Vaccine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Measles seroprevalence in Chiradzulu district, Malawi: Implications for evaluating vaccine coverage

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ARTICLE INFO

Article history:
Received 31 March 2015
Received in revised form 24 June 2015
Accepted 6 July 2015
Available online xxx

Keywords:
Measles
HIV
Malawi
Vaccination
Immunization

ABSTRACT

Introduction: Self-reported measles vaccination coverage is frequently used to inform vaccination strategies in resource-poor settings. However, little is known to what extent this is a reliable indicator of underlying seroprotection, information that could provide guidance ensuring the success of measles control and elimination strategies.

Methods: As part of a study exploring HIV infection and measles susceptibility, we conveniently sampled consenting HIV-uninfected patients presenting at the HIV voluntary counselling and testing centre, and HIV-infected patients presenting for regular care, in Chiradzulu district hospital, Malawi, between January and September 2012.

Results: A total of 2106 participants were recruited between January and September 2012, three quarters of whom were HIV positive. Vaccination cards were available for just 7 participants (0.36%). 91.9% of participants were measles seropositive.

Older age (OR = 1.11 per year increase in age; 95%CI: 1.09–1.14) and being female (OR = 1.90; 95%CI: 1.26–2.87) were both associated with significantly increased odds for seroprotection. Prior vaccination history was associated with lower odds (Odds Ratio (OR) = 0.44; 95% confidence interval (CI): 0.22–0.85) for confirmed seropositivity. Previous measles infection was not significantly associated with seroprotection (OR = 1.31; 95%CI: 0.49–3.51).

Protection by history and serological status were concordant for 64.3% of participants <35 years old. However, analysis by age group reveals important differences in concordance between the ages, with a greater degree of discordance among younger ages.

Vaccination and/or infection history as a predictor of seropositivity was 75.8% sensitive, but just 10.3% specific.

Conclusion: Reported vaccination and previous infection were poor predictors of seropositivity, suggesting these may be unreliable indicators of seroprotection status. Such serosurveys may be indicated in similar settings in which overestimation of the proportion of seroprotected individuals could have important ramifications if used to guide vaccination strategies.

1. Introduction

Measles vaccination was estimated to prevent 15.6 million deaths between 2000 and 2013, although approximately 145,000 deaths still occur each year, mostly in children under 5 years of age [1]; more than 95% of these deaths occur in resource-poor settings in Africa and Asia [2]. In recent years, enormous progress towards measles elimination has been made in some of the most affected countries, leading to a huge reduction in measles-related morbidity and mortality [2]. However a resurgence of measles in some sub-Saharan African countries has been documented [3].

Malawi introduced one dose of measles containing vaccine (MCV) for infants at (or soon after) 9 months of age into the routine immunization programme in 1979 [4]. The routine programme was supplemented with a non-selective catch-up campaign

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http://dx.doi.org/10.1016/j.vaccine.2015.07.007

targeting all children 9 months to 14 years of age in 1998, regardless of prior vaccination history. Follow-up campaigns targeting children 9–59 months were conducted in 2002, 2005 and 2008. In 2010, a Demographic and Health Survey estimated that 93% of children 12–23 months of age had received MCV [5].

A large and unexpected measles outbreak occurred in Malawi in 2010, during which a total of 134,039 cases and 304 deaths were reported [4]. 42% of the reported cases were under 5 years of age and 30% of cases were reported in children aged 5 to 14 years and 28% in adults (aged 15 years and older). A vaccination coverage survey after the reactive vaccination campaign targeting children 6 months to 14 years of age in Chiradzulu district showed 98.0% coverage (95% CI: 97.4–98.5%) [4] by card confirmation and oral reporting.

As part of a larger study on measles serological protection in HIV infected and uninfected individuals in Chiradzulu district [6], we collected data on measles vaccination and disease history. Our aim was to explore self-reported measles protective status, and comparing this with measles serological result, in order to inform local assessments of vaccine coverage and provide important guidance on how these assessments could be improved to ensure control strategies are successful.

2. Methods

A facility-based study was conducted to assess differences in levels of measles antibodies between HIV-infected and uninfected individuals in Chiradzulu district, Malawi [6]. A secondary objective of this study was to correlate self-reported measles protective status with measles serological result. The sample size was calculated based on the primary objective of the study.

Eligible participants were those aged 18 months and older who were able to understand the patient information sheet and who gave informed consent to participate. All individuals meeting the inclusion criteria attending voluntary counselling and testing services or presenting for follow-up care at Chiradzulu District Hospital were invited to participate. A convenient sample of all consecutive individuals consenting to participate who presented during the study period was enrolled until the desired sample size was reached.

2.1. Sample collection and processing

Venous blood samples were collected from each participant by a qualified phlebotomist. Serum samples were extracted and stored at −20 °C until tested for measles IgG antibodies at the National Institute for Communicable Diseases (NICD) in Johannesburg, South Africa.

Quantitative measurement of measles IgG was performed using an enzyme linked immunosorbent assay (ELISA; Enzygnost Anti-Measles IgG, Dade Behring, Germany). The assay was calibrated against the international reference preparation. Kit dependent parameters were used to express results as an antibody concentration (mIU/ml) derived from the optical density (OD) according to the manufacturer's instructions. Samples were categorized as seropositive (IgG titre > 330 mIU/ml), seronegative (IgG < 120 mIU/ml) and equivocal (IgG titre 120–330 mIU/ml). Equivocal samples were retested and classified accordingly. Those still equivocal after retest were considered negative as equivocal results are below the 330 mIU/ml protection threshold.

2.2. Interview

Information on demographic characteristics, previous measles vaccination and previous measles infection were collected from each participant using a structured questionnaire administered by trained interviewers in Chichewa, the local language. When available, vaccination cards were used to complement recall of previous vaccination.

Following the verbal histories, participants were categorized as "protected" (reported previous vaccination and/or infection), "susceptible" (reported no previous vaccination and no previous infection), and 'unknown' (missing information for previous vaccination and previous disease).

"Protected" participants were categorized as protected by vaccination if protection was established from vaccination only; or as protected by disease if they declared a past measles infection independently of reported vaccination.

2.3. Data collection

Anonymized data were double-entered into an EpiData database mask (EpiData Association 2010). Data were cleaned and exported to Stata 13.0 (College Station, TX, USA) for analysis.

2.4. Statistical analysis

MCV seroprevalence and descriptive analysis of measles antibodies included all study participants with known titres (analysis A). In a second analysis (analysis B), logistic regression models were used to calculate the odds of seroprotection according to measles vaccination and infection history, age, sex and HIV status in univariable and multivariable models. In these analyses only participants aged <35 years of age for whom a measles history questionnaire was completed were included. Participants aged ≥35 years old were excluded from this analysis because they had not been targeted by MCV vaccination activities.

Serological results were log-transformed to obtain a more normal distribution. Differences on geometric mean titres (GMTs) amongst groups were analysed using linear regression.

Additionally, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of reported vaccination status/previous infection were calculated using measles seropositivity as the 'gold-standard' reference measure.

2.5. Ethical considerations

This study adhered to the principles that govern biomedical research involving human subjects. The study protocol was approved by the National Health Sciences Research Committee of Malawi. The Declaration of Helsinki was followed, aiming to provide assurance that the rights, integrity, and confidentiality of trial subjects were protected.

Informed consent was sought from the study participants or from their parent/guardian if they were under the age of 18 years. Participation in the study was voluntary, entailing no obvious benefits or risks.

3. Results

In total 2106 participants were recruited from the District Hospital in Chiradzulu district, Malawi, between January and September 2012. A measles serological result and complete questionnaire are available for 1929 individuals. The mean age of enrolled participants was 36.9 years (median = 37) with a sex ratio of male/female of 0.6. There were only 9 participants in the 18 months to 4 years age group. On interview, only 7 participants (0.36%) showed a vaccination card to the interviewer. Three quarters of the participants were HIV positive (Table 1).

Overall, 61.8% of participants (1192) reported having received a measles vaccine. Reported measles vaccination was high, even amongst participants aged ≥35 years old with no opportunities

Please cite this article in press as: Polonsky JA, et al. Measles seroprevalence in Chiradzulu district, Malawi: Implications for evaluating vaccine coverage. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.07.007

Table 1
Participant characteristics.

Characteristic	*N* (%)	GMT* in mIU/ml (95% CI)
Measles serological status		
Seropositive	1772 (91.9)	2807 (2693–2926)
Seronegative	157 (8.1)	138 (122–157)
Age		
18 m–14 y	95 (4.9)	395 (298–525)
15–29 y	388 (20.1)	1207 (1055–1382)
30–44 y	915 (47.4)	2709 (2534–2896)
≥45 y	531 (27.5)	3223 (2990–3475)
Sex		
Male	702 (36.4)	1964 (1785–2160)
Female	1224 (63.5)	2345 (2198–2502)
HIV status		
Negative	507 (26.3)	1832 (1642–2045)
Positive	1422 (73.7)	2344 (2204–2492)
Vaccination history		
Vaccinated	1.192 (61.8)	2127 (1980–2285)
Not vaccinated	311 (16.1)	2508 (2205–2854)
Unknown	426 (22.1)	2182 (1968–2419)
Previous measles infection		
Yes	325 (16.9)	3182 (2862–3538)
No	1604 (83.2)	2038 (1918–2165)

* Geometric mean titre.

Table 2
Measles seroprevalence and geometric mean titre (GMT) by category, participants <35 years old.

Category	*N*	*N* protected (%)	GMT (95% CI)
Unprotected	144	132 (91.7)	1733 (1395–2154)
Protected by vaccination	413	317 (76.7)	1037 (902–1193)
Protected by disease	104	96 (92.3)	2670 (2118–3441)
Unknown status	147	127 (86.4)	1378 (1130–1679)
All	808	672 (83.2)	1354 (1229–1491)

for measles vaccination. 16.9% of participants ($n = 325$) reported a previous measles infection and 87.4% of these ($n = 284$) reported a measles infection within the previous 24 months. A total of 494 participants (25.6%) reported a measles infection in a member of their household within the previous 24 months.

From serological results, 91.9% of participants ($n = 1772$) were classified as measles seropositive. Mean GMT was 2082 IU/ml (range 8–18,479). GMTs were significantly higher with increased age and females had a higher GMT than males.

A measles infection within the last 24 months was not associated with higher GMT than those that reported measles infection longer in the past ($p = 0.504$). However, reporting a measles infection within the household in the previous 24 months was strongly associated with a higher GMT, even after adjusting for age, sex and HIV status ($p = 0.007$).

3.1. Measles history and serological status amongst participants <35 years of age

Amongst participants aged <35 years of age, considered as having had vaccination opportunities, over three-quarters of those categorized as protected by vaccination, and over 90% of those that reported a previous measles infection, were seropositive (Table 2). GMTs were significantly higher amongst the protected by disease group than the unprotected group (2670 vs. 1733, $p = 0.012$). However, GMTs were significantly lower in the vaccinated group compared to the unprotected. There were no significant differences in GMTs in relation to the number of measles doses received ($p = 0.833$).

Prior vaccination history was associated with lower odds (odds ratio (OR) = 0.44; 95% confidence interval (CI): 0.22–0.85) for confirmed seropositivity (Table 3). Having declared a previous measles infection was associated with higher odds for seroprotection (OR = 1.31; 95% CI: 0.49–3.51), however this was not statistically significant. Older age (OR = 1.11 per year increase in age; 95% CI: 1.09–1.14) and being female (OR = 1.90; 95% CI: 1.26–2.87) were both associated with significantly increased odds for seroprotection.

Table 3
Factors associated with seropositivity in participants <35 years of age.

Characteristic	Univariable OR (95% CI)	Multivariable OR (95% CI)
Measles verbal history		
Unprotected	Ref	Ref
Protected by vaccination	0.30 (0.16–0.57)	0.44 (0.22–0.85)
Protected by disease	1.09 (0.43–2.77)	1.31 (0.49–3.51)
Unknown status	0.58 (0.27–1.23)	0.24 (0.29–1.14)
Age		
18 m–14 y	Ref	Ref
15–33 y	5.72 (3.62–9.01)	4.77 (2.94–7.73)
34–44 y	43.23 (22.55–82.91)	39.64 (20.35–77.22)
≥45 y	59.23 (27.37–128.19)	53.17 (24.24–116.65)
Sex		
Male	Ref	Ref
Female	1.96 (1.35–2.85)	1.90 (1.26–2.87)
HIV status		
Negative	Ref	Ref
Positive	0.82 (0.56–1.20)	0.60 (0.38–0.93)

N = 808 in univariable and multivariable analysis.

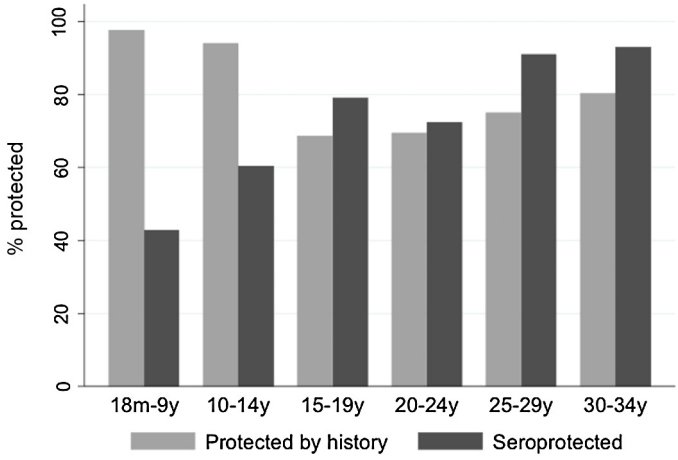

Fig. 1. Proportion of participants <35 years of age protected by history and/or serological status, according to age group.

3.2. Validity of measles protection history as a predictor of seropositivity

Protection by verbal history was higher in the <15 years old (91.6%; 95% CI: 83.9–95.8%) and lowest in the 15–29 years old group (59.6% protected; 95% CI: 55.7–63.3%). However serological results showed that the young population has the lowest proportion of seropositivity (47.4%; 95% CI: 37.4–57.6).

Protection by history and serological status were concordant for 64.3% of participants <35 years old. However, analysis by age group reveals important differences in concordance between the ages, with a greater degree of discordance among younger ages (Fig. 1). Concordance was 74.0% in the 25–34 years old group, but just 50.5% among those aged <15 years.

The sensitivity of vaccination and infection history as a predictor of seropositivity was 75.8%. The PPV was 79.9%. However, the specificity and NPV were 10.3% and 8.3%, respectively. Amongst

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Table 4
Sensitivity, specificity, positive predictive value and negative predictive value of reported measles protection compared to serological.

Participants*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
<35 years (n = 661)	75.8	10.3	79.9	8.3
<15 years (n = 91)	93.8	2.3	51.7	25.0

* Excluding unknown protection status by history.

participants <15 years of age, sensitivity was 93.8%, but again, specificity, PPV and NPV value were poor (Table 4).

4. Discussion

The majority of participants included in this study were seroprotected against measles and this increased with age. Amongst participants <35 years of age, who had opportunities for measles vaccination, only 77% of those that declared previous vaccination were seropositive. This was lower amongst the young. In this study, reported vaccination and previous infection were poor predictors of seropositivity. Age and gender were the main factors associated with seroprotection, with older age and female gender associated with higher odds of seropositivity.

A similarly high seroprotection amongst an adult population was found in a study in Kenya, among whom infection or viral exposure was postulated to have likely contributed to the high antibody levels seen amongst older age groups [9]. Indeed, in this study GMTs were significantly higher amongst those that declared a recent measles infection within their household, indicating a boost in IgG antibodies induced by anamnestic response.

Measles vaccine efficacy for a single dose in similar settings has been estimated at approximately 84% [24]. In our study, this imperfect vaccine efficacy may have led to an underestimation of the true discordance between vaccination status and seroprotection, as a proportion of those reporting having been vaccinated would not have been immunized by the vaccination. Assuming all study participants reporting having been vaccinated would have received just one dose, this would suggest an expected 1001 (84% of 1192) immunized participants, which is more discordant than the 1772 observed to be seroprotected (immunized). However, as second and third doses greatly improve measles vaccine efficacy, the true proportion immunized by vaccination may have been substantially greater than 84%.

Some studies have investigated the validity and reliability of self-reported vaccination status against measles and other antigens. A recent systematic review [10] of the validity of vaccination cards and parental recall in estimating vaccination coverage identified five studies conducted in low and middle income countries, of which just one was from Africa (Guinea-Bissau) [11]. Our results are in a similar range to those reported among low-middle income countries in this systematic review, which reported median concordance of 54%, median sensitivity and specificity of 53% and 69%, respectively, and median PPV and NPV of 94% and 13%, respectively.

Among other antigens, reported influenza vaccination status was reported to be a generally highly sensitive measure of vaccination status, but had variable specificity [12–16]. In three studies, reported pneumococcal polysaccharide vaccination status was reported to have high sensitivity and specificity [14,17,18], while another study reported high sensitivity but poor specificity of this measure [15]. Reported HPV vaccination status was shown to have a high sensitivity and specificity relative to provider-reported vaccination status among adolescent females in the USA [19], while another study reported high levels of inaccuracy between self-reported and actual vaccination status [20].

These results must be interpreted with caution, particularly as the great majority of participants were adults, potentially leading to substantial recall bias and/or misclassification due to the long time between vaccination and recall. Therefore, these results apply primarily to adults in similar settings, and further studies would be required for better understanding of such effects among children and younger adults, at whom measles vaccination strategies are generally targeted.

A high proportion of participants declared being vaccinated against measles. This was even the case for older participants that were less likely to be targeted by vaccination activities. It is likely that vaccination status was not correctly identified for part of these participants. Moreover, a relatively low number of participants reported having had a measles infection. This is particularly surprising amongst older participants, born before widespread use of vaccination where, with circulating virus, much of the population would have been infected by a young age [7]. Measles vaccination and infection generally occur early on in life and there may have been problems with accurate recall, particularly among the older study participants.

The low immunity found in children <15 years of age in this study is surprising, especially because the study was conducted soon after a reactive mass vaccination campaign that reached high vaccination coverage. Similar protection levels were also found in a seroprevalence study in Bangui, Central African Republic, despite high reported vaccination coverage [8]. The selection of study participants in these studies might have played a role as both studies included a high proportion of children recruited at clinic visits, which may have introduced selection bias in the sample, with an increased probability of selecting sick or unvaccinated children. Furthermore, vaccination cards were only available for a small minority and vaccination status might have been overestimated.

Another limitation of this study is that we used ELISA for determining measles IgG antibody titres, which has been shown to be both sensitive and specific [21,22]. However, PRNT is the gold-standard test [23], but is much more expensive, requires specialised training, and was not available at NICD at the time of study implementation. While not as sensitive and specific as PRNT, ELISA is the most commonly used test for determining measles antibody titres.

In conclusion, the results of the study presented here have important implications for measles control programs. As the correlation between reported vaccination and seroprotection was weaker than expected, reported vaccination and/or infection status may be an unreliable indicator of seroprotection status. In settings implementing measles control and elimination strategies, or in which measles outbreaks arise, it may be worthwhile to conduct similar serosurveys, as systematic overestimation of the proportion of seroprotected children could have major ramifications if used to guide vaccination strategies. This information can help to guide control programs in order to ensure that progress in measles control continues.

Acknowledgements

We would like to acknowledge the support of various individuals, who assisted in approving the study design and setting up the study, in particular Davie Zolowee at the Malawian Ministry of Health, Florence Fermon and Elisabeth Szumilin at Médecins Sans Frontières in Paris, and Musa Hamdan at Médecins Sans Frontières in Malawi. We also thank the participants of the study and the members of the Médecins Sans Frontières field team in

Please cite this article in press as: Polonsky JA, et al. Measles seroprevalence in Chiradzulu district, Malawi: Implications for evaluating vaccine coverage. Vaccine (2015), http://dx.doi.org/10.1016/j.vaccine.2015.07.007

Chiradzulu. All funds for this study were provided by Médecins Sans Frontières—Operational Centre Paris. Epicentre receives core funding from public fundraising for MSF.

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