Population immunity to measles virus and the effect of HIV-1 infection after a mass measles vaccination campaign in Lusaka, Zambia: a cross-sectional survey

Sara A Lowther, Frank C Curriero, Brian T Kalish, Timothy M Shields, Mwaka Monze, William J Moss

Summary

Background Measles control efforts are hindered by challenges in sustaining high vaccination coverage, waning immunity in HIV-1-infected children, and clustering of susceptible individuals. Our aim was to assess population immunity to measles virus after a mass vaccination campaign in a region with high HIV prevalence.

Methods 3 years after a measles supplemental immunisation activity (SIA), we undertook a cross-sectional survey in Lusaka, Zambia. Households were randomly selected from a satellite image. Children aged 9 months to 5 years from selected households were eligible for enrolment. A questionnaire was administered to the children’s caregivers to obtain information about measles vaccination history and history of measles. Oral fluid samples were obtained from children and tested for antibodies to measles virus and HIV-1 by EIA.

Findings 1015 children from 668 residences provided adequate specimens. 853 (84%) children had a history of measles vaccination according to either caregiver report or immunisation card. 679 children (67%) had antibodies to measles virus, and 64 (6%) children had antibodies to HIV-1. Children with antibodies to HIV-1 were as likely to have no history of measles vaccination as those without antibodies to HIV-1 (odds ratio [OR] 1.17, 95% CI 0.57–2.41). Children without measles antibodies were more likely to have never received measles vaccine than with antibodies (adjusted OR 2.50, 1.69–3.71). In vaccinated children, 33 (61%) of 54 children with antibodies to HIV-1 also had antibodies to measles virus, compared with 568 (71%) of 796 children without antibodies to HIV-1 (p=0.1).

Interpretation 3 years after an SIA, population immunity to measles was insufficient to interrupt measles virus transmission. The use of oral fluid and satellite images for sampling are potential methods to assess population immunity and the timing of SIAs.

Funding Thrasher Research Fund.

Introduction

Substantial progress in measles control has been made in Africa as a consequence of implementation of WHO and UNICEF’s strategy for measles mortality reduction.1 This strategy consists of sustaining more than 90% routine measles vaccine coverage, ensuring that all children receive a second opportunity for measles vaccination through supplementary immunisation activities (SIAs; ie, mass measles vaccination campaigns), establishment of effective case-based surveillance, and provision of appropriate clinical management to children with measles.2 Measles deaths in Africa decreased by an estimated 91% from 2000 to 2006, accounting for 70% of the global decline in measles mortality.1

In 2005, as part of the Global Immunization Vision and Strategy, the World Health Assembly set a 5-year goal to reduce measles mortality by 90% compared with 2000 levels.3 This goal is achievable but will need sustained resources and efforts, and further reductions in measles mortality face several obstacles.4 Measles control is especially challenging in densely populated urban areas of Africa and Asia, where several factors converge to exacerbate measles virus transmission; these include difficulties in maintenance of high levels of vaccination coverage,5,7 high prevalence of HIV-1 infection,4 and potential clustering of susceptible people.6 Zambia has one of the highest HIV-1 prevalence rates in the world, and was prone to large outbreaks of measles until the national SIA was done in June, 2003.9 To assess the level of population immunity to measles virus in three urban townships of Lusaka 3 years after this campaign, and the potential effect of the HIV-1 epidemic and clustering of susceptible children, we undertook a cross-sectional, community-based survey with a satellite image-based sampling design and oral fluid specimens to measure the frequency of antibodies to measles virus and HIV-1.
satellite image obtained from DigitalGlobe Services (Denver, CO, USA). The image was imported into ArcGIS version 9.2 and locations of potential households were

identified and enumerated manually. 16 105 structures of appropriate size (larger than a vehicle) and of regular polygonal shape were identified as potential households, of which 750 were randomly selected without replacement.

A pilot exercise had been done to show the feasibility of correctly finding the selected structures by use of satellite photographs. The survey teams, which consisted of community health workers and students, used satellite photographs and knowledge of the study area to locate the randomly selected structures. If a selected structure was ineligible because it was not a residence, no eligible children lived in the home, or no adult was available, the survey team proceeded to the structure to the right. If an eligible residence was not found after three attempts, the team proceeded to the next randomly selected structure. If children between the ages of 9 months and 5 years lived in the household and a guardian or caregiver was present, the team requested written informed consent from the caregiver. After informed consent was obtained, a questionnaire was administered to obtain information about demographic and socioeconomic characteristics of the household, the educational and vital status of the parents, and the health status of the child, including vaccination history and history of measles. Under-5 immunisation cards were reviewed if available.

The study was approved by the University of Zambia Research Ethics Committee and the Johns Hopkins University Bloomberg School of Public Health Committee on Human Research.

Oral fluid samples were obtained with Oracol oral-specimen collection devices (Malvern Medical Developments, Worcester, UK). In accordance with the manufacturer’s protocol, the child’s gums were swabbed for 1 min. The collection devices were transported in

Figure 1: Study profile
*If a selected structure was ineligible because it was not a residence, no eligible children lived in the home, or no adult was available, the survey team proceeded to the structure to the right. If an eligible residence was not found after three attempts, the team proceeded to the next randomly selected structure.

<table>
<thead>
<tr>
<th>Table 1: Summary of characteristics of children included in analyses</th>
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</thead>
<tbody>
<tr>
<td><strong>N=1015</strong></td>
</tr>
<tr>
<td>Age (years, median [IQR])</td>
</tr>
<tr>
<td>Respondent (n [%])*</td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Education level (years, mean [95% CI])†</td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>Dead parent (n [%])‡</td>
</tr>
<tr>
<td>Mother</td>
</tr>
<tr>
<td>Father</td>
</tr>
<tr>
<td>Both parents</td>
</tr>
<tr>
<td>Under-5 immunisation record card available (n [%])</td>
</tr>
</tbody>
</table>

*N=1010, owing to missing data. †Assumption that children within the same household have the same parents. (Number of families (N=668), not individual children.)
cold boxes within hours to the local clinic where 1 mL of transport buffer (phosphate-buffered saline with 10% fetal calf serum, 0·2% Tween 20 [polysorbate 20], 0·5% gentamicin, and 0·2% amphotericin B) was added and the sample stored in a cold box. The specimens were transported the same day to the Virology Laboratory at the University Teaching Hospital, Lusaka, where they were centrifuged at 2000 rpm for 5 min and the fluid removed and stored at −80°C until testing.

We tested oral fluid specimens for antibodies to measles virus with an IgG capture EIA (Microimmune, Brentford, Middlesex, UK) validated for oral fluid. According to the manufacturer, the assay sensitivity is 93% and specificity 98% compared with serum. Antibodies to HIV-1 were detected by the Oral Fluid Vironostika HIV-1 Microelisa System (BioMérieux, Durham, NC, USA) according to the manufacturer’s instructions. Because of the difficulty in assessing the quality of oral fluid samples—ie, whether sufficient oral fluid was obtained—specimens in which antibodies to both measles virus and HIV-1 were undetectable were assayed for total IgG by EIA (Bethyl Laboratories, Montgomery, TX, USA). Oral fluid specimens with total IgG concentrations less than 0·125 mg/L were judged to be of poor quality and were excluded from analyses, according to recommendations of the manufacturer of the measles IgG EIA.

**Statistical analysis**

The sample size was estimated to detect a 30% absolute difference in the proportion of HIV-1-infected and HIV-1-uninfected children with antibodies to measles virus. 60 HIV-1-infected children were required to detect this difference with a power of 0·90 and α of 0·05. On the assumption of an HIV-1 infection rate of 5% in children, and that every household had on average two eligible children, 600 households with 1200 children would include 60 HIV-1-infected children.

Data were double entered, checked, and validated in Microsoft Access, and analysed by Stata version 10. Categorical variables were compared by use of the χ² test or Fisher’s exact test. Proportion and 95% CIs were adjusted for within-household correlation by robust variance estimation known within Stata as the Huber/White/Sandwich estimate of variance.11–13 For age-specific proportion, 95% CIs were estimated by exact binomial methods. Multivariable logistic regression was used to identify predictors of measles vaccination status, lack of antibodies to measles virus, and presence of antibodies to HIV-1, and to control for potential confounding variables. Distance in metres was log-transformed in the regression models. Residual spatial variation from reported logistic regression models were examined by variogram analysis,14 and estimated effect standard errors were adjusted when necessary.

To complement the logistic regression analysis, we estimated and mapped the variation in spatial distributions using the ratio of kernel spatial intensities for unvaccinated children without antibodies to measles virus compared with vaccinated children with antibodies to measles virus, and for children with antibodies to HIV-1 compared with those without antibodies to HIV-1. Kernel spatial intensity estimation is a statistical method to estimate the expected number of events per unit area for a spatial point pattern dataset.15 When the events can be labelled as two types (eg, unvaccinated children without antibodies compared with vaccinated children with antibodies), the ratio of these expected number of events, as a function of location, provides an estimate for the variation in spatial distribution of the ratio for the associated outcomes.16
Role of the funding source
The funding source had no involvement in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows numbers of study households and children. During 3 weeks in July and August, 2006, 1069 children from 691 residences were enrolled. An additional 233 households with potentially eligible children were not enrolled, mainly because consent was refused. Basic demographic information was available for 32 (14%) of the non-enrolled families: these households were more likely to have piped water, a vehicle, and to own their home than were enrolled households.

We analysed data for 1015 children from 668 residences who provided an adequate oral fluid specimen and whose caregiver completed the interview. Table 1 shows the characteristics of these children.

853 (84%) of the 1015 children had a reported history of measles vaccination, 137 (13%) had no reported history of measles vaccination, and 25 (2%) had unknown measles vaccination status. Verbal caregiver reports provided history of routine measles vaccination for 461 (54%) of 853 children; the remaining children’s vaccination history was documented on under-5 immunisation record cards. Additionally, 272 (27%) of the 1015 children were reported to have been vaccinated in the SIA in June, 2003; 259 (95%) had a history of routine measles vaccination by either verbal report (n=178) or documented on the under-5 card (n=81), ten children (4%) were reported to have received measles vaccine during the SIA only, and an additional three (1%) children had unknown routine measles vaccination status.

To assess misclassification of measles vaccination status by caregiver report, we examined measles antibody status for 408 children younger than 35 months (born after the SIA in 2003) with no history of measles and compared two groups of children: those whose caregivers provided a verbal report of measles vaccination and those whose under-5 card was available. 150 (70%) of 215 children with measles vaccination documented on their under-5 card had detectable antibodies to measles virus compared with 117 (61%) of 193 children with a history of measles vaccination by verbal report, suggesting 10% misclassification by caregiver report.

Although measles vaccination is recommended at 9 months of age, it was given before that age to 30 (8%) and after 12 months to 76 (20%) of the 378 children with a documented date of measles vaccination on their under-5 card (figure 2). For 943 children with complete data for measles vaccination status (by card and caregiver report) and measles history, lack of measles vaccination was associated with low levels of caregiver education (adjusted odds ratio [OR] for 0–6 years of education 2·2, 95% CI 1·4–3·4) and young age of the child (adjusted OR for 1-month increase in age 0·93, 0·92–0·95).

679 (67%) of 1015 children had detectable antibodies to measles virus. The proportion of children who did not have detectable antibodies to measles virus rose with later years of birth (figure 3), and was 16% for children born in 2001, 32% for those born in 2002, 27% for those born in 2003, 39% for those born in 2004, and 42% for those born in 2005 (p<0·001 for trend).

For the 943 children with complete data for measles vaccination status and measles history, absence of detectable antibodies to measles virus was strongly associated with no history of measles vaccination (table 2). Children with a history of measles were unlikely to lack detectable measles antibodies (adjusted OR 0·37, 0·15–0·93). 64 (6%) of 1015 children had antibodies to

<table>
<thead>
<tr>
<th>History of measles vaccination</th>
<th>Measles antibodies present (627 children)</th>
<th>Measles antibodies absent (316 children)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes (N=807) 567 (70%) 240 (30%)</td>
<td>Reference</td>
<td>Reference</td>
<td>2.98 (2.03–4.37)</td>
<td>2.50 (1.69–3.71)</td>
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<tr>
<td>No (N=126) 60 (44%) 76 (56%)</td>
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<td>Reference</td>
<td>0.62 (0.42–0.93)</td>
<td>0.60 (0.40–0.92)</td>
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<thead>
<tr>
<th>History of measles</th>
<th>Measles antibodies absent (316 children)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (N=901) 509 (65%) 276 (35%)</td>
<td>Reference</td>
<td>Reference</td>
<td>0.60 (0.40–0.92)</td>
</tr>
<tr>
<td>Yes (N=42) 36 (85%) 6 (14%)</td>
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<td>Reference</td>
<td>1.41 (0.84–2.35)</td>
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</table>

<table>
<thead>
<tr>
<th>Age categories</th>
<th>Measles antibodies absent (316 children)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months of age</td>
<td>Reference</td>
<td>Reference</td>
<td>0.93 (0.90–0.96)</td>
</tr>
<tr>
<td>1-month increase in age†</td>
<td>22 (41%)</td>
<td>Reference</td>
<td>2.01 (1.56–2.61)</td>
</tr>
</tbody>
</table>

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<tr>
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<th>Measles antibodies absent (316 children)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (N=882) 591 (66%) 310 (34%)</td>
<td>Reference</td>
<td>Reference</td>
<td>0.97 (0.96–0.99)</td>
</tr>
<tr>
<td>Yes (N=42) 36 (85%) 6 (14%)</td>
<td>Reference</td>
<td>Reference</td>
<td>1.60 (1.20–2.10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibodies to HIV-1 in oral fluid</th>
<th>Measles antibodies absent (316 children)</th>
<th>Crude OR* (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
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<tr>
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Data are n (%). OR, odds ratio. *Standard errors adjusted for clustering by household. †Age was modelled to compare 9 months of age to 1-month increments.

Table 2: Factors associated with the absence of antibodies to measles virus in oral fluid from 943 Zambian children
HIV-1. The proportion of children with antibodies to HIV-1 fell from 18% of 55 children 9–11 months of age to 9% of 297 children 12–23 months of age and 4% of 663 children older than 24 months (p=0.002 for trend). Children with antibodies to HIV-1 were more likely to be young, have visited a clinic in the past 3 months because they were sick, and have a dry mouth and mouth sores reported at the time of specimen collection than children without antibodies (data not shown).

The proportion of children without a history of measles vaccination did not differ between those with (ten [16%] of 61) and without (126 [14%] of 882) antibodies to HIV-1 (OR 1.17, 0.57–2.41). In vaccinated children, 33 (61%) of 54 children with antibodies to HIV-1 had detectable antibodies to measles virus, compared with 568 (71%) of 796 children without antibodies to HIV-1 (p=0.1, adjusted for clustering).

44 (4%) of the 1015 children had a reported history of measles; two of the 44 had antibodies to HIV-1. Six children with a reported history of measles lacked detectable antibodies to measles virus (none of them had antibodies to HIV-1). The median age of reported measles was 22 months (IQR 12–35). Three of the 44 children with a reported history of measles had never received measles vaccine, two had unknown vaccination status, and three had measles either before or within the same month as receipt of measles vaccine. One measles case was reported in 2001, three were reported in 2002, seven in 2003, four in 2004, five in 2005, and 15 up to July 31, 2006 (dates of the remaining cases were not

Figure 4: Temporal and spatial distributions of measles cases within the three study townships, Lusaka, Zambia
(A) Temporal distribution of measles cases from July, 2002, to July 31, 2006. Only cases for which the month and year were reported are shown. (B) Spatial distributions of measles cases from 2003 to July 31, 2006, for which the year was reported. 35 cases of measles were reported from Jan 1, 2006, to July 31, 2006. Only 13 locations are marked because in two households, two children were reported to have measles.
All measles cases reported in 2003 occurred before the SIA in June. Reported cases of measles were distributed throughout the study area over the 4 years, but yearly spatial patterns differed.

Unvaccinated children without antibodies to measles virus (ie, susceptible children) were distributed throughout the study area (figure 5). However, regions of increased spatial intensity were present in the north and south of the study area where the ratio of unvaccinated, susceptible children to vaccinated, protected children was as high as 0·3 per km², by contrast with areas with as few as 0·05 unvaccinated, susceptible children for every vaccinated, protected child per km².

The spatial variation in children with antibodies to HIV-1 did not overlap areas of measles susceptibility, and a greater proportion of children with antibodies to HIV-1 lived within the middle of the study area. The ratio of children with antibodies to HIV-1 to those without was as high as 0·12 per km² in the middle of the study area, by contrast with as few as 0·05 per km² at the perimeters (figure 5).

Discussion

We have shown that 3 years after a successful SIA that substantially reduced measles incidence and mortality in Zambia, only 84% of children within the study townships had a history of measles vaccination and 67% had detectable antibodies to measles virus in oral fluid samples, suggesting a build-up of susceptible children and a population at risk for measles outbreaks. After adjustment for the reported sensitivity and specificity of the oral fluid assay, the estimated proportion of children with detectable antibodies to measles virus was 70%. In Zambia, the number of reported measles cases increased from 35 in 2004 (the year after the SIA) to 459 in 2006, and a follow-up SIA was done in July, 2007. One of the challenges to continued progress in reducing measles incidence and mortality is the need for repeated mass measles vaccination campaigns. These campaigns require the sustained commitment of resources and personnel, are typically done within 3–4 years of the initial campaign, and target a narrower age-group than initial catch-up campaigns. Cross-sectional surveys such as this, using oral fluid specimens and satellite images for sampling, could be useful to identify the optimum timing of repeat SIA before large outbreaks of measles occur.

HIV-1-infected children did not contribute substantially to the pool of susceptible children. The proportion of vaccinated children with detectable antibodies to measles virus was 10% lower in HIV-1-infected children than in HIV-1-uninfected children. This finding might indicate a true difference, although the statistical evidence for this effect is not strong. We previously reported that HIV-1-infected children lost neutralising antibodies 2–3 years after measles vaccination. However, static and dynamic models of the effect of the HIV-1 epidemic on population immunity to measles suggest that the high mortality of untreated HIV-1-infected children counterbalances their waning immunity, preventing the build-up of susceptible children.
Our findings accord with the hypothesis that HIV-infected children, in the absence of high coverage with antiretroviral therapy, do not contribute substantially to an epidemiologically significant pool of susceptible children. By contrast with our previous finding in a hospital-based, case–control study, no differences in vaccination status were seen between children with and without antibodies to HIV-1.

Spatial clustering of individuals susceptible to measles has been responsible for recent outbreaks of the disease in the USA and Europe and will become increasingly important in sub-Saharan Africa and Asia as measles virus transmission is reduced. Few studies have investigated spatial clustering of susceptible children within urban centres in sub-Saharan Africa. We noted some clustering of susceptible children in the northern and southern sections of the study area, but the number of reported measles cases was insufficient to predict measles outbreaks on the basis of the spatial distribution of susceptible children.

29% of the non-enrolled households declined participation. Limited information from 15% of the non-enrolled households with potentially eligible children suggests that caregivers who declined participation were more likely to have a higher level of household assets than those who participated. Non-enrolled households might have differed from enrolled households with respect to HIV infection or measles vaccination status. Under-5 immunisation cards were available for only 48% of the 1015 children, and we were not able to confirm measles vaccination status for those children without cards. Reported history of measles might be unreliable, particularly in low-transmission settings. We estimated that 10% of children were not vaccinated against measles despite being reported as such by their caregivers; this misclassification might have stemmed from the caregivers’ tendency to tell the interviewers what they thought they wanted to hear.

A further limitation of our study is that the oral fluid assay is less sensitive than assays that use plasma or serum, and underestimates the proportion of children with antibodies to measles virus. We noted that oral fluid testing is less sensitive than assays that use plasma or serum, and underestimates the proportion of children with antibodies to measles virus.

References


