFR than those infected by someone of the same sex (Table 7) (Aaby et al. 1986b). This tendency did not depend on the classification of who infected whom, for it could be shown that mortality for children aged 6-59 months was higher in houses where one boy and one girl had measles together (26%) than in those with two boys or two girls (ll%) (RR=2.65; 95% CI: 1.20 - 5.84). Something similar seems to have occurred in Copenhagen at the beginning of this century (Aaby 1991b). Mortality was significantly higher ($p<0.05$, Mantel-Haenszel, $\chi^2=4.36$) in families where one boy and one girl caught measles during the same outbreak than in those where two boys or two girls fell ill (RR=1.85; 95% CI:1.04-3.30).

Table 7
Case fatality ratio among secondary cases of measles by age and by sex of infecting child, Guinea-Bissau 1979–84

Age (Months)	Case Fatality Ratio % (deaths/no.ill)							
	Same-sex transmission				Cross-sex transmission			
	Male to Male		Female to Female		Male to Female		Female to Male	
6–35	26	(9/35)	16	(5/31)	49	(22/45)	36	(16/45)
36–59	10	(1/10)	6	(1/16)	20	(3/15)	18	(3/17)
Total	22	(10/45)	13	(6/47)	42	(25/60)	31	(19/62)

Source: Aaby et al. (1986b)

This tendency has been examined in a number of studies. In a small outbreak in Keneba, in The Gambia, where the children were under close medical observation, and there was no mortality, individuals infected by someone of the opposite sex were more likely to suffer pulmonary complications than those infected by their own sex (RR=2.82, 95% CI:0.9-9.7; Aaby and Lamb 1991). Since this result could be influenced by the severity of the index case, the effect of sex differences on the increase in severity from index to secondary case was also examined. Secondary cases infected by the opposite sex were significantly more likely to show increased severity, relative to the index case, than were those infected by someone of their own sex (p=0.026).

In Niokholonko, a rural area of Senegal under demographic surveillance since 1970, 243 deaths were registered during three separate outbreaks of measles. Unfortunately the total number of cases was not recorded, and so it was not possible to document the immediate source of infection where a death had occurred. However, on the assumption that this was most likely to be a maternal sibling, we examined the mortality risk, by sex composition of sibships, in families with only two maternal siblings under ten years of age. When significant background factors were taken into consideration, the relative risk of dying of measles during an outbreak was 1.81 times greater (95% CI: 1.17-2.82) in sibships consisting of one boy and one girl than in those containing two children of the same sex (Pison et al. 1992).

A similar pattern has been detected in several other studies in Kenya (Aaby and Leeuwenburg 1991), Senegal, Greenland and Germany (author's unpublished observations). Published case reports of

measles fatalities, giving the sex of both index and secondary cases, also reveal higher mortality from cross-sex infection (Aaby et al. 1986b). There are indications that this pattern may also occur where other infections are concerned since we have found that twin pairs of unlike sex suffer higher post-neonatal mortality than do same-sex twins (Aaby and M¿lbak 1990).

There is no simple explanation for the higher mortality associated with cross-sex infection. It is not obvious that children of opposite sexes have more intensive contact with each other. In fact, the available studies indicate that the reverse is the case (Aaby et al. 1986b). It thus seems probable that a biological mechanism is involved. Since viruses take material from the cells they have grown in, it may be that those grown in male or female cells have a different potential for infecting cells of the opposite sex (Aaby et al. 1986b).

Delayed impact of measles and intensive exposure

The importance of the transmission approach may transcend the immediate outcome of the infection. Most studies have only dealt with acute measles mortality (within one month of the rash), but some recent work has suggested that measles may have a profound effect on morbidity and mortality beyond this period (Aaby, Clements and Cohen 1987). Though there are few studies of the determinants of such 'delayed impact', it is likely that it arises from intensive exposure during the period of acute infection. For example, among the children hospitalized in Copenhagen, secondary cases had a higher risk of dying after the first 30 days of measles infection (3/152) than did index cases (3/472) (RR=3.11; 95% CI: 0.7-14.0). In rural Senegal, the secondary cases had a significantly higher risk of dying in the year following measles infection than did the index cases (RR=3.5) (Table 8) (Garenne and Aaby 1990).

Table 8
Post-measles mortality rate (6–52 weeks) by age and intensity of exposure, Niakhar 1983–1986

Age (months)	Case fatality ratio % (deaths/no. of survivors)	
	Index cases in compound	**Secondary cases in compound**
0–5	0 (0/4)	5 (1/210)
6–41	2 (2/107)	7 (25/356)
42–65	1 (1/79)	2 (3/184)
66+	0 (0/122)	1 (2/275)
Total	**1 (3/312)**	**4 (31/836)**
Odds ratio	**1.0**	**3.5**

Source: Garenne and Aaby (1990)

In Guinea-Bissau, we also found that children who had been exposed to measles at home during the first six months of their lives had a mortality between ages six months and five years which was three times higher than community controls (34% vs 11%) (Aaby et al. 1990a). In a Cox regression analysis, taking the known background factors into consideration, the mortality hazards ratio was 5.7 times higher (95% CI:2.7 - 12.0) among the exposed children than the controls. The difference in mortality was significant in each of the age intervals 6–11, 12–23 and 24–35 months. This delayed excess mortality was found both among children who had had measles (despite being below six months of age) and among those who had been exposed without showing clinical symptoms. The latter were particularly likely to die of diarrhoea.

These tendencies have been revealed systematically in several outbreaks in Guinea-Bissau (Aaby et al. 1990a) but have not been examined elsewhere. The observation of delayed mortality among children exposed to measles early in life—without showing clinical symptoms—suggests that measles may be responsible, indirectly, for a much larger share of childhood mortality than is usually assumed. The mechanisms underlying this longer-term relationship require further study, but some form of persistent infection and immunosuppression may be involved. Its effect may go even further. In two outbreaks in Guinea-Bissau, it was found that children of mothers exposed to measles during pregnancy had a significantly higher perinatal mortality (Table 9) (Aaby et al. 1988b) as well as an increased post-perinatal mortality (Aaby et al. 1990b).

Table 9
Perinatal mortality among children of mothers exposed to measles during pregnancy, Bandim, Guinea-Bissau, 1979

Type of mortality	Perinatal mortality risk % (deaths/no. at risk)		
	Exposed	Controls	O.R. (95% C.I.)[a]
Stillbirths	6.5 (7/107)	1.4 (5/346)	4.8 (1.7–13.8)
Died in first 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)

[a]Odds ratio (95% confidence interval)

While these tendencies have not been studied elsewhere, there are indications that early exposure may have consequences for health in later life. The delayed fatal form of measles known as subacute sclerosing panencephalitis (SSPE) is most frequent among children who had measles early in life, suggesting that the victims are more likely to have been intensively exposed as secondary cases (Aaby et al. 1984d). A study from Denmark found that the frequency of cancers and immunoreactive diseases among adults with no history of childhood measles was four times higher than that of controls with such a history (R¿nne 1985). Since all the controls had measles antibodies, it is most likely that they had been exposed to the virus at a very early age when still partly protected by maternal antibodies or immunoglobulin. It thus seems that early intensive exposure is connected with excess morbidity in later life.

Testing the contrasting hypotheses: the impact of measles vaccination

In seeking to explain any given problem the hypothesis we adopt must be able to account for all observed variations in our data and to resolve the contradictions inherent in competing interpretations. Measured against these criteria there is little to indicate that host factors such as malnutrition and young age at infection play a major role in determining the severity of measles infection. Host-factor hypotheses cannot explain major contrasts in measles mortality, and some of their predictions are contradicted by the known epidemiology of severe measles.

On the other hand, transmission factors appear to explain much more of the variation in mortality; differences in mortality between historical periods, according to the degree of crowding, between regions, and between rural and urban areas, all correspond to differences in the intensity and type of exposure. Patterns which conflict with the host factor hypotheses, for example the differences between

Africa and Asia, and between rural and urban areas, are compatible with the transmission factor approach.

Table 10
Efficacy of measles vaccine against death: different studies

Country	Age at vaccination	Period of follow-up	Mortality %	Vaccinated	Vaccine efficacy against death (95% C.I.)
Nigeria (Hartfield and Morley 1963)[c]		18 months	12[b] (25)	0 (23)	100
Zaire (Kasongo Project Team 1981)[d]	7–9 months	30 months	7–9.5[a]	3.8	46–60
Guinea-Bissau (Aaby et al. 1984c)[e]	6–35 months	12 months	14.3[a] (70)	1.9 (361)	87 (70–94)
Guinea-Bissau (Aaby et al. 1989)[f]	7–24 months	24 months	13.2[b] (53)	4.8 (124)	63 (2–86)
Guinea-Bissau (Aaby, Knudsen et al. 1990)[g]	9–23 months	24 months			66 (32–83)
Senegal (Garenne and Cantrelle 1986)[h]	6–35 months	30 months	33.6[a]	23.2	31
Haiti (Holt et al. 1990)[i]	6–13 months	9–39 months	6.6[a] (1056)	1.3 (235)	85 (36–96)
Bangladesh (Clemens et al. 1988)[j]	9 months	9–60 months		(8135)	36 (21–48)
Bangladesh (Koenig et al. 1990)[k]		9–60 months	(8135)[a]		46 (35–54)

Note: [a] Unvaccinated

[b] Placebo

[c] A small placebo study carried out at the beginning of the 1960s.

[d] The study in Zaire was carried out in the mid-1970s. Vaccination was introduced in one area and mortality compared with a comparable neighbouring area and with data from the same two areas prior to vaccination being introduced.

[e] The study was carried out in 1980 in the capital of Guinea-Bissau. Mortality has been compared for children who attended a child examination and were vaccinated against measles and children who did not attend, mostly because they were temporarily absent.

[f] The study carried out in 1984–86 represents a 'natural experiment'. When blood samples taken in connection with vaccination were analysed two years later, it was found that, during a short period, none of the children had seroconverted. They can thus be considered to have received a 'placebo'.

[g] The study carried out between 1984 and 1987 compared mortality for children who received vaccination and those who did not in two districts in the capital of Guinea-Bissau.

[h] Two systematic measles vaccination campaigns were carried out in a rural area of Senegal, in 1965 and 1967. Mortality was compared with an area where vaccination was not available.

[i] The study compares mortality for children who had participated in a serological study in 1982. The estimation of vaccine efficiency against death takes account of background factors with a significant effect on mortality (socioeconomic status, literacy, knowledge and use of oral rehydration therapy, and birth intervals).

[j] The study from the Matlab area in 1982–84 compares vaccination status for 536 children who died with 1072 controls.

[k] This study of 8135 vaccinated children and controls from the Matlab area covers 1982–85. The study overlaps partly with the previous study.

In health-related matters, the ultimate test of a hypothesis lies in its implications for prevention, and our two competing hypotheses imply very different assessments of the value of specific disease interventions (vaccination, immunoprophylaxis). If measles is primarily a killer of weak and malnourished children, then immunization might have only a limited effect on survival because those whose lives are thereby saved would have a high risk of dying from other diseases (Hendrickse 1975; Kasongo Project Team 1981; Mosley 1985). However, if intensity of exposure is the major determinant of measles' severity then there is no reason why weaker children should be particularly at risk (Aaby et al. 1984c), and in this case immunization should have a significant impact on overall survival.

Community studies available from Nigeria, Guinea-Bissau, Senegal, Zaire, Bangladesh and Haiti all indicate at least a 30 per cent reduction in child mortality after the age of vaccination, and seven of the studies found a reduction of at least 45–50 per cent (see Table 10). None have failed to find a marked effect on mortality, although it is true that most suffer from potential methodological problems because they are not randomized double-blind trials. However, one study found that mortality among children who seroconverted was only a third of that of children failing to seroconvert because they had received an ineffective vaccine as a placebo (Aaby et al. 1989).

In all studies the reduction in mortality was greater than expected from the direct contribution of measles deaths to overall child mortality. For example, in Bangladesh, the reduction in mortality between ten and 60 months of age was 36 per cent although measles accounted only for four per cent of all deaths among the controls (Clemens et al. 1988). Thus measles immunization seems to be highly effective in preventing both acute and delayed mortality from the disease.

Lessons for the past

Although no other infection has been studied systematically from the transmission-factor perspective, there are indications that the mechanisms emphasized here may apply more widely (Aaby et al. 1985), and I shall argue, using four examples, that the transmission perspective has a general importance for the understanding of historical data on mortality and morbidity.

Measles mortality decline in the industrialized world

The contrasting hypotheses outlined above provide quite different interpretations of the process of measles mortality decline. In England, for which the best data and analyses are available thanks to Reves (1985), a very important fall in measles mortality took place between 1900 and 1930 (Table 11) which was attributed to improvements in nutrition (Mayer 1969). The main evidence for this attribution is a correlation between low social status, as measured by the number of rooms occupied by the family, and measles CFR (Morley 1973). However, this correlation does not necessarily indicate that poor children had a higher case fatality rate because they were malnourished. There are no specific data linking nutritional changes with improved survival rates among those infected, and it could equally well be that children living in small apartments had a higher risk of intensive exposure to the infection.

It has also been hypothesized that the decline in the industrialized world's measles mortality at the beginning of this century reflected a rise in the age at infection (Reves 1985). English fertility fell dramatically—from 6.7 children per woman in 1875 to 2.6 in 1925—and it has been assumed that this increased the average age at infection because children in smaller families were older when they first encountered the virus (*The Lancet* 1985; Reves 1985). However, this effect may have been offset by a contemporary increase in the risk of early infection outside the family due to greater urbanization, improvements in transport, and the spread of schooling and public child care.

Table 11
Age-specific measles mortality rate (per million), England and Wales 1911–1930

Age (years)	Period			
	1911–15	1916–20	1921–25	1926–30
<1	3,130	1,931	1,337	1,284
1–4	2,905	1,861	1,182	999
5–9	205	190	95.9	95.9
10–14	17.1	12.7	6.5	10.3
15–19	9.4	12.8	2.4	3.6
20–24	7.1	10.0	1.7	1.6

Source: Reves 1985

There are no data for England as a whole to show any increase in the age at infection in this period (Reves 1985). The few available community studies and reports of notifications suggest no major change, and the proportion of cases under three years of age has been remarkably constant (Aaby et al. 1988c). At a time when measles in the United Kingdom was severe, Picken (1921) noted that variations in mortality could not be explained by differences in age distribution, and it is known that the mean age at infection in England and Wales fell from 5.5 to 4.4 years between 1944 and 1968 (Anderson and May 1982).

Thus it remains true, as Lancaster (1952) noted, that there is no adequate explanation for the decline in CFR in the industrialized world before the advent of antibiotics. However, the decline may be better understood—from a transmission perspective—in terms of reductions in the frequency of intensive exposure and a feedback process. Data from England and Germany, together with hospital studies from Copenhagen (Aaby 1988a), dating from the period of severe measles mortality show that this was higher for secondary cases than for index cases whilst community studies from Sunderland in 1885 (Aaby et al. 1986a) and rural Germany in 1861 (Pfeilsticker 1863) suggest that the proportion of secondary cases in Europe was as high as that found in present-day Africa.

Although there are no proper epidemiological studies of measles transmission in contemporary industrialized countries, it seems likely that smaller families and changes in schooling and public child care have significantly reduced the proportion of secondary cases since the beginning of this century. Factors such as increased urbanization, universal primary education and the spread of public child care will have raised the likelihood of early infection by taking the child out of the family and increasing its contact with other children. The earlier immunity thus acquired will also have reduced the risk of children becoming infected at home as secondary cases should school-age siblings bring the virus into the home.

Thus the social processes stemming from industrialization contributed to breaking the older pattern of transmission in which children experienced their most numerous contacts with susceptible peers on entering school, and school-aged children brought the virus home intensively infecting their susceptible younger siblings. The importance of this pattern seems to have been recognized by Brownlee (1920), the leading contemporary epidemiologist, who proposed that schools maintain registers of all their pupils' siblings. Thus, when measles broke out in the school, teachers would be able to advise parents to board out any small siblings with relatives until the epidemic had passed. This proposal constitutes a dramatic recognition of the importance of preventing intensive exposure at home. I do not know if it

was ever implemented but it seems likely that social processes were more effective in this respect than any school-based public-health measures over the first decades of this century.

It may also have been significant that doctors in the 1920s and 1930s began using convalescence serum (and later gamma-globulin) to prevent, or modify, measles infection. This treatment would have been aimed precisely at the high-risk group for measles mortality, namely small children exposed to a sibling at home, and its impact has not been properly assessed. Gamma-globulin has had a marked effect on the CFR in virgin-soil epidemics among indigenous peoples who all contract measles at the same time (Aaby et al. 1987).

Undoubtedly the most important contribution was made by reduced family size, leading to fewer secondary cases and thus to lower mortality, but this cannot explain the entire reduction in mortality. Secondary cases still occur in the developed countries, but their mortality is virtually nil. However, as the proportion of secondary cases falls, the index cases will themselves become milder, having been infected by mild index cases rather than severe secondary cases. Thus, secondary cases too may have become milder, and the general severity of measles in the community been gradually reduced, through a process of positive feedback.

In order to examine this question further we have used records from the infectious diseases hospital in Copenhagen. Table 12 shows that children infected at day care institutions had a significantly lower mortality than did index cases contracting measles from another child in the same apartment building. Presumably exposure was less intense in the kindergarten because children sick with measles were kept at home, whereas children at home may have maintained contact with infected playmates. Since children infected in kindergartens also had much lower mortality, the establishment of such institutions may have contributed to the fall in measles mortality by reducing the proportion of secondary cases.

Table 12
Measles case fatality ratio according to source of infection and age, Copenhagen 1915–1925

Age (years)	Day care		Neighbours, playmates		Secondary cases	
	%		%		%	
0	13	(5/40)	40	(4/10)	29	(16/55)
1	5	(3/64)	22	(5/23)	29	(24/84)
2	6	(2/31)	22	(4/19)	20	(9/44)
0–2	7	(10/135)	25	(13/52)	27	(49/183)

Source: Aaby (1988a)

It may also have promoted the transmission of measles in a milder form. Table 13 shows marked annual variations in both measles mortality and the proportion of children infected in day-care institutions between 1915 and 1925. When this proportion was high the overall CFR tended to be low. This was only partly due to the lower mortality of children infected at kindergarten, because as the table shows, children under three, infected elsewhere, also had a reduced CFR in years when the proportion of kindergarten infections was high (logistic regression, p=0.001 χ^2=10.88, 1 df). It is possible that in some years the epidemic was dominated by transmission among kindergarten children, whilst in others transmission at schools and apartment buildings was more important. These observations support the suggestion that an increase in mild cases in the community reduces the absolute number of severe cases. It may be a process of this kind which generated the considerable annual variation in CFR, a variation explained by contemporary epidemiologists in terms of changing pathogenic virulence.

Table 13
Case fatality ratio according to age, year and frequency of children infected in day-care institutions, Copenhagen, 1915–1925

Year	Case fatality rate (no. of cases)							
	All cases		Children <3 years		Children >3 years not in day care		Children <3 years infected in day care	
	%		%		%		%	
1915	10	(114)	16	(49)	20	(35)	29	(49)
1916	20	(295)	29	(123)	31	(116)	6	(123)
1917	10	(100)	21	(42)	20	(38)	10	(42)
1918	8	(153)	18	(66)	19	(58)	12	(68)
1919	14	(172)	23	(84)	25	(72)	14	(84)
1920	18	(244)	23	(125)	24	(115)	8	(125)
1921	8	(72)	10	(30)	11	(28)	7	(30)
1922	8	(14)	14	(69)	16	(57)	17	(69)
1923	16	(304)	29	(96)	30	(90)	6	(96)
1924	9	(275)	14	(108)	16	(83)	23	(108)
1925	10	(312)	12	(160)	14	(125)	22	(160)
Total	**13**	**(2208)**	**20**	**(952)**	**22**	**(817)**	**14**	**(952)**

There are few well-documented accounts of fundamental changes in CFR from developing countries. The three series we have, from Kenya, Gambia and Guinea-Bissau, all indicate that neither nutritional changes nor variations in age at infection were responsible, but that fundamental changes occurred in the transmission patterns and reduced the proportion of secondary cases (Aaby 1990). Furthermore, the extension of vaccination coverage proved to be essential in each study. Experience from Africa suggests that vaccinated children often have milder infections with lower CFR (Aaby et al. 1986c). It is therefore likely that they contribute to the transmission of milder infection in the community.

To sum up, it seems likely that the most important causes of measles mortality decline were social changes which diminished the risk of intensive exposure within the family. Chief among these were the fall in family size and greater social contact among young children which increased the risk of infection outside the home. Furthermore, the continual reduction in the numbers of fatal cases has reduced the risk of transmission of measles in a severe form.

The strength of the weaker sex: the social production of 'biology'

> 'Men are more often colour blind than women,' said Joanna. 'It's one of those sex-linked things,' she added, with an air of erudition. 'You know, it passes through the female and comes out in the male.' 'You make it sound as though it was measles,' said Emlyn Price.
> (Agatha Christie, *Nemesis* 1974).

Western popular beliefs have been characterized by a complementary view of the sexes; men are seen as being endowed with greater physical strength, while women are more resistant biologically. More boys are born, but in the end it is the women who survive (Mims 1976). Scientific studies of infectious diseases have supported this belief by showing many infections, including measles (see Table 14), to be more severe in males (Karzon et al. 1961; McGlashan 1969; Denny et al. 1977). Such findings are usually explained in terms of 'sex determined immune capacity' and 'hormonal differences influencing immunity' (Mims 1976).

The pattern observed in the Western world has come to be seen as the 'biological' or 'natural' one, and it causes little surprise if boys have higher mortality. On the other hand, where girls have higher mortality we are in need of an explanation. Usually the reference is to differential treatment (Bhuiya et al. 1987). However, for a biological constant there are some surprising irregularities in the pattern even within the Western world. For example, as also illustrated in Table 14, beyond a certain age females experience higher risks of measles mortality than do males. The reason that fewer girls die overall is that they have lower mortality in the youngest years, where the CFR is particularly high, and not because they have an advantage at all ages. This pattern of early female advantage, being reversed at older ages, has also been found in other infections such as polio (Hall, Nathanson and Langmuir 1957).

Table 14
Measles case fatality ratio and relative risk for females by sex and age, registered cases 1883–1902, Aberdeen.

Age (years)	Case fatality ratio %				Relative risk for females %
	Cases	Males	Females	Total	
0	3034	14.5	13.6	14.0	0.94
1	5222	10.9	9.2	10.1	0.85
2	5195	3.6	3.2	3.4	0.89
3	5053	1.5	1.7	1.5	1.13
4	4836	0.9	0.9	0.9	0.92
5	5352	0.7	0.7	0.7	1.01
6	4628	0.4	0.5	0.5	1.42
7	2818	0.3	0.7	0.5	2.27
8–14	3155	0.3	0.4	0.4	1.27
15+	1081	0.6	1.0	0.8	1.76

Source: Wilson (1905)

The lower mortality among females may be due less to sex-determined immunological strength than to the fact that infection 'passes through the female and comes out in the male', as pointed out by Agatha Christie. Since severity is associated with intensive exposure and cross-transmission of infection, sex differences in these respects might explain the sex difference in mortality. In fact these two mechanisms would tend to work together. If members of one sex are more likely to become secondary cases, they will also be more likely to be infected by a member of the other sex, since it is these who will comprise the bulk of index cases. Thus small inter-sex variations in the risk of becoming a secondary case may result in much larger variations in severity and CFR.

In European culture there are several indications that girls catch measles and other infections at a younger age than males (Aaby et al. 1984d). One dramatic illustration of this is the age-distribution of viral infections in Denmark, where females outnumber males by more than two to one in the first year of life (Table 15). Since the reporting rate has been high (50%), and the total number of males and females is the same, biased reporting is unlikely to be responsible for this pattern. Since there is no indication that girls are more likely to be infected if exposed at home, it seems likely that they have a higher risk of infection elsewhere. This may be due in part to differences in behaviour, as girls appear to have closer face-to-face contact with their playmates as early as kindergarten age, and this could facilitate the transmission of infection. Furthermore, we have found in Guinea-Bissau that girls tend to have fewer maternal antibodies against measles which would render them susceptible at any earlier age than boys (author's unpublished observations). Both of these tendencies would lead girls to contract

infection at a younger age than boys, predisposing the latter to a higher risk of domestic infection as a secondary case which may be one reason for the higher mortality of boys in the industrialized countries (Aaby et al. 1983).

Table 15
Reported cases of measles by sex and age, Denmark 1963–1969

Age (years)	Males %	Females %
0	3.09	6.35
1–6	86.05	95.09
7–14	48.61	39.75
15+	3.57	2.80
Total	**141.32**	**143.99**

Source: Hertz, S¿rensen and Vejerslev (1977)

Higher measles mortality for girls has been reported from several communities, usually with a Muslim culture (Monastiri 1961; McGregor 1964; Bhuiya et al. 1987; Fargues and Nassour 1988). It seems likely that girls are more bound to the home in these communities and that boys have a greater chance of getting out and thus of being infected outside the home. As a consequence, girls suffer a dual disadvantage: a higher risk of becoming a secondary case as well as a higher risk of being infected by someone of the opposite sex. In a study in rural Senegal, girls were found to have 30 per cent higher CFR than boys, and virtually all of this difference could be explained with reference to the transmission pattern. There were slightly more secondary cases among the girls, and they were significantly more likely to be infected by the opposite sex. When these differences were taken into consideration, there was only a five per cent higher CFR among the girls (author's unpublished observations).

Thus, before assuming that sex differences are based on biology, or differential treatment, it may well pay to examine the mode of transmission in that particular environment. There are very few studies where the sex of both the infected and the infecting child has been documented, but they have shown that girls were more likely to be the index case, or that boys were more likely to be infected by a member of the opposite sex (Pfeilsticker 1863; Asano et al. 1977; Aaby and Lamb 1991). The higher risk among older girls could be related to a lower degree of schooling, or to the way in which their role in child care exposes them more intensively to infection from siblings.

Virgin-soil epidemics

> It seems that the Mandans were surrounded by several war parties of their more powerful enemies the Sioux, at that unlucky time, and they could not therefore disperse upon the plains... they were necessarily enclosed within the piquets of their village, where the disease [smallpox] in a few days became so very malignant that death ensued in a few hours after its attacks; and so slight were their hopes when they were attacked, that nearly half of them destroyed themselves with their knives, with their guns, and by dashing their brains out by leaping head-foremost from a thirty foot ledge of rocks in front of their village. The first symptoms of the disease was a rapid swelling of the body, and so very virulent had it become, that very many died in two or three hours after their attack, and that in many cases without the appearance of the disease upon the skin (Catlin 1841).

Five hundred years ago, the Amerindian population may have numbered as many as 100 million, or one fifth of the world's population (Crosby 1976; McNeill 1976). Where there are reliable data, they imply that the indigenous groups diminished by 90–95 per cent, or vanished completely, during the first 100–150 years of contact. Virgin-soil epidemics of diseases like smallpox, measles, influenza, whooping cough and typhoid fever—occurring where no one had immunity and thus everyone succumbed at once—were the major cause of this reduction and the prime means by which Europe acquired the Americas. They were also important on the islands of the Pacific basin.

There is no indication that the Indians were malnourished (Black et al. 1971), and, as in Catlin's account of the Mandan, the epidemics' dramatic impact has usually been ascribed to the Indians' lack of immunity (Black et al. 1971), or to the breakdown of nursing when everybody became sick simultaneously (Crosby 1976). But several features of these epidemics are inconsistent with such hypotheses, and the possibility of an unusually severe form of infection has been little considered.

The excessive epidemic mortality has fuelled speculation concerning the Indians' lack of immunity, or 'constitutional weakness' on their part. In support of such views, it was claimed in some older literature that mestizos often fared better than pure Indians (Smellie 1846; Bridges 1950). In modern terms, the suggestion is that Amerindians' susceptibility was increased because they 'lack certain genetic traits which have become common in other populations through prolonged selective pressure' (Black et al. 1971). Although the specific traits making non-Indians more resistant have not been demonstrated, it has been emphasized that in most studies of measles vaccination, Indians and Innuits displayed a stronger febrile response (0.4-0.5^{o} higher fever) than did populations with prior measles experience (Black et al. 1971).

A further argument in favour of increased genetic susceptibility is provided by the observation that death in the prodromal phase (before the appearance of the rash) seems to be a distinctive feature of virgin-soil epidemics, as is also implied by Catlin's account. Normally measles deaths are thought to arise from complications due to secondary infections, most of which occur after the appearance of the rash. In the first measles epidemic on Greenland in 1951, 32 per cent of all deaths (25/77) occurred in the prodromal phase (Christensen et al. 1953).

The genetic hypothesis is difficult to test because the relevant traits and immunological mechanisms remain unknown, but such a hypothesis may not be necessary. In many epidemics among Europeans and Africans with long experience of measles the CFR has been as high as those documented for virgin-soil outbreaks among Indians and Innuits (Table 16). The epidemics have shared other features with the latter, occurring in institutions or closed communities where transmission was rapid and incidence universal. For example, during the Paris Commune the Garde Mobile had a measles CFR of 40 per cent (86/215) (Squire 1877), and outbreaks in institutions and refugee camps have often had CFRs of 25-50 per cent (Gannelon 1892; Godfrey 1928).

Table 16
Measles mortality in virgin-soil epidemics among Indians and Innuits

Locality	Year	Medical care	Gamma-globulin	Cases	Case fatality rate %
Fort York, Canada (Smellie 1846)	1846	Yes	No	145	27.6
Tierra Del Fuego (Bridges 1950)	1884		No	1000	60.0
S.W. Greenland (Christensen et al. 1953)	1951	Yes	Yes	4247	1.8

Ungava Bay	1952	Yes	No	900	7.4
Baffin Island	1952	Yes	Yes	900	2.0
(Peart and Nagler 1954)					
Xingu, Brazil	1954	Yes/No	No	654	17.4
Xingu, Brazil		Yes/No			9.6
Xingu, Brazil		No	No		26.8
(Nutels 1968)					
Yanomamo, Brazil	1968	Yes	No	480	8.8
(Neel et al. 1970)					

Prodromal deaths are also found elsewhere, but are much less likely to be diagnosed as measles in the absence of the rash. The higher fever response among vaccinated Amerindians, not previously exposed to the disease, could well be due to the controls having a low level of antibodies which displayed a modified fever reaction to the vaccine. It has been a common feature of the few well described virgin-soil epidemics that the disease was usually relatively mild to begin with, becoming much more severe with the progress of time (Squire 1877). This does not suggest that genetic susceptibility was particularly important—and the same feature has characterized measles outbreaks in institutions (Picken 1921)—whilst subsequent epidemics in the same isolated communities were often much milder. This again fails to support the genetic hypothesis since too little time had elapsed for genetic selection of 'certain traits' to have taken place.

The most commonly accepted explanation for heightened severity is the social breakdown which can occur during virgin-soil epidemics (Morley 1973; Crosby 1976). In support of the view that lack of nursing was the primary contributor to surplus mortality, several studies have suggested that even minimal provisioning for sick people could reduce mortality (Peart and Nagler 1954; Neel et al. 1970). For example, Table 16 shows that the CFR was lower in those epidemics with some medical care.

It is quite likely that fear of imminent death, fatalism and neglect of sick relatives may have contributed to the high CFRs observed in virgin-soil epidemics. However, the CFR has been equally high in situations where complete social breakdown did not occur. For example, in the Scottish Highland Division at Bedford in 1914–1915, 12 per cent (65/529) of the adult males stricken with measles died. In child institutions in New York, mortality was as high as 24 per cent in the period 1916–1918 (Godfrey 1928). While these institutions may well have been under stress due to the simultaneous occurrence of many cases of measles, there is no indication that basic necessities like food and water were not provided.

Furthermore, there are a number of features of virgin-soil epidemics which are difficult to relate to social breakdown. Lack of nursing and medical care can probably not produce prodromal deaths, and several accounts of virgin-soil epidemics have stressed that the disease was particularly severe for adult females (Corney 1913; Christensen et al. 1953). Though this could reflect womens' greater risk of being inadequately nursed while sick, it seems also to hold in Greenland where care was sufficient to secure a relatively low level of overall mortality (see Table 16). Adult women aged 15–54 had significantly worse mortality, and a higher rate of complications, than did their male age-mates (Christensen et al. 1953).

All of these features, which fail to fit the genetic or social breakdown hypotheses, appear to be compatible with the transmission factors which we emphasized hitherto:

(a) In a virgin-soil epidemic, where there is no prior immunity, the proportion of individuals infected within the home will be much higher. The Mandans, for example, had large huts with as many as 40 inhabitants. In a reanalysis of data from the first measles epidemic on Greenland, secondary cases displayed a higher CFR than index cases (author's unpublished data).

(b) A progressive increase in mortality, from an initially low level, would be predicted from the mechanism of amplification of severity. As the proportion of severe secondary cases rises, subsequent cases will become even more severe.
(c) The higher mortality of adult females is hard to reconcile with the notion that they have a greater immunological capacity. Pregnancy, which is immuno-suppressive and connected with more severe infections, might explain some of the difference, but in the Greenland epidemic non-pregnant women also had a higher CFR than their male age-mates (Christensen et al. 1953). It seems simpler to explain this in terms of womens' role at home, taking care of domestic tasks and sick family members, which is likely to have increased their risk of intensive exposure.
(d) Prodromal deaths and a shorter period of incubation have been noted in several virgin-soil epidemics. These phenomena are compatible with lack of genetic resistance to the infection, but also with the higher dose of infection which is likely to result from more intensive exposure and is known to reduce the period of incubation.
(e) The impact of medical care and gamma-globulin. Table 16 suggested that medical care could reduce mortality, but this seems to have been the case particularly where gamma-globulin was used prophylactically. When it is given just before exposure, or in the early phase of incubation, some of the invading virus will be neutralized, the period of incubation prolonged, and the severity reduced. For example, when measles attacked the Innuits and Indians around Hudson Strait in Canada, the CFR was as high as 7.4 per cent (67/900) of the total population on the southern side (Ungava Bay). Here, no one received gamma-globulin, while other kinds of treatment and care were provided by the Indian health service. When measles reached the other side of the strait (Baffin Island) medical supplies were dropped by parachute. These included gamma-globulin, and there were no deaths among the 269 persons who received it ($p<0.001$).

The key factor in these cases seems to have been a reduction in infective dose, rather than either basic nursing care or genetic susceptibility. By implication, excessive doses of infection are likely to have been a major factor in producing the excess mortality that has characterized virgin-soil epidemics.

European mortality decline: the role of smallpox vaccination

> The children whose death might be prevented by measles vaccine are at risk of dying not because of the severity of measles *per se,* but because they are on 'the road to death' and their nutritional status is so poor that they are likely to die of any infectious disease. Thus, preventing a death among these children may not necessarily save a life, but only change the cause of death (Mosley 1985).

McKeown's explanation of the decline of mortality throughout Europe since the eighteenth century has been widely accepted, even in medical circles, despite his minimization of medicine's contribution before the advent of antibiotics in the 1930s (McKeown and Brown 1955; McKeown and Record 1962; McKeown et al. 1972; McKeown, Record and Turner 1975). McKeown argued that, theoretically, the reduction in mortality from the late eighteenth century and throughout the nineteenth century could be due to one or more of the following factors: medical measures for preventing and treating disease in the individual; a spontaneous decline of mortality due either to decreased virulence or increased resistance; improvements in environmental conditions.

He discarded the contribution of medical measures because the nature of infectious disease was not understood until 1850, and specific prevention or treatment was unlikely to have had much influence on the national death rate before the introduction of chemotherapy. Spontaneous mortality decline was also ruled out as being unlikely to have contributed much to the decline. Thus McKeown concluded that it was changes in environment, particularly improvements in diet and the results of sanitary

reforms, which were responsible. To a large extent this conclusion was reached negatively, by excluding all the (perceived) alternatives. The data in favour of improved diet as the main cause of reduced mortality are not very convincing, and as has been pointed out by others (Razzell 1974), it is actually questionable to what extent diet did improve over the period. Furthermore, there are no data to indicate that improvements of the kind that may have occurred would have affected the causes of death most implicated in the decline.

However, what is more critical is the apparent ease with which McKeown et al. (1972) dismissed the eighteenth-century role of inoculation against smallpox followed by that of vaccination after 1800. The former role was dismissed on the grounds that it required a much greater effectiveness for the technique than would be accepted by virologists, and that it attributed to this crude measure an influence on total mortality which would not be expected from any modern immunization procedure. The argument against vaccination was that control of smallpox contributed little to the decline of mortality between 1838 and 1900. However, what happened after Civil Registration in 1838 is a poor guide to events in the first decades of the century.

The available data suggest a very dramatic drop in mortality, related to vaccination, in the first decades after the practice became widespread, or even compulsory (Razzell 1974; Mercer 1985). The arguments against the effectiveness of inoculation seem to be erroneous in the light of data from England, Copenhagen and Boston which suggest that it was highly effective when used during epidemics. Furthermore, the time trend of mortality also suggests that inoculation contributed to a decline in smallpox deaths (Mercer 1985). These data have been presented more fully by others and will not be discussed in detail here.

What is more interesting in the present context is McKeown et al.'s (1972) claim that the control of smallpox has been erroneously credited with 'an influence on total mortality which would not be expected from any modern immunization procedure'. This seems to reflect *a priori* beliefs, rather than specific investigations, and to be based on the assumption that no single infection can ever have had such an influence because its victims would always have been drawn from the weakest and most vulnerable sections of the population.

However, if experiences with measles and measles vaccination is any guide to what we can expect in relation to smallpox and smallpox vaccination, McKeown was certainly wrong. Measles immunization may help to reduce total mortality in several distinct ways:

(a) Acute deaths are prevented, and there is no indication that those saved from measles are more likely to die from other causes afterwards.

(b) Vaccinated children who subsequently contract measles have a much lower CFR, probably because the vaccine has induced some partial immunity.

(c) Measles gives rise to some delayed mortality, and this mortality is also prevented by immunization.

(d) Unvaccinated children who catch measles have a lower CFR than they would otherwise do because the degree of clustering and the risk of intensive exposure have been reduced; such cases also contribute to the transmission of milder measles thus lowering the CFR still more.

(e) Early exposure to measles is connected with much higher mortality later on in childhood; immunization should reduce the risk of this kind of exposure.

(f) Exposure to measles during pregnancy is connected with much higher perinatal and post-perinatal mortality. Immunization should reduce this kind of exposure.

Of these possible mechanisms, only the first three relate to the effect of immunization on individual survival. All the available studies suggest that the effect of measles vaccination on overall mortality, a reduction of some 40–50 per cent after the age of vaccination, was much larger and could

be explained by the proportion of all deaths attributable directly to the disease. To these gains should be added those obtained by eliminating the long-term effects of early exposure and exposure during pregnancy. Experience from Guinea-Bissau suggests that these may produce excess deaths equal in total to 50 per cent of those from acute measles.

I am not aware of the extent to which measles and smallpox can be compared in terms of their determinants and effects, but they appear to be similar in at least some respects. Smallpox was as fatal to well-nourished individuals as to the poorly-nourished (Mercer 1985). Severe cases transmitted a more severe form of infection. Immunized individuals had a much lower CFR if they contracted the infection. Contemporary opinion connected smallpox to many later complications, for example consumption (Mercer 1985), and it may thus have functioned like measles. However, I am not aware of any study which has actually measured the size of the delayed mortality after acute smallpox, nor is there, to my knowledge, any study which has examined the impact of early exposure or exposure during pregnancy.

There seem to be rather consistent data from several European countries, at the turn of the eighteenth century, to show that smallpox deaths constituted 10–15 per cent of all deaths (Mercer 1985). This is likely to be an underestimate since many smallpox deaths may not have been properly registered as such. If those who died of smallpox did not also display higher risks of dying from other infections, then immunization should have reduced overall mortality by at least 10–15 per cent, and maybe by much more if smallpox was also associated with delayed mortality.

It should be worthwhile to examine whether smallpox gave rise to other than acute deaths. Given the level of mortality attributed to smallpox, and the parallel with the impact of measles control, the disease may well have been a prime mover in the European mortality decline from the eighteenth century. It is likely that McKeown's critiques (Razzell 1974; Mercer 1985) may have underestimated the impact of smallpox control. If there is anything to the contemporary notion of an association between smallpox and consumption (Mercer 1985), the much improved control of smallpox in the early nineteenth century could partly explain the major drop in tuberculosis mortality in its central decades.

Most epidemiological and historical research has searched for external factors to explain severe infection, assuming in Mosley's words that infection was not severe *per se.* Thus severe infection is seen as a reflection of other problems, which has consequences for our explanations of mortality change as well as for public-health policy. However, experience with measles suggests that, under certain conditions of exposure, some infections may indeed be a problem *per se* and may induce long-term consequences. Smallpox may belong to this category. If so, the main point may be, not to explain why smallpox was severe under certain conditions, but that the absence of smallpox may itself explain many other health phenomena, in particular the mortality decline which started 200 years ago.

Conclusion

There are undoubtedly many other aspects of past morbidity and mortality which may be fruitfully examined or reanalysed from the perspective of the transmission process. For example, Reves (1985) noted as a contradiction that diarrhoea mortality among children in England started falling, not at the time of the sanitary reforms, but at the same time as other forms of child mortality related to pneumonia, measles and whooping cough. Some of the important diarrhoea pathogens may also be influenced by the crowding together of many susceptibles, in which case they would have displayed the same reduction in severity as did measles and whooping cough following the fall in family size and the associated changes in transmission patterns.

However, diarrhoea death is probably often a symptom, rather than a result of some specific pathogen. For example, among children in Guinea-Bissau who were exposed to measles under six months of age, most of the excess deaths in later childhood were related to diarrhoea. Such children

had a risk of diarrhoea death which was eight times higher than that of controls. It is likely that diarrhoea death is related to previous measles infection, though this has not actually been demonstrated, and that intensive exposure to measles induces an immunodeficiency leading to elevated risk later in childhood. It is therefore not at all contradictory that diarrhoea mortality should decline at the same time as measles mortality.

Some other aspects of measles mortality are harder to understand. Contemporary accounts of measles in developing countries consistently report higher CFRs in rural than in urban areas, but British records usually indicated the reverse. This contrast could usefully be explored further to see whether it might be explained by differences in number of offspring, spacing and degree of crowding, or in the number and size of rooms, between urban and rural areas in Britain.

In the attempt to combine biological and social realities to obtain some kind of understanding of the variations in morbidity and mortality, discussion has been dominated by a rather limited set of host, disease and treatment factors believed to determine the severity of infectious diseases. The underlying assumption has usually been that there is something distinctive about those who die, that they are somehow the weak ones. I have argued here that a better insight might be obtained by asking whether the infection itself could vary in severity such that the essential question is not the distinction between children who die and those who survive, but that between a fatal infection and a less severe one.

In this paper I have mainly emphasized factors relating to the intensity of exposure, but synergistic relations between several infections occurring at the same time may also have had substantial effects on the severity of each of them. This is an aspect that I have not been able to study in any detail, but is seems worth pursuing in the future. It is likely that there was an important interaction between tuberculosis and measles in the past, such that measles paved the way for tuberculosis, and tuberculosis aggravated the severity of acute measles infection. The point has not been to suggest that host factors have no importance; they have. However, exploring the implications of the transmission-factor approach for historical data may provide many more lessons for both the past and the present.

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