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Response to measles revaccination among Bolivian school-aged children

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Abstract

The response to measles revaccination was evaluated in 1994 among 202 Bolivian school-aged children whose antibody levels were below 200 miu (milli-international units) by haemagglutination inhibition (HI) in a large-scale serosurvey conducted in Santa Cruz one year earlier. Of the 202 revaccinated children, 164 (82%) had seroconverted between the 1993 serosurvey and the pre-revaccination blood sample. A measles outbreak occurred in Santa Cruz 6 months before the revaccination. Among the seroconvertors, only 6% gave a history of measles, and 15% a history of contact with a case of measles. All 20 children with undetectable HI antibody pre-revaccination, and all 6 children with levels below 100 miu, seroconverted after revaccination. The geometric mean titres by HI at 4 weeks after revaccination were 2018 miu (95% confidence limits [95% CL] 1143, 3564) and 398 miu (95% CL 254, 625) in the 2 groups, respectively. Six of 9 children with pre-revaccination antibody titres of 100–199 miu also seroconverted. No child demonstrated a measles-specific immunoglobulin M response. Among the 29 children who seroconverted and were followed up at one year after revaccination, 15 (52%) showed a fourfold or greater decline in antibody levels, which in 8 fell to levels below 200 miu. This study confirmed the observation that revaccination is successful in producing an antibody response in children with low or undetectable pre-revaccination titres, but it also confirmed that vaccine-induced immunity wanes rapidly.

Keywords: measles, vaccination, revaccination, antibody response, children, Bolivia

Introduction

The availability of an effective measles vaccine has enabled vaccination programmes substantially to reduce measles morbidity and mortality, and has raised the possibility of interrupting measles transmission (HOPKINS *et al.*, 1982; DE QUADROS *et al.*, 1996). Countries aiming to interrupt measles transmission administer more than one dose of measles vaccine, either through a routine two-dose schedule (BOTTIGER *et al.*, 1985; BOTTIGER, 1993) or periodic mass campaigns (DE QUADROS *et al.*, 1996). The cost- effectiveness and longer-term effect of mass campaigns on immunity to measles have not yet been established.

A community-based cluster survey conducted in Santa Cruz, Bolivia, in April 1993 showed that 87% of sera from a sample of 1654 children aged less than 15 years contained measles-specific immunoglobulin (Ig) G detectable by haemagglutination inhibition (HI) assay (CUTTS *et al.*, 1995). Among school-aged children, only 7% had no detectable measles IgG, but 30–40% had antibody levels below 200 miu (milli-international units). Other studies have shown that measles neutralizing antibody levels below 200 miu are not fully protective against infection or disease (CHEN *et al.*, 1990). With the agreement of the Santa Cruz regional health authority, we conducted a study in 1994–1995 to evaluate the response to revaccination among Bolivian children with low or absent measles antibody levels by HI. Ethical approval for the study was obtained from the London School of Hygiene and Tropical Medicine.

Materials and Methods

Children whose antibody levels were below 200 miu by HI in the 1993 serosurvey (196 aged 5–9 years and 150 aged 10–14 years) were eligible. Children younger than 5 years were excluded because they might have received measles revaccination in a campaign aimed at that age group in May 1993. After obtaining written informed consent from the head of the household, these children were revaccinated in March 1994 and a short questionnaire was administered. The vaccine used was a Schwarz standard titre vaccine (Morbilvax®, Chiron–Biocine, Siena, Italy), as used in the routine programme in Bolivia at the time of the study. Five mL of blood were collected by venepuncture immediately before vaccination (T0) and 4 weeks later (T1). From children who were later shown to have a pre-revaccination antibody level below 500 miu a further sample was obtained one year after vaccination (T2). Blood samples were transported each day in cool boxes to the health unit laboratory in Santa Cruz. Sera were separated, divided into aliquots and stored at –20°C until transported, on dry ice, to the Department of Molecular Biology of the University of Siena, Italy. A subsample of sera was sent to the Public Health Laboratory Service (PHLS), London, UK.

Laboratory assays

All serum samples were tested for measles-specific IgG using an HI assay in the Department of Molecular Biology of the University of Siena, as previously described (CUTTS *et al.*, 1995). Assays were standardized to the second international standard antimeasles serum (FORSEY *et al.*, 1991; FORSEY, 1992) and the results of individual sera expressed as miu/mL. Serum samples from children with a measles IgG level <500 miu by HI, from whom sufficient sera remained (n=35), were also assayed by plaque reduction neutralization (PRN) assay at the PHLS (CALVERT *et al.*, 1996). Serum samples collected 4 weeks after vaccination (T1) were assayed for measles-specific IgM at the University of Siena by enzyme-linked immunosorbent assay (EIA), using a commercially available kit (Enzygnost Measles®, Behringwerke AG, Marburg, Germany). We defined seroresponse as a fourfold or greater increase in antibody titre from pre-vaccination to post-vaccination levels, or a detectable post-vaccination antibody level in an individual who had had no detectable antibody before vaccination.

Results

Of the 346 eligible children, 101 (28%) could not be located in 1994. Among the remaining 245 children, informed consent was obtained from the head of household for 82%; thus 202 children entered the study. All had a verbal history of vaccination in early childhood, and none gave a history of vaccination since the 1993

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survey. Blood samples were obtained from 191 children (95%) at T1. Samples were obtained at T1 from 49 of the 54 children (91%) with pre-revaccination antibody levels below 500 miu, and at T2 from 37 children (69%).

Antibody levels before revaccination

Although all of the 202 children in the study had measles antibody levels below 200 miu in 1993, 148 (73%) had high measles antibody levels at the time of revaccination in 1994, ranging from 500 to 8000 miu by HI. In 1993, 18% of these children had undetectable measles antibody, while in 1994 only 10% had undetectable levels ($P<0{\cdot}05$). Geometric mean titres (GMT) among children with detectable antibody were substantially higher in 1994: 973 miu (95% confidence limits [95% CL], 831, 1139) in 1994, compared to 112 miu (95% CL 107, 118) in 1993. There was no significant difference in antibody levels between females and males in either 1993 or 1994 (respectively, 116 vs. 108 miu in 1993; 1021 vs. 986 miu in 1994).

Overall, 82% of children had seroresponded between the 1993 survey and collection of the pre-revaccination blood sample in 1994. Among the 164 seroresponders, only 6% gave a history of clinical measles since 1993 (none of the 36 non-convertors had a history of measles). A history of contact with a case of measles was obtained from 15% of seroresponders and 6% of non-convertors ($P=0{\cdot}1$). GMT of antibody in 1994 did not differ among children with a history of measles or contact with measles, and those without (data not shown).

Response to revaccination

All 20 children with undetectable HI antibody pre-revaccination seroresponded, with a GMT at T1 of 2018 miu (95% CL 1143, 3564) (Table). Similarly, all 6 children with pre-revaccination antibody levels below 100 miu seroresponded, but with a much lower post-revaccination GMT of 398 miu (95% CL 254, 625). The proportion of children seroresponding decreased sharply at higher pre-revaccination antibody levels, from 6 of 9 children with pre-revaccination titres of 125 miu to one of 14 with titres of 250 miu and 6 of 82 with pre-revaccination titres of 500–1000 miu. None of 60 children with pre-revaccination titres of 2000 miu or above had an increase in antibody level after vaccination. No child demonstrated a measles-specific IgM response to revaccination. There was no difference in the rate of seroresponse between females and males.

Persistence of antibody

The increase in antibody level after revaccination was short-lived in most children (Fig. 1). A serum sample was obtained at T2 from 29 of the 32 children with a pre-revaccination antibody level below 200 miu who had seroresponded at T1. Of these, 15 (52%) demonstrated a fourfold or greater decline in antibody level between T1 and T2, with levels falling below 200 miu in 8 children; these 15 children had all had pre-revaccination titres <100 miu. A similar pattern was seen in plaque reduction neutralization (PRN) assays (Fig. 2), although the magnitude of the changes in antibody levels was somewhat smaller. GMTs by PRN were 693 (95% CL 506, 951) at T0, 1750 (95% CL 1341, 2284) at T1, and 923 (95% CL 691, 1231) at T2.

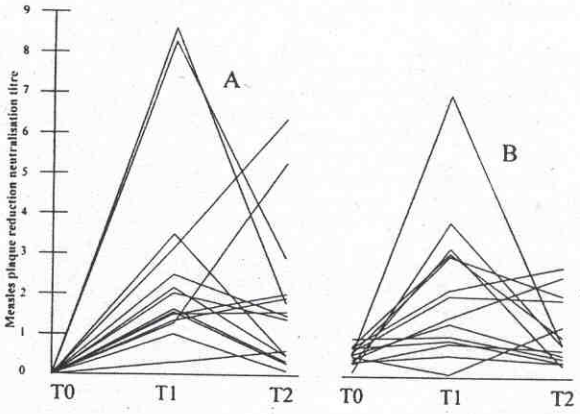

Fig. 2. Measles plaque reduction neutralization antibody titres at baseline (T0) and 4 weeks (T1) and 12 months (T2) after measles revaccination. A, no detectable antibody at T0; B, low antibody titre at T0. Titres are shown in international units/mL.

Table. Haemagglutination antibody response to measles revaccination according to pre-revaccination antibody level

	Pre-revaccination antibody level (miu/mL)			
	Undetectable	60–99	100–199	200–1000
Proportion seroconverted 4 weeks after revaccination	20/20(100%)	6/6(100%)	6/9(67%)	7/96(7%)
Titre at 4 weeks (miu/mL)[a,b]	2018(1143,3564)	398(254,625)	562(449,705)	3266(2548,4186)
Proportion with fourfold or more decline in titre 12 months after revaccination[b]	11/17(65%)	4/6(66%)	0/6	Not evaluated

[a]Geometric mean titre (95% confidence limits in parentheses).
[b]Among those who had seroconverted at 4 weeks.

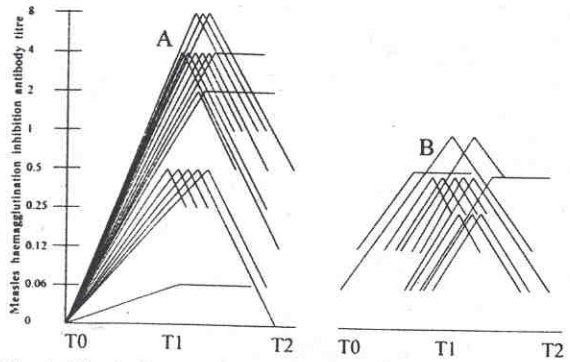

Fig. 1. Measles haemagglutination inhibition antibody titres at baseline (T0) and 4 weeks (T1) and 12 months (T2) after measles revaccination. A, no detectable antibody at T0; B, low antibody titre at T0. Titres are shown in international units/mL.

Discussion

This study aimed to assess the response to revaccination among children who had low or undetectable measles-specific antibody levels in a previous large-scale community survey in Santa Cruz. By the time of this study, one year after the baseline survey, 82% of 202 children who were available for study had a marked increase in measles antibody titres, either seroconverting (8%) or showing a fourfold or greater increase in titre (74%). The assay used in both surveys was the same. The increase in measles antibody titres may be related

to a measles outbreak that occurred in Santa Cruz approximately 6 months before revaccination, during September–November 1993 (Santa Cruz regional health authority, unpublished data). Although only 6% of seroconvertors gave a history of measles and 15% a history of contact with a case of measles, community spread of wild virus during the outbreak could have led to asymptomatic infection among the other children (OZANNE & D'HALEWYN, 1992).

In accordance with previous observations (STETLER *et al.*, 1986; ORENSTEIN *et al.*, 1987), 100% of children with pre-revaccination HI antibody levels below 100 miu seroresponded after revaccination. Among children with pre-revaccination levels of 100–199 miu, 67% responded, but very few children with higher levels before revaccination showed a significant increase in titre. As in previous studies (BASS *et al.*, 1976; DESEDA-TOUS *et al.*, 1978; MARKOWITZ *et al.*, 1992), the persistence of antibody after revaccination was short-lived. Approximately half of the seroresponders at 4 weeks had a significant decline in measles antibody titre by one year after vaccination, with titres often returning to antibody levels close to those before revaccination. Unlike previous studies, this pattern was particularly marked among those who were seronegative before revaccination. Given the absence of an IgM response in these children, it appears that they were also showing a secondary immune response to vaccine, with rapidly waning antibody levels after the initial rise.

Overall, of 49 children with pre-revaccination antibody levels below 500 miu, 33 (67%) seroresponded after revaccination. It is difficult to know how many of these children would have developed measles after contact with wild virus. Although secondary vaccine failure (clinical measles in vaccinated children who had a documented antibody response to the vaccination) has been reported (REYES *et al.*, 1987; MATHIAS *et al.*, 1989; AMMARI *et al.*, 1993; HIDAKA *et al.*, 1994), data from outbreak studies suggest that it occurs in 5% or less of those vaccinated, and does not play an important role during a measles epidemic (OZANNE & D'HALEWYN, 1992). Our findings were in agreement with this, since, although 82% of evaluated children had a significantly higher antibody level in 1994 than in 1993, only 6% of these had a history of symptomatic measles-like illness. Nonetheless, since asymptomatic reinfection with wild virus results in a much greater and more sustained increase in antibody levels than does revaccination (DAIBIN *et al.*, 1991; AMMARI *et al.*, 1993), the potential impact of waning vaccine-induced immunity on measles control should continue to be monitored as measles transmission is reduced world-wide.

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