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Exploring HIV infection and susceptibility to measles among older children and adults in Malawi: a facility-based study

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SUMMARY

Background: HIV infection increases measles susceptibility in infants, but little is known about this relationship among older children and adults. We conducted a facility-based study to explore whether HIV status and/or CD4 count were associated with either measles seroprotection and/or measles antibody concentration.

Methods: A convenience sample was recruited comprising HIV-infected patients presenting for follow-up care, and HIV-uninfected individuals presenting for HIV testing at Chiradzulu District Hospital, Malawi, from January to September 2012. We recorded age, sex, and reported measles vaccination and infection history. Blood samples were taken to determine the CD4 count and measles antibody concentration.

Results: One thousand nine hundred and thirty-five participants were recruited (1434 HIV-infected and 501 HIV-uninfected). The majority of adults and approximately half the children were seroprotected against measles, with lower odds among HIV-infected children (adjusted odds ratio 0.27, 95% confidence interval 0.10–0.69; $p = 0.006$), but not adults. Among HIV-infected participants, neither CD4 count ($p = 0.16$) nor time on antiretroviral therapy ($p = 0.25$) were associated with measles antibody concentration, while older age ($p < 0.001$) and female sex ($p < 0.001$) were independently associated with this measure.

Conclusions: We found no evidence that HIV infection contributes to the risk of measles infection among adults, but HIV-infected children (including at ages older than previously reported), were less likely to be seroprotected in this sample.

1. Introduction

Enormous progress towards measles control and elimination has been made in recent years, due largely to sustained efforts to increase vaccination coverage among children worldwide with a cheap, safe, and highly efficacious vaccine.[1–3] As a result, measles incidence and mortality in Sub-Saharan Africa decreased by approximately 90% between 2000 and 2010.[2,4,5] However, outbreaks continue to occur in areas where high vaccination coverage has not been achieved or maintained.[3,6–8] For example, in Malawi, following a reduction from 162 000 measles cases in 1980 to fewer than 200 per year between 2005 and 2009, a large outbreak occurred in 2010, with a reported 134 039 cases and 304 deaths.[8]

Although measles is typically a disease of young children (those aged less than 5 years),[6] an unexpected feature of this Malawian outbreak was that the majority of cases occurred among individuals aged 5 years and older, with 28% of cases among those aged 15 years and older.[8] A similar age distribution has been

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observed in other recent measles outbreaks in Sub-Saharan Africa.[5,7,9]

There are several possible explanations for this phenomenon, including low vaccination coverage in subpopulations despite high national coverage,[10] extensive vaccine failure (possibly due to the logistical difficulties of maintaining a functioning cold-chain in these contexts),[11] waning immunity among previously seroprotected individuals,[12] and impaired immunogenicity to measles vaccine due to health-related factors known to influence the immune response to vaccination, such as malnutrition.[13] Additionally, the reduction in circulating measles virus levels associated with successful measles control may limit or eliminate the immune-boosting effect of frequent re-exposure.

Another possible factor in the unusual age distribution could be the high prevalence of HIV infection in Malawi.[14] Several studies have reported associations between measles antibody concentration and HIV infection and exposure; for example, infants born to HIV-infected women have lower levels of measles-specific transplacental antibodies (which wane faster), potentially leaving these infants at greater risk of infection before they receive the scheduled measles vaccination at 9 months.[15–18] Other reports have shown that HIV infection is associated with greater severity of measles disease,[19] higher mortality from measles,[20] and prolonged measles virus shedding.[21]

Few studies have addressed the role of HIV infection in measles infection risk among adults and children after infancy:[18,22] one study concluded that measles vaccine-derived antibodies decline more rapidly in HIV-infected adults ($n = 48$);[23] a further three studies reported finding no difference in measles seropositivity between HIV-infected adults at different stages of disease progression (as measured by CD4 count).[24–26] A study among Kenyan adults in Nairobi found no statistical difference in measles IgG seroprevalence and concentration between HIV-infected and HIV-uninfected adults, and concluded that reduced immunity among HIV-infected adults was not a major contributor to measles resurgence in that country.[22]

An association between HIV infection and measles susceptibility in individuals over 18 months of age could have wide-ranging implications throughout areas of high HIV prevalence in Africa and Asia that remain at risk for measles outbreaks,[10] where achieving measles control goals may need to include specific guidance for HIV-infected individuals. To investigate this possible association, we assessed measles antibody levels according to HIV status and CD4 count among individuals presenting at a hospital-based outpatient clinic in a rural district of southern Malawi.

2. Materials and methods

2.1. Study design, setting, and participants

We investigated the relationship between HIV status (both serostatus and CD4 count) and measles antibody concentration. This cross-sectional study was conducted between January and September 2012 at Chiradzulu District Hospital in Malawi, the nominal catchment area of which includes all people living within Malawi's Chiradzulu District.

A convenience sample of HIV-uninfected participants was recruited from among individuals who voluntarily presented for HIV counselling and testing during the study period: all people who presented and who were subsequently found to be HIV-uninfected were referred to the study recruiters. Meanwhile, a convenience sample of HIV-infected participants was recruited from patients already on HIV treatment and who presented for follow-up care during the study period: all people who presented for such care were referred, after their medical consultation, to the study recruiters.

The study recruiters explained the study purpose and design to all individuals (or their guardians if they were younger than 18 years old) referred to them. Those who gave informed consent to participate were recruited into the study. Eligibility for inclusion was restricted to individuals aged 18 months or older at the time of recruitment to minimize the potential influence of maternal antibodies acquired either transplacentally or through breastfeeding.

2.2. Variables

The primary outcome measure of this study was measles seroprotection status (seroprotected vs. not seroprotected), and for this purpose, we set the seroprotected threshold (the antibody concentration considered protective against disease) at 330 mIU/ml.[27,28] The secondary outcome was measles IgG antibody concentration among HIV-infected participants only, measured as a continuous variable.

To explore predictors of measles seroprotection status, the exposure variable of interest was HIV infection status (HIV-infected vs. HIV-uninfected), while for measles antibody concentration among HIV-infected participants, the CD4 count was the exposure variable of interest. Additional predictors, potential confounders, and effect-modifiers included for both outcomes were age and sex,[27] time on highly active antiretroviral therapy (HAART),[18,27,29] and reported measles vaccination and infection status.[1]

2.3. Data sources and measurement

Samples of venous blood were collected from each participant for CD4 counts and measles serology. The manufacturer's instructions were followed for all analytical procedures. CD4 counts were determined on site by standard flow cytometry with Cyflow (Partec, Münster, Germany) analysis within 1–6 h of specimen collection.

Serum samples were obtained from whole blood and stored at −20 °C at Chiradzulu District Hospital until transfer to the National Institute for Communicable Diseases in South Africa, where measles serology was performed. Measles IgG antibody concentrations were assessed quantitatively by ELISA (Enzygnost Anti-Measles Virus IgG; Siemens, Marburg, Germany), using kit-dependent parameters.

For each participant, we recorded age, sex, reported measles infection status (ever having had measles), and reported measles vaccination status (ever having been vaccinated against measles). The treatment programme identification number of HIV-infected participants was also recorded to enable linking to the HIV treatment database to include duration of treatment on HAART in the analyses.

2.4. Bias

In order to limit potential sources of bias, all laboratory staff were blinded to the HIV status of participants.

2.5. Study size

Obtaining representative samples of hard-to-reach individuals is a major challenge for epidemiological studies and surveillance.[30] Traditional sampling methods often involve very large sample sizes, which are prohibitive due to operational and cost difficulties. Most importantly, carrying out home-based studies in this context is hindered by ethical considerations, as individuals may not disclose their HIV status, if known, to family members and friends. Like many other studies of this type, we used convenience