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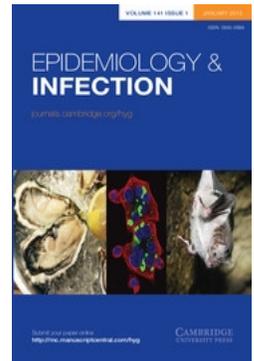S. YAMAGUCHI, A. DUNGA, R. L. BROADHEAD and B. J. BRABIN (2002). Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. Epidemiology and Infection, 129, pp 361-369 doi:10.1017/ S0950268802007458

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Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998

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SUMMARY

Measles surveillance data in Blantyre, Malawi were reviewed for 1996–8 to describe the epidemiology of infection and to estimate vaccine efficacy (VE) by the screening method. A total of 674 measles cases were reported to the Blantyre District Health Office during this period. Age distribution showed that 108 (16·1%) of the cases were aged less than 1 year. The median age was 5 years. Eighty percent of the cases between 1 and 19 years had been previously vaccinated. VE was 68·6% (95% CI, 52·7–79·2) for children 12–23 months of age and 67·3% (95% CI, 48·3–79·3) for infants 9–11 months of age. Reasons for this low vaccine efficacy are discussed. Previous vaccination history was negatively associated with the risk for developing cough during measles infection (odds ratio (OR), 0·30; 95% CI, 0·09–0·91), diarrhoea (OR, 0·64; CI, 0·44–0·95) and pneumonia (OR, 0·40; CI, 0·25–0·62). Logistic regression analysis showed that pneumonia in adults was negatively associated with vaccination history. The passive surveillance system for measles in Malawi was useful to describe the epidemiology of measles.

INTRODUCTION

Measles has been a killer disease throughout human history. Although the Expanded Programme on Immunization (EPI) has been operating since 1974, measles still causes 31 million cases and one million deaths annually in the world [1]. Most of these cases occur in developing countries. In Malawi, measles was reported as the third cause (20·6%) of mortality in the second year of life [2], although measles vaccination coverage was high as shown in Figure 1. Although the incidence of measles in Malawi has dropped dramatically since 1993, several thousand measles cases were still reported annually until the mass measles

vaccination campaign took place in October 1998 [3]. The reason why measles had been prevalent despite the high vaccination coverage in Malawi in mid-1990s is worth considering. One of the possible explanations is a falsely high estimate of vaccination coverage. The other is low vaccine efficacy (VE). In Malawi, measles vaccine is given after 9 months of age as in other developing countries. It has been reported that measles VE was 95% at 9 months in Niger [4], and more than 90% in Mozambican refugee camps in Malawi [5]. However, measles accounted for 10·4% of hospital admissions (the fourth cause), and 8·7% of in-patient mortality (the fifth cause) in children under 5 years in 1992 [6]. These statistics for measles cases were high in view of a reported 80–90% vaccination coverage. Therefore, it is important to confirm that measles vaccination coverage and VE in Malawi was
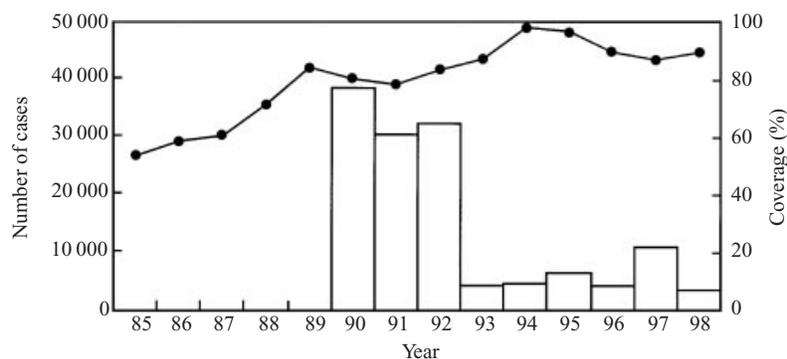
Fig. 1. Measles vaccination coverage and number of reported cases in Malawi. Line, measles vaccination coverage; bars, number of cases (incidence data before 1990 were not available). (Source: Malawi EPI Unit.)

actually as high as reported and comparable with reported efficacy. This study was carried out to describe the epidemiology of measles in Blantyre District, Malawi where Blantyre, the most thriving city in the country, is located. A further aim was to calculate measles VE by the screening method in view of the significant reported morbidity and mortality despite good vaccination coverage.

METHODS

This study reviewed measles case records in Blantyre District, Malawi for the 3-year period 1996–8. The population in Blantyre District was 782226 in 1998, 39% of whom lived in rural areas [7]. This proportion is lower than the national average of 89%, because Blantyre is the most thriving city in Malawi and the district is relatively well developed. Measles Outbreak Investigation Forms (MOIF) used for reporting measles cases by health centres and hospitals to the Blantyre District Health Office (DHO) were reviewed. This form collects information on the name, age, village, date of onset of rash, vaccination history, age (month) at vaccination, presence of cough, runny nose, red eyes, diarrhoea, pneumonia, and death for each measles case.

In Malawi, measles has been diagnosed by health facility staff according to the standard case definition of the WHO [8], which is 'Any person with: generalized maculopapular rash *and* a history of fever of 38 °C or more *and* at least one of the following: cough, runny nose or conjunctivitis; *or* any person in whom a health professional suspects measles.' Aaby et al. reported that measles has been feared in the community in Guinea–Bissau and there was good correspondence between parental diagnoses and clinical records and with serological surveys [9]. Because measles has also been prevalent and feared in Malawi, we believe that diagnoses of measles by the health

facility staff in Blantyre District were reasonably reliable. MOIF were reported when more than five measles cases occurred in a week at each health facility in the entire district. Therefore if less than five cases occurred in 1 week at a site, those cases were not usually reported to the DHO and not included in this study. However, several health facilities have reported measles cases when less than this cut-off.

The data were analysed with Epi-Info version 6.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and StatView version 5 (SAS Institute Inc. Cary, NC, USA). Proportions were compared using the χ^2 test or Fisher's exact test. The Mann–Whitney U test was used to compare the median of a variable for non-normally distributed data. Multiple logistic regression analysis was used to compare clinical symptoms by stratified age groups with adjustment for possible confounding. The Edwards test, which fits a sine curve to monthly incidence data, was used to assess the epidemic pattern of measles [10]. Measles VE was calculated by the screening method [11]. It has been reported by an active surveillance in Malawi that measles vaccination coverage was 67·9% in infants and 88·3% in children 12–23 months of age in 1996 [12]. Age-stratified vaccination coverage was only available for these two age groups. Other coverage data available were based on the ordinary EPI reports, which estimate coverage by dividing the number of vaccine doses used by the size of target population. Because such figures may not have been sufficiently accurate, we used the coverage data from active surveillance only. The percentage of cases vaccinated (PCV) was derived from the case record review.

RESULTS

Descriptive epidemiology

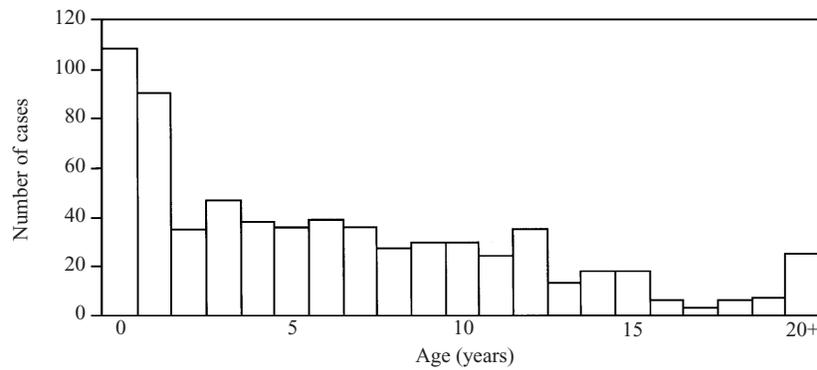A total of 674 measles cases were reported to the

Fig. 2. Age distribution of measles cases. Three cases whose ages were unknown were excluded.
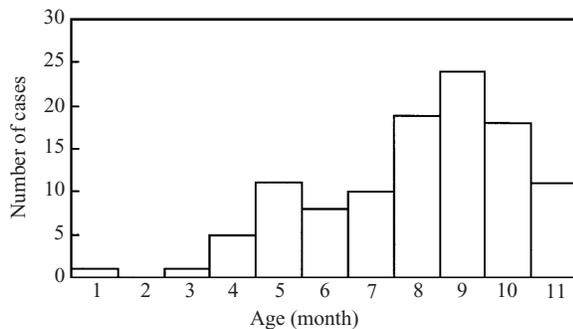

Fig. 3. Age distribution of measles cases in infants.

Blantyre DHO during the 3-year period. The age distribution of the cases is shown in Figure 2. Measles occurred most frequently in children below 2 years of age: 108 (16·1%) cases were less than 1 year, and 55 (8·2%) less than 9 months old. The median age was 5 years. There was an even distribution for children between 2 and 12 years. Twenty-five (3·7%) cases occurred in adults older than 19 years of age. The male to female ratio was 1·09. Figure 3 shows the age distribution in infants. Fifty-one percent of infants were less than 9 months, 34% between 6 and 8 months.

The monthly distribution of measles cases is shown in Figure 4. We defined an epidemic as the period of high measles incidence which is spaced by more than 3 months of very low incidence (< 5 cases/month). The first and the third epidemics had their peaks on 27 April and 28 June, respectively (Edwards test) [10]. The peak of the second epidemic was on 30 October. This minor epidemic had a shorter epidemic period of 4 months. These annual peaks were all highly significant when tested for seasonal variation ($P < 0.001$, Edwards test).

Figure 5 shows the annual incidence of measles by age group. The population for each age group in 1997 and 1996 was extrapolated from the 1998 census data using a 2·6% annual growth rate in Blantyre District [7]. Annual incidence of measles for each age group

was derived by dividing the number of cases by the population of each age group in respective years. In 1997, the annual incidence fell for children 0–4 years of age, but less for older children 5–14 years of age. This indicated that the 1997 minor epidemic occurred mainly in older children, whereas the larger 1996 and 1998 epidemics occurred mostly in younger children. The median age in each year was 3, 9 and 5 years in 1996, 1997 and 1998, respectively. The median age of measles cases in 1997 was significantly higher than that for the 1996 and 1998 epidemics ($P < 0.001$ for both comparisons).

Vaccination status of the cases

Vaccination status of the cases by age group is shown in Figure 6. This status was recorded in MOIF according to the parental memory or immunization record if available. The age at vaccination ranged from 7 to 14 months with a median of 10 months. Of 60 cases under 1 year of age whose vaccination status and age at vaccination were known, 7 children had presented measles in the same month of vaccination. There was no way to know whether these children had presented with measles within 14 days of vaccination, during which period the vaccine cannot confer protection. In the 9–11 months age group, 16 of 39 (41·0%) children, whose vaccination status was known, had been vaccinated. On average, 79·7% of measles cases between 1 and 19 years of age had been previously vaccinated. The PCV by age group is shown in Figure 6. The age group over 20 years showed a low PCV, reflecting the fact that the EPI has been in operation in Malawi for about 15 years.

Vaccine efficacy

PCV was 41·0% (16/39) for the cases aged 9–11 months, and 70·3% (45/64) for those 1 year of age. Measles vaccination coverage has been reported as
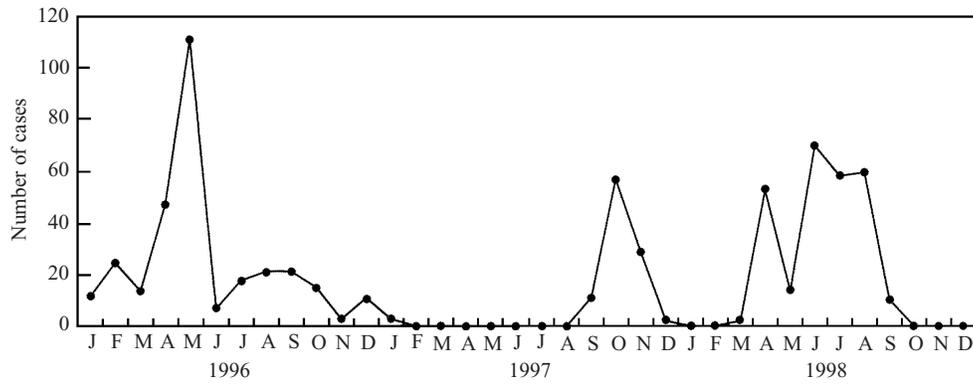
Fig. 4. Reported measles cases by month. Data are based on the date of onset of rash.
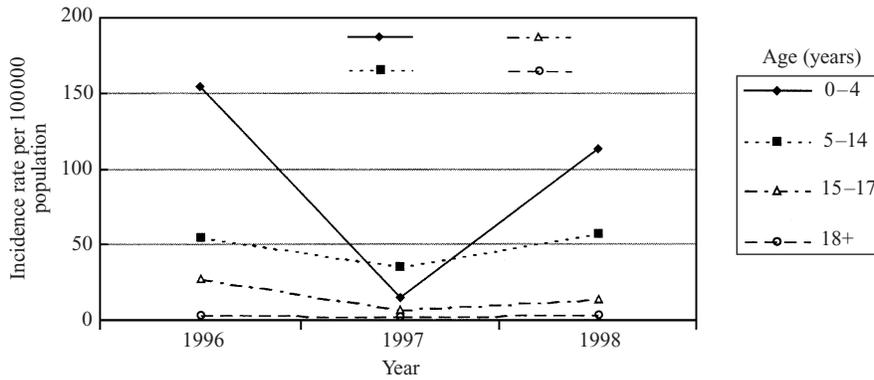
Fig. 5. Annual incidence of measles by age group.

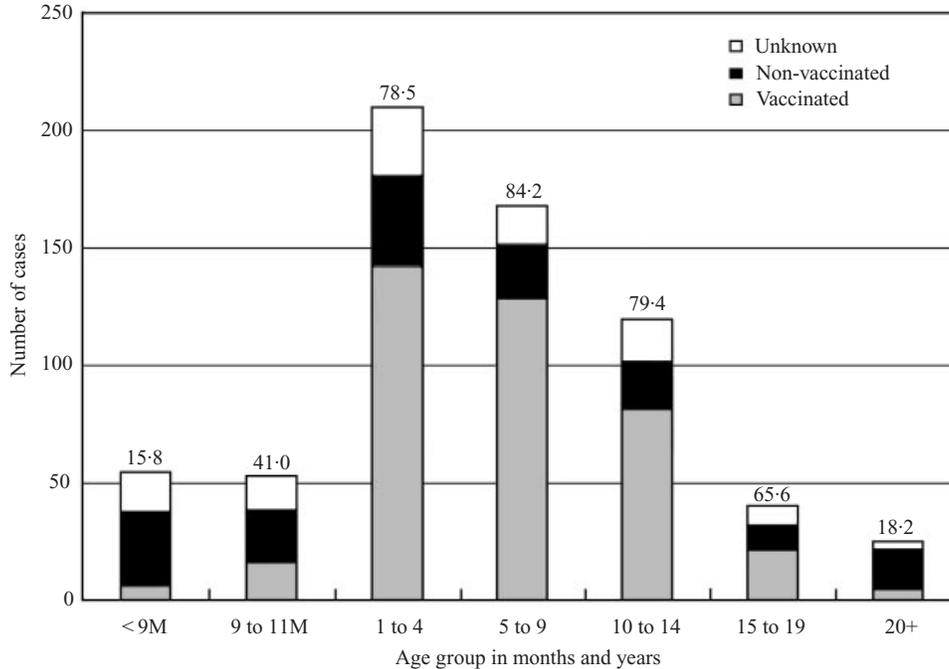**Fig. 6.** Vaccination status of measles cases by age group. Percentage case vaccinated (PCV) is shown above bars.

67·9% for the former, and 88·3% for the latter age group in Malawi [12]. These coverage data were derived from active surveillance and were only available for the 9–11 and 12–23 months age groups. Using these data, VE was calculated as 67·3% (95% CI, 48·3–79·3) and 68·6% (95% CI, 52·7–79·2) for

Table 1. *Proportion of measles cases with specific symptoms or mortality by age group**

Age group	Cough	Runny nose	Red eyes	Diarrhoea	Pneumonia	Death
0	76/80 (95·0)	69/77 (89·6)	64/79 (81·0)	30/78 (38·5)	15/72 (20·8)	1/71 (1·4)
1–4	171/184 (92·9)	164/184 (89·1)	160/185 (86·5)	89/182 (48·9)	38/166 (22·9)	7/166 (4·2)
5–9	152/160 (95·0)	141/158 (89·2)	141/160 (88·1)	71/149 (47·7)	37/140 (26·4)	2/146 (1·4)
10–14	97/106 (91·5)	80/108 (74·1)	103/112 (92·0)	44/99 (44·4)	29/94 (30·9)	1/100 (1·0)
15–19	39/40 (97·5)	32/40 (80·0)	35/40 (87·5)	27/39 (69·2)	9/34 (26·5)	0/35 (0·0)
20+	24/24 (100·0)	20/24 (83·3)	22/24 (91·7)	13/24 (54·2)	10/24 (41·7)	2/24 (8·3)
Total	559/594 (94·1)	506/591 (85·6)	525/600 (87·5)	274/571 (48·0)	138/530 (26·0)	13/542 (2·4)

* Figures in parentheses are percentages.
Cases with missing data were excluded.

Table 2. *Relationship between vaccination and symptoms in measles cases*

	Cough	Runny nose	Red eyes	Diarrhoea	Pneumonia	Death
Odds ratio	0·30	0·85	1·32	0·64	0·40	0·34
95% CI†	0·09–0·91	0·48–1·49	0·75–2·32	0·44–0·95	0·25–0·62	0·10–1·17
P value	0·030*	0·629	0·360	0·024*	< 0·001*	0·053

* Indicates significant association with vaccination.
† 95% CI, 95% confidence interval.

Table 3. *Comparison of the proportion with pneumonia between different age groups with an adjustment for vaccination history*

Comparison	Risk	χ^2	*P* value	OR†	95% CI‡
Age group	Age 20+	3·37	0·067	2·65	0·94–7·49
0 and 20+	Vaccination	0·86	0·355	0·56	0·17–1·90
Age group	Age 20+	0·58	0·447	1·50	0·53–4·29
1–4 and 20+	Vaccination	3·89	0·049*	0·45	0·20–0·99

* Significant at 95% confidence level.
† OR, odds ratio.
‡ 95% CI, 95% confidence interval.

each age group. If the seven cases are excluded who presented with measles in the same month of vaccination, assuming that they had got the disease within 14 days of vaccination, PCV for the 9–11 months group would have been 28·1% and VE 81·6% (95% CI, 51·8–85·10). Confidence intervals of VE by the screening method were calculated following Farrington [13].

Morbidity and mortality

The frequencies of symptoms and mortality are shown in Table 1. Cases with missing information were excluded from the analyses. The proportion of cases with cough, runny nose, and red eyes were not significantly different among the age groups. The age group over 20 years showed a significantly higher rate of pneumonia (41·7%) than for those under 5 years ($P < 0·05$).

The relationship between measles vaccination history and morbidity or mortality is shown in Table 2. Measles vaccination was negatively associated with the risk for developing cough, diarrhoea and pneumonia. Vaccinated cases tended to show a lower mortality rate than non-vaccinated, although this did not reach statistical significance in view of the small number of deaths.

Table 3 shows a logistic regression analysis for pneumonia as an outcome comparing two age groups with adjustment for previous vaccination history. The age group over 20 years showed no significant difference in the risk for developing pneumonia compared with the other age groups, however vaccination history was negatively associated with pneu-

monia in the comparison between the 1–4 and over 20 years age groups.

The overall case fatality rate (CFR) was 2·4%. CFR in infants was 1·4%, which was not significantly higher than for the older age groups. CFR in children under 5 years was 3·4%. The highest CFR was observed in the age group over 20 years (8·3%). No significant difference in CFR was shown among the age groups, possibly because of the small number of deaths.

The proportion of reported cases without any of the three symptoms (cough, runny nose and red eyes) was 3·0%. At least two symptoms were present in 93·2% of the cases (results not shown). The relationship between mortality and specific symptoms showed that mortality was significantly associated with diarrhoea ($\chi^2 = 9·7$, $P < 0·01$) and pneumonia ($\chi^2 = 20·8$, $P < 0·001$) (results not shown).

DISCUSSION

Epidemiology

The surveillance data in this study were reported by the health facility staff when they identified more than five measles cases in a week. Not all cases with measles may have attended the health facilities in Blantyre District. Thus, there would have been some unreported cases that were not included in this study. It has also been reported that patients with rubella are often misdiagnosed as measles [3]. Therefore, there is no reason to believe that the diagnosis for measles by the health facility staff was always accurate. Vaccination history might not have been confirmed by written records. Therefore, interpretation of our data should take into account these limitations which are consequences of the passive surveillance system. However, we believe that the information obtained by the MOIF were reasonably reliable because our results agreed well with previous findings in terms of age distribution, the negative association of vaccination history with symptoms, and seasonal trend [14–16].

The age distribution of the cases showed a low but fairly even distribution between 2 and 12 years of age. The shift in age distribution of measles cases after the implementation of mass-immunization was well described in the review by Cutts et al. [14]. They summarized the proportion of reported measles cases in older children > 5 years as 31–62% for four sub-Saharan African countries. The proportion for our sample was 53%, which is comparable to these other studies. However, they described measles cases which

occurred in older children as mostly among those who were unvaccinated. In our study, about 80% of cases between 1 and 19 years of age had been previously vaccinated. This observation is clearly different from these previous reports probably because previous studies were performed in the late 1980s when the EPI had not been operating for long. In Malawi, where EPI has been in operation since 1983, a susceptible population, should have accumulated, because of low VE, and resulted in a shift of age distribution mostly among vaccinated children.

However, measles most frequently occurred in children less than 12 months of age. It is noteworthy that 34% of the infant cases were between 6 and 8 months. Figure 3 shows that the incidence of measles increased from 4 months of age, indicating that Malawian infants start losing maternally acquired measles antibody around this age. It has been reported that 12% of infants in Bangladesh maintained a protective antibody level at 5 months of age, and 5% at 8 months [17]. Loss of maternal antibody may be greater in babies born to mothers who are HIV-seropositive [18], and HIV seropositivity in women of child-bearing age in Malawi is about 25%. These observations would support the initial use of measles vaccine at 6 months of age in this population. AIK-C measles vaccine strain would be a promising candidate, as it has been reported to be effective at 6 months of age in Ghanaian children [19]. It should also be noted that 59% of the cases between 9 and 11 months with known vaccination history occurred in non-vaccinated infants (Fig. 6). Thus, it is also important to strengthen the standard schedule of vaccination at 9 months of age.

The monthly distribution of measles cases showed annual epidemics (Fig. 4). The age-group specific incidence indicated that the second epidemic occurred mostly in older children (> 4 years), while the preceding and the subsequent epidemics occurred mainly in young children (0–4 years) (Fig. 5). This shift in age groups over consecutive years may indicate that there is a biennial pattern in the younger age group and a relatively stable incidence in older age groups. In the pre-immunization era, measles epidemics occurred biennially in England and Wales [16] and it was possible that virus transmission remained unchanged following the introduction of the national measles immunization programme in the United Kingdom in 1968. Although 3 years of observation was not enough to conclude that there was a biennial pattern in the younger age group, this possibility is

important because it may imply that measles virus transmission remained unchanged in Malawi during the study period. After Malawi conducted a mass vaccination campaign for measles in October 1998, transmission of the virus would have been affected significantly [3] thus changing this pattern. It will be useful to continue to analyse passive surveillance data from Blantyre to establish the importance of on-going measles transmission.

Vaccine efficacy

The accuracy of vaccination history is essential in calculation of VE by the screening method. We could not trace each case record in health facilities and there was no way to determine whether the data were based on written documents. This should be taken into account in the interpretation of the MOIF. Considering the negative association between vaccination history with cough, diarrhoea and pneumonia, which would be expected, we believe that the data on vaccination history were reasonably accurate. Based on vaccination coverage data derived from active surveillance in Malawi [12], estimated VE was 67·3% for children aged 9–11 months and 68·6% for children aged 12–23 months. If we excluded those cases which presented within the same month of vaccination, PCV would be 28·1% for the children 9–11 months old and VE would be 81·6%. Therefore, VE estimates for children 9–11 months of age ranged between 67·3 and 81·6%. There was no case in the 12–23 months age group who presented with measles within the same month of vaccination. VE for this age group was low at 68·6%. The possible explanation(s) for the low VE may relate to:

HIV infection

HIV-infected children show a lower seroconversion rate following measles vaccination [20], and about 6–9% of Malawian children in this area will be HIV-infected [21].

Interferon

An increased level of interferon in a febrile child may interfere with the host immune response to vaccine virus [22]. The WHO recommendation to vaccinate even mildly febrile children may be justified in these settings, but could play a role in reducing measles VE.

Waning immunity

Reyes et al. reported one measles case who had previously shown a documented seroconversion [23]. Their study suggested that measles might occur even in successfully vaccinated children because of subsequent waning immunity.

Maternal antibody

Transplacentally acquired maternal antibody may reduce VE, although early loss of passive maternal antibody in developing countries may reduce the magnitude of this factor.

Low vaccine potency

Due to breakdown of the cold chain.

Limitation of MOIF data

The use of MOIF, which only include data where more than five cases were identified in a week, could result in lowering the sensitivity for case detection. This could reduce the precision of the estimate of VE if the proportion of the vaccinated and non-vaccinated differ significantly in the unreported cases.

Misdiagnosis

Cases such as rubella may have been misdiagnosed as measles and this would result in lower specificity for case definition. This would lead to substantial underestimates of VE, as measles vaccine cannot protect against other diseases.

The screening method provides a simple, rapid and cheap surveillance tool. Its limitations are that the proportion of the population vaccinated cannot usually be tested and detailed analysis of risk factors for low VE may not be possible [13]. Nevertheless, it is the basis for deciding whether more methodologically rigorous investigations are required [11]. Our figure of 68·6% for the 12–23 months age group would suggest the necessity for further investigations such as a cohort or case-control study to confirm the low measles VE in Malawi.

Morbidity and mortality

Table 2 shows that vaccinated measles cases were less likely to develop cough, diarrhoea or pneumonia,

which is consistent with the evidence that vaccinated children experience milder measles infections [15].

The higher rate of pneumonia in the age group over 20 years compared with those of 1–4 years was associated with low vaccination coverage in the adult age group (Table 3), and pneumonia was significantly associated with mortality ($P < 0.001$). The highest mortality rate (8·3%) was also observed in this age group, although only small numbers were available for the analysis (Table 1). It is noteworthy that non-vaccinated adults without past measles infection are at risk of developing serious measles, for measles in non-immune adults is severe [24].

The CFR in this study ranged between 0 and 8·3%, and in children under 5 years it was 3·4%. These rates might be underestimates because children dying of measles at home would not have reported to health facilities. In Niger an overall measles CFR of 2·4% was reported for children under 5 years in a large-scale retrospective cohort study ($n = 6919$) [4]. Their infant CFR was 1·5% compared with 1·4% in our study. This similarity may suggest reasonable reliability in the measles surveillance system in Blantyre District in Malawi.

The MOIF surveillance system was useful to describe the epidemiology of measles over a 3 year period for this one district in Malawi. The systematic analyses of data at the national EPI level is strongly recommended. A further study is required to confirm the low VE reported in this study, in order to facilitate measures to improve VE.

ACKNOWLEDGEMENTS

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