Measles immunization research: a review*

P. Aaby[1] & C. J. Clements[2]

Most global estimates indicate that more than 1 million children a year die from acute measles. The actual number of deaths may, however, be considerably higher than this. In addition, the impact of delayed mortality as a result of measles infection is only now being realized. Many months after they contract measles, children continue to experience higher levels of mortality and morbidity than those who do not.

Immunization of children against measles therefore prevents mortality and morbidity not only during the acute phase but also during subsequent months. The impact of measles immunization programmes may therefore have generally been underestimated.

The effects of measles infection on children during the early months of life are more damaging than those experienced by older children. Children should therefore be immunized against measles as early in life as possible, given the limitations of existing vaccines.

Introduction

The WHO Expanded Programme on Immunization (EPI) estimates that 1.6 million children die from measles each year in developing countries (excluding China),[a] making it the biggest killer among the six EPI target diseases. Other workers have estimated that measles is responsible for 0.9–1.5 million deaths per year in developing countries (*1*, *2*). Globally, around 70 million cases occur annually. Opinion has varied not only as to real death toll from measles but also about the value of immunization against the disease.

Since, on the one hand, measles mortality is usually associated with both poor living conditions and malnutrition, it has often been suggested that the disease mostly kills children who, in any case, are likely to die from other infections (*3*, *4*). In consequence, measles immunization may increase child survival only to a limited extent, if at all, because prevention of deaths from measles through immunization may result in children surviving, only to die from other causes. On the other hand, many children are weakened and become malnourished after measles infection, so that the disease may lead to excess delayed mortality (*5*, *6*). If so, the number of children who survive because of being immunized should exceed the number of acute measles deaths that are prevented.

These contrasting hypotheses have implications for the emphasis given to measles control within primary health care programmes and have prompted us to undertake this review of the available data on the case fatality rates for measles and the mortality impact of measles infection and measles immunization.

Mortality from measles

Magnitude of deaths from acute measles

Official estimates of the number of deaths from acute measles infection may be too low. EPI calculates that the case fatality rate (CFR) for acute infection among persons of all ages in developing countries is 2–4%, that the CFR throughout Africa and Asia is 3–4%, and that it is 2% in the majority of countries in South America. It is very difficult, however, to estimate the rate in many of these areas because

* A fuller version of this article (unpublished document EPI/GAG/87/WP.10) is available upon request from: Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland.

[1] Lecturer, Institute of Anthropology, University of Copenhagen, Copenhagen, Denmark, and Chief of Research Station, MINSAP/DCA Primary Health Care Project, Guinea-Bissau.

[2] Medical Officer, Expanded Programme on Immunization, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this author.

[a] See, for example, *EPI Update*, February 1989.

Reprint No. **4997**

registration of cases is unreliable. Data from longitudinal community studies indicate that the CFR ranges from 34% to 0% in rural Africa (*7–11, 20, 21*),[b] from 21% to 6% in urban Africa (*4, 12, 13*), and from 5% to 0% in other studies (*14–19*). With few exceptions (*16, 18, 19, 21*), CFRs from these longitudinal community studies are higher than EPI estimates, at least during the initial stages of an investigation (*20, 21*). In particular, for Africa, the difference between official estimates and the observed CFRs is considerable. Notably, for West and Central Africa, mortality from measles in the community may well be two or three times higher than the estimated 3%.

Delayed impact on mortality and morbidity

Available data strongly suggest that children who have previously been infected with measles have a significant excess morbidity and mortality compared with community controls. If measles should continue to have an effect on a child after the period of acute infection, it may have a considerably greater influence on mortality than is usually assumed (*5*). Unfortunately very few studies have examined the impact of previous measles infection on later morbidity and mortality, and in those that have, the comparison between previous cases and controls is associated with serious methodological problems.

Hull et al. reported an outbreak of measles in a village in the Gambia which they re-visited 3 and 9 months later to assess the impact of the disease (*22, 23*). The results indicated that for children who had contracted measles, the excess risk of dying after the acute infection was highly significantly greater than that of community controls. Deaths were distributed throughout the 8-month follow-up period. The excess mortality seemed to be particularly high for the children under 1 year of age. Other studies in the Gambia (*24*), Nigeria,[c] and Burkina Faso (*25*) suggest an increase in mortality for some months after infection with measles. Furthermore, a study in Guinea-Bissau (*6*) has reported that the excess mortality extends also to the following year; similar observations of excess mortality that was delayed for more than a year were also made in Guinea-Bissau during 1984 for an epidemic that began early in 1983.[d]

Delayed morbidity after measles infection has been investigated in at least two studies (*26, 27*). In one of these, measles cases had 10 times more days of illness than controls, with the difference being particularly marked during the first 3 months after the infection.

Future studies should control for background factors that might increase both the risk of measles infection and of mortality due to other causes. From existing data, however, the differences in mortality reported are so large that it seems improbable that unsuspected background factors could account for them.

Available data suggest that the risk of delayed mortality is particularly increased for children who become infected with measles before reaching 1 year of age. Most studies have emphasized that the period of 1 month to 3–6 months after infection is critical in this respect. However, the possibility that the difference in risk may continue for an even longer period has not been sufficiently evaluated.

Measles infection

Early exposure to measles virus

Children who are exposed to measles during the early months of life experience more damaging effects than those who contract the disease when they are older. For example, in Guinea-Bissau (*28*), the mortality rate throughout childhood among children who lived in houses where measles occurred during the first 6 months of their life was three to four times higher than that of community controls. This trend has been documented several times in Bissau, the capital, following measles outbreaks. Should this be documented elsewhere, it would suggest that infants under 6 months of age are particularly vulnerable, and that a considerable proportion of deaths in childhood may be related to primary measles infection.

There is obviously a need to confirm these findings in other settings and to define more precisely the difference in mortalities in relation to the age of exposure to measles. If future studies confirm these tendencies, the implication would be that measles has a considerably greater impact on mortality than previously assumed and would strengthen the importance of measles control, especially to protect the very young.

Effect of nutritional status

It has usually been assumed that the severity of measles is mainly determined by adverse

[b] **Stephens, P.W.** *Reliability of lay-reporting of morbidity and cause-of-death data: an evaluation of reported cases and deaths from measles in rural Senegal.* Paper presented at the International Union for the Scientific Study of Population. Seminar on Comparative Studies of Mortality and Morbidity: Old and New Approaches to Measurement and Analysis, Siena, 1986.

[c] **Osagie, H.F.** *Delayed mortality and morbidity 12 months after measles in young children in Nigeria.* M.Sc. thesis, University of London, Institute of Child Health, 1986.

[d] **Aaby, P. et al.** [*Report on preventive efforts in Bandim I*]. Unpublished document, 1984 (in Portuguese).

environmental factors, in particular by nutritional status. Accordingly, it has been claimed that measles immunization would not make a great deal of difference to overall mortality rates because the immunized children are likely to die from other causes, such as malnutrition. However, the results of recent community studies, that the state of nutrition before the onset of measles may not be associated with the severity of the disease (*7*, *29*) or the risk of dying, question such claims. Intensity of exposure and overcrowding may be much more potent predictors of outcome (*12*, *18*, *30*). If it is not the particularly weak who die of measles, then immunization against the disease may have more effect on survival than was previously thought. Indeed, the number of lives saved by immunization may be greater than the number of acute measles deaths that are averted, because children may be more likely to die from other causes for an extended period after acute measles.

Measles immunization

Effect on mortality and morbidity

The impact of measles immunization on mortality and morbidity is difficult to gauge because of the difficulty in selecting controls. The only study of this type that has been reported was carried out by Hartfield & Morley (*31*) before the introduction of measles immunization on a large scale. They observed that over an 18-month follow-up period no one died in the small study group of 23 children who received measles vaccine, whereas three children died (two from measles) among the 25 controls who received pertussis/tetanus vaccine ($P = 0.27$; Fisher's exact test).

A major comparative study was carried out in Kasongo, Zaire (*4*). The overall mortality reported from measles was 1.8–2.5 times lower among the immunized group than that among three control groups during the critical age period for child mortality (7–35 months), which corresponds to a 45% to 60% reduction in mortality.

Re-analysis of data from the Khombole area in Senegal (*32*) also showed that children who had been immunized against measles had an overall mortality risk that was 31% lower than that of controls for a period between 6 months and 3 years ($P = 0.028$). Furthermore, studies in Bangladesh (*17*, *33*, *34*)[e,f] and Guinea-Bissau (*6*, *7*, *35*) suggest that the reduction in mortality following immunization is greater than that expected simply from a reduction in measles deaths.

At least two studies have examined the effect on mortality of immunizing children against measles upon admission to hospital (*36*, *37*). In one of these, the total hospital mortality rate fell to half of that which it had been in the previous year. No other major change in treatment practice was introduced that could have explained this reduction.

Measles immunization also has a positive effect on morbidity as well as mortality (*38*, *39*).[g] Several studies suggest this effect is particularly pronounced for children who are immunized at a young age (*4*, *6*, *32*, *35*).[e] Also, in Zaire (*4*) and Guinea-Bissau (*6*), measles immunization of children under 9 months of age without subsequent re-immunization was highly protective against death.

As many deaths from measles may occur within a year of contracting the disease as occur during the acute phase of the disease (*22*).[h] In areas where the protective efficacy of measles immunization is greater than the proportion of deaths attributed to acute measles, a major reason for this is probably the delayed excess mortality among previous measles cases. Also, measles immunization may be immunostimulating (*6*, *39*). It therefore appears that a well-executed measles immunization programme will protect children dying from the disease both during the acute phase as well as months later—deaths which appear to be from other causes but are, none the less, attributable to measles (*32*).[f]

Optimum age for immunization

The delayed effect of contracting measles at under 1 year of age is particularly marked (*6*, *22*).[h] Also, reduction in mortality is particularly impressive in children who have been immunized at a young age (*4*, *6*, *32*, *35*).[e] While these observations need to be studied further, the available data add another dimension to discussions of the appropriate age for immunizing against measles in developing countries. The evidence suggests that measles in the very young must be prevented at all costs.

It has been a common expectation that as immunization coverage becomes greater, the average age of children who are infected with measles would increase, and, at the same time, the risk of exposure before 9 months of age would diminish considerably (*40*). Were this to be the case it might be possible to

[e] **Uddin, N. et al.** *Studies on measles vaccination.* Report to Overseas Development Administration, London, June 1986.

[f] **Clemens, J.D. et al.** *Impact of measles vaccination upon childhood mortality in rural Bangladesh.* Unpublished document WHO/EPI/GAG/86.

[g] **Andersson, N. et al.** *Acute respiratory infections in early childhood and immunization against measles.* Centro de Investigación de Enfermedades Tropicales, Universidad Autónoma de Guerrero, Guerrero, Mexico.

[h] See footnote *c*, p. 444.

raise the age of immunization to 12 months, when seroconversion is more efficient (*41*). However, these expectations have not always been fulfilled. Studies indicate that, in urban African areas with immunization programmes, as many as 20–45% of measles cases occur among children aged under 9 months (*40*, *42*, *43*). In such circumstances, between 5% and 10% of children may contract measles before the age of 9 months, which is similar to the proportion of cases among under-9-month-olds in community studies carried out in areas where immunization has not been introduced (*30*, *44*).

It is disappointing that, at intermediate levels of immunization coverage, no major drop occurs in the risk of measles infection for children under 1 year of age. Model studies by McLean & Anderson (*45*) predict that even high levels of coverage in older children may not be protective for those aged under 9 months in environments where transmission rates of measles are high. There is a need for further studies of the incidence of measles in children under 9 months of age, of the factors that contribute to the high risk of transmission in this age group, and of interventions to reduce the transmission among such children. For the present, it therefore seems unrealistic to expect that the recommended age for measles immunization can be raised; however, there is every reason to pursue strategies that would lower it.

One of the most attractive alternatives is a one-dose vaccine that can be used to immunize children aged 4–5 months or younger, even in the presence of maternal antibodies. The Edmonston–Zagreb measles vaccine holds such a prospect, and there is increasing evidence that it is more immunogenic than the Schwarz vaccine (*46–49*).[f] However, before the Edmonston–Zagreb vaccine can come into general use, further studies are needed of its clinical efficacy in children aged under 9 months, including investigations of the optimal dose and the optimal age to administer it (*50*).

Until alternative measles vaccines become available, a viable strategy might be to use a two-dose immunization schedule for areas where measles transmission is high—the first dose being given probably at 6–7 months of age and the second at perhaps 9 months. Although initial predictions obtained in model studies suggest that no benefit is to be gained by adopting a two-dose schedule (*45*), further investigation is clearly required.

[f] See footnote *e*, p. 445.

Résumé

Le point de la recherche en matière de vaccination antirougeoleuse

Le Programme élargi de Vaccination estime que 1 600 000 enfants meurent chaque année de la rougeole. Ces chiffres en font la plus mortelle des six maladies cibles du Programme. Même ainsi, les taux officiels de mortalité par rougeole sont peut-être sous-estimés puisque les données d'études communautaires donnent des taux de létalité encore plus élevés. En outre, ce n'est que tout récemment qu'on s'est rendu compte que la rougeole avait des effets à retardement importants sur la morbidité et la mortalité. Au bout de plusieurs mois, la mortalité et la morbidité sont plus élevées chez les enfants ayant contracté la rougeole que chez les autres. Des rapports provenant de Guinée-Bissau indiquent que cet effet peut se prolonger pendant plus d'un an.

Par conséquent, la vaccination des enfants contre la rougeole prémunit contre la morbidité et la mortalité non seulement au cours de la phase aiguë de la maladie, mais aussi pendant les mois qui suivent. Les données de l'étude de Kasongo au Zaïre laissent à penser que, même sans cet effet à retardement sur la morbidité et la mortalité, cette dernière est de 1,8 à 2,5 fois plus faible dans les groupes d'enfants vaccinés, ce qui correspond à une diminution de la mortalité de 45 à 60%. L'impact des programmes de vaccination antirougeoleuse a donc peut-être été généralement sous-estimé.

Les enfants qui contractent la rougeole au cours des tout premiers mois de la vie sont beaucoup plus sérieusement atteints que ceux qui la contractent à un âge plus avancé. Il faudrait donc pratiquer la vaccination antirougeoleuse aussitôt que possible, compte tenu des limites imposées par les vaccins actuels.

References

1. **Walsh, J. & Warren, K.S.** Selective primary health care. *New England journal of medicine*, **301**: 967–974 (1979).
2. **Assaad, F.** Measles: summary of worldwide impact. *Reviews of infectious diseases*, **5**: 452–459 (1983).
3. **Hendrickse, R.G.** Problems of future measles vaccination in developing countries. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **69**: 31–34 (1975).
4. **The Kasongo Project Team.** Influence of measles vaccination on survival pattern of 7–35-month-old children in Kasongo, Zaire. *Lancet*, **1**: 764–767 (1981).

5. **Aaby, P. et al.** Measles vaccination and child mortality. *Lancet*, **2**: 93 (1981).
6. **Aaby, P. et al.** Measles vaccination and reduction in child mortality: a community study from Guinea–Bissau. *Journal of infection*, **8**: 3–21 (1984).
7. **Aaby, P. et al.** Determinants of measles mortality in a rural area of Guinea–Bissau: crowding, age and malnutrition. *Journal of tropical pediatrics*, **30**: 164–169 (1984).
8. **Pison, G. & Bonneuil, N.** Increased risk of measles mortality for children with siblings among the Fula Bande, Senegal. *Reviews of infectious diseases*, **10**: 468–470 (1988).
9. **McGregor, I.A.** Measles and child mortality in the Gambia. *West African medical journal*, **14**: 251–257 (1964).
10. **Lamb, W.H.** Epidemic measles in a highly immunized rural West African (Gambian) village. *Reviews of infectious diseases*, **10**: 457–462 (1988).
11. **Morley, D.C. et al.** Measles in West Africa. *West African journal of medicine*, **16**: 24–31 (1967).
12. **Aaby, P. et al.** Overcrowding and intensive exposure as determinants of measles mortality. *American journal of epidemiology*, **120**: 49–63 (1984).
13. **Aaby, P. et al.** Measles mortality: further community studies on the role of overcrowding and intensive exposure. *Reviews of infectious diseases*, **10**: 474–477 (1988).
14. **Gordon, J.E.** Measles in rural Guatemala. *Journal of pediatrics*, **66**: 779–786 (1965).
15. **Mata, L.J.** *The children of Santa Maria Cauqué: a prospective field study of health and growth.* Cambridge, MA, MIT Press, 1978.
16. **Sinha, D.P.** Measles and malnutrition in a West Bengal village. *Tropical and geographical medicine*, **29**: 125–134 (1977).
17. **Koster, F.T. et al.** Synergistic impact of measles and diarrhoea on nutrition and mortality in Bangladesh. *Bulletin of the World Health Organization*, **59**: 901–908 (1981).
18. **Bhuiya, A. et al.** Measles case fatality among underfives: a multivariate analysis of risk factors in a rural area of Bangladesh. *Social science and medicine*, **24**: 439–443 (1987).
19. **Reddy, V. et al.** Relationship between measles, malnutrition, and blindness: a prospective study in Indian children. *American journal of clinical nutrition*, **44**: 924–930 (1986).
20. **Muller, A.S. et al.** The impact of measles in a rural area of Kenya. *East African medical journal*, **54**: 364–372 (1977).
21. **Leeuwenburg, J. et al.** The epidemiology of measles. In: van Ginneken, J.K. & Muller, A.S., ed. *Maternal and child health in rural Kenya*. London, Croom Helm, 1984, pp. 77–94.
22. **Hull, H.F. et al.** Measles mortality and vaccine efficacy in rural West Africa. *Lancet*, **1**: 972–975 (1983).
23. **Williams, P.J. & Hull, H.F.** Status of measles in the Gambia, 1981. *Reviews of infectious diseases*, **5**: 391–394 (1983).
24. **Hull, H.F.** The effect of crowding on measles mortality in the Gambia, 1981. *Reviews of infectious diseases*, **10**: 463–467 (1988).
25. **van de Walle, E.** Anatomie d'une épidémie de rougeole vue par la lorgnette d'une enquête à passages répétés. In: Cantrelle, P. et al., ed. *Estimation de la mortalité du jeune enfant (0–5 ans) pour guider les actions de santé dans les pays en développement*. Paris, Institut national de la Santé et de la Recherche médicale (INSERM), 1986, pp. 419–428 (Séminaire INSERM, Vol. 145).
26. **Shahid, N.S. et al.** Long-term complications of measles in rural Bangladesh. *Journal of tropical medicine and hygiene*, **86**: 77–80 (1983).
27. **Bhaskaram, P. et al.** Effect of measles on the nutritional status of preschool children. *Journal of tropical medicine and hygiene*, **87**: 21–25 (1984).
28. **Aaby, P. et al.** Delayed excess mortality after exposure to measles during the first six months of life. *American journal of epidemiology* (In press).
29. **Bhaskaram, P. et al.** Immune response in malnourished children with measles. *Journal of tropical pediatrics*, **32**: 123–126 (1986).
30. **Aaby, P. et al.** High measles mortality in infancy related to intensity of exposure. *Journal of pediatrics*, **109**: 40–44 (1986).
31. **Hartfield, J. & Morley, D.** Efficacy of measles vaccine. *Journal of hygiene*, **61**: 143–147 (1963).
32. **Garenne, M. & Cantrelle, P.** Rougeole et mortalité au Sénégal: étude de l'impact de la vaccination effectuée à Kḥombole 1965–1968 sur la survie des enfants. In: Cantrelle, P. et al., ed. *Estimation de la mortalité du jeune enfant (0–5 ans) pour guider les actions de santé dans les pays en développement.* Paris, Institut national de la Santé et de la Recherche médicale (INSERM), 1986, pp. 515–532 (Séminaire INSERM, Vol. 145).
33. **Chen, L.C. et al.** Anthropometric assessment of energy–protein malnutrition and subsequent risk of mortality among preschool aged children. *American journal of clinical nutrition*, **33**: 1836–1845 (1980).
34. **Chen, L.C. et al.** Epidemiology and causes of death among children in a rural area of Bangladesh. *International journal of epidemiology*, **9**: 25–33 (1980).
35. **Aaby, P. et al.** Child mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatric infectious disease journal* (In press).
36. **Harris, M.F.** The safety of measles vaccine in severe illness. *South African medical journal*, **55**: 38 (1979).
37. **Glyn-Jones, R.** Measles vaccine and gammaglobulin in the prevention of cross-infection with measles in an acute paediatric ward. *Central African journal of medicine*, **18**: 4–9 (1972).
38. **Natu, M. et al.** Measles vaccination. Prevention strategy for malnutrition. *Indian pediatrics*, **22**: 597–600 (1985).
39. **Bhaskaram, P. et al.** Immunological response to measles vaccination in poor communities. *Human nutrition, clinical nutrition*, **40C**: 295–299 (1986).
40. **Heymann, D.L. et al.** Measles control in Yaoundé: justification of a one dose, nine-month minimum age vaccination policy in tropical Africa. *Lancet*, **2**: 1470–1472 (1983).
41. **Halsey, N.A. et al.** Response to measles vaccine in Haitian infants 6 to 12 months old. Influence of maternal antibodies, malnutrition, and concurrent ill-

nesses. *New England journal of medicine*, **313**: 544–549 (1985).

42. **Loening, W.E.K. & Coovadia, H.M.** Age-specific occurrence rates of measles in urban, peri-urban, and rural environments: implications for time of vaccination. *Lancet*, **2**: 324–326 (1983).
43. **Taylor, W.R. et al.** Measles control efforts in urban Africa complicated by high incidence of measles in the first year of life. *American journal of epidemiology*, **127**: 788–794 (1988).
44. **Aaby, P.** Malnutrition and overcrowding-exposure in severe measles infection. A review of community studies. *Reviews of infectious diseases*, **10**: 478–491 (1988).
45. **McLean, A.R. & Anderson, R.M.** The predicted impact of mass vaccination. *Epidemiological information bulletin*, **100**: 419–442 (1988).
46. **Whittle, H. et al.** Immunisation of 4–6-months-old Gambian infants with Edmonston–Zagreb measles vaccine. *Lancet*, **2**: 834–837 (1984).
47. **Khanum, S. et al.** Comparison of Edmonston–Zagreb and Schwarz strains of measles vaccine given by aerosol or subcutaneous injection. *Lancet*, **1**: 150–153 (1987).
48. **Aaby, P. et al.** Trial of high-dose Edmonston-Zagreb measles vaccine in Guinea–Bissau: protective efficacy. *Lancet*, **2**: 809–811 (1988).
49. **Whittle, H. et al.** Edmonston–Zagreb measles vaccine in the Gambia: antibody response and side-effects. *Lancet*, **2**: 811–814 (1988).
50. **Expanded Programme on Immunization, Global Advisory Group.** *Weekly epidemiological record*, **64** (2): 5–10 (1989).