Predicted impact of the HIV-1 epidemic on measles in developing countries: results from a dynamic age-structured model

Susana Scott, 1* Joel Mossong, 2 William J Moss, 3 Felicity T Cutts 1 and Simon Cousens 1

Accepted 7 January 2008

Background Although measles incidence has been reduced to low levels in many countries, the potential exists for HIV-1 infection to enhance measles virus (MV) transmission and hinder measles control and elimination efforts.

Methods HIV-1 infection was incorporated into an age-structured, deterministic compartmental model of MV transmission. Parameter estimates were obtained from published studies. The model was then adapted to simulate the introduction of antiretroviral therapy (ART).

Results The model suggests that prior to the introduction of ART, HIV-1 infection has little impact on the transmission dynamics of MV. High mortality rates in HIV-1-infected children without access to ART counteract the higher rates of vaccine failure, shorter duration of maternal antibody protection and longer duration of infectiousness in HIV-1-infected children, as many of these children die before they are able to contribute to MV transmission. The introduction of ART into the model resulted in an increase in measles prevalence.

Conclusions High overall mortality among HIV-1-infected children without access to ART limits the impact of the HIV-1 epidemic on MV transmission and may help to explain the initial success of measles control strategies in Africa. The scaling-up of ART should improve children’s survival but could lead to an increase in measles prevalence in the absence of sustained measles control efforts. Further study of the duration of immunity in HIV-1-infected children receiving ART and their response to revaccination is needed to determine whether a second dose of measles vaccine will protect these children and further reduce MV transmission.

Keywords Measles, HIV-1, mathematical model, disease transmission, antiretroviral therapy, measles vaccine, Africa

1 London School of Hygiene and Tropical Medicine, London, UK.
2 Laboratoire National de Santé, Luxembourg, Luxembourg.
3 Department of Epidemiology and W. Harry Feinstone Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.

* Corresponding author. Infectious Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. 
E-mail: susana.scott@lshtm.ac.uk
Introduction

Although there is a safe and effective vaccine, measles remains an important cause of child mortality in sub-Saharan Africa, where over one-third of the estimated 345,000 measles deaths in 2005 occurred. With almost two thirds of the estimated 33.2 million HIV-1-infected individuals in the world living in sub-Saharan Africa, the potential exists for HIV-1 infection to impact on measles control and elimination.

HIV-1 infection causes immune deficiency and may alter how measles virus (MV) is transmitted within a population. HIV-1-infected children may not develop the characteristic measles rash which could result in unrecognized transmission of MV. They may have prolonged shedding of MV and hence increased duration of infectiousness. Children born to HIV-1-infected mothers have lower levels of maternally acquired antibodies increasing the period during which they are susceptible prior to routine measles vaccination at age 9 months. HIV-1-infected children may have lower levels of protective antibody levels after measles vaccination compared with uninfected children, which could lead to a greater proportion of susceptible children.

Successful measles control in much of Africa suggests the HIV-1 epidemic is not an insurmountable barrier to measles mortality reduction. An important factor limiting the impact of HIV-1 infection on MV transmission has probably been the high mortality of HIV-1-infected children in the absence of antiretroviral therapy (ART), limiting the time during which HIV-1-infected children contribute to the pool of susceptibles. With the scaling up of ART in sub-Saharan Africa, HIV-1-infected children should have improved life expectancy, which could affect their contribution to MV transmission. To investigate the hypothesis that treatment of HIV-1-infected children with ART could increase the number of measles cases and deaths, we modelled the potential impact of HIV-1 infection and ART on the transmission dynamics of MV infection.

Methods

Model framework

The age-structured, deterministic compartmental model of MV transmission in a developing country, first proposed by McLean and Anderson, was extended to incorporate a subpopulation of HIV-1-infected children. The model allows for age-dependent survival rates and high population growth rates, important features of populations in low-income countries. We considered a vaccination programme in which children receive a single dose of standard-titre measles vaccine at age 9 months (the routine age for vaccination in developing countries). A detailed specification of the model can be found in the Appendix.

Briefly, the equations describe the transmission of infection from infectious to susceptible individuals in a population subject to demographic processes (birth and death) and a single dose of measles vaccine at 9 months of age. The standard model comprises six compartments: protected by maternal antibodies (M); susceptible to MV infection (S); latent MV infection (E); infectious individuals (I); immune following infection (R) and immune following vaccination (V).

In the absence of HIV-1 infection, immunity is assumed to be lifelong after infection or effective vaccination. We further divided the population into two subgroups, HIV-1-infected and uninfected, each with six compartments. Age structure in the model was implemented using the partial differential approach. As described below, we allowed model parameters to differ between HIV-1-infected and HIV-1-uninfected individuals based on estimates from published reports, and examined the effect of varying these parameters in sensitivity analyses.

Protection from infection by maternal antibodies

Based on data from Kenya, our model assumes that 18% of HIV-1-infected children are susceptible to measles at birth compared with 7% of HIV-1-uninfected children (Table 1). Data from Zambia suggest that the duration of protection from maternal antibodies is shorter in HIV-1-infected children. Our model assumes that the average duration of protection from passively-acquired antibodies in HIV-1-infected infants is 2 months, compared with 4 months in HIV-1-uninfected children.

Duration of infectiousness

We assume an average duration of infectiousness for HIV-1-uninfected children with measles of 7 days. HIV-1-infected children may have prolonged shedding of MV, which could increase their duration of infectiousness. We assume that the duration of infectiousness is doubled in children with HIV-1 infection (Table 1).

Protection afforded by vaccination

Based on data from an immunogenicity study conducted in Lusaka, Zambia, we assume a vaccine efficacy of 94% among HIV-1-uninfected children, with lifelong immunity. Also based on this study, we assume that HIV-1-infected children have a similar primary response to measles vaccination and explore the effect of varying this assumption in sensitivity analyses. However, waning of vaccine-induced immunity in HIV-1-infected children was observed over a 27-month period following vaccination. By 3 years of age, only 43% of seven HIV-1-infected children who initially responded to measles vaccine had protective antibody levels. Assuming an exponential rate of decay, the estimated rate of loss of
vaccine-induced immunity in HIV-1-infected children was 0.282 per year (Table 1), and this decay rate was incorporated into the model.

### All-cause mortality

Demographic characteristics resembling those of Lusaka, Zambia were used. Mortality rates for children not infected with HIV-1 were obtained from publicly available life tables for Zambia for the year 2004 (Table 1). In the absence of ART, mortality in HIV-1-infected children is much higher than in uninfected children. For HIV-1-infected children, we assumed an annual mortality rate of 280/1000 in the absence of ART, yielding a mean life expectancy of \(3.6\) years.  

#### Table 1: Parameter value description and estimates used in the measles model

<table>
<thead>
<tr>
<th>Parameter name</th>
<th>HIV-1-infected group</th>
<th>HIV-1-uninfected group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter name</td>
<td>Value estimate — rates per year</td>
<td>Value estimate — rates per year</td>
</tr>
<tr>
<td>Birth rate(^a)</td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>Age-specific death rates(^a,b)</td>
<td>(\mu_{\text{hiv}}(a)) (= 0.28)</td>
<td>(\mu(a))</td>
</tr>
<tr>
<td>&lt;1</td>
<td>(0.11184)</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>(0.02305)</td>
<td></td>
</tr>
<tr>
<td>5–9</td>
<td>(0.00668)</td>
<td></td>
</tr>
<tr>
<td>10–14</td>
<td>(0.00298)</td>
<td></td>
</tr>
<tr>
<td>15–19</td>
<td>(0.00242)</td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>(0.00802)</td>
<td></td>
</tr>
<tr>
<td>25–29</td>
<td>(0.01663)</td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>(0.0296)</td>
<td></td>
</tr>
<tr>
<td>35–39</td>
<td>(0.03803)</td>
<td></td>
</tr>
<tr>
<td>40–44</td>
<td>(0.0339)</td>
<td></td>
</tr>
<tr>
<td>45–49</td>
<td>(0.02895)</td>
<td></td>
</tr>
<tr>
<td>50–54</td>
<td>(0.03003)</td>
<td></td>
</tr>
<tr>
<td>55–59</td>
<td>(0.03245)</td>
<td></td>
</tr>
<tr>
<td>60–64</td>
<td>(0.03498)</td>
<td></td>
</tr>
<tr>
<td>65–69</td>
<td>(0.04803)</td>
<td></td>
</tr>
<tr>
<td>70–74</td>
<td>(0.07065)</td>
<td></td>
</tr>
<tr>
<td>75–79</td>
<td>(0.10408)</td>
<td></td>
</tr>
<tr>
<td>Proportion of newborns without protective maternal antibodies</td>
<td>(\kappa_{\text{hiv}}) (= 17.6% (7–100))</td>
<td>(\kappa) (= 7%)</td>
</tr>
<tr>
<td>Rate of loss of maternal antibody protection(^c)</td>
<td>(\delta_{\text{hiv}}) (= 6 (3–24))</td>
<td>(\delta) (= 3)</td>
</tr>
<tr>
<td>Effective vaccination coverage assuming 78% coverage</td>
<td>(\nu_{\text{hiv}}) (= 73.2% (73–39))</td>
<td>(\nu) (= 73.2%)</td>
</tr>
<tr>
<td>Rate of loss of vaccine-induced immunity</td>
<td>(\omega_{\text{hiv}}) (= 0.282 (0.28–0))</td>
<td>(-)</td>
</tr>
<tr>
<td>Rate at which latent become infectious(^d)</td>
<td>(\sigma_{\text{hiv}}) (= 52)</td>
<td>(\sigma) (= 52)</td>
</tr>
<tr>
<td>Recovery rate(^d) for measles infection</td>
<td>(\gamma_{\text{hiv}}) (= 26 (6.5–52))</td>
<td>(\gamma) (= 52)</td>
</tr>
<tr>
<td>Case fatality ratio (CFR)</td>
<td>(\alpha_{\text{hiv}}) (= 12.5%)</td>
<td>(\alpha) (= 2.5%)</td>
</tr>
</tbody>
</table>

\(^a\)Birth rate in combination with age-specific death rates yields an overall growth rate of 2.2% per year.  
\(^c\)Rate \(= 1\)/duration of protection (20): 2 months for HIV-1-infected children and 4 months for uninfected children.  
\(^d\)Rate \(= 1\)/duration of latent period (20) (7 days = 0.019 years) or period of infection (7 days for HIV-1 uninfected individuals and 14 days for HIV-1-infected individuals).  
\(^e\)Mortality rates ranging from 0.12 to 0.4 per year were applied to HIV-1-infected children under 1 year of age in sensitivity analysis, while keeping the mortality rates in HIV-1-infected children older than 1 year the same as those in HIV-1 uninfected individuals.
Anti-retroviral therapy (ART)
ART is assumed to improve the survival of HIV-1-infected children. We explored an extreme scenario in which we assumed that all HIV-1-infected children start ART at age 1 year and thereafter have the same all-cause mortality as HIV-uninfected children. Since ART is administered at an age after measles vaccination, and recent studies suggest that children vaccinated before ART continue to have waning anti-MV antibody levels, we assumed that ART will have no effect on immunity induced by measles vaccination. The rate of loss of vaccine-induced immunity in HIV-1-infected children could be reduced by ART, but there are no data to support this. We also assumed that the duration of infectiousness in HIV-1-infected children with measles remained the same with and without ART, and examined the sensitivity of the model results to this assumption.

Measles-associated mortality
The World Health Organization (WHO) estimates a measles case fatality rate (CFR) in developing countries of 1–5%. We assumed a CFR of 2.5% for HIV-1-uninfected children. For HIV-1-infected children, hospital-based studies have reported CFRs between 5% and 50%. Since hospital-based studies are likely to be biased toward more severe cases, we assumed a measles CFR of 12.5% for HIV-1-infected children. We assumed that measles deaths occur only during the infectious period and not during the incubation period.

Prevalence of HIV-1 infection
In southern Africa, approximately 30% of mothers are HIV-1-infected, and mother-to-child transmission is about 30% in the absence of antiretroviral treatment. We therefore assumed that 10% of newborns will be HIV-1-infected. We do not distinguish HIV-1 transmission through breast milk or other modes of transmission. As we simulated a ‘worst case’ scenario from the point of view of MV transmission, we did not model the reduction in HIV-1 prevalence in infants as a consequence of prevention of mother-to-child transmission or provision of ART to pregnant women.

Vaccination coverage
Measles vaccination coverage was assumed to be 78% among both HIV-1-infected and uninfected children, based upon the WHO estimate for measles vaccination coverage in Zambia in 2003. Effective vaccination coverage was defined as the product of vaccination coverage and the proportion of children who develop protective immunity (at the time of the initial response to vaccination). We examined the sensitivity of the model results to varying assumptions of measles vaccine responses (Table A1).

Varying the vaccination coverage resulted in similar model outputs (data not shown). Model assumptions and details of the model parameters are presented in the Appendix. The model was coded and compiled using Compaq Visual Fortran 6.5 (Compaq Computer Corporation). Model outputs included estimates of the force of MV infection, the average age of MV infection, and the proportion of the population immune. We report prevalence of infectious measles cases rather than incidence, as prevalence is important in terms of MV transmission dynamics; however, similar results would be obtained for measles incidence for this acute infectious disease.

Sensitivity analyses
Sensitivity analyses were conducted to assess the impact of varying assumptions on model outputs. For each model parameter, a range of values were explored (Table A1) while constraining other parameters to the values shown in Table 1, with the exception of mortality rates after 1 year of age, which were set to be equal in HIV-infected and uninfected children, i.e. representing the situation where ART is available.

Results
The model was run to achieve equilibrium before introducing an effective measles vaccination coverage of 78%. As expected, the annual force of infection decreased from 34.1% to 10.9% following the introduction of measles vaccination into the model, and the average age of infection increased from 2.9 to 6.5 years (Table 2).

The impact of HIV-1 on MV transmission dynamics in the absence of ART
HIV-1 infection (without ART) was introduced into the model once equilibrium had been reached following the introduction of measles vaccination. In the presence of HIV-1 infection, the force of infection increased slightly to 11.8% and the average age of infection decreased to 5.9 years (Table 2). HIV-1-infected children had a lower average age of infection (3.0 years) than HIV-1-uninfected children (6.3 years), reflecting the short life expectancy (3.6 years) of HIV-1-infected children in the absence of ART. Figure 1 shows population immunity by age under varying assumptions. There is little difference between the model with no HIV-1 infection and the model with 10% of infants born HIV-1-infected, with little change in the proportion of the population susceptible to MV. In the absence of HIV-1 infection, 2.3% of the population were susceptible to measles at 25 years of age and 34.5% were immune as a result of wild-type MV infection (Figure 1b). When 10% of children were assumed to be HIV-1-infected at birth, 1.9% were susceptible to measles at 25 years of age.
Table 2 Outcome parameters before and after vaccination and HIV-1 infection has been introduced into the model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No vaccination, no HIV-1</th>
<th>78% vaccination coverage at 9 months of age, no HIV-1</th>
<th>78% vaccination coverage at 9 months of age &amp; 10% born HIV-1 infected, ART provided from 1 year of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Force of infection per year (%)</td>
<td>34.1</td>
<td>10.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Average age of measles (years)</td>
<td>2.9</td>
<td>6.5</td>
<td>5.9</td>
</tr>
<tr>
<td>Overall prevalence of infectious cases (per 100000)</td>
<td>69.3</td>
<td>22.1</td>
<td>23.9</td>
</tr>
<tr>
<td>Proportion of measles cases that are HIV-1 infected</td>
<td>–</td>
<td>–</td>
<td>12.2</td>
</tr>
<tr>
<td>Proportion of population susceptible</td>
<td>10.9</td>
<td>10.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Proportion remaining susceptible by 25 years of age</td>
<td>0</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Proportion acquiring immunity via exposure to wild type MV</td>
<td>100</td>
<td>34.5</td>
<td>35.1</td>
</tr>
</tbody>
</table>

Figure 1 Immune status profile for (a) prior to introduction of measles vaccination, (b) 78% measles vaccine coverage, and 78% measles vaccination coverage and 10% of children born HIV-1-infected without (c) and with (d) ART starting at 1 year of age
and 35.1% acquired immunity via infection by wild-type MV (Figure 1c).

**The impact of HIV-1 infection on the age-specific prevalence of infectious measles cases**

Small changes in age-specific measles prevalence were observed when 10% of the population are born HIV-1-infected (Figure 2). Measles prevalence per 100,000 in infants <9 months of age increased from 117 in the absence of HIV-1 infection to 138 with HIV-1 infection. For children aged between 9 and 23 months, the prevalence increased from 62 to 71 per 100,000. The difference in prevalence between populations with and without HIV-1 declined with age, largely as a result of the high mortality rates in HIV-1-infected individuals (Figure 2).

**Figure 2** Predicted age-specific measles prevalence by age group and scenario. Black bars: No measles vaccination; grey bars: measles vaccination at 78% coverage; diamond pattern: 78% vaccination coverage and 10% of infants born HIV-1-infected; horizontal stripes: 78% vaccination coverage, 10% of infants born HIV-1-infected and ART starting at 1 year of age.

**The impact of ART on MV transmission dynamics**

The yearly force of infection increased from 11.8% without ART to 15.5% with ART starting at 1 year of age. This in turn increased the prevalence of measles from 23.9 to 31.4 per 100,000 population. The proportion of measles cases that were HIV-1-infected increased from 12% without ART to 29% with ART (Table 1). Figure 1d shows the population immunity profile by age. By 25 years of age, 1% remained susceptible to wild-type MV infection with ART compared with 1.9% in the absence of ART. Seven per cent of infants acquired infection before the age of routine vaccination (9 months) in the population with ART compared with 5.5% without ART. By 25 years of age, the proportion that was immune as a result of infection with wild-type MV increased from 35% without ART to 42% with ART. Less than 0.1% of the individuals younger than 25 years with wild-type MV immunity were HIV-1-infected without ART, compared with 17.5% with ART (Figure 1). Introduction of ART led to an increase in MV transmission and thus to both an increased prevalence of measles in all age groups (Figure 2), including children younger than 9 months of age, and a slight decrease in the proportion susceptible to measles (9.5%, Table 2). HIV-1-infected children constituted a larger proportion of all measles cases when ART was available than in the absence of ART (Figure 3).

**Measles vaccination coverage**

Assuming 94% of children respond to measles vaccination, irrespective of HIV-1-infection status, then 100% vaccination coverage in children aged 9 months of age resulted in a yearly force of infection of 2.6%. There was a slight increase in the yearly force of infection in a population with 10% of children born HIV-1-infected and no ART (3.9%) and a further...
increase when all HIV-1-infected children receive ART at 1 year of age (8.5%; Figure 4). At this level of coverage, the prevalence of measles was 17/100,000 population compared with 8/100,000 in a population without HIV-1 infection.

Sensitivity analysis
The results of the sensitivity analysis in the presence of ART are summarized in Table A1. Within the ranges we explored, the parameter that had most impact on the model outputs was duration of infectiousness. The yearly force of infection increased from 12% when the duration of infectiousness was the same for HIV-1-infected and uninfected children (7 days) to 22% when the duration of infectiousness was increased to 1 month in the HIV-1-infected children. The proportion of the population susceptible also decreased from 11% when the duration of infectiousness was 7 days to 7.5% when the duration of infectiousness was increased to 4 weeks. Age-specific measles prevalence also varied with varying duration of infectiousness. This was most marked in infants <9 months of age. Measles prevalence increased from 132/100,000 infants under 9 months when the duration of infectiousness was 7 days to 288/100,000 persons when the duration of infectiousness was 4 weeks (Figure 5).

Mortality rates in HIV-1-infected children younger than 1 year of age had an important effect on the model outputs. The force of infection decreased slightly from 16%, when the mortality rate for HIV-1-infected and uninfected children was assumed to be 111/1000, to 14.9% when the mortality rate in the HIV-1-infected group was increased to 400/1000. In the sensitivity analysis, HIV-1-infected children older than 1 year of age have the same all-cause mortality as non-HIV-infected children. Increasing these rates reduced the time HIV-1-infected individuals were in the model, i.e. more closely resembling the situation without ART (data not shown).

As the rate of loss of vaccine-induced immunity decreased in the HIV-1-infected group, the force of infection decreased and the average age of measles increased. Model outputs were not sensitive to assumptions about other model parameters (Table A1).

Discussion
Using an age-structured, deterministic model we found little impact of HIV-1 infection on MV transmission dynamics in the absence of ART. This suggests that the high mortality rates in HIV-1-infected children without access to ART counteract the higher rates of vaccine failure, shorter duration of maternal antibody protection and longer duration of infectiousness among HIV-1-infected children. This finding is consistent with recent experience in southern Africa, where increased routine measles vaccine coverage and supplementary immunisation activities have been successful in substantially reducing measles incidence and mortality despite high HIV-1 prevalence. These results also are consistent with those of a static model of the impact of the HIV-1 epidemic on measles. However, our dynamic model represents an advance as we model immunity due to infection as well as vaccination and also explore the effect of ART on measles transmission. Our model also explores the model parameters with the greatest impact on the transmission dynamics of measles infection by fully taking into account the changes in the force of infection with varying parameter estimates.

Although there was little overall effect of HIV-1 infection on MV transmission in our model, the model predicts a higher prevalence of measles in children younger than 9 months of age (the routine age for measles vaccination) when HIV-1 is prevalent.
in the population. This is in accordance with the higher proportion of hospitalised measles cases in Lusaka younger than 9 months of age observed among HIV-1-infected children compared with HIV-uninfected children.25,29

When ART was introduced into the model, there was an overall increase in measles prevalence. Our assumption that all HIV-1-infected children began ART at one year of age and subsequently had the same survival as HIV-1-uninfected children, but with the same rate of waning vaccine immunity as HIV-infected children, reflects a ‘worst case’ scenario in terms of MV transmission. This is a rather unrealistic scenario for the current situation in sub-Saharan Africa. Detection and confirmation of HIV-infection before 18 months of age requires the use of tests that are not readily available in low-income countries for routine diagnosis.33 The median age of starting ART in children in Lusaka is 81 months,34 by which age most HIV-1-infected children have already died, and the achievement of 100% coverage of ART is unlikely. It is also unrealistic to assume high access to ART in children but none in mothers, such that vertical transmission rates remain unchanged.

The proportion of measles cases that were HIV-1-infected increased from 12% in the absence of ART to 29% after the introduction of ART, which could increase the burden on health services if measles in HIV-1-infected children is more severe, as reported in the absence of ART.3 Further studies are required to compare the severity of measles in HIV-1-infected individuals with or without ART. We assumed that vaccine-induced protection waned in HIV-1-infected children irrespective of ART.21–23 If vaccine-induced immunity persists longer after ART, this would lessen the impact on MV transmission (Table A1).

In sensitivity analyses, increasing the duration of infectiousness had a substantial effect on MV transmission. In a study in Zambia, MV RNA was detected in 91% of 11 HIV-1-infected children 38 days after onset of rash compared with 53% of 36 HIV-1-uninfected children ($P=0.02$). The presence of viral RNA suggests recent MV replication. However, it remains unclear whether the presence of MV RNA correlates with infectiousness. Varying the duration of measles immunity acquired from vaccination or protection from maternal antibodies had little impact on the estimated dynamics of MV transmission.

The MSEIR model assumes random mixing within the population. This seems reasonable for Lusaka, which is densely populated with large households and overcrowding.35 This approach is similar to previous models of measles in developing countries.18,19,36–38 as mixing patterns are likely to be less dependent on age than those in developed countries. Clustering of HIV-1-infected children in the population would have an effect on mixing patterns between susceptible and infectious individuals. However, in the absence of reliable data on mixing patterns, random mixing was the simplest model assumption. Future research should include the collection of data on mixing patterns to better understand measles virus transmission between age groups in urban developing country settings.

The model also assumed that each individual had an equal chance of being vaccinated. In a recent study of children hospitalised with measles in Lusaka, Zambia, HIV-1 infection was associated with incomplete immunisation with DTP and OPV (OR: 1.9, 95% CI 1.1, 3.3).39 This finding is consistent with another study in Uganda.40 The likely impact on MV transmission of lower vaccination rates in HIV-1-infected children would be similar to reduced effective vaccination coverage (Table A1).

We assumed that all HIV-1-infection occurred in utero or at delivery and did not model mother-to-child transmission arising from breast milk. We observed similar immune responses in children who acquired HIV-1 infection before and shortly after measles vaccination, although the number of children studied was small.10 We did not model HIV-1 infection in adults. Most HIV-1-infected adults experience natural infection or received measles vaccine before becoming HIV-1-infected, and despite increasing immunodeficiency due to progressive HIV-1 infection, humoral immunity to natural measles infection appears durable.8,41,42

In conclusion, high overall mortality in HIV-1-infected children without access to ART limits the impact of HIV-1 on MV transmission and may help to explain the initial success of current measles control strategies in southern Africa.17,31 The scaling-up of ART should improve children’s survival. However, immune reconstitution following ART is likely to be with naïve rather than memory T-cells. If children vaccinated before ART still have higher vaccine failure rates than HIV-1-uninfected children,21–23 in settings in which only one dose of measles vaccine is provided, increasing provision of ART to HIV-1-infected children could lead to an increase in measles cases. The WHO recommends that countries provide two opportunities for measles vaccine, through a routine second dose or periodic supplementary campaigns.43 Further study of the duration of immunity in HIV-1-infected children receiving ART and their response to revaccination is needed to determine whether a second dose of measles vaccine will protect these children and reduce MV transmission in regions of high HIV-1 prevalence.

Supplementary material
Supplementary data (colour image for figure 1) are available at IJE online.

Acknowledgements
We thank Rita Helfand for the many discussions on the basic concepts of the measles model. We thank
the project staff in Zambia who assisted with the study of the immunogenicity of measles vaccine in HIV-1-infected and uninfected children, which provided many of the parameter estimates used in our models. We also thank the children and their parents for their participation.

**KEY MESSAGES**
- High mortality rates in HIV-1-infected children without access to ART counteract the higher rates of vaccine failure, shorter duration of maternal antibody protection and longer duration of infectiousness in HIV-1-infected children, as many of these children die before they are able to contribute to measles virus transmission.
- This may explain the initial success of measles control strategies in Africa. The scaling-up of antiretroviral therapy in Southern Africa should improve children’s survival, but may lead to an increase in measles prevalence if high levels of measles vaccine coverage are not maintained.
- Further study of the duration of immunity in HIV-1-infected children receiving ART is needed to determine whether a second dose of measles vaccine will protect these children.

**References**


**Conflict of interest:** None declared.

**Sources of funding:** The Wellcome Trust-Burroughs Fund Infectious Disease Initiative (GR059114MA).
Appendix

The model of measles in developing countries\textsuperscript{18,19} was extended by incorporating separate compartments for individuals with HIV-1 infection acquired at birth. The model differs from the standard measles model in a number of aspects that relate to HIV-1 infection status and demographics of a developing country.

Model structure

The model was written as a system of partial differential equations:

\[
\begin{align*}
\frac{dM}{dt} + \frac{dM}{dt} &= -\left(\mu(a) + \delta\right)M(a, t) \\
\frac{dS}{dt} + \frac{dS}{dt} &= \delta M(a, t) - \left(\mu(a) + \lambda(t)\right)S(a, t) \\
\frac{dE}{dt} + \frac{dE}{dt} &= \lambda(t)S(a, t) - \left(\mu(a) + \sigma\right)E(a, t) \\
\frac{d\mathcal{I}}{dt} + \frac{d\mathcal{I}}{dt} &= \alpha E(a, t) - \left(\mu(a) + \gamma + \alpha\right)\mathcal{I}(a, t) \\
\frac{dR}{dt} + \frac{dR}{dt} &= \gamma I(a, t) - \mu(a)R(a, t) \\
\frac{dV}{dt} + \frac{dV}{dt} &= -\mu(a)V(a, t) \\
\frac{dM_{uv}}{dt} + \frac{dM_{uv}}{dt} &= -\left(\mu_{uv}(a) + \delta_{uv}\right)M_{uv}(a, t) \\
\frac{dS_{uv}}{dt} + \frac{dS_{uv}}{dt} &= \delta_{uv}M_{uv}(a, t) + \omega V_{uv}(a, t) - \left(\mu_{uv}(a) + \lambda(t)\right)S_{uv}(a, t) \\
\frac{dE_{uv}}{dt} + \frac{dE_{uv}}{dt} &= \lambda(t)S_{uv}(a, t) - \left(\mu_{uv}(a) + \sigma\right)E_{uv}(a, t) \\
\frac{d\mathcal{I}_{uv}}{dt} + \frac{d\mathcal{I}_{uv}}{dt} &= \alpha E_{uv}(a, t) - \left(\mu_{uv}(a) + \gamma + \alpha\right)\mathcal{I}_{uv}(a, t) \\
\frac{dR_{uv}}{dt} + \frac{dR_{uv}}{dt} &= \gamma I_{uv}(a, t) - \mu_{uv}(a)R_{uv}(a, t) \\
\frac{dV_{uv}}{dt} + \frac{dV_{uv}}{dt} &= -\left(\mu_{uv}(a) + \omega\right)V_{uv}(a, t)
\end{align*}
\]

Let \( a \) be the age of infection with HIV-1 and let \( t \) be the time. The model includes the following parameters:

- \( \mu(a) \): natural death rate
- \( \delta \): HIV-1 infection rate
- \( \lambda(t) \): force of infection due to measles
- \( \sigma \): measles-induced death rate
- \( \gamma \): recovery rate
- \( \alpha \): HIV-1-induced death rate
- \( \omega \): loss of memory B cells

For further details, please refer to the original paper.
Here the quantities $M, S, E, I, R, V$ denote the immune status of maternally protected, susceptible, latent, infectious, recovered and vaccinated individuals, respectively. The subscript ‘hiv’ denotes individuals who have acquired HIV-1 infection at birth.

The following boundary conditions determine the immune status of newborn children:

$$
M(0, t) = (1 - p)(1 - \kappa) \int_0^\infty bN(a, t) da
$$

$$
M_{\text{hiv}}(0, t) = p(1 - \kappa_{\text{hiv}}) \int_0^\infty bN(a, t) da
$$

$$
S(0, t) = (1 - p)\kappa \int_0^\infty bN(a, t) da
$$

$$
S_{\text{hiv}}(0, t) = p\kappa_{\text{hiv}} \int_0^\infty bN(a, t) da
$$

where $p$ is the proportion of individuals who acquire HIV-1 infection at birth, $\kappa$ and $\kappa_{\text{hiv}}$ is the proportion born without maternal antibodies among individuals without and with HIV-1 infection acquired at birth, respectively, $b$ is the per capita birth rate, $N(a, t)$ represents the total population of age $a$ at time $t$. All other variables are set at 0 for age $a = 0$.

The force of infection was $\lambda(t)$ assumed to be independent of age as mixing patterns in developing countries are likely to be less dependent on age than those in developed countries:

$$
\lambda(t) = \frac{\int_0^\infty \beta (I(a', t) + I_{\text{hiv}}(a', t)) da'}{\int_0^\infty N(a', t) da'}
$$

where $\beta$ is the effective contact rate between susceptible and infectious individuals. Note that $\beta$ was chosen so that the force of infection was approximately equal to 0.2 units per year with 50% vaccine coverage and no HIV-1 infection.

Vaccination was implemented by transferring a proportion $v$ and $v_{\text{hiv}}$ of children who reach 9 months of age from the susceptible compartments $S$ and $S_{\text{hiv}}$ to the vaccinated compartments $V$ and $V_{\text{hiv}}$, respectively. Maximum age in the model was restricted to 80 years.

### Parameter estimates

Empirical data from a measles vaccine study in Lusaka, Zambia and from Kilifi, Kenya were used to provide estimates for the model parameters, summarised in Table A1 and discussed in the methods section.

### Further model assumptions

1. Random mixing within the population.
2. No migration into or out of the population, i.e. the population increases through births only and decreases through deaths only.
3. Each individual has an equal chance of being vaccinated.
4. Infants not effectively vaccinated are susceptible to MV infection.
5. The effective contact rate between susceptible and infectious individuals, $\beta$, is the same for both HIV-1-infected and HIV-1-uninfected individuals, and between these two HIV-1 status groups.
6. Everyone has had measles or been vaccinated before they are exposed to HIV-1 through non-vertical transmission routes.
**Table A1** Sensitivity analysis with varying model parameters in the HIV-1 infected group only

<table>
<thead>
<tr>
<th>Model parameter ranges(^a)</th>
<th>Force of infection</th>
<th>Prevalence per 100 000</th>
<th>% measles cases HIV-1 infected</th>
<th>Average age of measles infection (years)</th>
<th>% susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of infectiousness (weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12.4</td>
<td>25.1</td>
<td>16.9</td>
<td>6.3</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>15.5</td>
<td>31.4</td>
<td>28.5</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>4</td>
<td>21.5</td>
<td>43.7</td>
<td>43.2</td>
<td>4.6</td>
<td>7.5</td>
</tr>
<tr>
<td>8</td>
<td>33.9</td>
<td>68.7</td>
<td>58.4</td>
<td>3.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Mortality rate per 1000 in the under ones (&gt;1 year same as the HIV-1 uninfected group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>118.4</td>
<td>16.4</td>
<td>33.2</td>
<td>31.6</td>
<td>5.4</td>
<td>9.3</td>
</tr>
<tr>
<td>280.4</td>
<td>15.5</td>
<td>31.4</td>
<td>28.5</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>400</td>
<td>14.9</td>
<td>30.2</td>
<td>26.3</td>
<td>5.7</td>
<td>9.6</td>
</tr>
<tr>
<td>Proportion born susceptible to measles infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7%</td>
<td>15.4</td>
<td>31.4</td>
<td>28.4</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>17.6%</td>
<td>15.5</td>
<td>31.4</td>
<td>28.5</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>50%</td>
<td>15.5</td>
<td>31.4</td>
<td>28.6</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>100%</td>
<td>15.5</td>
<td>31.5</td>
<td>28.7</td>
<td>5.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Duration of maternal antibody protection (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>15.4</td>
<td>31.3</td>
<td>28.4</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>15.5</td>
<td>31.4</td>
<td>28.4</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>0.5</td>
<td>15.5</td>
<td>31.5</td>
<td>28.7</td>
<td>5.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Proportion who responds to vaccination (with a 78% vaccination coverage)(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94%</td>
<td>15.5</td>
<td>31.4</td>
<td>28.5</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>90%</td>
<td>15.5</td>
<td>31.4</td>
<td>28.5</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>70%</td>
<td>15.6</td>
<td>31.6</td>
<td>28.9</td>
<td>5.4</td>
<td>9.5</td>
</tr>
<tr>
<td>50%</td>
<td>15.7</td>
<td>31.8</td>
<td>29.2</td>
<td>5.3</td>
<td>9.5</td>
</tr>
<tr>
<td>Rate of loss of vaccine-induced immunity (per year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.282</td>
<td>15.5</td>
<td>31.4</td>
<td>28.4</td>
<td>5.6</td>
<td>9.5</td>
</tr>
<tr>
<td>0.170</td>
<td>15.2</td>
<td>30.9</td>
<td>27.7</td>
<td>5.9</td>
<td>9.5</td>
</tr>
<tr>
<td>0.074</td>
<td>14.5</td>
<td>29.5</td>
<td>25.4</td>
<td>6.4</td>
<td>9.6</td>
</tr>
<tr>
<td>0.003</td>
<td>11.9</td>
<td>24.2</td>
<td>14.5</td>
<td>6.2</td>
<td>10.1</td>
</tr>
</tbody>
</table>

\(^a\)For each HIV-1-related parameter, a range of values were explored (column 1) while constraining other parameters to the values shown in Table 1 except for mortality rates. <1 year of age; mortality rate is 280/1000, >1 year of age all cause mortality rates are the same as in the non-HIV infected individuals.

\(^b\)Effective vaccination coverage = % who initially respond to vaccination × vaccination coverage.