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Predicting the extinction of HIV-2 in rural Guinea-Bissau

Helen R. Fryer[a], Carla Van Tienen[c,e], Maarten Schim Van Der Loeff[f,g], Peter Aaby[h], Zacarias J. Da Silva[h], Hilton Whittle[c,i], Sarah L. Rowland-Jones[b] and Thushan I. de Silva[c,d]

Objective: This article predicts the future epidemiology of HIV-2 in Caió, a rural region of Guinea Bissau; and investigates whether HIV-2, which has halved in prevalence between 1990 and 2007 and is now almost absent in young adults in Caió, can persist as an infection of the elderly.

Design: A mathematical model of the spread of HIV-2 was tailored to the epidemic in Caió, a village in Guinea-Bissau.

Methods: An age-stratified difference equation model of HIV-2 transmission was fitted to age-stratified HIV-2 incidence and prevalence data from surveys conducted in Caió in 1990, 1997 and 2007. A stochastic version of the same model was used to make projections.

Results: HIV-2 infection is predicted to continue to rapidly decline in Caió such that new infections will cease and prevalence will reach low levels (e.g. below 0.1%) within a few decades. HIV-2 is not predicted to persist in the elderly.

Conclusion: HIV-2 is predicted go extinct in Caió during the second half of this century.

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Keywords: age, epidemiology, extinction, HIV-2, incidence, mathematical model, prevalence

Introduction

HIV-2 is thought to have entered humans in Guinea-Bissau around 1940 [1] and has since become endemic in parts of West Africa [2–6]. Although less transmissible and less pathogenic than HIV-1 [7–12], HIV-2 nevertheless kills 2–3% of infected individuals, each year [9]. Surveys carried out in Guinea-Bissau since 1987 [4,8,13–16] have provided a detailed description of the epidemiology of HIV-2, showing that 8.9% of adults were infected in 1987 [8], but that prevalence almost halved by 2007 [5,13]. HIV-2 epidemiological studies outside of Guinea-Bissau are rare and limited to the neighbouring countries of Senegal and The Gambia where the epidemics have been similarly in decline [5,6].

Previous studies indicate that the majority of HIV-2 decline in Guinea-Bissau resulted from changes in risk behaviour over the last few decades [17,18]. It is thought that the war of independence (1963–1974) promoted the

[a]Department of Zoology, The Institute for Emerging Infections, The Oxford Martin School, Oxford University, [b]Nuffield Department of Medicine, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford, United Kingdom, [c]Medical Research Council Laboratories (UK), Fajara, The Gambia, [d]Department of Infection and Immunity, The University of Sheffield Medical School, Sheffield, United Kingdom, [e]Erasmus Medical Centre, Medical Microbiology and Infectious Diseases, Rotterdam, [f]Health Service of Amsterdam (GGD) and Academic Medical Center, [g]Department of Internal Medicine, Division of Infectious Diseases, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, Meibergdreef, Amsterdam, The Netherlands, [h]Projecto de Saúde de Bandim, Apartado 861, Bissau Codex, Guinea-Bissau, and [i]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom.

Correspondence to Helen R. Fryer, Department of Zoology, South Parks Road, Oxford OX13PS, UK.

E-mail: helen.fryer@zoo.ox.ac.uk
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early spread of HIV-2 through an increase in prostitution and expansion of medical infrastructure [3,19]. Greater access to vaccinations and blood transfusions likely facilitated the iatrogenic spread of HIV-2 through needle reuse and unscreened blood [19–21]. Following the war, prostitution probably receded and hygienic medical practices became more widespread. Concurrently, HIV-1 began to spread in Guinea-Bissau, reaching a prevalence of 3.6% by 2007 [4]. HIV-1 is thought to compete with HIV-2 [17,18,22] primarily through both strains being more prevalent in high-risk individuals [notably commercial sex workers (CSWs)], meaning that HIV-1 preferentially removes HIV-2-infected individuals from the population. Modelling work has attributed only a minority of the decline in HIV-2 from its peak to competition with HIV-1 [17].

Despite the marked reduction in HIV-2 prevalence since the late-1980s, the future of the HIV-2 epidemic in Guinea-Bissau remains unclear. In 2007, infection amongst young adults was low (<1% amongst ages 15–34) [4]. However, infection has remained prevalent amongst older adults (12% amongst over 45 years) [4], susceptibility of women is believed to increase with age [23] and it has been suggested that HIV-2 may persist as an infection of the elderly [13].

We predict the future epidemiology of HIV-2 in Caió, a rural region of Guinea-Bissau, by analysing temporal, age-stratified incidence and prevalence data [4,14,16]. Specifically, we ask whether HIV-2 is likely to go extinct in Caió or whether it will persist in the elderly. Furthermore, we predict how HIV-2 prevalence will change over time and when, if at all, HIV-2 will go extinct. To address these questions, we have developed a mathematical model of the spread of HIV-2 amongst an age-stratified population and fitted it to data.

Materials and methods

HIV-2 data from Caió

Around 1990 (1989–1991) [14], 1997 (1996–1998) [16] and 2007 (2006–2007) [4], HIV surveillance studies amongst adults (over 15 years) were conducted in Caió, a rural region of Guinea-Bissau with a population of approximately 4000 adults. Fieldworkers visited all adults in their homes and offered testing for HIV-1 and HIV-2. Efforts to trace patients were not dependent upon known HIV status. The three surveys were held in a similar manner. More details of the surveys and HIV diagnostics have been previously described [4]. For each survey, participation was high (mean 74% of census-registered individuals) and both incidence and prevalence was measured amongst five different age categories (15–24, 25–34, 35–44, 45–54, ≥55 years). They reveal that HIV-2 prevalence in adults reduced from 8.3% in 1990 to 4.7% in 2007 (Fig. 1a, circles). Despite this overall reduction, prevalence remained higher amongst older individuals over the same period (Fig. 1b, circles). For example, in 1997 and 2007, prevalence amongst individuals aged over 45 years was 22 and 12%, respectively. By comparison prevalence amongst individuals aged 15–34 years was 3 and 0.9%, respectively. Incidence has also remained highest amongst individuals aged 45–54 years despite declining considerably amongst younger adults (Fig. 1c). The most striking observation, however, is that broadly across ages, both incidence and prevalence have reduced over time.

Modelling the spread of HIV-2

To predict the future epidemiology of HIV-2, a model (Fig. 2, Tables S1 and S2, http://links.lww.com/QAD/A764) of the spread of infection in an age-structured population was developed and tailored to the epidemic in Caió from 1990. The population is segregated into two infection states (susceptible and infected) and 70, one-year age groups (15–84 years). The age structure allows the model to account for changes in susceptibility to HIV-2 with age and to be fitted to the age-stratified incidence and prevalence data (Fig. 1b and c). Thus, we can evaluate whether HIV-2 is likely to persist in the elderly and can account for age dependency in sexual partner choice. Although iatrogenic transmission is thought to have contributed significantly to the early spread of HIV-2, improvements in medical practice make heterosexual intercourse the likely major transmission route over the period modelled. Accordingly, the spread of infection, adapted from [24–26], is modelled as frequency-dependent transmission without recovery, with contacts occurring more frequently between individuals who are similar in age than between individuals with a large age gap [23]. This represents a system wherein transmission is predominantly sexual. The average rate of partner exchange (the number of sexual partners per year) varies in such a way that the relative rates of partner exchange across different ages remains fixed over time, whereas the overall rate of partner exchange varies with time.

The population undergoes individual turnover. Hosts are born into the population and can leave the population (through death or emigration). Net removal rates vary with age and HIV-2 infection status (Text S3 and Table S2, http://links.lww.com/QAD/A764); furthermore, they vary with time to account for changes in therapy and HIV-1 prevalence (Fig. 1d), and thus account for competition from HIV-1 in the form of preferential removal of high-risk individuals. Removal rates of untreated HIV-1, HIV-2 and dually infected individuals are estimated from data [9,10] (Table S2, http://links.lww.com/QAD/A764). Other mechanisms of competitive exclusion of HIV-2 by HIV-1 are not modelled. Evidence for protective cross-immunity from superinfection is lacking [27], and the observation that

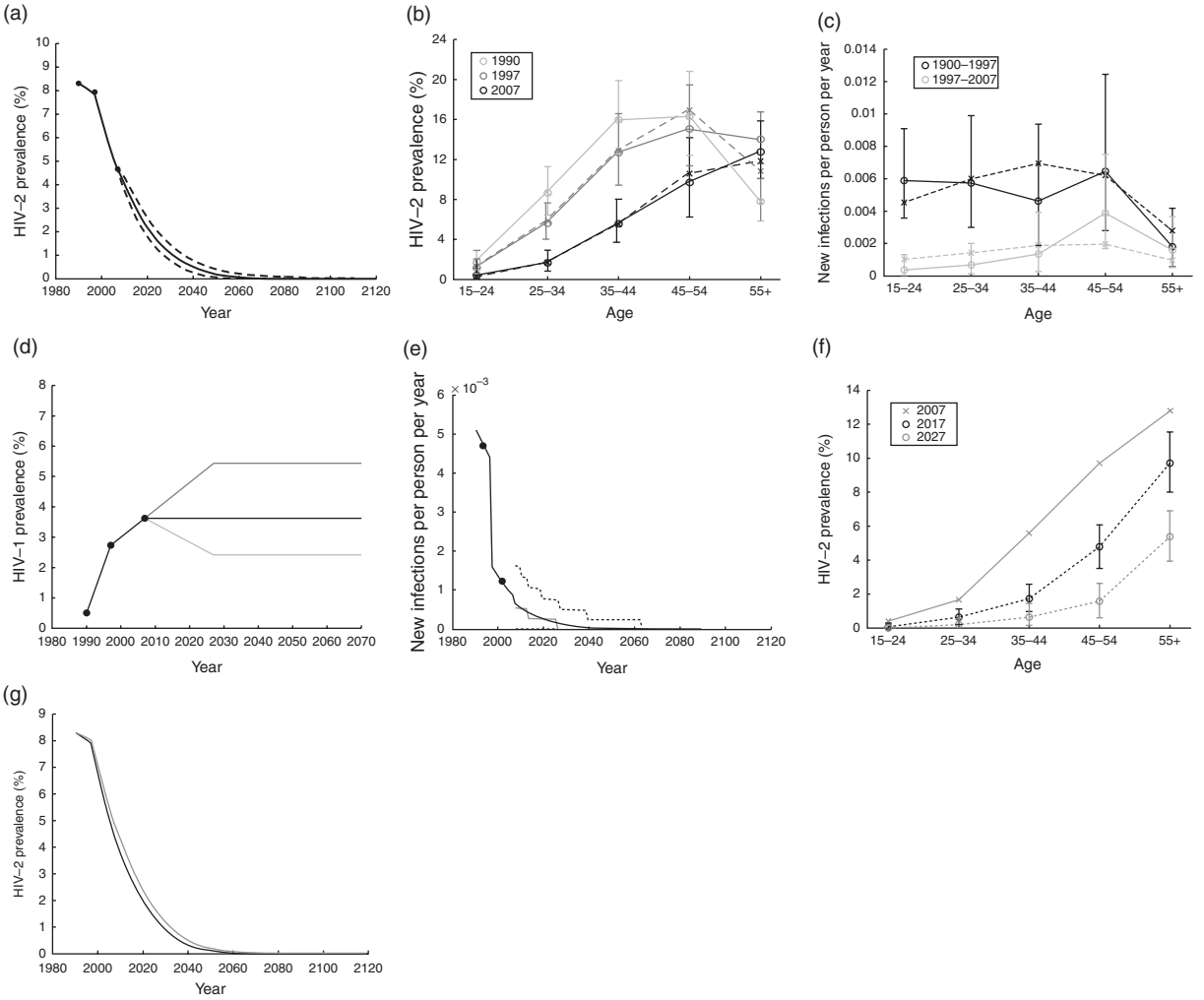

Fig. 1. Data and model predictions of the incidence and prevalence of HIV-2 infection in Caió. (a) The prevalence of HIV-2 infection amongst individuals aged over 15 years. Observations are represented as circular markers. Between 1990 and 2007, the deterministic result is shown. Beyond 2007, the median and 95% confidence intervals of 5000 stochastic simulations are shown as solid and dashed markers, respectively. (b) The prevalence of HIV-2 (including dual HIV-1/2) stratified by age in 1990, 1997 and 2007. Owing to the fact that the initial conditions of the model were fixed to observations, the observations and model predictions for 1990 are identical. (c) The yearly incidence per person of HIV-2 stratified by age in the periods 1990–1997 and 1997–2007. In (b) and (c), the model predictions are shown using dashed lines and crosses, whereas the data are shown with solid lines and circles. The univariate 95% CI surrounding the data is also provided. (d) The prevalence of HIV-1 assumed in the model. Between 1990, 1997 and 2007, the assumed prevalence is interpolated from observations (black circles). Beyond 2007, the black line represents our primary assumption that HIV-1 prevalence remains constant. The dark grey and light grey represent the assumption of the sensitivity analyses that the prevalence of HIV-1 is 50% larger or 30% smaller by 2027 and remains fixed thereafter. (e) The yearly incidence per person of HIV-2 in Caió amongst individuals aged over 15 years. The yearly incidences estimated during two periods (1990–1997 and 1997–2007) from data in Caió are plotted at the midpoints of these periods (circles). Between 1990 and 2007, the deterministic model predictions (solid black line) of yearly incidence are shown. Beyond 2007, the mean (solid black line), median (grey solid line) and 95% confidence intervals (dashed lines) of 5000 stochastic simulations are shown. Note that the lower 95% interval is zero for all years. (f) Stochastic model predictions and 95% confidence intervals of the prevalence of HIV-2 amongst different age groups in 2017 and 2027. For comparison, the 2007 prevalence data are also presented. (g) Model predictions of HIV-2 prevalence assuming HIV-1 is absent in the population (grey line). For comparison, our primary model prediction assuming HIV-1 is present in the population is shown in black.

dual infections occur frequently [4] suggests that any protective effect that exists is small. Within-host competitive outgrowth of HIV-1 has been cited as reducing viral loads – and by inference transmissibility – of HIV-2 amongst dually infected individuals with low $CD4^+$ cell counts [28,29]. However, averaged across all $CD4^+$ cell counts [28,29], HIV-2 viremia is equal in those harbouring single or dual infection suggesting that this mechanism would not significantly affect HIV-2 transmission.

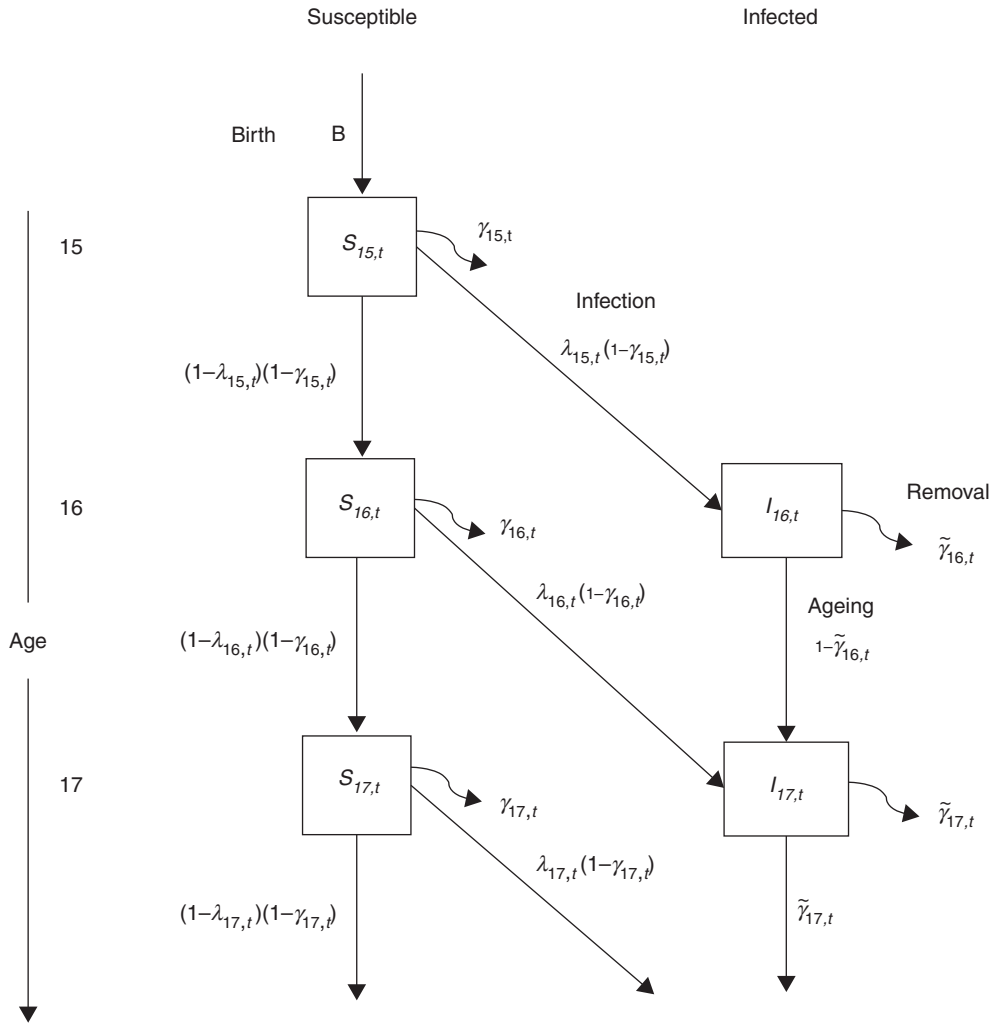

Fig. 2. A schematic representation of a difference equation model of the spread of infection through an age-stratified population. In the model, the population is segregated by age and infection status (susceptible and infected). There are 70 one-year age categories representing individuals aged 15–84. During year t a fraction, $\gamma_{a,t}$, of susceptible hosts aged a ($S_{a,t}$) are removed from the population through emigration or death. The remaining hosts move into the next age category, a fraction, $\lambda_{a,t}$, of whom become infected. During year t, a fraction, $\tilde{\gamma}_{a,t}$, of infected hosts aged a ($I_{a,t}$) are removed from the population through emigration or death and the remainder move into the next age category. During year t, a total of B susceptible individuals, aged 15 years are born. A description of the model equations and parameters are provided in the supplementary material.

Therapy for HIV started in Caió in 2007 and therefore would not have contributed to the observed decline of HIV-2. No surveys were conducted in Caió after 2007, but to model the impact of therapy beyond 2007, mortality rates of treated HIV-1 and HIV-2-infected individuals were inferred from other studies in West Africa [30,31]. Based upon data from The Gambia indicating that 79% of individuals alive after 36 months of therapy had undetectable viremia [31] treatment effectiveness, both in terms of reducing the infectiousness of HIV-2-infected individuals and preventing HIV-2 infection in singly HIV-1-infected individuals, was assumed to equal 0.79. The fact that partnerships are more likely to be made with high-risk individuals who in turn are more likely to be HIV-1 positive and therefore are also more likely to be receiving therapy is accounted for (Text S4, http://links.lww.com/QAD/A764) [32,33].

Removal rates for each host category (age and HIV-2 infection status) at each time were estimated to be the weighted average of treated HIV-1-infected, untreated HIV-1 infected and HIV-1-uninfected removal rates amongst that host category. The weightings represent the fraction of that host category estimated to be in each of these three states (Figure S1, Table S2, Text S3, http://links.lww.com/QAD/A764).

The model, formulated using difference equations (Text S1, equations 1–4, http://links.lww.com/QAD/A764), was fitted using maximum likelihood estimation (Text S5, http://links.lww.com/QAD/A764) to the incidence and

prevalence data from the HIV surveys conducted in Caió in 1990, 1997 and 2007, under an assumption of independence. A stochastic version (Text S7, equations 19–22, http://links.lww.com/QAD/A764) was also formulated by allowing death and infection to be governed by probabilistic methods. This was used with 5000 simulations to make our projections.

Tailoring the model to the epidemic in Caió

Model parameters achieving the global maximum of the likelihood function were used for projections. HIV-2 infections declined in prevalence between 1990 and 1997 before declining at a greater pace between 1997 and 2007 (Fig. 1a). Our model was best able to reproduce this pattern under the assumption that the risk of transmission was lower between 1997 and 2007 than between 1990 and 1997. This perhaps represents improvements in medical practices and/or reductions in sexual risk (e.g. reductions in unprotected sex, partner exchange rates, the concurrency of partnerships or commercial sex work) over the nineties. Nevertheless, for simplicity, we model the apparent reduction in risk behaviour as a stepwise reduction, estimated to be a factor of 2.6 in the average number of sexual partnerships per year applied across all age groups occurring in 1997 (Figure S2, http://links.lww.com/QAD/A764). Confidence in this estimate provides support for a positive reduction [95% confidence interval (CI): 1.7–4.3]. This finding is not dependent upon the assumption of independence of incidence and prevalence data during model fitting (Text S6, http://links.lww.com/QAD/A764). Estimations indicate that the effective reproductive number, defined as the average number of secondary infections generated by one primary infection, declined from 0.9 between 1990 and 1997 to 0.4 between 1997 and 2007 (Text S8, http://links.lww.com/QAD/A764).

Data from Guinea-Bissau [34] are used to specify how the rate of partner exchange varies with age in the period 1990 to 1997. Individuals aged 20–24 have the highest average number of partners per year (3.7) and partner numbers decline with age (0.7/years amongst ages 70–74 years). Individuals aged 75–84 are assumed to have no sexual partnerships. The age difference between sexual partners is assumed to be less than 20 years for 81% of partnerships (Text S4, http://links.lww.com/QAD/A764) [23]. The remaining 19% of partnerships are distributed across hosts of all ages.

Two parameters defining how the probability of infection per partnership between an infected individual and a susceptible individual depends upon the age of the susceptible individual were fitted to the incidence and prevalence data. Assuming that the frequency of coitus is independent of age, the probability of infection per partnership can be taken as a proxy for susceptibility with age. As such, an attribute of our model is that it allows us to investigate how age influences susceptibility to HIV-2, while accounting for cohort effects and age dependency of partner exchange rates. Previous studies have suggested that susceptibility to HIV-2 increases with age [23], but our findings indicate any such effect that exists is small. Individuals aged 74 years are estimated to be 1.4 times as susceptible as individuals aged 15 years (Figure S2, http://links.lww.com/QAD/A764). The 95% CI (0.8–2.6) shows that it cannot be ruled out that susceptibility is independent of age, decreases a little with age or increases more significantly with age. Susceptibility to infection does not need to increase with age to reproduce higher HIV-2 prevalence amongst older individuals. Such a pattern can be simply explained by the modest mortality rates associated with HIV-2 [9,10,35], combined with the fact that as individuals get older, more time has passed for them to become infected. Model predictions of the future epidemiology of HIV-2 are the same when susceptibility to HIV-2 is independent of age and when its age-dependency optimizes the model fit (Table S4, http://links.lww.com/QAD/A764). We therefore assume for simplicity that susceptibility to HIV-2 is independent of age. Additional details about the model are provided in the supplementary text, http://links.lww.com/QAD/A764.

Between 1990 and 2007, HIV-1 prevalence was fixed to levels interpolated from data (Fig. 1d); beyond 2007, prevalence was assumed to remain constant. This simplistic assumption was made because epidemic growth was slowing between 1990 and 2007. The fraction of HIV-1, HIV-2 and dually infected individuals receiving therapy was assumed to remain fixed beyond 2007 at levels estimated from clinical records from 2014 (Table S3, http://links.lww.com/QAD/A764).

Figure 1 shows that the optimal model fit is closely able to reproduce the age-stratified prevalence data (Fig. 1b) and broadly reproduce the age-stratified incidence data (Fig. 1c). The model is not able to reproduce the high incidence amongst individuals aged 45–54 years across both observational periods (1990–1997 and 1997–2007) whilst simultaneously producing markedly lower incidence amongst younger adults across the second of these periods. Owing to aging of individuals and mixing between individuals of different ages, our model predicts that trends in incidence or prevalence will be broadly consistent amongst all age groups. Nevertheless, the better fit of the model to the prevalence data is consistent with their tighter CIs as compared with the incidence data. The optimal model fit lies within the univariate 95% CIs surrounding the incidence and prevalence data for each age category, providing broad support for the model.

Results

The model predicts that HIV-2 will continue to decline in prevalence and become extinct in Caió this century.

Prevalence is expected to fall below 0.1% by 2050 (95% stochastic CI: 2042–2065) (Fig. 1a). New infections are predicted to cease around 2043 (2027–2075) (Fig. 1e) but complete extinction is expected to take longer. Mortality rates for HIV-2 are slower than for HIV-1 [9,10], meaning that the last few individuals to acquire infection may survive for decades. Extinction is expected to occur around 2068 (2053–2099). By 2027, HIV-2 should be almost absent in young adults (<0.1% amongst 15–34 years; Fig. 1f). Although HIV-2 will be more prevalent amongst older adults at any particular point in time, over time prevalence in older adults will continue to decline. Thus, infection will not persist indefinitely in the elderly. In agreement with the earlier work [17], competition by HIV-1 is estimated to account for only a minority of the decline of HIV-2 prevalence – 13% between 1990 and 2007 (Fig. 1g). This suggests that risk reductions, for example reductions in iatrogenic spread or war-related CSW, have turned a growing epidemic in the 1960–1980s into a declining one by the 1990s.

All of the parameters in the model are derived from data, however, mortality rates because of HIV-2 vary across data sources [9,10,35] and data on the extent to which contacts are segregated by age in Guinea-Bissau are limited [23]. Sensitivity analysis (Table S4, http://links.lww.com/QAD/A764) reveals that plausible univariate changes to parameter values defining these processes and others reduce the fit of the model to the data and change the predicted median time to extinction by 7 years at most.

Thus far, it has been assumed that beyond 2007, therapy prevalence and HIV-1 prevalence remain unchanged. Arguably, HIV-1 prevalence could decline from this level before equilibrating because of saturation effects, or it could continue to increase from it – older HIV-1 epidemics in Africa often exceed the 3% prevalence observed here. Therapy rates are estimated from clinical records from 2014, not a population survey, and therefore may vary compared with our best estimates (Table S3, http://links.lww.com/QAD/A764; Fig. S1d). Future changes in therapy uptake are also plausible. It could increase with future improvements to healthcare, although it will always be limited by undiagnosed infections. Population surveys have now ceased in Caió meaning that diagnoses and therefore treatment rates could alternatively decline in the future. The sensitivity of our results to plausible increases or decreases in treatment rates and/or HIV-1 rates (Table S4, http://links.lww.com/QAD/A764) suggests that the median year of extinction would vary by no more than 1 year. This additionally suggests that ignoring the timing of treatment during infection [32] will not significantly affect our findings.

It is noteworthy that a better fit of the model to the incidence data can be achieved by applying the contact rate reduction in 1997 only to younger cohorts, for example those born after 1952. A possible explanation for this finding is that younger generations have been adopting safer sexual practices since 1997, compared with previously, whilst sexual practices of older generations have remained largely unchanged. Whether such changes have taken place is uncertain but, nevertheless, the model's predictions remain qualitatively unchanged. Such an assumption adds an extra degree of freedom to the model and does not significantly improve the fit, according to a likelihood ratio test (P value = 0.18). The optimal fit under this assumption is therefore presented in the supplementary material (Figure S3, http://links.lww.com/QAD/A764). As this model provides a better fit to the very low incidence observed amongst younger adults between 1997 and 2007, it predicts that new infections would cease sooner (2036) and prevalence would decline more rapidly (0.1% by 2047). Extinction would occur around 2064.

How representative are our predictions for Caió of the epidemiology of HIV-2 elsewhere? The best data from outside Caió comes from a large HIV survey between 1987 and 2006 in urban areas of Bissau, the capital of Guinea-Bissau [8,13] which show almost identical HIV-2 dynamics to those observed in Caió. Prevalence amongst adults has dramatically declined from the late-1980s (8.9, 7.4 and 4.4% in 1987, 1996 and 2006, respectively, compared with 8.3, 7.9 and 4.7% in 1990, 1997 and 2007, respectively, in Caió) and it is now almost absent amongst young adults (1.5% in 2006 amongst 15–34 years, compared with 0.9% in 2007 in Caió). Our model predictions of the prevalence in Caió are independent of population size (Fig. 1a), and given that the epidemic there appears representative of the rest of Guinea-Bissau, our prevalence predictions are relevant throughout the country. Over large populations extinction takes longer and is less predictable, but our model (parameterized by the Caió data) adapted to a population the size of Guinea-Bissau (approximately 1 million adults) predicts that new infections would cease around 2097 (95% CI: 2081–2130) and infection would persist until 2123 (2106–2154). (Figure S4, http://links.lww.com/QAD/A764).

Discussion

The aim of this study was to investigate whether HIV-2 is likely to go extinct in Caió or it will instead persist in the elderly. We infer that HIV-2 cannot now sustain itself in Caió, new infections will cease within a few decades (median: 2043) and the infection is likely to go extinct in this region during the second half of this century (median: 2068). The observations that infection is more prevalent amongst the elderly and incidence has remained fairly stable amongst individuals aged over 45 between 1990

and 2007 does not preclude this. Furthermore, this prediction is independent of future changes in HIV-1 or antiretroviral prevalence in the region, of our parameter assumptions and our particular assumptions about risk changes during the 1990s. At most, these model assumptions change the timescale over which extinction is predicted to occur.

The fact that all of our model parameters are taken from data and, in particular, those defining the transmission dynamics are based upon data from an unusually comprehensive series of Caió surveys adds confidence to the model predictions. It is, however, acknowledged that the model is a simplified representation of the spread of HIV-2. For example, concurrency of partnerships, the duration of partnerships, two sexes and heterogeneous contact patterns within and between different risk groups are not explicitly modelled. HIV-2 prevalence amongst the elderly is higher amongst women than men [4,23] and CSWs have elevated infection levels [16]. Such heterogeneities can affect epidemic dynamics [33], but since the model is fitted to incidence and prevalence data, the average effect of these heterogeneities on transmission rates will be accounted for in the transmission parameters and therefore also in our predictions. The average effect of heterogeneities is a reasonable approximation because there will be mixing between the groups (e.g. between men and women and between CSWs and non-CSWs; 36% of men in Caió report ever having had sex with a CSW [16]) and the surveys did not exclude particular risk groups, but spanned a large majority of the population. Arguably, men who have sex with men would have more distinct contact networks, but they too were not excluded from the surveys and prevalence was lower in men than women [4]. Thus, no separate HIV-2 epidemics are likely to be flourishing in the community. Furthermore, the average effects of these heterogeneities on transmission dynamics are unlikely to vary significantly over the period that is modelled because of limited effects of infection saturation during this period of declining HIV-2 prevalence. The specific impact of core groups on treatment impact is accounted for. In summary, the model simplifications will not affect the qualitative predictions and are unlikely to significantly affect the quantitative predictions.

Infection amongst children was also not modelled. Mother-to-child transmission of HIV-2 is rare [36,37] and the observation that HIV-2 prevalence is low amongst 15–25 years (Fig. 1a) suggests that infections in children have limited impact upon infections in adults. Furthermore, because our model and data both relate to adults, infections in children should not significantly affect our results.

Although HIV-2 epidemiological data from elsewhere in West Africa are scarce, wherever available, they indicate a similar decline [5,6]. However, the emergence of a more transmissible strain in the future is possible. An HIV-2 recombinant, CRF01_AB, has been isolated from three individuals with advanced disease from Nigeria, Ghana and Japan [38]. A similar recombinant from Cote d'Ivoire was described in 1994 [39], but the distribution and transmissibility of these variants are unknown.

In summary, whilst we cannot rule out the persistence of HIV-2 further afield or through future changes in risk behaviour or strain transmissibility, our prediction is that HIV-2 is rapidly declining in prevalence and will eventually go extinct in Caió and neighbouring regions. In recent years, HIV-2 epidemiological surveys have been lacking, but we advocate their resurrection in order to test this hypothesis.

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Author contributions: H.F. developed the mathematical model, performed the modelling work and wrote the manuscript. C.V.T. generated hypotheses to be tested and contributed to data collection, data interpretation and writing the manuscript. Z.D.S. contributed to data interpretation and reviewed the manuscript. H.W. contributed to data collection, data interpretation and reviewing the manuscript. S.R.J. had overall responsibility for the laboratory and epidemiological studies on HIV-2 infection in Caio, and reviewed the manuscript. M.S.V.D.L. contributed to data collection, data interpretation and reviewed the manuscript. P.A. was responsible for the demographic surveillance in Caio. T.D.S. generated hypotheses to be tested and contributed to data interpretation and writing the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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