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Measles vaccination effectiveness among children under 5 years of age in Kampala, Uganda

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Abstract

Measles control remains a great challenge in Uganda. We conducted a prospective study among household contacts aged 9–59 months to assess measles vaccination effectiveness. Index cases were measles patients seen in Kampala hospitals in 1999. Measles was diagnosed in 37/43 (86%) of unvaccinated and in 33/145 (23%) of vaccinated exposed contacts, respectively. Vaccination effectiveness was 74% (95% CI; 64–81), which was lower than expected. This may indicate the need for strengthening of the cold chain and/or introduction of a second opportunity for measles vaccination, either as part of the routine immunization program or in the form of supplementary immunization activities.

Keywords: Measles vaccination effectiveness; Attack rates; Filter paper blood samples

1. Introduction

Measles is a leading cause of vaccine-preventable deaths worldwide [1], with Uganda being one of the countries with the highest morbidity and mortality figures [2,3]. Measles vaccination coverage in Uganda is low: WHO and UNICEF estimated a national coverage of 63% for 2003 (www.who.int, vaccine surveillance: statistics and graphs). In the Kampala district mass vaccination campaigns against measles were organized in 2000, which resulted in an initial decline in the numbers of cases followed by a period with morbidity and mortality numbers exceeding pre-campaign levels [3]. Hospital-based case-fatality ratios during the period 1997–2001 ranged from 5 to 17% [3].

Besides insufficient vaccination coverage, there are also indications that measles vaccination effectiveness (VE) may be low in Uganda. In the early 1990s, a community-based measles outbreak investigation in Kampala revealed a VE of 55–75% [4], and similar results of low VE have been found in urban as well as rural districts of other African countries [5–9]. Reduced VE in developing countries has often been attributed to poor cold chain maintenance or poor handling of measles vaccine in the field [5,10]. In addition, vaccination at an early age contributes to reduced VE [11].

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In order to assess VE, we evaluated measles attack rates (ARs) in vaccinated and unvaccinated household contacts of measles patients in Kampala.

2. Materials and methods

2.1. Study design

Between March and September 1999, a measles household contact study was conducted in Kampala, Uganda. Kampala is the largest city of Uganda, with a population of over 1.2 million residents. Index cases were children admitted to three Kampala hospitals: Mulago (the main public hospital in Kampala), Nsambya and Rubaga (both missionary hospitals). Measles patients were diagnosed by the physician on basis of clinical symptoms and laboratory-confirmed by detection of measles virus (MV)-specific IgM antibodies. Household contacts were defined as children aged 9 months to 5 years living in households of the index cases, exposed to the index case for at least one day in the 4 days before the index case developed rash, and who had a vaccination card documenting measles vaccination status 14 days prior to the onset of measles in the index case. Household contacts were excluded if the parent reported that the child had already had measles before the first visit to the household.

In each household, caretakers and household contacts were interviewed in the local language using a standardized questionnaire, including whether or not the household contact slept in the same room as the index case and how many days the contact was exposed to the index case. Date of birth, vaccination status and age at measles vaccination were obtained for each child from a vaccination card. In the absence of records for index cases, parental reports or life events were used to estimate the child's age or date of birth. Children were only classified as vaccinated if measles vaccine had been given at a minimum of 9 months of age and at least 14 days prior to the onset of measles in the index case. Contacts were evaluated in their homes within the first 3 days and again on the 14th day after hospital admission of the index patient. Household contacts that had prodromal symptoms of measles on second visit were also evaluated after 21 days. A secondary case was defined as a household contact with onset of rash 7–18 days after onset of rash in the index case. Any child found to be seriously ill was referred to Mulago Hospital for admission.

Informed consent was obtained from parents or caretakers. As all non-immunized children had been exposed to measles infection for more than 72 h, vaccination for preventing measles was not indicated. The study protocol was approved by the Uganda National Council for Science and Technology, the Research and Ethics Committee of the Faculty of Medicine, Makerere University and participating hospitals.

2.2. Sample collection and handling

During the first visit, whole blood was collected by finger prick from all household contacts (except where the caretaker refused), and spotted onto filter paper to soak an area at least 1 cm in diameter. After collection, filter papers were dried at room temperature and stored at −20 °C in leak-proof containers. During the second and third visits, blood was collected by venepuncture from any household contact meeting the WHO clinical case definition for measles [12], and serum was stored at −20 °C.

2.3. Measles serological testing

IgM measurement in serum were done at the Uganda Virus Research Institute (UVRI) Entebbe in March 2000, while IgG testing in filter paper blood samples was done at the Erasmus MC in Rotterdam, the Netherlands, in November 2001. At UVRI, MV-specific serum IgM antibodies were detected using a commercial measles IgM ELISA (Enzygnost, Dade Behring, Marburg, Germany). At Erasmus MC, baseline MV-specific IgG levels were determined using an in-house indirect ELISA assay based on coating with β-propiolactone-inactivated MV antigen [13]. Total IgG1 levels were determined in reconstituted filter paper samples as a control on the effectiveness of reconstitution [13]. Results were expressed in international units per milliliter (IU/mL), based on standard dilutions of the international standard serum for measles run in parallel with each assay.

2.4. Data analysis

Vaccination effectiveness (VE) was derived from ARs in household contacts and calculated according to the following formula: $VE = 100 \times [1 - (\text{AR in vaccinated/AR in non-vaccinated})]$ [14]. Children were considered to be in an overcrowded environment if they lived in a house with two or more persons per room including living and bedrooms and kitchen [15]. The association of categorical variables with the risk of measles was assessed using the χ^2-test. Logistic regression was used to analyze the effects of age, sex, vaccination status, overcrowding, IgG antibody level at baseline, number of children in each household, whether or not contacts slept in one room with the index case, number of rooms occupied in each household, number of windows in each household and the total number of people in each household on risk of developing measles in univariate analysis. Backward elimination was used to the final multivariate model, beginning with the following variables: exposed child slept in one room with index patient, immunization status, age, IgG status at baseline and overcrowding. Statistical analyses were performed using Epi-Info and SAS software.

3. Results

3.1. Cohort characteristics

One hundred and twenty-seven index cases and 223 household contact cases were recruited. Three household contacts

Table 1
Measles attack rates among household contacts with different MV-specific IgG levels at the moment of vaccination

Baseline IgG (IU/ml)	Overall attack rate		Attack rate in vaccinated children		Attack rate in unvaccinated children	
	Contacts[a]	Measles cases (attack rate)[b]	Contacts	Measles cases (attack rate)	Contacts	Measles cases (attack rate)
<0.05	41	35 (85)	14	9 (64)	27	26 (96)
0.05–0.125	23	16 (70)	10	7 (70)	13	9 (69)
0.125–0.2	12	5 (42)	9	3 (33)	3	2 (67)
0.2–1	51	8 (16)	51	8 (16)	0	0 (0)
>1	61	6 (10)	61	6 (10)	0	0 (0)
Total	188	70 (37)	145	33 (23)	43	37 (86)

[a] Number of household contacts in MV-specific IgG-level subgroup.
[b] Number of measles cases in baseline antibody subgroup (attack rate: measles cases as percentage of total number of household contacts in subgroup); χ^2 for linear trend = 77.597, $p < 0.0001$.

could not be traced during follow-up, 18 were excluded because they were above 5 years of age and two because they had been vaccinated at the age of 6 months. Of the remaining 200 household contacts, 55 (28%) were reported to be unvaccinated. However, 11 of these had serum IgG antibody levels above 0.2 IU/ml, indicative of prior vaccination or MV infection, and one had no serum sample collected at baseline to determine antibody level; therefore, these were also excluded from the study. Of the 188 household contacts finally included in the study, 145 (77%) were vaccinated and 43 (23%) were unvaccinated.

The group of index cases had a median age of 18 months; 62 (49%) were females, and 29 (23%) had been vaccinated against measles. The group of household contacts had a median age of 36 months; 103 (55%) were females. Most (98%) of the vaccinated household contacts had received their vaccination at 9 months of age.

3.2. Measles attack rates

Measles attack rates in vaccinated and unvaccinated household contacts in relation to MV-specific IgG levels measured in filter paper blood samples collected during the first visit are shown in Table 1. Overall, 70/188 (37%) household contacts contracted measles, of which 33 had been vaccinated and 37 were unvaccinated. Overall VE was 74% (95% confidence interval [CI]; 64–81). Vaccination effectiveness was higher in younger than in older age groups (see Table 2, χ^2 for linear trend vaccine effectiveness = 5.296, $p < 0.05$). Attack rates were inversely related to specific IgG level at baseline (see Table 1, χ^2 for linear trend = 77.597, $p < 0.0001$).

3.3. Statistical analysis

In univariate analysis, risk factors for developing measles included immunization status, specific IgG level at baseline, and age. Although the effect of overcrowding was not significant in univariate analysis, it was included in the multivariate analysis because of its recorded importance in measles transmission [16,17]. In multivariate analysis, adjusting for immunization status, age, overcrowding and IgG sero-status at baseline, only immunization status ($p < 0.01$) and specific IgG level at baseline ($p < 0.01$) remained significant.

4. Discussion

Measles vaccination effectiveness is expected to be at least 85% in children immunized at 9 months of age [18,19]. However, in the present study we found a VE of 74% in Kampala, Uganda. Similarly low VE has previously been observed in Uganda [6,20] and other developing countries [5,7], suggesting that factors contributing to reduced VE have not changed and occur region-wide.

Table 2
Measles age-specific attack rate among household contacts

Age (months)	Attack rate in vaccinated children		Attack rate in unvaccinated children		Vaccine effectiveness
	Contacts[a]	Measles cases (attack rate)[b]	Contacts	Measles cases (attack rate)	VE (95% CI)
9–11	1	0 (0)	6	5 (83)	100 (100, 100)
12–23	19	4 (21)	14	12 (86)	75 (40, 90)
24–35	34	9 (26)	12	9 (75)	65 (33, 82)
36–47	47	9 (19)	6	6 (100)	81 (66, 89)
48–59	44	11 (25)	5	5 (100)	75 (58, 85)
Total	145	33 (23)	43 (23)	37 (86)	74 (64, 81)

[a] Number of household contacts in age subgroup.
[b] Number of measles cases in baseline antibody subgroup (attack rate: measles cases as percentage of total number of household contacts in subgroup); χ^2 for linear trend vaccine effectiveness = 5.296, $p < 0.05$.

The reduced VE mainly resulted from high secondary attack rates in vaccinated children, which could be attributed to a combination of factors. Poor vaccine storage and/or handling during routine services may be an important factor, since problems in cold chain maintenance have been reported previously [21]. Another contributing factor could be intensity of exposure due to overcrowding, which has previously been identified as an important risk factor for contracting measles [5,16].

Virus-neutralizing (VN) MV-specific serum antibodies are the most important correlate of protection from clinical measles [22]. However, in the present study VN antibodies could not be measured since only filter paper blood samples were available. Serological data obtained from filter paper blood samples should be interpreted semi-quantitatively, since the exact volume of blood spotted on filter paper remains uncertain [13]. However, several studies have demonstrated the usefulness of filter paper blood samples for IgG serology by comparison with paired serum samples [23–26]. In addition, the major advantage of filter paper blood samples is the relative ease of collection and storage. The baseline samples from household contacts were collected from healthy children: parents and children would not easily agree to collection of blood by venepuncture, but had no objections to finger prick. MV-specific IgG levels measured in filter paper blood samples collected from household contacts during the first visit proved to be strongly associated with protection. However, the absence of detectable specific IgG antibodies did not necessarily mean that subjects are unprotected: also in the low or undetectable antibody subgroups ARs were not 100%, which is in agreement with previous reports and should probably be attributed to cellular immunity [22,27]. The ARs in children with high antibody levels were higher than expected from earlier studies [5,22,27], possibly because of the intensity of exposure.

VE was high in the youngest infants, lowest in the age group of 24–35 months and higher again in older children. This pattern suggests waning immunity in the first years after vaccination followed by boosting by subclinical infections in the subsequent years [28,29]. However, other factors could also have played a role, and numbers of subjects per age group were relatively low. During follow-up, two unvaccinated children died of measles complications (pneumonia and diarrhea), while no deaths were recorded among vaccinated contacts. Although our study was not powered for (or aimed at) studying disease severity, this observation suggests that despite low VE vaccination may have helped to reduce mortality and severity of disease.

This study had a number of limitations. Some children in the households could not be included because of missing vaccination cards. In addition, MV-specific IgM was only tested in household contacts who met the WHO clinical case definition for measles. Unapparent infections may have been missed, so that the measles ARs obtained could be an underestimate. No testing for serum antibodies to human immunodeficiency (HIV) was performed, so a potential role of HIV in influencing protection levels against measles could not be assessed. However, the study clearly emphasizes that evaluation of VE continues to be an essential tool to monitor ongoing measles control programs.

Our findings suggest that in addition to failure to vaccinate, vaccination failure may be an important cause of the severe recurrent measles outbreaks and epidemics that have been occurring in Uganda. A reduced VE appears to have persisted for several years. In other regions of the world implementation of a two-dose schedule for measles vaccination has proven necessary to achieve measles control [1,30]. This approach offers a second opportunity for those children that might have missed their first immunization, and could result in a boost of immunity in those with waning immunity. The planned implementation of a second opportunity for measles immunization in Uganda [31] will therefore hopefully limit the number of susceptible individuals, boost immunity levels and reduce measles-related mortality.

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