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What really is a concentrated HIV epidemic and what does it mean for West and Central Africa? Insights from mathematical modelling

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Abstract

Background/Objective: HIV epidemics have traditionally been classified as "concentrated" among key populations if overall HIV prevalence was below 1%, and as "generalised" otherwise. We aimed to objectively determine the utility of this classification by determining how high overall HIV prevalence can reach in epidemics driven by unprotected sex work (SW), and how estimates of the contribution of SW to HIV transmission changes over time in these epidemics.

Methods: We developed a deterministic model of HIV transmission specific to West and Central Africa (WCA) to simulate 1,000 synthetic HIV epidemics where SW is the sole behavioural driver that sustains HIV in the population (i.e. truly concentrated epidemics), and based on a systematic extraction of model parameters specific to WCA. We determined the range of plausible HIV prevalence in the total population over time and calculated the population attributable fraction (PAF) of SW over different time periods.

Results: In 1988 and 2008 HIV prevalence across the 1,000 concentrated HIV epidemics ranged (5th-95th percentile) between 0.1%-4.2% and 0.1%-2.8%, respectively. The maximum HIV prevalence peaked at 12%. The PAF of SW measured from 2008 over one year was <5% to 18% compared to 16-59% over twenty years in these SW driven epidemics.

Conclusion: Even high HIV-prevalence epidemics can be concentrated and driven by unprotected SW. Overall HIV prevalence and the short-term PAF are poor makers of underlying transmission dynamics and underestimate the role of SW in HIV epidemics, and thus should not be used alone to inform HIV programmes.

Introduction

The term "concentrated" epidemic has been commonly used in the HIV public health literature to describe epidemics where HIV prevalence is disproportionately higher (> 5%) among key subgroups of the population (including female sex workers [FSWs], men who have sex with men [MSM] and people who inject drugs [PWID]) than in the general population (HIV prevalence <1%)[1](Table 1). Accordingly, "generalized" epidemics have traditionally been defined as those where HIV prevalence exceeds 1% in the general population, which are usually represented by antenatal clinic attendees. This dichotomy has been used to inform the design of HIV surveillance systems, the allocation of HIV prevention resources, and to decide which risk groups should be prioritized[1,2]. For example, it is recommended that key populations (KPs) are prioritized in "concentrated" HIV epidemics, whereas in "generalized" epidemics, the recommendations have focused on HIV programmes supporting all segments of the population, assuming that resources would be accessible to KPs without tailored KP programmes[3,4]. Whilst this traditional classification is not necessarily wrong when used to describe HIV epidemic patterns, it may be misleading when used to inform the design and content of HIV surveillance and prevention programmes, and resource allocation[5-8]. Studies suggest that the traditional, descriptive classification system does not reflect the underlying transmission dynamics of the epidemic, especially in higher prevalence settings[5-10]. This is because HIV prevalence reflects HIV acquisition, and does not provide information on relative risks of onward transmission to and from subpopulations[11,12].

A key question relevant for HIV programming in Sub-Saharan Africa (SSA) is the extent to which unprotected sex work, and unprotected sex or needle exchange among other KPs, contributes to the HIV epidemic. The traditional classification of epidemics and output from the UNAIDS Modes of Transmission model[5,7,13] may have been misinterpreted and thus, underestimated the role of sex work (SW) on overall HIV transmission in SSA and potentially devalued the importance of focusing HIV prevention on FSWs and their clients[8,14]. In West and Central Africa (WCA), HIV prevalence in female sex workers and the total population ranges from 7-52%, and from 0.1-15%, respectively, based on sub-national data collected between 2006 and 2009[14-18]. Thus, many of these regional epidemics would be classified as "generalized". Yet recent studies suggest that even in settings where HIV prevalence exceeds 1%, epidemics may be truly concentrated[2,12,19] – i.e. in the absence of transmission during SW, the HIV epidemic would never have occurred and/or it could not be sustained (Table 1). For example, in Cotonou, Benin, it is estimated that more than 93% (range, 84-98%) of all HIV infection between the start of the epidemic and 1993 may be attributable to unprotected SW, despite an estimated HIV prevalence of 3.3% and 3.4% overall among males and females in 1998, respectively[9,20-22]. It has also been estimated that the SIDA1/2/3 programme focused on FSWs in Benin since 1993, and extended to clients in 2000, may have averted 33% (range, 20-46%) of all HIV infections between 1993 and 2008 in the overall population, highlighting the

relevance of a tailored KP-intervention even in some "generalized" epidemic settings[9]. Although these studies suggest that SW could be the main behavioural driver of some HIV epidemics with prevalence exceeding 1% in the general population, it remains unknown how big an HIV epidemic driven only by SW can get. Answering this question could improve our understanding of the epidemiology of HIV, our interpretation of HIV prevalence patterns in WCA, and what we can infer about underlying transmission dynamics from overall HIV prevalence.

The objectives of this study are to i) develop a dynamic mathematical model of HIV transmission informed by the systematic extraction of most of the relevant behavioural and epidemiological parameters specific to WCA; and ii) use this model to simulate a large family of realistic, data-driven, synthetic epidemics to determine how high overall HIV prevalence can reach in epidemics driven solely by SW (i.e. "truly" concentrated HIV epidemics), and how the contribution of SW to HIV transmission (the population attributable fraction, PAF) changes over time in these concentrated HIV epidemics (Table 1).

Methods

Approach

We generated 1,000 synthetic HIV epidemics using the best available epidemiological and sexual behaviour data from WCA (see Appendix 1 for list of countries). For clarity, we conducted the study prior to wide-scale antiretroviral treatment (ART) access to better answer the research question, since effective ART can increase HIV prevalence via increased survival of persons with HIV and on ART. ART coverage remained below 28% in West Africa by 2008[23], and thus, we generated synthetic epidemics by drawing upon data collected on or before 2008.

Dynamic Mathematical Model

We developed a dynamical deterministic mathematical model of HIV transmission by extending a previously described dynamic model of commercial sex work (CSW)[7]. The simulated population is stratified into two age-groups (less than 24, and ≥24 years), and by sexual activity into low-activity, individuals who engaged in multiple partnerships (high-volume and low-volume), high-volume FSWs/clients, and low-volume FSWs/clients, and former FSWs/clients and individuals who used to engage in multiple partnerships (former high-activity class whose behaviour is now assumed to be the same as others in the low-activity class). The model is represented by a set of ordinary differential equations detailed in Appendix 1. Individuals enter the simulated population at onset of sexual activity into the low-activity or multiple-partnership classes; from which they can enter SW (as FSWs or clients) at a rate dependent on the fraction likely to enter SW and replace those who exit SW. Individuals in the higher-activity classes (including those engaged in SW) retire into the former high-

4

activity classes. Individuals enter the simulation as susceptible (HIV un-infected), and may become infected with HIV with a force of infection dependent on partnership type, partner change rate, HIV prevalence of partners and the disease/infectivity stages of infected partners, STI, number of sex acts, probability of transmission per sex acts, male circumcision and condom use. Individuals then progress through four stages of untreated HIV reflecting CD4 decline and differential HIV infectivity. The model includes HSV-2 co-infection at a stable prevalence, wherein HSV-2 increases HIV infectiousness and susceptibility, per sex-act[24-28] and was included to enable further transmission heterogeneity across activity-classes. The model includes baseline male circumcision, which reduces HIV susceptibility in males by 60%[29,30] and is assumed to remain stable over time.

The model includes five types of sexual partnerships to reflect the variability in partnership dynamics from the sexual behaviour data from WCA. Each type of partnership has a different number of sex acts/year and levels of condom-use: SW with occasional clients; SW with regular/repeat clients; transactional (financially-motivated but not formal SW[31,32]); casual sex; and main partnerships. Table 2 summarises the different risk-groups, types of partnerships, and with whom those partnerships are formed. Condom-use within each partnership type increased linearly from zero at the start of the epidemic to the first estimates obtained from the data syntheses (range in time-period, 1991 to 2000), after which condom-use increased via a logistic function to saturate at the most recent estimate (data from 2005 to 2008), remaining stable thereafter.

Data from West and Central Africa for Model Parameterization

To ensure that the simulated synthetic epidemics were plausible, we comprehensively reviewed and extracted behavioural data (including condom-use), HIV and HSV-2 prevalence data for sex work and other sexual partnerships in WCA to parameterize the model. Because most HIV programmes are implemented at the province or state level (usually with adult population size >250,000-500,000), we extracted data at the sub-national level where available to more adequately capture heterogeneity between locales. The details of the systematic searches and comprehensive review are described in Appendix 1. In short, we performed a three-stage data synthesis to extract parameter values in the two main domains: biological (such as male circumcision and HSV-2 prevalence) and sexual behaviour. The first stage involved an expansion of a previous systematic review[14] to obtain data on sexual behaviour within commercial sex, HSV-2 and HIV prevalence on FSWs from 1985 onwards. The second stage involved extraction of raw data from the demographic health surveys (DHS[33]) to obtain sexual behaviour data on non-commercial partnerships. The third part involved a grey literature search from the UNAIDS country reports for data on overall HIV prevalence across provinces/states and for reports on 'non-commercial' multiple partnerships, supplemented by drawing from published systematic reviews of parameters relevant to non-commercial partnerships and populations. Parameters, which were assumed constant between locales within WCA - such as the biological

transmission probability of HIV per sex act, and untreated HIV progression - were drawn from the literature. The ranges of extracted parameters used in the model and their sources are shown in Appendix 1, with parameters related to partnership type shown in Table 3.

Sampling and Plausibility Checks

We used Latin hyper-cube sampling with a uniform distribution of the parameter range. As much as possible, correlations between parameter values were accounted for by using ratios and relative risks (such as with HSV-2 prevalence and contact rates within specific risk-groups). Generating relative risks and ratios was governed by data availability for the same province/state or within the same source (publication or survey). To ensure that we sampled enough parameter sets where there was no sex work (to mimic locales where the data might truly suggest there is no CSW), we set 15% of sampled parameter sets to have zero FSWs (and thus, values of zero for all sex work parameters). This was also done to ensure that we did not bias the study towards all synthetic epidemics including some (even if very small networks of) sex work. We then conducted plausibility checks of sampled parameter combinations as follows:

1) The relative size of risk-groups remained relatively stable; i.e. that they did not vary by more than 15% of their value at the start of the epidemic (HIV seeding).
2) Client population size would not exceed 35% of the male population. This was based on the largest sub-national estimate from the systematic review[14], using the indirect method of estimating client population size[34].
3) The total population did not exceed a 5% annual growth rate[35].
4) The balancing of partnerships did not produce large changes in the partner change rates (of more than 15% of their input value) of a given partnership type in each activity-class.
5) FSW incidence would not exceed 50% in the first two years of seeding HIV. This was based on pre-2002 HIV incidence measurements of 10-30% per year[36]. These empirical estimates were measured among women who had already been in sex work for >2 years, and estimated after 1994; thus we used 50% as our upper bound for feasibility checks.
6) An epidemic established when all condom-use was set to zero from the start of the epidemic. That is, each synthetic epidemic satisfied the following condition in the absence of condom-use: total HIV incidence exceeded 1 per 1000 people per year (as per Granich *et al* working definition for local elimination[37]) at 50 years from HIV seeding.

Generating plausible synthetic HIV epidemics based on data from West and Central Africa

Each simulation that passed the plausibility checks was run to 50 years post-seeding and the epidemic type (i.e. concentrated or not) was determined for each simulation. To determine whether or not the

epidemic was concentrated, we simulated the same parameter set with the following counterfactual: *w*here HIV transmission during SW was set to 0 in both directions (i.e. from clients to FSWs and from FSWs to clients, during SW partnerships). In this counterfactual, condom-use within transactional sex, casual sex, and main partnerships were also set to zero to ensure we did not incorrectly label a non-concentrated epidemic as concentrated because of increasing condom-use in non-SW partnerships. An epidemic was considered concentrated if in the counterfactual, the annual HIV incidence in the total population was less than one case per 1,000 people per year[37] at 50 years after seeding. The fifty-year time frame was chosen after checking the sensitivity of the classification to assessment post-seeding.

Although the goal was not to fit the model to a specific locale within WCA, we restricted model outputs to the observed epidemics in WCA. Thus, we bounded the simulations by imposing constraints using the upper bound of the documented FSW and province/state-level overall or ANC population HIV prevalence ranges for each region by time-period (<1990, 1990-1995, 1996-2000, 2001-2005, 2005-2008). We used the overall HIV prevalence data to bound HIV prevalence in young females (excluding FSWs), but did not bound client HIV prevalence. Parameters were re-sampled and the above steps repeated until 1,000 CSW-driven synthetic HIV epidemics were obtained.

Analyses: Estimated maximum epidemic size

First we estimated the maximum HIV prevalence in the total population, measured at any time after the start of the epidemic and before 2009, from each synthetic epidemic. These results provide a theoretical estimate of how big an epidemic can get. We also conducted a sensitivity analysis where the general population females (females excluding FSWs) were used. Because results were not very different (less than 10% relative difference in the maximum), we present the overall HIV prevalence (in the total population).

Analyses: Population attributable fraction of SW to concentrated HIV epidemics

The cumulative PAF of SW is a measure of the contribution of SW to direct and indirect HIV transmission [6,9,10,38-40]. We measured the cumulative PAF of SW in the synthetic epidemics by 'turning off' (i.e. setting to zero) HIV transmission during occasional and regular/repeat commercial sex partnerships from time *t0* onwards, and comparing the relative difference in the cumulative number of new HIV infections acquired in the total population over *x* years. This approach was exactly the same as that taken for determining if epidemics were concentrated, with the following exception: for the PAF, condom-use in other (non-SW) partnerships was allowed to rise. The cumulative PAF of SW is measured from the model outputs as:

$$PAF_{t0+x} = 100 \left(\frac{\int_{t0}^{t0+x} new\ HIV\ infections\ _{total}^{SW} - \int_{t0}^{t0+x} new\ HIV\ infections\ _{total}^{no\ SW}}{\int_{t0}^{t0+x} new\ HIV\ infections\ _{total}^{SW}} \right)$$

We measured the PAF_{1988+x} and PAF_{2008+x} for different values of x, to determine how the cumulative PAF in concentrated HIV epidemics varies over the course of the epidemic (early in the HIV epidemic [1988] and later in the epidemic [2008]), and how it changes over time (from $x=1$ to $x=20$ years). We then explored the relationship between condom-use levels (weighted average of condom-use with occasional and regular clients) achieved by 2008, stratified by overall HIV prevalence, with the cumulative PAF over 20 years.

Results

Figure 1A shows the predicted HIV prevalence over time from the 1,000 simulated epidemics. Figure 1B shows the range of empiric estimates of consistent condom-use with clients in the previous 30-90 days as reported by FSWs, and which increases over time. Figure 1A shows that in absence of HIV transmission during SW, no HIV epidemic would occur (blue line at 0% prevalence), reflecting that SW is the main driver of all the simulated epidemics under study.

HIV prevalence in the total population in concentrated HIV epidemics varies from 0.1 - 4.2% (5th-95th-percentile range) in 1988, and reaches a maximum of 12% HIV prevalence (Figure 1A). HIV prevalence ranges between 0.1-2.8% (5th-95th-percentile range) in 2008 even if condom use during SW has reached a relatively high level in most synthetic epidemics in 2008 (median of the weighted average for occasional and regular commercial sex, 74%). These results suggest that HIV epidemics can be sustained by SW even if overall HIV prevalence is as high as 12%. No epidemic exceeds 15% HIV prevalence.

Figure 2 shows the PAF_{t0+x} of cumulative HIV infections due to SW from t_0=1988 onward or t_0=2008 onward over different time periods x. Since all the synthetic, concentrated HIV epidemics are driven by SW, the $PAF_{start\ of\ epidemic\ +large\ x}$ of cumulative HIV infections from the start of the epidemic is, by definition, 100%. Despite this, the PAF_{t0+x} measured from 1988 or from 2008 varies substantially when measured, over different time periods (x years) and across simulated epidemics. The longer-term PAF_{1988+x} are larger than the one year PAF_{1988+1}; the latter fails to account for chains of secondary transmission from FSWs and their clients to subsequent partners (and vice versa). The median PAF_{1988+x} increases from less than 5% over one year, to 33% over 5 years, and to 58% over twenty years (Figure 2A). The PAF_{t0+x} is also larger when measured earlier in the HIV epidemic ($PAF_{1988+20}$ = 58%) than later ($PAF_{2008+20}$ = 32%) because condom-use during SW was always higher later in the epidemic (Figure 1B). There is wide variation in the PAF across epidemics. For example $PAF_{2008+20}$ ranged from 16-59% (Figure 2B). Figure 2C shows a weak negative association of the $PAF_{2008+20,}$ on the level of condom-use achieved by 2008 during SW. $PAF_{2008+20}$ can be very different across epidemics of similar HIV prevalence and even condom-use levels. The $PAF_{2008+20}$ can also be very similar in epidemics of very different prevalence levels, reflecting the influence of other elements of the underlying transmission chains (i.e. other determinants and model parameters that were varied in the simulations).

Discussion

We conducted a mathematical modelling exercise using the best available data from WCA to explore the potential size of concentrated HIV epidemics (driven by SW) and to examine the properties of the population attributable fraction of SW to HIV epidemics. The study provides key insights (Box 1) and adds new knowledge to previous studies by suggesting that HIV epidemics driven and sustained by SW could achieve higher overall HIV prevalence than typically assumed[7,9,10]. To our knowledge, this is the first modeling study that draws on the best available data across a wider region of SSA to clarify and explicitly demonstrate that concentrated HIV epidemics can achieve an HIV prevalence exceeding 1%, and which may be as high as 12%. None of the synthetic, concentrated HIV epidemics exceeded HIV prevalence of 15%, suggesting that it may be much less likely that SW could be the sole behavioural driver in regions experiencing such high HIV prevalence. However, as alluded to in previous studies, unprotected SW could still contribute substantially to onward HIV transmission in regions with HIV prevalence exceeding 15%[2,7,12,19,41]. Although it has recently been recommended to restrain the use of the 1% threshold for classifying epidemics due to its rigidity and potential for confusion, it is still often used as a descriptor of epidemics[42]. The results here provide a scientific rationale for abandoning the 1% threshold for inferring underlying transmission dynamics and guiding prevention. Our results have important implications for improving our understanding of the epidemiology of HIV in WCA.

Our results on the short-term and long-term PAF demonstrate its subtlety. The PAF_{t0+x} measured after the start of the epidemic as typically done in many studies [40,43] varied greatly across concentrated HIV epidemics, where by definition, the $PAF_{start\ of\ epidemic\ +\ large\ x}$ =100%. The PAF can be difficult to interpret because different estimates can be obtained from epidemics with similar HIV prevalence and even similar condom-use levels. The short-term PAF (e.g. over one year typically used in studies [10,14,18,40,44]) remains consistently lower that the longer-term PAF because the former fails to account for chains of secondary transmission from (and to) FSWs, their clients, and subsequent partners. Like the overall HIV prevalence, the short-term PAF is a poor marker of epidemic type and cannot be used to infer the behavioural drivers of HIV epidemics - i.e. those risk behaviours that enable HIV to establish and spread in the population and in absence of which the epidemic would eventually fade out[39].

What is a concentrated epidemic? Our results suggest that a more meaningful definition of a "truly" concentrated epidemic would reflect which behaviours (e.g. SW) are necessary for HIV to establish and persist in a locale, such that it is necessary to focus on these behaviours to control the local HIV epidemic (Table 1). In other words - and going back to early HIV epidemic theory[19,45-47] - concentrated epidemics should be defined as one where vulnerabilities and risk-behaviours in a small fraction of a population can lead to a disproportionate amount of HIV transmission and sustain

onward transmission. According to this new definition, our results suggest that it would be theoretical possible for concentrated epidemics in WCA to be as large as 10-12%.

With sub-national HIV prevalence ranging between 0.1 and 15% in the overall population, many HIV epidemics in WCA may be concentrated. However, overall HIV prevalence alone will not be helpful to identify "truly" concentrated epidemics, whereas the design of HIV surveillance, prevention/care programmes, and resource allocation should be aligned with the best possible characterization of the underlying transmission dynamics and behavioural epidemic drivers[2,12]. Thus, it remains critical to identify in which locales, HIV epidemics are driven by SW (or other KP-behaviours). Such information would tell us that in these locales, it is necessary, sufficient, and more efficient (especially under constrained resources) to focus HIV prevention and treatment efforts on FSWs and clients in order to control the local HIV epidemic[39]. Further work is required to identify combination of epidemiological parameters that would help identify SW driven epidemics and develop new and validated tools to classify epidemics in a way that identify the real, and programmatically-meaningful, behavioural epidemic drivers and better reflect the underlying transmission dynamics of the epidemic, especially in higher prevalence settings[12,19].

Major strengths of our analysis include developing synthetic epidemics based on the best available epidemiological and behavioural parameters representative of WCA and taking into account various SW partnerships types. The study was designed to theoretically and objectively explore the discordance between traditional epidemic classifications and the underlying transmission dynamics (Table 1), rather than to specifically replicate or make direct inferences about specific sub-national HIV epidemics in WCA. Despite using the best data, our conclusions on the maximum size of SW driven epidemics should be interpreted with some caution, in the light of the mathematical model used, which did not include duration of partnerships or long-term concurrency and may have over- or underestimated the epidemic size, respectively. Although our model did not include ART, it is unlikely to alter our conclusions, which were based on data prior to 2008 (when ART coverage was still low). This needs to be taken into account when interpreting future empirical HIV prevalence estimates. Our results tell us the theoretical maximum size of HIV epidemics. However, they cannot be used alone to determine if an epidemic of a given size is concentrated or generalized. In other words, if HIV prevalence is below 12% in WCA, this does not necessarily mean that SW drives them, but that it is plausible. Such inference requires detailed modelling analysis with sufficient high-quality data in the locale of interest to estimate the $PAF_{\text{start of epidemic +large x}}$ due to specific behaviours, as performed in a recent analysis for Cotonou, Benin[9]. Future work includes detailed and multivariate sensitivity analyses of key parameter combinations that influence overall HIV epidemic size, and an exploration across other behaviours and KPs.

In conclusion, we cannot make inferences about the underlying transmission dynamics of HIV epidemics based on overall HIV prevalence alone. A more meaningful definition of a concentrated epidemic would capture the transmission dynamics of HIV(Table 1). HIV epidemics in WCA that exceed 1% (up to 12%) HIV prevalence may still be driven and sustained by SW, and warrant a revisit to more appropriately characterize the contribution of SW (and other KP-behaviours) to overall HIV transmission. Only then will governments have the information needed to determine the appropriate scale and content of HIV prevention, treatment, and care programs for different populations at risk of acquiring and transmitting HIV.
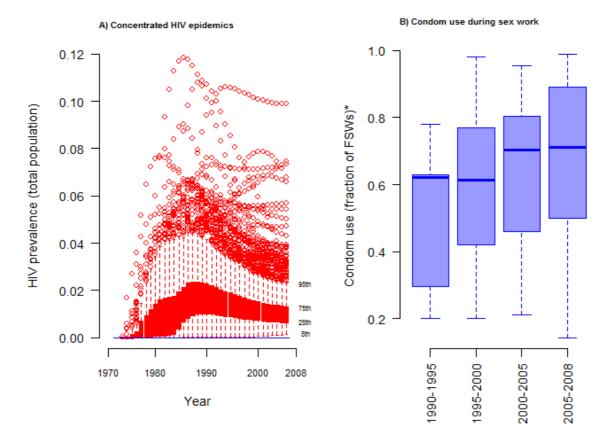
Author contributions: MCB originally formulated the research question. MCB and SM conceived of, and designed the study. SM designed, developed, and analyzed the mathematical model and conducted the systematic and comprehensive reviews and the data syntheses. MCB and SM wrote the manuscript. MP contributed significantly to the study and model design and development. MA, SM, and JFB contributed original data to the data syntheses. All authors provided critical intellectual input into the interpretation of results and edited the manuscript.

Figures

Figure 1: HIV prevalence in synthetic, concentrated HIV epidemics driven by SW (Panel A) and empiric data on condom-use reported by FSWs in West and Central Africa (Panel B). Panel A shows the overall HIV prevalence in the total population from 1,000 synthetic HIV epidemics using the best available data from WCA, where the solid red bars indicate the inter-quartile range, the dashed lines indicate the 5-25 percentiles and the 75-95 percentiles, and the red circles indicate the >95th percentile. The blue line shows that HIV prevalence would have remained at 0% in the overall population in absence of HIV transmission during sex work from epidemic onset. Panel B summarizes the data from the different surveys on condom-use reported by FSWs in WCA (min, median, interquartile range, max). * The fraction of FSWs reporting consistent (always) condom-use in the last 30-90 days, where the x-axis reflects the year of data collection. SW (sex work); FSW (female sex worker).
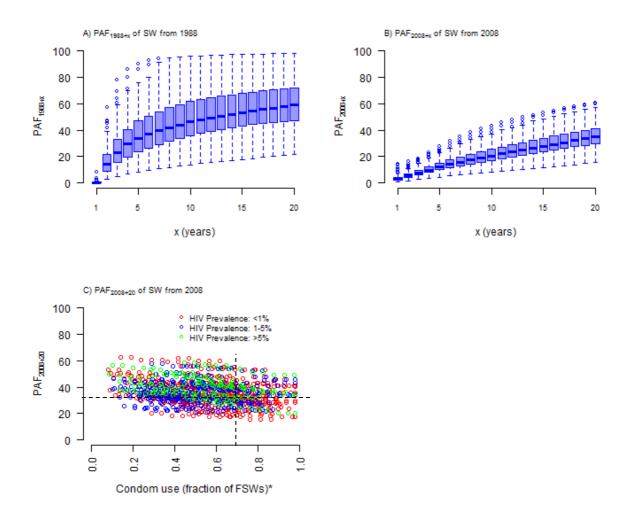
Figure 2. **Population attributable fraction of SW (directly and indirectly due to unprotected sex work in the total population) derived from the 1,000 synthetic, concentrated HIV epidemics.** The ranges (5th,25th, 50th, 75th, 95th percentiles) of predicted population attributable fraction (PAF$_{t0+x}$) of SW to cumulative HIV infections acquired in the total population over *x* years, measured from t_0=1988 in A) and from t_0=2008 in B). In C) PAF$_{2008+20}$ measured from 2008 over x=20 years, by level of SW condom use* achieved by 2008 in the synthetic epidemics, stratified by overall HIV prevalence. The dotted lines represent the median PAF$_{2008+20}$ and the median estimate of the level of condom-use by 2008. * Proportion of SW partnerships (a weighted average of condom- use with occasional and regular/repeat clients) where condoms were used in the synthetic epidemics, by 2008 and stable thereafter. SW (sex work); FSW (female sex worker)