Measuring the Utility of Surveillance Data For Monitoring the HIV/AIDS Epidemic In Sub-Saharan Africa

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Abstract

Since the early 1980s in sub-Saharan Africa (SSA), substantial human and financial resources have been dedicated to monitoring the HIV/AIDS epidemic. Throughout, surveillance data collected at antenatal care (ANC) clinics have been a key data source.

ANC surveillance data are well-known to be biased when quantifying population HIV prevalence levels in SSA. Nonetheless, a routinely-accepted, although rarely-tested assumption has been that the data are representative of population-level HIV prevalence trends. More recently, HIV testing data from prevention of mother-to-child transmission (PMTCT) programmes have been proposed as a substitute for ANC surveillance, although these data can be subject to temporal biases too.

The primary objective of this thesis is to add to the limited evidence regarding the representativeness of HIV testing data from pregnant women to monitor population-level HIV prevalence trends. Empirical analyses from repeated household-based population surveys and ANC surveillance were done for seven countries in SSA from 2000 to 2010 and among youth aged 15 to 24 years in Manicaland, Zimbabwe from 1985 to 2003. Also, a mathematical model was used to explore temporal bias in ANC surveillance trends in epidemics similar to those in Botswana, Côte d'Ivoire and rural Zimbabwe from 1985 to 2030. Finally, PMTCT programme data were assessed for their representativeness as compared to ANC surveillance data in Manicaland, Zimbabwe from 2006 to 2008.

Results showed the representativeness of ANC surveillance data to vary by time period and setting, although trends among youth were more robust than those

among adults aged 15 to 49 years across settings, and particularly so among men. Representativeness in the ART-era depends on coverage and scale-up, the setting, and the potential for changing fertility patterns among ART users. PMTCT data for surveillance purposes was of limited use in Manicaland, Zimbabwe from 2006 to 2008. In summary, caution is needed when using HIV testing data from pregnant women to monitor population HIV prevalence trends in SSA.

Declaration

I declare that the work in this thesis is my own, except as otherwise indicated in the section below describing contributions.

Contributions

Each of the chapters in this thesis has been written under the helpful guidance of my supervisors. Examiners of this thesis also provided substantial suggestions to improve the integrity and interpretation of the work. All analyses have relied on data collected by others.

For Chapter 2, WHO and CDC staff provided comments on the literature review describing biases in PMTCT programme data for surveillance purposes in preparation for submission of a WHO-commissioned white paper on the topic.

Discussions by Ministry of Health country staff at two meetings in Ethiopia and Geneva also informed the conclusions drawn from these studies. Anonymous reviewers provided helpful comments for a final published article about using PMTCT data for surveillance purposes.

For Chapter 3, UNAIDS staff gave permission to include ANC surveillance data provided by them on behalf of countries. UNAIDS staff also provided comments on a similar chapter included in a UNAIDS-commissioned study on temporal biases in ANC surveillance-based HIV prevalence trends.

For Chapter 4, Dr. Tim Hallett wrote all of the C++ code for the mathematical model, following joint discussions on the model's primary objectives. He, along with staff from UNAIDS, provided comments on a draft version of this chapter as part of the previously-mentioned UNAIDS-commissioned study.

Chapter 5 benefitted from early discussions with Professor Christl Donnelly regarding approaches to statistical analyses of repeated population survey data. Also, methods for analysing proportional change with complex variance structures were developed jointly. This chapter also reflects the suggestions and comments made by anonymous reviewers in preparation for publication.

Chapter 6 was initially discussed with WHO staff as part of a contract to Professor Gregson exploring the uses of PMTCT data for surveillance purposes.

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Acronyms and abbreviations

AIDS	**Acquired Immune Deficiency Syndrome**
ANC	**Antenatal Care**
APR	**Adjusted Prevalence Ratio**
ART	**Antiretroviral Therapy**
ASFR	**Age-specific Fertility Rates**
CDC	**The Centers for Disease Control and Prevention**
CI	**Confidence Interval**
DHS	**Demographic and Health Surveys**
EPP	**Epidemic and Projections Package-Spectrum**
HIV	**Human Immunodeficiency Virus**
MOH	**Ministry of Health**
MOHCW	**Ministry of Health and Child Welfare [Zimbabwe]**
OR	**Odds Ratio**
PMTCT	**Prevention of Mother-to-Child Transmission**
POP	**Household Population Survey**
PR	**Prevalence ratio**
SSA	**Sub-Saharan Africa**
STD	**Sexually transmitted diseases**
STI	**Sexually transmitted infections**
TFR	**Total fertility rate**
UAT	**Unlinked Anonymous Testing**
UNAIDS	**Joint United Nations Programme on HIV/AIDS**
UNICEF	**United Nations Children's Fund**
US	**United States of America**
WHO	**World Health Organization**

Chapter 1: Introduction

1.1 Background

Thirty years ago, in the summer of 1981, the Centers for Disease Control and Prevention (CDC) published an article about what would later become the first reported cases of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in the United States (US) [1]. The article described *pneumocystis carinii pneumonia* among five previously healthy young men in Los Angeles. The report's authors also identified a set of risk factors associated with the newly-recognized infection that would subsequently be used as the preliminary case definition for future disease reporting purposes.

Not long after the publication of the 1981 article, reports of additional cases from across the US were received by CDC, followed closely by case reports from Haiti [2], Uganda [3] and several countries in Europe [4-6]. By 1983, the CDC had received notification of 3064 AIDS cases in the US [7]. Reports of these US cases, along with those from Canada, Haiti, Zaire, 15 European countries, and seven Latin American countries, were compiled and published in a report at the World Health Organization's (WHO) inaugural meeting to assess the global AIDS situation [7]. The 1983 report represented the first attempt to monitor the epidemic through a fledgling global HIV/AIDS surveillance system.

Since this first WHO report, substantial financial and human resources have been invested to monitor and disseminate information about the epidemic and how it is changing over time. Accurate estimates of new and existing cases of HIV are arguably the most important measure of the success or failure of a country's response to control transmission [8, 9]. When countries fall short in their measurements of HIV incidence and prevalence, it can have devastating consequences. Failure to document increases in the number of persons newly

infected and living with HIV can result in inadequate allocation of resources for prevention, treatment and care programs. Conversely, overestimation of the number of HIV-infected individuals will unnecessarily draw scarce resources away from other public health priorities, result in wasted expenditures, and generate scepticism about future resource needs [10-12].

Beginning in the late 1980s, as the true scale of the epidemic was emerging, the impracticality of relying on HIV and AIDS case reporting alone became evident, particularly in sub-Saharan Africa (SSA) where the provision of health care services and public health infrastructure were weak [13-15]. In place of -- or at least in complement to -- case reporting, WHO recommended in 1988 that countries set up surveillance of HIV infections in sentinel populations. These populations included high risk groups, such as patients at sexually transmitted infection (STI) clinics, and groups more representative of the general population, such as pregnant women attending antenatal care clinics (ANC). It was suggested that ultimately, ANC surveillance could produce the most accurate data for monitoring HIV prevalence trends (i.e., relative changes in the number of HIV-individuals over time) in resource-constrained settings with severe HIV burdens [16]. There was also considerable evidence at the time to suggest that ANC surveillance data could be used to monitor population prevalence levels (i.e., the proportion of HIV-infected individuals in the population at any given time).

Although the transition to ANC sentinel surveillance systems in the late 1980s represented a considerable improvement in the quality and timeliness of data, bias in ANC surveillance estimates resulting in inconsistencies between estimates of HIV prevalence among pregnant women and the population generally were increasingly flagged as problematic. Starting in 2001, to respond to the need for more accurate

estimates of HIV prevalence in the population, many countries in SSA began adding anonymous HIV testing to nationally-representative population-based surveys [17].

Since the early 2000s, WHO has recommended that countries use testing data from nationally-representative population surveys to determine HIV prevalence levels in countries in SSA. Given the cost and complexity of conducting such surveys, though, countries would still need to use ANC surveillance data to monitor population prevalence trends [18]. In the last few years, many countries in SSA also have begun to explore the potential for using HIV prevalence estimates from prevention of mother-to-child transmission (PMTCT) programmes to complement, or in some cases, replace ANC surveillance data to monitor HIV prevalence trends in the population [19].

Despite the continued reliance on surveillance data from pregnant women as the primary data source for monitoring population prevalence trends in SSA, there has been relatively limited, and definitely not systematic, research into whether trends in HIV prevalence from pregnant women accurately reflect population prevalence trends. This is especially true in recent years where the epidemic has been marked by changes in prevalence and incidence in many countries in SSA [20-22]. These changes, which are due to the natural dynamics of the epidemic, the scale-up of prevention programmes, and the rapid expansion of antiretroviral therapy (ART) programmes, [17, 22-24] have the potential to alter the magnitude and direction of bias that has previously observed in ANC prevalence estimates. Also, improvements in the way that PMTCT services are delivered may mean that participation biases change from year to year.

1.1.1 Overall aims and key research questions of this thesis

Although the dynamics of the HIV epidemic in the general population have been well-described, relatively less is known about the dynamics of the HIV epidemic among pregnant women and women at risk of becoming pregnant specifically. Therefore, the first aim of this thesis is to contribute to an improved understanding of whether HIV surveillance data among pregnant women attending ANC clinics can be used to monitor population-level HIV prevalence trends in sub-Saharan Africa. Further to this aim, the key research questions that this thesis will address are (i) have historical trends in HIV prevalence among pregnant women mirrored those in the population in selected countries in SSA?; and (ii) can ANC surveillance data be used to reliably monitor future population HIV prevalence trends? Underlying each of these questions is whether or not changes in the natural dynamics of the HIV epidemic or a country's response to the epidemic through the scale-up of prevention and treatment programmes bias ANC surveillance data over time.

As a second aim, the feasibility of using HIV testing data from PMTCT programmes to replace or complement ANC surveillance data to monitor population prevalence trends will be considered, based on an assumption that repeated estimates of HIV prevalence among pregnant women will mirror those in the general population. With regard to this secondary aim, key research questions are: (i) do estimates of HIV prevalence among women participating in PMTCT programmes accurately reflect HIV prevalence among ANC attendees?; and (ii) what factors related to the geographic scale-up of PMTCT services or selective participation (either being offered or accepting testing) by HIV status might bias these estimates? A variety of analytic approaches, including mathematical modelling and analysis of data from demographic and health survey (DHS) and a population-based cohort

study with parallel ANC surveillance data in Manicaland, Zimbabwe, are used to inform responses to these questions.

1.1.2 Structure of this thesis

By way of introduction, this chapter provides background information on the important role that HIV/AIDS surveillance data have played in mobilizing a response to the epidemic. In Chapter 2, the types of bias that can influence the accuracy of HIV prevalence levels using (a) ANC data and (b) PMTCT data are explored, along with how these biases might change with time.

With regard to the specific aims and key research questions described in the previous section, Chapters' 3 through 5 address the representativeness of ANC surveillance data to monitor population prevalence trends. Chapter 3 uses data from seven countries in SSA with repeated DHS and DHS-like surveys and ANC surveillance data to assess the representativeness of ANC data during the 2000s. Chapter 4 addresses the historical reliability of ANC surveillance trends from 1985 through 2002 using a mathematical model of HIV/AIDS epidemics similar to those in Botswana, Côte d'Ivoire and rural Zimbabwe. In each of these settings, the model is also used to explore the potential for the introduction and scale-up of ART from 2003 to 2030 to cause further shifts in temporal bias in ANC data due to a change in fertility patterns and increased survival among users. Chapter 5 considers the historical representativeness of ANC data in Manicaland, Zimbabwe, where parallel cohort and ANC surveillance data were available at three time points from 1998 to 2005. The final analytical chapter, Chapter 6, addresses the second aim of this thesis by exploring the extent to which HIV prevalence data from PMTCT

programme records can be used for HIV surveillance purposes in Manicaland, Zimbabwe. Geographic, socio-demographic and behavioural risk determinants of testing and HIV status are described in the ANC surveillance and population survey data.

The main findings from each chapter and directions for future research are summarized in the final chapter, Chapter 7. Appendix A, containing summary tables of the key studies about bias included in the literature review in Chapter 1, Appendix, B, with a description of the parameters used in the mathematical model in Chapter 4, and Appendix C, which includes published manuscripts based on work from Chapters' 2 and 5 of this thesis, follow the complete list of citations referenced in Chapters' 1 through 7. Three commissioned reports for the WHO and UNAIDS, upon which Chapters' 2 through 6 were based, are available upon request but not included in this thesis due to their length.

1.2 Aims and organization of the chapter

In this introductory chapter, the trajectories of the HIV/AIDS epidemic globally and in SSA are described. In subsequent sections, methods that have been commonly used to collect HIV surveillance data, along with the strengths and limitations that characterize them, are reviewed. This critique serves as a useful starting point for subsequent chapters in this thesis, which explore the extent to which data from HIV surveillance from pregnant women can be used to monitor levels and trends in HIV prevalence among the wider population.

1.3 The HIV/AIDS epidemic globally and in sub-Saharan Africa

HIV/AIDS has had a devastating impact on the health of the population globally, especially in SSA where the burden of HIV infection is most severe. In 2009, UNAIDS estimated that there were 30.8 million [Uncertainty bound (UB): 29.2 million - 32.6 million] adults aged 15 and over worldwide living with HIV [22]. Of these, nearly two thirds, or 20.3 million [UB: 19.0 million -21.6 million] of all HIV-infected people were living in SSA. Although the rate of new infections has slowed over time, the estimate of the number of newly infected individuals is still high. In 2009, of the 2.6 million [UB: 2.3 million – 2.8 million] new infections, just under 70% were in SSA [1.8 million; UB: 1.6 million – 2.0 million]. This number outpaces the estimated 1.8 million [UB: 1.6 million – 2.1 million] individuals, including adults and children, in 2009 who died from an AIDS-related condition. An estimated 28% of these deaths were estimated to have occurred outside SSA.

Although statistics describing HIV prevalence, incidence and mortality are commonly provided for SSA as a whole, in aggregate, they can mask important differences in sub-regional and country-specific epidemics and how these epidemics are evolving over time. In southern Africa, for example, the most severe infection levels were observed in Swaziland, with an estimated HIV prevalence of 25.9% [UB: 24.9%-27.0%] in adults aged 15 years and older in 2009 [22]. High levels of HIV prevalence above 20% have also been observed in Botswana, Lesotho, and Zimbabwe [22]. Although the HIV prevalence estimate in South Africa of 17.1% [UB: 16.7% - 17.5%] was not among the highest in SSA, it had the greatest number of infected persons of any country [22]. In Southern and Eastern Africa, HIV prevalence was lowest in Angola at 1.9% [UB: 1.4% - 2.4%] and Eritrea at 1.2% [UB: 0.9% - 1.5%], respectively [22].

In Western and Central Africa, where the epidemic has been less severe, HIV prevalence in 2009 was highest in Cameroon at 5.3% [UB: 4.9% - 5.8%] and above 3% in Central African Republic, Côte d'Ivoire, Gabon and Nigeria [22]. The remaining countries in Western and Central Africa (Benin, Burkina Faso, Democratic Republic of the Congo, Gambia, Ghana, Liberia, Mali, Mauritania, Niger, Senegal and Sierra Leone) had an HIV prevalence of less than 2% among adults [22].

The 2009 HIV prevalence estimates reflect the changes in HIV incidence and mortality due to the introduction of ART, the scale-up of effective behaviour change and biomedical interventions, and the natural evolution of the epidemic [22, 24-27]. In several countries in SSA, HIV incidence rose rapidly during the 1980s before peaking in the mid to late 1990s [20]. Between 2001 and 2009, UNAIDS estimates that incidence fell by more than 25% in 22 countries in SSA [22].

With regard to AIDS mortality, the estimated number of deaths over time has decreased gradually, primarily due to the introduction of ART[22]. By the end of 2009, 37% of the population in need of ART (based on a CD4-count threshold of 350) were receiving it, contributing to a decline in number of AIDS-related deaths in SSA from 740 000 [670 000- 820 000] in 2004 to 610 000 [530 000 – 700 000] in 2009 [22]. Of those countries most severely impacted in SSA, Rwanda, Botswana, and Namibia have achieved ART coverage levels upwards of 75% by 2009. In six countries in SSA (Côte d'Ivoire, Ghana, Mozambique, South Africa, United Republic of Tanzania, and Zimbabwe), however, ART coverage was still less than 40% [22].

1.4 Methods for conducting HIV/AIDS surveillance in sub-Saharan Africa

In the most general sense, public health surveillance has been defined as “the ongoing systematic collection, analysis and interpretation of outcome-specific data for use in the planning, implementation, and evaluation of public health practice.” [28]. This definition has guided the public health practice of surveillance for diseases ranging from smallpox in the 1970s to avian influenza in the late 2000s.

In 1990, Jim Chin, the first chief of the Surveillance, Forecasting and Impact Assessment unit at the Global Programme on AIDS at the WHO, suggested that methods typically used to conduct public health surveillance of other infectious diseases should be considered equally useful for monitoring the HIV/AIDS epidemic globally [14]. However, the WHO recognized at the time that HIV/AIDS was not just another infectious disease that could be monitored by adding it to a list of notifiable conditions. Key attributes of the disease, including its long incubation period, geographic differences in disease burden, and, in particular, the widespread stigma associated with being identified as infected, would make the process of monitoring the epidemic especially challenging.

Since the early 1990s, surveillance data have been used to varying degrees of success to monitor the HIV/AIDS epidemic. As Chin originally suggested in his 1990 article, these sources can be categorized into five systems as outlined in Teutsch and Churchill’s 1994 book, Principles and Practice of Public Health Surveillance, with some allowances made for the “exceptionalism” of the HIV/AIDS epidemic [29]. These five systems are (i) notifiable disease and disease registry reporting systems, (ii) routine vital statistics systems; (iii) sentinel surveillance systems; (iv) surveys; and (v) programme-specific monitoring systems. A description of the methods and contributions of each of the systems to monitoring the HIV/AIDS

epidemic is described below, with a particular focus on the use of these systems in SSA.

1.4.1 Notifiable disease and disease registry reporting systems

As mentioned in the background section of this chapter, case-based notifiable disease reporting systems were first used to monitor the HIV/AIDS epidemic internationally. In most countries, including those in SSA, AIDS case reports were filled out by local health care providers and then sent via a reporting system to the national level for aggregation and reporting to WHO. Case reports typically consisted of basic socio-demographic information, such as the gender and age of the individual, laboratory data, and any known risk factors for transmission. In areas without access to diagnostic HIV testing, a points-based clinical case definition using AIDS-defining symptoms called the Bangui definition was used to confirm cases beginning in 1985 [30].

Despite the contribution of this early system to gaining some initial insight into transmission patterns, AIDS case-based reporting was heavily criticized in SSA as an inadequate method for monitoring HIV prevalence in the population [13]. The two biggest concerns regarding the accuracy of estimates were under-reporting and delays in reporting cases [13]. This was particularly true in non-urban health care facilities where reporting systems were weak and timeliness of reporting often depended on a functioning transportation system. Missed diagnoses, or false diagnosis were also problematic, as many clinics in SSA did not have the laboratory capacity to conduct HIV testing. As evidence of these problems, the WHO estimated the number of AIDS cases globally at over 350 000 in 1988 using a mathematical

model, but the number of confirmed case reports received by the agency during that year was less than half that number [13].

A further limitation of relying on an AIDS case-based reporting system was that this focus provided only a snapshot of transmission patterns which, due to the long asymptomatic period, had occurred five to ten years earlier [31]. To address this problem, many countries added HIV to their notifiable disease reporting system. While this might have provided a better strategy for determining the true proportion of the population infected, lack of testing opportunities and the stigma associated with testing positive meant that most HIV infections continued to go undiagnosed. As a result, in most countries in SSA, the reliance on HIV and AIDS case reporting declined, although in limited instances, this system is still used by some to describe basic shifts in risk and demographic characteristics of HIV infection in the population [32].

1.4.2 Routine vital statistics systems

Because the time from AIDS to death is relatively short (in the absence of ART), at first, death registries were also considered a potential source of surveillance data for monitoring the epidemic [33]. In many countries where national vital reporting systems were well-developed and specified causes of death were certified by physicians, the number of AIDS-related deaths could be used to approximate infection levels in the population using back-calculation [34] and other methods [35].

Ultimately in SSA, however, two factors prevented the use of national vital registry systems for surveillance purposes. In the first instance, vital reporting systems were often weak, with few national systems collecting and analysing death

events [33]. In the second instance, coding and classification of disease done by a physician may not have identified AIDS-related conditions as a primary or secondary cause of death, either through simple misclassification or intentional obfuscation [36]. As a result, very few countries in SSA found national vital reporting systems of sufficient quality to be useful.

As an aside, some public health researchers have been able to use trends in the number of reported deaths nationally, as well as locally available data from burial societies, to better quantify AIDS-related mortality in a geographic area [36-38]. In particular, vital reports have been used to estimate the number of AIDS deaths based on changes in mortality rates over time in South Africa [36]. Additionally, in some longitudinal community-based surveys, verbal autopsies of deceased persons have been carried out with previous caregivers to quantify the proportion of deaths that were likely due to AIDS [37, 38]. In most cases, however, these methods have not been used systematically at a national level or across countries in SSA given the intensity of resources required to conduct these types of studies.

1.4.3 Sentinel surveillance systems

To address limitations in data quality from case-based and vital reporting systems in SSA, in 1988, the WHO recommended that countries consider implementing sentinel surveillance to monitor HIV infection levels and trends [16]. In draft guidance released at the IV International Conference on AIDS in Stockholm, Sweden, the organization outlined a method by which selected population groups at chosen sites would be anonymously tested for HIV antibodies using leftover blood collected for other diagnostic purposes on a repeated basis [16]. Using leftover blood collected

would not require individuals to consent to testing, thus estimates would not be biased by selective participation.

The main purpose of the initial sentinel surveillance activities was to detect trends in infections for specific population groups and not necessarily to estimate infection levels in the population as a whole [16]. In most countries in SSA, HIV surveillance among pregnant women, STI patients, military conscripts, and blood donors was considered relatively straightforward to implement since blood samples and routine socio-demographic data were collected during visits to health facilities [39]. Also, facilities were chosen in a convenient, rather than systematic manner, with more accessible, better-resourced areas typically included [16]. Facilities where HIV prevalence was expected to be higher (e.g., in urban areas with good transportation networks or in areas where higher sexual risk behaviour was previously documented) were also given preference for inclusion.

After several years of conducting surveillance in a variety of facilities, it was observed that estimates of HIV prevalence among pregnant women attending ANC clinics were a reasonably good approximation of HIV prevalence in the community, especially where contraceptive use was low and uptake of ANC services was high [13, 40, 41]. Data from pregnant women relative to sexually active women in general, however, were found to be subject to three types of systematic bias: (i) the purposeful selection of participating clinics; (ii) the self-selection of women who choose to access antenatal care, and (iii) the impact of testing only women who became pregnant [42]. Generally, due to the first bias, ANC estimates systematically overstated HIV prevalence at the national level (e.g., among men and women combined) due to over-representation of clinics in urban areas [43-46]. In community level comparisons, however, the more usual pattern was for ANC data to understate

prevalence among older women in the population due to HIV-related sub-fertility biases and to overestimate prevalence among women under age 25 due to bias in ANC data from selection for high risk sexual activity [42, 47-54]. Where uptake of ANC was low or contraception was high, biases in ANC data relative to the surrounding female population were less consistent [55, 56]. To improve their accuracy, demographic and statistical methods were proposed to adjust for these biases [42, 45, 57]. Countries were also encouraged to collect behavioural data as part of a "second-generation" surveillance effort to aid in the interpretation of changes in the HIV epidemic over time [58-60].

Since the mid-1990s, most countries in SSA have adopted similar methodologies for conducting HIV surveillance among pregnant women. According to WHO and UNAIDS recommendations, ANC surveillance protocols typically dictate that surveillance occurs over a one or two month period on an annual or bi-annual basis at a convenience sample of selected clinics [39]. The number of participating clinics can vary from country to country, but range from as low as six clinics to hundreds or more [31, 61].

In the last ten years, many countries have expanded the number of participating ANC clinics in an attempt to increase the geographic representativeness of urban and rural estimates [31, 61-63]. Despite this change, and the availability of standardized protocols and guidance, a recent study in 2009 by Garcia-Calleja and colleagues found the quality of the ANC surveillance systems across SSA to be variable [63]. In nine countries in SSA, HIV surveillance systems were described either as being of low quality or non-functioning. The reason for this designation in many countries was that there were long gaps between surveillance rounds.

ANC surveillance is usually conducted using an unlinked and anonymous (UAT) testing protocol [39]. Protocols relying on UAT use leftover blood from syphilis testing, which usually occurs at a woman's first prenatal visit. Routinely-collected information regarding a woman's socio-demographic and fertility characteristics at the time of the visit, which in most countries includes her age, residence, parity, gravidity, educational level and marital status, are used to aid in the interpretation of trends in HIV prevalence [39]. Women are often excluded from participating in ANC surveillance if they are not attending their first prenatal care visit or have been referred from another facility.

In each ANC surveillance round, data from approximately 200 to 300 women is collected at each participating clinic over a four to eight week period [39]. An overall sample size target of 300 women per age group across all clinics is set. Based on UNAIDS recommendations also, some countries in SSA have oversampled younger women aged 15 to 24 years (with a goal of approximately 3000 women across all clinics) as a proxy for monitoring trends in new infections [39]. Because HIV-related morbidity and mortality in recently infected women is low, HIV prevalence should be a reasonably good indicator of underlying HIV incidence among young people, including men and women [64].

With regard to interpretation and presentation of ANC surveillance data, UNAIDS recommends that countries report HIV prevalence among all pregnant women as the median clinic estimate from the survey round, followed by the lower and upper range of clinic-specific estimates so as to highlight any disparities in sub-regional HIV prevalence [39]. Countries with repeated estimates of HIV prevalence greater than 1% in pregnant women (e.g., sustained transmission in the population) from ANC sentinel surveillance are considered to have generalized HIV epidemics,

while countries with HIV prevalence of less than 1% (e.g., in select high-risk groups only) are categorized as having concentrated epidemics. In SSA today, 39 of the 45 countries are described as having a generalized HIV epidemic [63]. Those countries in SSA with concentrated epidemics are Comoros, Madagascar, Mauritius, Mauritania, Senegal and Somalia [63].

Although ANC surveillance data have provided a relatively reasonable indicator of community-level HIV prevalence, the accuracy of ANC surveillance data to describe national-level HIV prevalence was, as previously mentioned, eventually found to be lacking [65]. In particular, the effect of choosing ANC clinics disproportionately located in more urban areas proved difficult to quantify and adjust for systematically across countries [44]. Beginning in the early 2000s, UNAIDS and WHO recommended that countries in SSA replace ANC surveillance data with data from nationally-representative household-based surveys in men and women to more accurately estimate HIV prevalence [65, 66]. Nevertheless, UNAIDS has recommended that ANC surveillance data, despite its limitations, still serve as the primary means by which trends (i.e., changes in population prevalence over time) in the epidemic are monitored [41, 65]. The methods used to produce country and global estimates and projections of HIV prevalence and incidence are described in more detail in Section 1.5.

1.4.4 Surveys

Concerns about the representativeness and accuracy of national HIV estimates derived from ANC surveillance in the early 2000s, along with the increased availability of financial and human resources to monitor the epidemic, created an

increased demand for nationally-representative estimates of population HIV prevalence [65, 66]. To meet this demand, many countries, beginning with Mali and Zambia in 2001, added HIV testing to household-based nationally-representative surveys, such as the DHS [67].

DHS and DHS-like surveys typically use census-driven sampling frameworks to select enumeration areas in which all, or a select sample, of participants domiciled in households are interviewed on basic demographic and health indicators [68]. Sample sizes typically range from 5000 to over 10000 men and women aged 15 to 49 years, depending on the size of the country [68]. Individuals selected to participate are also asked to provide blood for HIV and other testing [69].

Since 2001, upwards of three dozen DHS and DHS-like surveys with HIV testing have been carried out in SSA. While most countries have published results from at least one survey, seven countries have reported on two (Botswana, Kenya, Lesotho, Mali, Niger, Tanzania, and Zambia) and Sierra Leone and South Africa have reported on three.

Due to the complexity and expense of carrying out population surveys, nationally-representative surveys are typically conducted every five to 10 years [39]. Also, given their complexity, high levels of technical support and longer periods of time are often required to clean, interpret and publish results. As a result, data collected from these systems are not available as frequently as those obtained from ANC surveillance.

Not unlike the ANC surveillance data, the accuracy of estimates from population surveys can be of concern, especially if refusal rates at the household and individual levels are high and differentially associated with HIV status [39, 70, 71]. Garcia-Calleja and colleagues, in a review of national population-based HIV

prevalence surveys from 19 countries in SSA from 2001 to 2005, found that household refusal rates ranged from less than 1% to 17%, with higher individual-level refusal rates typically observed in men (ranging from 4.6% to 37.8%) as compared to women (ranging from 2.7% to 31.8%) and in urban as compared to rural areas [44]. Of the 19 countries, rates of refusal were the highest in South Africa, for both men and women [44], and especially in the province of KwaZulu-Natal, where 59.1% of individuals refused to provide a blood sample [72, 73].

In Garcia-Calleja's 19 country study, it was not possible to directly measure the impact of bias due to refusals, although the authors suggested that countries with high refusal rates may find significant differences between observed and actual population prevalence estimates, assuming that those refusing were twice as likely to be HIV infected than those participating. To assess the impact that refusal bias might have had on estimates of HIV prevalence from the population survey in the KwaZulu-Natal province in 2005, in particular, researchers developed a mathematical model that sought to infer HIV prevalence among non-testers from background mortality rates among HIV infected and uninfected individuals in the surrounding population in the pre-ART era [73]. Mortality rates were available separately for HIV infected and uninfected individuals via a series of demographic health studies in the province.

From the model, HIV prevalence, adjusted for refusers, was estimated to be 27.5% (95% CI 23.6–31.3), or approximately 7% higher than the observed prevalence of 19.7% (95% CI 19.6–21.3) among testers only. Analysis also showed that some proportion of this bias likely resulted from refusers who already knew their HIV serostatus to be positive, since relative to HIV negative individuals, persons testing positive at an earlier round were 23% less likely to test in the follow-up 2005

survey round. This latter finding was similar to a study conducted in Malawi, which showed that individuals who knew their HIV status to be positive were five time more likely to refuse to participate in testing than those who had previously tested negative [71]. A greater increase in refusals among women previously testing positive in rural South Africa was also noted, but crude adjustment methods to account for this bias had a negligible influence on the population prevalence estimate [56]. As access to HIV testing expands, it is conceivable that household surveys could increasingly understate HIV prevalence in the population in the future due to issues related to repeat testing refusals, but evidence that this will have a measurable impact on changes in bias in estimates is still limited.

Although the finding for bias from the population survey estimates in KwaZulu-Natal was not surprising given the high and differential refusal rates by persons assumed to be HIV positive, this result contrasts with those from a larger study by Mishra and colleagues using DHS and DHS-like data from 14 countries. Results from this analysis suggested that the effect of individual-level non-response bias (including absentees) on population estimates was likely to be minimal [74], One key limitation to the study's conclusions was that the accuracy of the adjusted population prevalence estimates were only valid to the extent that the socio-demographic and behavioural characteristics included in the multivariate statistical analysis correlated with the risk of HIV infection. Evidence from the regression models in the countries suggested that these variables did a relatively poor job at predicting HIV prevalence among testers, with only 20% of the variation in prevalence explained by over 30 predictor variables. For this reason, it is possible to conclude that population based estimates may not always be a perfect 'gold standard' when refusal biases are very high, and that analyses relying on this method of adjustment may not produce more

accurate estimates of underlying population prevalence under this circumstance. In Zambia, an analysis of DHS data suggested that HIV prevalence would have needed to be at least 41% higher among non-respondents to have a significant effect on the estimate of prevalence from the national survey [70].

A second concern beyond refusals and non-response at the individual level is that population surveys may be biased by the exclusion of high risk groups, such as prisoners, military personnel, homeless persons, or migrant workers, not domiciled in a permanent household. In the previously described 14 country study, which also considered this potential source of bias, household response rates and census data from five countries with varying rates of HIV infection (Cambodia, India, Ghana, Uganda and Lesotho) were used to explore the impact of excluding non-household populations on survey-based HIV prevalence estimates.

To do this, estimates of the proportion of the non-household populations who were adults was constructed, assuming three scenarios where: (i) household and non-household prevalence estimates were the same (e.g., baseline); (ii) non-household members comprised 66.7% of non-household population, and the HIV prevalence among the non-household adults, as compared to adults in households, was 10 times in India and Cambodia, five times in Ghana, two times in Uganda, and one and a half times in Lesotho; and (iii) the non-household adult population was 75.0%, with HIV prevalence among non-household adults as compared to household adults, 20 times in India and Cambodia, 10 times in Ghana, four times in Uganda, and two times that in Lesotho.

Results from these analyses indicated that exclusion of non-household adults was likely to have only a minimal effect on the observed national HIV prevalence estimates from the surveys, regardless of the non-household proportion and infection

level assumed. In India, for example, even under the most extreme scenario (scenario iii), the adjustment for missing adults would have resulted in an increase in population prevalence from 0.28% to 0.35%. In countries with higher HIV prevalence, such as Uganda and Lesotho, the exclusion of a substantial proportion of the non-household based adult population would not change HIV prevalence overall in the countries.

Even given the potential for inaccuracies described above, the benefits from population-based household surveys have increasingly outweighed any limitations as a means for estimating overall HIV prevalence in a country, because most importantly, they are often the only source of data to describe HIV prevalence among men nationally. Population-based surveys also provide an opportunity to directly link socio-demographic, behavioural and health service use data to an individual's HIV status, thereby producing a more comprehensive understanding of the dynamics of the epidemic. Finally, repeated population-based surveys have been used most recently to monitor changes in HIV incidence by examining changes in mortality and HIV prevalence within age cohorts [75, 76]. In ANC surveillance, sample sizes are generally too small to provide stable estimates of incidence using these methods, while results from smaller, geographically-localized cohort studies likely would not be generalizable to the national level.

1.4.5 Programme-specific monitoring systems

Although population-based survey and ANC surveillance data are currently considered to be the best sources for monitoring HIV prevalence levels and trends respectively, in 2006, UNAIDS also recommended that alternative data sources,

such as from the scale-up of routinely-offered HIV testing through PMTCT programmes, be explored as possible proxies for ANC-derived HIV prevalence levels and trends [77]. In terms of the availability of PMTCT data, the roll-out of programmes to test pregnant women through routine pre-natal care services has been somewhat slow, but by 2008, about 28% of pregnant women in SSA had been tested during their ANC visit [78]. A variety of interventions, including the adoption of the 2007 WHO recommended provider-initiated 'opt-out' testing strategy have been credited with increasing uptake [79]. Studies have shown that the 'opt-out' strategy, where HIV testing is included in the battery of prenatal tests conducted during a woman's pregnancy unless she refuses, substantially increased testing uptake compared to when client-initiated or 'opt-in' testing strategies were used [80-87]. With 'opt-in' testing, although all women may have been informed about the benefits of HIV testing during their prenatal care, they would have been required to request the test from their health care provider. [79]

Using PMTCT data for surveillance purposes offers certain advantages over ANC surveillance in that (i) more ANC clinics can participate, (ii) ethical concerns of testing women without consent are avoided, and (iii) data on the number of women testing and their HIV status are routinely available as part of programme monitoring activities [88-90]. However, possible disadvantages have also been raised. Of greatest concern has been that HIV-infected women refusing or, conversely, preferentially seeking out HIV testing could bias PMTCT-based estimates [91, 92]. The impact of this participation bias on prevalence estimates could also vary in magnitude and direction with time as uptake levels increase or approaches to delivering HIV testing and counselling services change [93]. Finally, whether PMTCT data are sufficiently standardized across clinics, detailed enough for surveillance

purposes, and accessible in their current form has also been debated [77, 89, 94-96].

With regard to methods for collecting and analysing PMTCT data for surveillance purposes, a variety of approaches have been explored [88, 89, 93-98]. Initial recommendations for countries wishing to begin collecting and using PMTCT data for surveillance purposes have been developed, based on lessons learned from the studies conducted to date [19] . As part of these recommendations, countries were encouraged to prioritize collecting PMTCT data from the same sample of clinics that previously participated in ANC surveillance in order to be able to continue to monitor population prevalence trends. To avoid the possible influences of non-participation bias, it was also suggested that countries set minimum standards for the amount of time a clinic had to have been offering services and the level of uptake required before permitting the clinic to contribute PMTCT-based HIV prevalence estimates for surveillance purposes. Finally, issues regarding data collection methods and reporting systems were raised for further consideration, including what minimum set of data should be collected and whether PMTCT data should be collected during a specific surveillance period or abstracted from existing registries in the clinics on an on-going basis.

Preliminary guidelines for using PMTCT data for surveillance purposes have also been developed based on the recommendations references above [99]. If, during the process of evaluating the PMTCT programme data for surveillance purposes, the data are found to accurately reflect underlying HIV prevalence in countries, the guidelines encourage countries to transition from ANC surveillance to routine PMTCT reporting data. Chapter 2 provides more background on the types and magnitude of bias associated with PMTCT data that may complicate this

potential transition. In Chapter 6, these issues are discussed further with regard to the representativeness of PMTCT data for monitoring ANC prevalence in Manicaland, Zimbabwe.

1.5 Selected examples of how ANC surveillance data are used

As previously discussed, ANC surveillance data have played an important role in monitoring the HIV epidemic and the effectiveness of a country's response. In their crude form, ANC surveillance data from women aged 15 to 24 years have been used to monitor changes in HIV prevalence and incidence among youth [21]. In the absence of repeated population survey data and without the benefit of a reliable laboratory test for incidence, ANC surveillance data are the easiest way to monitor trends in this population. Accordingly, UNAIDS recommends that countries rely on these data under the assumption that trends in HIV prevalence among young pregnant women reflect trends in young men and women aged 15 to 24 years [64].

ANC surveillance data have also been used to determine why changes in the epidemic may be observed. For example, Hallett and colleagues used a counterfactual mathematical model to determine whether changes in HIV prevalence in countries with generalized HIV epidemics were caused by changes in sexual risk behaviour in eight countries [27]. In this example, HIV prevalence trends for each country were produced assuming no change and various levels of changes in transmission due to increased condom use, fewer partnerships, smaller age-disparities between partners, and other risk reduction behaviours. These curves were then fitted to ANC surveillance data to determine what changes in sexual behaviour would have been required in the population to produce the observed

changes in prevalence among pregnant women. The model assumes that ANC surveillance data are representative of underlying population prevalence trends, which is validated using the model also.

ANC surveillance data have also been used to measure the effectiveness of HIV programme services and to improve programme performance [100]. For example, Bolu and colleagues in 2005 used ANC surveillance data from Kenya, Ethiopia and Zimbabwe to calculate the proportion of HIV-infected women not participating in the PMTCT programme. As these proportion were high in Ethiopia and Zimbabwe (57% and 59%, respectively), recommendations were made to strengthen and improve a woman's first encounter with the PMTCT programme so as to increase participation [101].

Perhaps the most important use of HIV surveillance data from sentinel surveillance of HIV infections among pregnant women, and more recently, from population survey data, is to model the HIV epidemic in SSA. Results from country-specific mathematical models are used to describe estimates and short-term projections of HIV prevalence and incidence among adults aged 15 to 49 years [18, 39]. Depending on country needs, estimates and projections can also be produced separately for rural and urban areas or for sub-regions or specific population groups.

To generate national HIV prevalence estimates and short-term projections, most countries in SSA use the Estimates and Projection Package (EPP)-Spectrum software package developed and supported by UNAIDS and the UNAIDS Reference Group on Estimates, Modelling and Projections [102]. The UNAIDS Reference Group is a multi-disciplinary, multi-institution team of individuals who work to ensure the accuracy and comparability of estimates and projections globally [11]. Public health officials from countries typically convene alongside members of the UNAIDS

Reference Group at bi-annual workshops to produce models of their country's epidemic. Typically, these models are published in national and international surveillance reports and are also used to inform a wide-range of policy and funding decisions.

When using EPP-Spectrum to generate estimates and projections, the software provides users with an Excel-like spreadsheet to enter ANC surveillance and population survey data [103]. For the ANC surveillance data, the names of clinics located in urban areas are entered in a sheet separately from clinics in rural areas. Within each sheet, the names of ANC clinics are listed in the first column by row, with subsequent column headings representing years, dating back to the earliest ANC surveillance rounds.

For each clinic and year, the sample size and the number testing HIV-positive are entered. Where information on sample size is not available, the software assumes a default value of 300 women per clinic. The overarching purpose of entering the ANC surveillance data is to select which of the curves produced through the EPP-Spectrum model best fit the trends in these data.

For population survey data, the year in which the survey was conducted, the number of persons sampled, HIV prevalence in the group, and their standard errors are entered [103]. For the purposes of fitting the epidemic curve, population survey estimates are treated as if they were a separate ANC surveillance clinic. More detailed information on how population survey data are used to calibrate overall infection levels is discussed below.

In addition to the HIV surveillance data, country-specific demographic data and data on ART use are also entered into EPP-Spectrum to inform the construction of prevalence and incidence curves. These data include: the population living in rural

and urban areas over time, the ratio of males to females, sub-fertility, CD4 eligibility threshold for starting ART in the country, progression patterns to death among ART users, the rate of survival of individuals on ART over time, annual numbers of first-line and second-line ART users, and the coverage of the ART among sub-populations of interest, such as men versus women.

Based on the country-specific ART and demographic data, a simple compartmental mathematical model in EPP-Spectrum is used to derive an initial set of epidemic curves for a population of adults aged 15 to 49 years [102, 104-106]. The basic four parameters of the model are:

- r – the force of infection
- f_0 – the proportion of the population newly at risk
- t_0 – the start year of the epidemic
- ϕ – a behaviour change parameter representing increased or decreased levels of risk over time

Other parameters, including the time from infection to ART eligibility and from ART eligibility to death, are fixed.

To choose the combination of parameter values that best fits trends in the surveillance data, a method known as incremental mixture importance sampling (IMIS) is used [107]. In this method, a small set of randomly generated curves are initially produced from a distribution of values from the four parameters and then the resulting curves are evaluated for their fit to the surveillance data. Curves that best fit the data are assigned the highest weight, with special weight assigned to curves that fit data from ANC clinics which have participated in more surveillance rounds. Next,

the values for the four parameter estimates that produced the most heavily weighted curves are used as the starting point for producing additional curves. Through repeated sampling, this process eventually produces a single curve of HIV prevalence and underlying incidence, with uncertainty estimates that capture 95% of the distribution of all potential curves that could reasonably fit the surveillance data [102, 107].

While the final curve represents the best fit to the trend in the ANC (and population surveillance data when available), the overall level of the prevalence and incidence curves can be modified in special cases [103]. For example, countries without population survey data can calibrate a prevalence curve downward based on observed biases in ANC surveillance data for urban and rural areas. Countries can also modify prevalence curves to fit through specific point prevalence estimates, such as those estimated from repeated population surveys. Finally, countries can manually input incidence patterns over time based on other country-specific information, such as changes that might have occurred in a specific region or a sub-group population.

As the technical description of EPP-Spectrum demonstrates, ANC surveillance data are integral to selecting the best-fitting curves describing national and sub-national incidence and prevalence trends. For this reason alone, and apart from the many other ways countries use ANC surveillance data to monitor the HIV epidemic, it is critical to ensure that ANC surveillance data accurately reflect underlying changes in prevalence in the population over time. In Chapter 2, biases in ANC surveillance estimates and their sensitivity to changes in behavioural and biological determinants of HIV infection in an evolving epidemic are therefore examined in further detail.

Chapter 2: Assessing bias in levels and trends in HIV surveillance data from pregnant women

2.1 Aims and organization of the chapter

The central aim of this chapter is to provide a comprehensive review of published and unpublished literature describing (i) the types of bias that have previously been found to influence the accuracy of HIV prevalence levels and methods applied to adjust for them using (a) ANC surveillance data and (b) PMTCT data and (ii) how these biases may be changing with time to influence the representativeness of surveillance trends. Also, analytical methods for detecting changes in bias over time that have been used in previous studies are described as an introduction to the remaining analytical chapters. Finally, a description of the Manicaland HIV/STD Prevention project is provided, since subsequent chapters make extensive use of data from this project.

2.2 Bias in HIV prevalence levels from ANC surveillance data

As briefly discussed in Chapter 1, estimates of HIV prevalence from ANC surveillance data can be influenced by three types of bias. These biases are: (i) the purposeful selection of participating ANC clinics; (ii) the self-selection of women who access ANC services and (iii) only testing women who became pregnant [42]. Understanding the nature and direction of these biases is important even though UNAIDS no longer recommends using ANC surveillance data to estimate overall levels of population prevalence in a country. Without this understanding, it would be difficult to predict how changes in these biases over time could affect the representativeness of trends in HIV prevalence at a local or national level, for which ANC surveillance data are still used.

Studies describing the experiences of countries in SSA with regard to bias in ANC estimates are numerous. Studies included in this review were identified through an online search of published literature using Google Scholar and PubMed in February 2012. Search parameters included: *ANC sentinel surveillance, population surveys, HIV prevalence, measurement error and sub-Saharan Africa.* This search returned 746 references, of which all abstracts were reviewed for their relevance.

In total, nine of the 746 articles explored bias in ANC estimates relative to national population estimates or relative to estimates among adult men and women combined [40, 43, 45, 46, 48, 70, 108-110]. These studies are summarized in Appendix A, Supplemental Table 2.1. Ten studies were identified that primarily explored differences in HIV prevalence among ANC attendees relative to female population in community-based comparisons [47, 51-53, 55, 56, 111-114]. These articles are also summarized in Appendix A in Supplemental Table 2.2. In some instances, where population level data could be disaggregated to the catchment level, a few articles considered both types of comparisons [43, 46, 95, 110]. Summaries of findings for both comparisons are included in Supplemental Table 2.1.

Importantly, supporting articles for which bias in ANC estimates was considered a secondary topic or which provided context for the type of bias reported (e.g., most importantly those describing HIV-related fertility differences in women) are referenced in the text but not summarized in the supplemental table, unless the study attempted to quantify a magnitude of bias [47, 113, 114]. From this initial search, seven studies that directly address issues of bias in ANC surveillance data specific to trends were also identified. These studies are reviewed in Section 2.3 and summarized in Supplemental Table 2.3 of Appendix A [21, 27, 50, 113, 115-117].

2.2.1 The purposeful selection of participating ANC clinics

Based on findings from studies comparing HIV prevalence estimates from pregnant women attending ANC clinics and men and women living in the catchment areas of those communities, estimates of HIV prevalence in both groups have generally been found to be similar throughout SSA [40, 46]. However, due to resource and practical constraints, not all ANC clinics in a country can participate in ANC surveillance. Consequently, those clinics that are selected to participate in ANC surveillance must serve as reliable proxies for areas without participating clinics.

One of the biggest concerns when relying on only a sub-set of clinics is whether the chosen clinics will have sufficient spatial diversity to capture geographic differences in HIV prevalence that can occur [45]. For example, in most countries in SSA, HIV prevalence is higher in urban, more populated areas such as towns and commercial centres, and lower in rural, less populated areas such as subsistence farming areas [26, 45, 118]. Accordingly, clinics are usually identified as either representing urban or rural areas when constructing population prevalence trends. Associations between geographic location and HIV prevalence are often more nuanced, however, than just a division between rural and urban areas. For example, in Kenya, HIV prevalence levels were found to increase as the distance that women lived from a major road or to Lake Victoria declined, and these types of geographic differential in prevalence must also be anticipated when choosing ANC clinics [119].

Another concern is whether the sub-set of clinics selected to participate in ANC surveillance adequately reflect the unique mixture of cultural norms and behaviours that influence HIV transmission in specific geographic areas [120]. For example, an early ecological study of male circumcision and HIV prevalence showed that, in four countries in SSA (Côte d'Ivoire, Kenya, Tanzania and Zaire), geographic

areas where circumcision was either practiced or not could be defined [121]. In those areas where circumcision was not practiced, HIV prevalence was 2.0 to 4.5 times greater than in areas where circumcision was practiced. Religion is another factor that has been associated with differences in HIV infection levels by geographic area. In rural Manicaland, Zimbabwe, members of Apostolic churches living in some communities were found to have lower HIV prevalence levels than members of other religions living in other communities [122]. Given the limited number of clinics that can participate in ANC surveillance, it would be nearly impossible for this system to capture all of these differences.

A final, more recent concern is whether the sub-set of ANC clinics selected to participate accurately capture differences in geographic access to HIV prevention, treatment and care programmes [123]. This is especially of concern since populations with access to these programmes will experience higher levels of HIV prevalence due to extended survival [25] and lower HIV incidence due to reductions in onward transmission through decreased viral loads [102, 124]. As a case in point, ART and PMTCT programmes in South Africa were initially concentrated in urban clinics with better diagnostic and laboratory infrastructure while expansion to more rural clinics lagged behind [125-127]. Also, in some countries, ANC surveillance protocols dictate that clinics selected to participate must offer PMTCT services; thus, ANC surveillance prevalence estimates may be weighted more heavily towards populations with better access to PMTCT and ART programmes [128].

Given the above, it is not surprising that at a national level, ANC surveillance data from participating clinics have tended to overstate population HIV prevalence in most countries in SSA [43, 45, 46, 109] by about 20% on average [45]. Further stratification of these comparisons also revealed that the differential tended to be

greater in rural as compared to urban areas and in countries in western and central Africa as compared to countries in southern and eastern Africa. Despite these overarching commonalities, country-specific variations have also been observed. In Zimbabwe [108] and Zambia [70], for example, ANC surveillance estimates were found to be similar to those in the general population in surveys conducted in the early to mid-2000s. In Uganda, where estimates of population prevalence are believed to have stabilized in the mid-2000s [129], ANC surveillance estimates of HIV prevalence were observed to be lower than those in the general population [46]. In these three countries, either ANC surveillance estimates are not influenced (or in the case of Uganda, influenced differently) by the usual clinic selection biases observed in other parts of SSA, or, in contrast, other types of biases, such as those arising from the self-selection of women who access ANC services or from differences in who becomes pregnant, are more influential.

2.2.2 Self-selection of women who access ANC services

The WHO recommends that women have at least one, and preferably four or more, prenatal visits during pregnancy [130]. Findings from DHS have shown that ANC uptake is higher than might initially be expected in countries in SSA, with 72% of women reporting at least one prenatal visit and 43% reporting four or more between 2005 and 2009 [131]. In two countries with generalized HIV epidemics (Namibia and Rwanda) 95% or more of women reported at least one visit. In nine countries, (Botswana, Kenya, Lesotho, Malawi, Mozambique, South Africa, Uganda, Zambia and Zimbabwe), uptake ranged from 90% to 94%. Not all countries have been as successful at promoting the use of prenatal services. In Ethiopia and

Nigeria, only 28%, and 58% of women, respectively, reported attending at least one prenatal visit.

Socio-demographic factors associated with increased uptake of prenatal care in countries in SSA with generalized HIV epidemics have included higher education, being married, higher income, being employed, and having a history of obstetric complications [130, 132]. Age has also been associated with increased uptake, except among the youngest women (below aged 20 years) and older women (above aged 35 years) [130]. Women from urban areas have also been reported to be significantly more likely to use ANC services than women from rural areas [130, 132]. Higher parity and higher birth orders were negatively associated with use of ANC services, although not consistently [130, 132]. With the exception of being married, all of the above factors have also been shown to be associated with higher levels of HIV infection in SSA [51, 120, 133-135]. This latter finding suggests that, on average, ANC surveillance data might overestimate HIV prevalence due to self-selection bias, even among recently pregnant women in the surrounding community.

However, in the only study comparing HIV prevalence estimates of ANC attendees and recently pregnant women from the surrounding clinic catchment areas, which occurred in rural Manicaland, Zimbabwe, ANC surveillance data were actually found to underestimate HIV prevalence among recently pregnant women (21.7% in the ANC surveillance data versus 25.7% in recently pregnant women) [55]. The authors suggested that the most likely explanation for this difference was that women from rural areas with lower HIV prevalence were visiting clinics in towns where HIV prevalence was higher. Many of these women reported attending clinics in urban areas because they perceived that an urban clinic would offer better

services or because the clinic was located near an urban market that they also visited routinely.

Based only on this single study, and given the paucity of other studies to assess the associations between ANC uptake and HIV infection, it is difficult to generalize broadly about the magnitude or the direction that bias due to self-selection might exert on ANC surveillance estimates. At the national level, WHO recommends that countries carefully monitor changes in the socio-demographic characteristics of pregnant women participating in ANC surveillance or who report attending ANCs in DHSs to ascertain if self-selection biases are changing.

Although not specifically related to access to ANC uptake, socio-demographic factors associated with HIV infection and differently distributed between ANC clinics and the population have also been reported to have introduced a bias in ANC estimates. For example, in Zimbabwe, differences in the age structure and religious affiliations of ANC and study population participants in two areas of Manicaland exaggerated differences in HIV prevalence estimates from ANC clinics since women in their 20s with high HIV prevalence were over-represented in the ANC clinic, while women of apostolic faith with low HIV prevalence were under-represented [122]. Standardization of the estimates to the local population age distribution partially removed these differences, reducing prevalence in one of the areas from 24.3% to 18.4%. Differences in the distribution of age between ANC and population survey participants is common throughout sub-Saharan Africa, and as a result, comparisons of estimates between community and female population prevalence estimates is usually done adjusting for differences in age distributions between the two populations [48, 50, 51, 53, 56, 136]. As noted by Zaba [42] and Gregson [113], however age standardization can have the effect of reducing ANC estimates even

further by giving more weight to lower HIV prevalence among older pregnant women than what would have otherwise occurred in the crude estimates. As a result, age-standardization is not always appropriate when comparing ANC and female HIV prevalence estimates.

In addition to age, other socio-demographic factors in SSA that have been differently associated with HIV prevalence in ANC attendees as compared to sexually active women generally have included: marital status [51, 53], education [48, 116, 137, 138] and having moved within the last five years [53]. Women attending from rural areas, where HIV prevalence is typically lower, has also been identified as a factor in differentially biasing ANC estimates relative to the female population [138]. Various factors related to the use of contraception and other aspects of a woman's fertility history have been associated with bias in many of these studies, and these factors are discussed in more detail in the section below.

2.2.3 The effect of testing only women who become pregnant

In SSA, women's fertility rates are among the highest in the world, with an average total fertility rate (TFR) of 5.0 children per woman in 2009 [131]. Exceptions to these higher rates include countries such as Botswana, South Africa, Lesotho and Zimbabwe, where TFRs ranged from 2.5 to 3.5 children per woman [131]. In part, these lower fertility levels represent an underlying demographic transition independent of the HIV epidemic [139]. However, these lower fertility rates also reflect the high levels of HIV prevalence in these populations, which has tended to suppress overall fertility rates in HIV-infected women.

The extent to which HIV influences fertility in the population was heavily studied in countries in SSA so as to be able to interpret and predict how the demographic structure and economic security of the population might be changing as the epidemic grew [47, 113, 114, 138, 140-143]. At the community level, household-based population surveys from six countries in SSA in the early and mid-1980s showed TFRs that were from 25% to 40% lower in infected as compared to uninfected women [47]. These lower fertility levels among HIV-infected women resulted in estimates of HIV prevalence at ANCs that were 5% lower (ranging from 2% to 8%) than estimates of HIV prevalence in the surrounding female population. A subsequent review in 2004 of 19 settings also in SSA showed similar findings, with a population-attributable decline in total fertility of 0.37% (95% CI: 0.30% - 0.44%) for each percentage point increase in HIV prevalence [114]. More recently, using DHS data collected from 20 countries between 2003 and 2008, the age-specific fertility rate (ASFR) was higher for HIV-infected as compared to uninfected women aged 15 to 19 years (ASFR ratio: 1.20) but it then declined with increasing five year age intervals for women aged 20 to 44 years (ASFR ratio: 0.76, 0.71, 0.65, 0.59 and 0.53) [144].

In each of the studies summarized above, the authors highlighted the specific role that (i) selection for high-risk sexual activity, (ii) varying levels of contraceptive use, and (iii) sub-fertility in HIV-infected women might play in biasing ANC surveillance prevalence estimates. The potential direction and magnitude of these biases are explored in the sections which follow.

2.2.3.1 Selection for high-risk sexual activity

Comparisons of HIV prevalence estimates from ANC surveillance data and those estimates obtained from population surveys show that ANC data frequently overestimate HIV prevalence in women aged 15 to 19 year in SSA [117]. The primary reason for this is that many young women have little or no sexual experience, and therefore are highly unlikely to become pregnant or infected with HIV. However, the select group of young women who have initiated sex are at a much higher risk of HIV infection given that they often choose older men as partners, who are more likely to be infected [145-147]. These women also report less consistent use of condoms and other contraception, and thus are more likely to become pregnant [146, 147]. In a study in rural Tanzania, HIV-infected women aged 15 to 19 years had fertility rates that were 40% greater than uninfected women of the same age [54].

As evidence for the effect of selection for high risk sexual activity among young women on ANC-based estimates, HIV prevalence among pregnant women aged 15 to 19 years in Manicaland, Zimbabwe from 1998 to 2000 was more than twice that of females of the same age group in the surrounding population (15.7% among ANC attendees versus 7.0% in all women) [55]. Similar age-specific disparities among women aged 15 to 19 years have also been reported in, Zambia [116], eastern Malawi [53] and South Africa [56]. Using national DHS and ANC surveillance data, this bias can also be observed among women in the broader 15 to 24 year age group in Ethiopia, Malawi, Tanzania and Uganda [46] Typically, the later the age of sexual debut in a country, the more ANC surveillance will overestimate female population prevalence among those aged 15 to 19 years and 15 to 24 years also [117].

Although selection for sexual activity primarily introduces an upwards bias in ANC estimates among younger women, the opposite (i.e., a downwards bias) can occur in some countries for estimates among older women. In this latter group, HIV-infected women who have been widowed or divorced may either choose or are strongly encouraged through societal norms to not remarry or re-initiate sexual activity after losing a partner. As a result, they will be excluded from the ANC sample because of selection biases for sexual activity. Since the proportion of older women who are currently divorced or widowed in SSA is relatively small though, the influence of this bias is likely to be minimal. In practice, ANC surveillance estimates are typically biased downwards for older women because of the biological effect of HIV on fertility, and to a lesser extent, higher levels of contraceptive use at older ages. These scenarios are reviewed in more detail in the following two sections.

2.2.3.2 Contraceptive use

Contraceptive use among women has been shown to bias ANC prevalence estimates in SSA [55, 56]. The magnitude and direction of the bias depends on the type of contraceptive used -- either barrier (e.g., condoms) or hormonal (e.g., pills, injections, intrauterine devices) -- and the context in which they are used; that is, either at high- or low-risk encounters. These different facets of contraceptive use and their influence on HIV prevalence estimates from ANC surveillance data are discussed here separately.

In the case of barrier contraceptive use, studies have shown that condom use within stable partnerships is infrequent in SSA, where risk of HIV transmission is believed to be low and strong cultural norms make their use in such partnerships

unacceptable [148-151]. Conversely, condom use during high-risk or casual relationships has increased greatly since the start of the epidemic in SSA [152]. As a result, women engaging in higher-risk behaviour will be under-represented in ANC surveillance relative to women in lower-risk, stable relationships. In turn, ANC prevalence estimates will be biased downwards relative to those in the surrounding female population due to the exclusion of these women at higher risk.

An alternative, albeit less likely scenario, is that women begin using condoms at the start of sexual activity (when the likelihood of a previous infection is very low) and that they continue using condoms until they enter stable relationships and decide to become pregnant. Using a mathematical model, Gregson and colleagues demonstrated that, in this situation, HIV prevalence levels from ANC surveillance would overstate those in the community, since only higher risk women not consistently using condoms would be susceptible to pregnancy and HIV [113]. This model also highlighted the fact that ANC prevalence as compared to HIV prevalence in the surrounding female population will be more sensitive to increasing condom use.

Use of contraceptives other than condoms, such as hormonal pills, injections or intrauterine devices, has typically been limited throughout SSA. In some countries, however, including Botswana, South Africa, and Zimbabwe, between 50% and 65% of sexually active women have reported using these types of contraceptives [131]. In these settings, hormonal contraceptive use has frequently been a marker of low- rather than high-risk activity by women since contraceptives are frequently used within stable partnerships to reduce unwanted pregnancies or to space out births [153]. When young women use contraception effectively and at high levels, ANC surveillance prevalence estimates will over-estimate population HIV prevalence

because only high-risk women will be at risk of infection and pregnancy [55, 56, 153]. As Gregson and colleagues showed, this over-estimation also will persist among older age groups [55]. In one of the more extreme examples of this tendency, HIV prevalence estimates among women aged 30 to 34 years at six urban and peri-urban ANC clinics was 51.7% compared to 47.0% in the surrounding female population in KwaZulu-Natal, South Africa [56]. Among women aged 35 and older, the ANC surveillance estimate was 36.5% compared to 27.7% in the female population. Contraceptive use in the study area exceeded 50% in both age groups, and was identified as one possible explanation for the higher ANC estimates. Other sources of bias that might have contributed to this discrepancy include (i) the unrepresentative selection of ANC clinics, (ii) under-reporting of pregnancies within the study area, and (iii) the inclusion of women from outside the clinic catchment area at higher risk of infection.

When hormonal contraceptive use is low in a population, as it is throughout most of SSA, only those women most at risk of pregnancy will be motivated to regularly use contraceptives (hormonal or otherwise). Since hormonal contraception does not prevent transmission of HIV, however, ANC surveillance prevalence estimates would likely under-represent HIV prevalence in the female population, especially if women rely heavily on hormonal methods.

One final, more recent concern that has yet to be fully measured with regard to its potential impact on the representativeness of ANC surveillance estimates is the extent to which hormonal contraceptive use may place women at a greater risk of either acquiring HIV or experiencing more rapid disease progression [154]. If hormonal contraceptives are found to increase susceptibility or exacerbate illness, this association could result in an under-representation of HIV prevalence in the

population due to the exclusion of HIV infected women from ANC surveillance. This exclusion could occur either through the use of hormonal contraception to prevent pregnancy or through HIV-related sub-fertility due to biological or behavioural causes, as discussed further in Section 2.2.3.3.

Although early studies have found mixed evidence for the influence of contraceptives on HIV susceptibility and disease progression [154], a rigorous seven country study in SSA conducted from 2004 to 2010 has provided convincing evidence for a significant positive association between hormonal contraceptive use and HIV acquisition. In the study, female partners in serodiscordant couples using injectable and oral contraceptives were nearly twice as likely as non-users to become infected during the study period (adjusted hazard ratio: 1.98; 95% CI: 1.06-3.68) [155]. Although a major limitation of the study was that it relied on self-reported contraceptive use, the majority of women were using long-acting injectable hormones which, unlike daily oral contraceptives, would have been subject to fewer adherence issues. Also, HIV sero-conversion was highest in the group using injectable hormones.

In summary, because of the variety of contraceptive methods and manners in which they could introduce bias into ANC surveillance prevalence estimates, specific knowledge of these practices in a community and more information on the biological mechanisms through which contraceptive use influences HIV infection will be required. Additional information is also needed about the role that contraceptive use plays in either protecting or increasing the risk women have from acquiring HIV, along with better data on the magnitude of bias in estimates that is likely to occur because of this factor.

2.2.3.3 Sub-fertility due to HIV and other STIs

As discussed in Section 2.2.3, HIV infection has been associated with a range of adverse reproductive health outcomes, which can lead to lower fertility rates in HIV-infected women. The biological reasons for this are twofold. First, HIV-infected women may experience more difficulty than uninfected women in becoming pregnant. In a study of sequelae from HIV infection in 15 hospitals throughout Uganda, 26% of women reported amenorrhea due to severe weight loss from advanced infection [156]. Reductions in spermatozoa by HIV-infected male partners and reduced coital frequency in individuals with advanced HIV disease may also lower the likelihood of conception among HIV-infected women [113].

Second, where pregnancy does occur, spontaneous abortion, stillbirth and perinatal mortality have each been found to occur more frequently in HIV-infected as compared to uninfected women [157, 158]. Importantly, the risk of foetal loss has also been observed to increase as time since infection increases [158, 159]. Additionally, a history of, or co-infection with, bacterial STIs has also been identified to adversely impact a woman's fertility, although the strength of this association has depended on the type of STI [153, 160-162]. In a community-based study in Rakai, Uganda, HIV-infected women with syphilis were 1.5 times less likely to be pregnant as compared to HIV-infected women without syphilis [161]. However, neither gonorrhoea nor trichomonal infection were found to reduce the prevalence of pregnancy in this population. In another Ugandan study, a current bacterial STI co-infection had no significant impact on pregnancy rates, but previous bacterial STI infections were thought to be responsible for at least 50% of the total sub-fertility in HIV-infected women [162]. When left untreated, bacterial STIs can cause pelvic inflammatory disease, which in turn can cause twice the number of ectopic

pregnancies in women with histories of infection [160]. Where bacterial STI infections are infrequent in a population though, fertility differences among older HIV-infected and uninfected women will be reduced [153].

As a result of HIV-related sub-fertility, ANC surveillance prevalence estimates are typically lower than population prevalence among older women [55, 153], except as previously noted in South Africa and in Zimbabwe [55, 56, 108]. Most recently, in a comparison of DHS and ANC surveillance prevalence estimates from 2002 through 2005 from four countries (Ethiopia, Malawi, Tanzania and Uganda), HIV prevalence among women aged 35 years and older attending ANC surveillance clinics was 1.3 to 2.5 times lower than prevalence among women of a similar age living in the clinic catchment areas [46]. In part, these lower levels of HIV prevalence at ANC clinics could arise from the concentration of HIV infection among older ages as incidence falls and survival due to ART increases. The impact of expanding ART use on fertility patterns and ANC surveillance prevalence estimates are discussed further in Section 2.3.3 and in Chapter 4.

One final consideration regarding HIV-related sub-fertility is that, in its absence, HIV prevalence estimates among ANC attendees would almost always overstate female prevalence because HIV prevalence is highest in women with the highest fertility [115]. Typically, women aged 15 to 24 years represent half of all ANC attendees in SSA clinics. Among those women aged 15 to 24 years, however, the majority will be aged 20 to 24 years (except in settings where the age of sexual debut is very early) [117]. Along similar lines, there is also some evidence that pregnant women are at higher risk of HIV infection during their pregnancy, either due to behavioural or biological changes [163]. The influence of this factor on ANC estimates is likely to be minimal, provided the infection can be detected at ANC

surveillance clinics. If infection is too recent to be detected, ANC surveillance estimates will under-represent HIV prevalence among females generally.

2.2.4 Summary of bias in ANC surveillance HIV prevalence estimates

Table 2.1 summarizes the primary sources of bias that can influence the accuracy of HIV prevalence estimates from ANC surveillance data in SSA and their expected impact on the direction of bias in ANC estimates. These biases operate at multiple levels, however, so the relationship between ANC surveillance and estimates of HIV prevalence in the population can vary. At the national level, the most frequently documented bias in ANC estimates due to over-representation of urban clinics has historically resulted in an overstatement of prevalence in the population [43, 45, 46, 109], although more recent studies in a few countries, including Uganda and Zimbabwe, have found these estimates to be relatively similar [108, 110]. In contrast, when compared to women in the surrounding population, bias due to self-selection and testing only pregnant women more often results in an underestimate of HIV prevalence [42, 51-53, 137]; however, this relationship has been observed to vary by setting and especially for those areas with low fertility and high contraception levels, such as South Africa [56] and Zimbabwe [55, 108].

Type of bias	Factor	ANC attendance at clinic(s) relative to the female population	Direction of bias
Clinic selection*	More urban sites included in sample [45, 46]	More HIV-infected ANC attendees	ANC >POP
	More ART/PMTCT sites included in sample [123]	More HIV-infected ANC attendees	ANC>POP
Self-selection†	Socio-demographic characteristics (age, education) are associated with attendance at ANC clinics and HIV infection [51, 53, 122, 137, 164]	May work in either direction depending on factor	Depends on local context
	Women with planned pregnancies (at lower risk of HIV) attend ANC clinics [154, 155]	Fewer HIV-infected ANC attendees	ANC<POP
	Women from rural areas attend urban ANC clinics [55, 56]	Fewer HIV-infected ANC attendees	ANC<POP (in urban areas)
Testing only women who become pregnant†	Young women who have an early age of sexual debut are at higher risk of HIV infection and pregnancy than virgins[117]	More HIV-infected ANC attendees	ANC>POP (at younger ages)
	Some older, higher risk women stop having sex [113, 165]	Fewer HIV-infected ANC attendees	ANC<POP (at older ages)
	Condoms or hormonal contraceptives are used primarily by women at high risk [47, 113]	Fewer HIV-infected ANC attendees	ANC<POP
	Condoms or hormonal contraceptives are used primarily by women at risk [47, 113]	More HIV-infected ANC attendees	ANC>POP
	Hormonal contraceptives may place women at increased risk of infection [154, 155]	Fewer HIV-infected ANC attendees	ANC<POP
	HIV-infected women have reduced fertility with greater time since infection [158, 159]	Fewer HIV-infected ANC attendees	ANC<POP (at older ages)
	High prevalence of bacterial STIs in the population [115, 153]	Fewer HIV-infected ANC attendees	ANC<POP
	Peaks in natural fertility patterns overlap with patterns of HIV infection by age [115, 153]	More HIV-infected ANC attendees	ANC>POP
	Women who are pregnant may be more susceptible to HIV infection [166]	More HIV-infected ANC attendees (so long as infection is detectable)	ANC>POP

* Refers to comparisons of ANC surveillance including all clinics and the general female adult population aged 15 to 49 years in a country

†Refers to comparisons of ANC surveillance prevalence estimates from a single clinic and the general female adult population aged 15 to 49 years in the surrounding catchment area

Table 2.1 Selected factors common to the HIV epidemic in SSA and their expected impact on bias in ANC estimates.

For the most part, bias due to clinic selection and self-selection has been dealt with by making informed decisions about how ANC surveillance data are used. For example, the seemingly intractable problem of overestimating overall population prevalence due to non-representative clinic selection has led UNAIDS to discourage use of ANC surveillance data for this purpose [18]. In the case of self-selection biases, the WHO recommends that countries monitor DHS and the socio-demographic data from individual ANC surveillance clinics to look for potential factors that may differentially include or exclude women from accessing ANC depending on their HIV status [39]. When evidence suggests that an ANC clinic becomes unrepresentative of the population living in the catchment areas that surround it, possibly due to a shift in the economic welfare of a community or the influx of migrants, countries are advised to consider excluding these clinics from further analyses [39].

Bias from testing only pregnant women is not so easily dealt with because it depends on a complex and interwoven set of biological and behavioural factors that, at a minimum, can vary from woman to woman, and will most definitely vary from community to community. Section 2.4, however, summarizes adjustment methods that have been proposed to address these biases due to HIV-related fertility differences while, in the next section, Section 2.3, the potential for biases to change over time as a result of changes in the natural dynamics of the epidemic and behaviour change is considered .

2.3 Bias in HIV prevalence trends from ANC surveillance data

As previously mentioned in Chapter 1, relative to the literature describing the overall levels of bias in ANC surveillance estimates, there are remarkably few studies quantifying bias in ANC surveillance trends. From the previous search strategy described in Section 2.1, the 746 articles originally identified there were reviewed for their contribution to describing bias in ANC trends. In summary, seven articles were identified, of which four described mathematical models exploring bias [27, 113, 115, 117], two related results from comparisons of ANC and population prevalence trends from two community-based studies in Lusaka, Zambia and Kigera, Tanzania [50, 116] and one provided data on trends among youth aged 15 to 24 years in South Africa, Zambia and Zimbabwe [21].

Of the four modelling papers, Garnett [115] and Zaba [117] quantified bias in ANC data over time as one of the primary objectives of the study, whereas models by Hallett [27] and Gregson [104] only briefly explored this topic as part of a larger effort to assess how changes in sexual behaviour could influence population prevalence over time. The model by Zaba focused exclusively on women aged 15 to 24 years whereas the model for Garnett reported results for women of all reproductive ages. The two empirical studies occurred in smaller communities, with comparisons made to adult females and males separately and to the adult population overall. The other study explored differences in national-level estimates. Each of these studies is discussed in further detail in Sections 2.3.1 and 2.3.2 related to (i) changes in the natural dynamics of the epidemic (which can alter the age-structure of HIV-infected women in the population with time) [50, 115], and (ii) changes in patterns of behaviour (such as increases in age of sexual debut or

condom use, due to the scale-up of effective prevention interventions) [27, 113, 116, 117]. These studies are also summarized in Supplemental Table 2.3 in Appendix A.

One challenge that arises with regard exploring the current or future potential for bias in ANC estimates is that all of the seven studies identified above were conducted prior to the wide-scale introduction of ART in the regions. As suggested in Chapter 1, however, it is possible that ART could influence the fertility patterns of HIV-infected women through a variety of biological and behavioural mechanisms, and thereby introduce a temporal bias in ANC trends. The potential for this bias over time, which is as yet unmeasured in any study, is considered in Section 2.3.3. Four studies that have explored or documented the influence of ART on fertility patterns in SSA [165, 167-169] are described alongside other articles that document changes in factors due to the introduction of ART that could influence bias in ANC trends. Table 2.2 summarizes what is currently known according to the models and empirical evidence from these studies, and in the case of ART, what effect might be expected as access to therapy expands in SSA.

2.3.1 The natural dynamics of the epidemic

As discussed in Section 2.2.3.3, if not for HIV-related and other STI-related sub-fertility, HIV prevalence among ANC attendees would rise more rapidly than population HIV prevalence and remain at a higher level throughout the epidemic because prevalence of HIV is typically highest among women with the highest fertility rates. Due to HIV-related sub-fertility, however, ANC estimates are almost always lower than female prevalence estimates in the community. Nevertheless, variations

in the magnitude of bias in ANC prevalence trends can still occur as the average age of HIV-infection among women in the population changes.

In the mid-1990s, Garnett and Gregson developed an age-structured mathematical model of HIV transmission via heterosexual transmission to explore how changes in the natural dynamics of infection, including changes in the age of HIV-infected women and fertility patterns could influence the representativeness of ANC trend data. In the model, HIV prevalence among pregnant women and the general female population aged 15 to 49 years were compared during the first 30 years of a generalized HIV epidemic typical of SSA [115]. The model stratified the population by sex, sexual activity levels, and age. Age-specific fertility levels associated with HIV-infection, as compared to those among uninfected women, were assumed to be either 30% lower or progressively reduced from 10% to 25% to 60% to 80% until AIDS. An additional 50% reduction in fertility among women with the highest level of sexual activity was incorporated to represent morbidity due to pre-existing STIs and early mortality in the high-risk population.

Results from the model showed that, in the epidemic initially, the average age of the infected woman increased, which led ANC surveillance prevalence estimates to increase relative to female population prevalence over time. Gradually, however, as the average age of HIV-infected women increased beyond peak fertility ages, this overestimation would decline. At the same time, however, bias due to HIV-related sub-fertility and a reduction in fertility due to other STIs in high-risk groups was shown to result in an opposing underestimate of HIV prevalence in the population. As a result of these opposing biases, which cancel each other out, the authors suggest that ANC surveillance data would be reasonably representative of female population prevalence trends in SSA with similar fertility patterns and transmission

patterns. They also note, however, the potential for these biases to change over time depending on the extent to which HIV incidence might become concentrated in one age group as opposed to another, as an example.

An empirical study of bias in ANC trends, conducted under similar circumstances as those used to parameterize the Garnett and Gregson model, was carried out in the rural Kagera region of Tanzania in the early to mid-1990s [50]. The study findings also showed that ANC surveillance prevalence estimates may have been differentially biased over time, but not drastically so. It was suggested that the reasons why these biases were not more dramatic was because declines in prevalence occurred largely before large-scale prevention interventions reached the community [116]. Behaviour change and their influence on bias in trends in HIV prevalence among pregnant women are discussed in the following section.

2.3.2 Behaviour change

One of the key assumptions in the mathematical model by Garnett is that HIV incidence in the population remained relatively stable after the early and steep rise when the epidemic took off [115]. Similarly, in the Tanzania study, there was no apparent decline in incidence; instead, declines in prevalence were thought to have occurred due to high levels of mortality in the population [136]. When HIV incidence declines with time because of the expansion of effective behaviour change interventions, however, it is possible that these programmes may have a different influence on HIV prevalence among the ANC population than the population more generally. As a result, ANC estimates may be increasingly or decreasingly biased

over time. The magnitude and direction of the change in this bias will depend, in part, on the type of intervention responsible for introducing these declines.

In SSA, behaviour change campaigns have focused primarily on three approaches: abstinence (i.e. delay in sexual debut), faithfulness among married or cohabitating couples, and condom use at high-risk sexual encounters [27]. To investigate the impact of reductions in incidence due to delays in sexual debut and increased condom use among young women, Zaba and colleagues developed a mathematical cohort projection model that compared ANC and population surveillance estimates for young women aged 15 to 24 years over a 25 year period of a generalized epidemic [117]. The model included three scenarios in which declines in HIV incidence resulted from (i) reduced transmission due to changes in sexual activity (i.e., condom use and less risky partner selection), (ii) delays in sexual debut, and (iii) both reduction due to less risky sexual behaviour and delays in sexual debut [117].

As expected, biases in ANC estimates due to declines in transmission resulted in generally stable biases throughout the course of the epidemic. This was the case for the period of time when incidence was declining because, at young ages the limited influence of HIV-related sub-fertility and mortality excludes very few HIV-infected women from ANC surveillance. In the latter two scenarios, in which interventions led to rapid and substantial delays in sexual debut alone or in combination with reductions in risky behaviour, bias in ANC prevalence trends was particularly unstable. In both scenarios, HIV prevalence among pregnant women continued to rise even after the decline in incidence in the population was observed because the proportion of women who had been sexually active for a relatively long time initially increased as fewer younger women started sexual activity. After some

years, those who experienced the earlier pattern of sexual debut cease to dominate the population of pregnant women aged 15 to 24 years and are replaced by pregnant women with sexual activity that reflect the new, later pattern of age at first sex and the lower rates of transmission. Because women overall in the ANC population aged 15 to 24 years were still somewhat older than their peers in the corresponding age group, ANC prevalence trends were still higher than those in the population.

Gregson and colleagues also briefly explored the potential for increased condom use over time to introduce bias in ANC estimates within an age-structured cohort model [113]. In this case, the scale-up of condom use in the population was not limited to young people alone. Results from the model suggested that, as condom use increased over time and incidence declined, ANC surveillance would fail to capture the full extent of this decline because riskier women having unprotected sex would still be at risk of pregnancy. In Lusaka, Zambia, a study in a single urban clinic comparing trends in ANC surveillance and population survey estimates found that ANC trends under-estimated declines in prevalence in the population from 1995 to 2003 [116]. The authors show that the reason for this was changing fertility and education patterns among younger women.

2.3.3 ART use

Because of the relatively recent introduction of ART in SSA, there is limited understanding of how and to what extent treatment programmes could impact fertility patterns, and in turn, biases in ANC trends. Of the three studies that have explored the interaction between ART and fertility in SSA to date, two have reported increases in fertility rates among users [167, 168] while the third showed a negative association

[169]. If fertility rates among ART users rebounded as access to ART expanded, bias in ANC estimates relative to the population would be expected to decline since fewer HIV-infected women would be excluded. If, on the other hand, fertility rates among ART users declined further, possibly due to increased use of contraception, bias in ANC trends would become even greater with time.

In the first study offering evidence for a positive association, a significantly higher overall fertility rate among ART users compared to HIV-infected non-ART users (adjusted hazard ratio: 1.74; 95% CI: 1.19-2.54; median duration on pre-ART: 482 days; post-ART: 696 days) was found in six countries in SSA [167]. Fertility rates among ART users were also found to increase with time, in contrast with the stable and lower pregnancy incidence rates observed among HIV-infected treatment-naïve women. In the second study in eastern Uganda, pregnancy incidence among ART users was found to increase (p-value for linear trend over the 27 month study period: <0.001) even though 93% of ART users expressed no additional desire for children [168].

In the single study showing a negative association, ART users in western Uganda had fewer recognized pregnancies (OR: 0.56; 95% CI: 0.33-0.95) and live births (OR: 0.30; 95% CI: 0.13-0.66) compared to treatment-naïve women, but they did report a relatively greater fertility desire (OR: 2.99; 95% CI: 1.38-6.28) [169]. As ART had only been recently introduced at the time of the study, it is possible that fertility intention outpaced improvements in health, and that the direction of this association could change over time.

These findings somewhat contradict the early experiences of introducing ART in the US and Europe. In an early cohort of HIV-infected women in the 1990s, the introduction of ART appeared to have no impact on age-adjusted pregnancy

incidence trends [170]. Two studies in the US also showed lower incidence of pregnancy among women on ART compared to those that were not [171, 172]. Still, researchers noted a 20% increase in pregnancy among HIV-positive women (independent of ART status) from the 1992-1996 pre-ART period to the 1998-2001 ART period in the US, suggesting that women may have a more positive outlook toward pregnancy after seeing improvements in the quality of life and life expectancy of women on ART [171].

In 2006, recognizing the limited research on the impact of ART on fertility patterns, particularly in SSA, Kaida and colleagues suggested a framework for exploring this interaction [141] based on Bongaarts' proximate determinants of fertility model [173]. The extension of this framework was based on a previous adaptation of Bongaarts' model considering the impact of HIV on fertility in 1994 by Gregson [141]. Kaida's framework could be extended even further to explore possible changes in bias in ANC-based HIV prevalence estimates that might result from the introduction of ART over time. These changes can be considered within the original structure of biases observed from testing only those women who become pregnant, namely: (i) selection for sexual activity, (ii) varying levels and types of contraceptive use, and (iii) sub-fertility due to HIV-infection and other STIs. A brief discussion on bias related to self-selection due to ART and PMTCT programme scale-up follows the discussion of the first three types of bias related to testing only women who become pregnant.

2.3.3.1 Selection for sexual activity

The impact of ART on selection for sexual activity among youth is largely unknown. On one hand, it is possible that young people may be influenced by the availability of ART to increase the riskiness of sexual behaviour. On the other hand, the availability of ART is unlikely to be the only driver of the decision about whether or not to begin having sex or to marry thus would not likely have a large influence on ANC trends. . Regarding marital status at older ages, however, it is possible to consider a scenario where ART increases the reproductive lifespan by extending the quantity and the quality of years that an HIV-infected women stays in a partnership [165]. The impact of an extended reproductive lifespan could reduce some of the sub-fertility biases observed among older women, while bias in the youngest women (aged 15-19), who are unlikely to be married, would remain unaffected. As a consequence of these changes in fertility, it is unlikely that bias would change over time at the youngest ages so long as risk dis-inhibition was not a factor. However, among older women, bias in ANC surveillance trends could decline as the length of monogamous relationships increases, thereby increasing fertility.

2.3.3.2 Contraceptive use

The impact of ART on fertility and contraceptive choice, including induced abortions, is still unknown in SSA. In theory, women on ART or with access to PMTCT may choose to become pregnant based on the potential health benefits of treatment and prophylaxis for their unborn child. In addition, societal pressures to conceive may also greatly encourage pregnancies to replace children who died from HIV infection. At the same time, some women on ART may still consider the risk of

orphaning children too great or may be in a serodiscordant relationship [165]. In this latter scenario, fertility patterns may remain unchanged, even in light of the introduction of ART or PMTCT services. Ultimately, whether women on ART preferentially choose to use or avoid contraception will impact biases in ANC estimates, but it is difficult to predict the direction and magnitude of this bias. If bias does change with time due to changes in contraception, it would likely have little effect on the youngest women. In older women, depending on existing contraception levels and types, the effects of increasing hormonal contraception due to better linkages with family planning could be cancelled out by the reduction in contraceptive use that might occur from women wishing to become pregnant [174].

2.3.3.3 Sub-fertility due to HIV and other STIs

Given that access to contraception was low in the three studies thus far, it is likely that sub-fertility or rebound fertility is occurring due to improvements in health. In addition, more frequent access to health care systems could lead to earlier treatment of STIs, thus preventing pre-infection infertility. Finally, healthier women (and their partners) may also increase coital frequency, thereby further increasing the likelihood of pregnancy. Whether women might choose to breastfeed longer on ART, thereby decreasing fertility, or whether they continue to follow recommendations for a shortened breastfeeding period is unknown [165, 175].

Despite the potential decline in fertility owing to extended breastfeeding, it is possible that health-related improvements from ART could result in significant increases in fertility among HIV-infected women, particularly in women who have been infected longer where sub-fertility is greatest. In turn, ANC estimates of HIV

prevalence for these women could increase with time, reflecting not an actual increase in underlying HIV prevalence but rather fertility resumption or prevention of STI-related infertility.

Although the rationale for why biases could change with time is clear, whether these biases will be sufficiently large to distort ANC surveillance estimates is not so obvious. For example, if the benefits of ART occur most among women who have been infected longest, these women are also likely to be relatively older, thus a return to fertility in this age group may cause relatively small increases in the number of HIV pregnant women appearing in ANC clinics. Still, as Lee found, HIV-related fertility declines do begin to occur almost immediately after the onset of infection [159], suggesting that ART may benefit younger women as well as older women. Research from Braitstein and colleagues has also shown that women are more likely to access ART when they are younger and healthier, thus potentially preventing substantial HIV and STI-related sub-fertility and infertility [176]. Accounting for these relationships, once again, it is unlikely that the introduction of ART would introduce any biases into ANC trends among younger women. However, among older women, bias in ANC estimates could decline over time if natural fecundity increases; thus, ANC and population estimates should converge over time

2.3.3.4 Self-selection due to ART and PMTCT programme scale-up

As previously discussed, access to ART programmes, including PMTCT services, is increasing in many countries in SSA. Nonetheless, the scale-up of services has not always been geographically equitable owing to the limited availability of trained health care personnel and access to adequate laboratory infrastructure. As a result,

many clinics participating in ANC surveillance will have initiated ART or PMTCT services in the last three to five years, while other clinics may still be waiting to begin. As previously mentioned, in large part, this scale-up has occurred fastest in urban areas, with rural access to PMTCT and ART services lagging somewhat behind [177].

Fragmentation in the availability of services means that some women may seek prenatal services further away from their home if HIV-related services are not available at their nearest clinic. If ANC surveillance prevalence estimates come from sites that offer HIV services, they could preferentially attract HIV-infected women from outside the catchment area, which could lead in turn to an artificial increase in ANC-based HIV prevalence estimates over time. Conversely, declines in HIV prevalence from women at non-PMTCT sites could reflect the fact that women are choosing to access prenatal care elsewhere where HIV services are offered.

2.3.4 Summary of the potential for bias in ANC surveillance HIV prevalence trends

Table 2.2 summarizes the potential for bias in ANC surveillance trends due to changes in the natural dynamics of infection, behaviour change interventions, and the influence of introducing ART and PMTCT in the population.

Factor	Factor	Impact of factor on ANC attendance at clinic(s) over time	Expected direction of bias in ANC surveillance trends over time relative to the population
Natural change in the epidemic[115]	Average age of HIV-infected women increases	Increasing number of HIV-infected ANC attendees over time until the average age of the infected woman reaches the peak age of fertility	ANC HIV prevalence trends move toward population prevalence trends
		Decreasing number of HIV-infected ANC attendees over time after the average age of the infected women surpasses the peak age of fertility	ANC HIV prevalence trends move away from population prevalence trends
Behaviour change [27, 113, 116]	Increased condom use among youth	No change	Stable trends
	Delays in the age of sexual debut	Proportion of ANC attendees who are HIV-infected increases over time	ANC HIV prevalence trends move away from population prevalence trends until sexually active women age out and are replaced by lower risk women
	Increased condom use at all ages	Proportion of ANC attendees who are HIV-infected increases over time	ANC HIV prevalence trends move away from population prevalence trends
Introduction of ART (Based on HIV-related impact on determinants of fertility [140, 165, 173])	Length of span of marriage increases	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends
	ART leads to more partnerships or dis-inhibition	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends
	Increase in hormonal contraception due to family planning linkages	Decreasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move away from population prevalence trends
	Contraceptive use decreases as HIV-infected women increase fertility demand	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends
	Natural fertility returns	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends
	Better reproductive health care reduces influence of STIs	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends
	Increased number of women breastfeeding or period of time increased	Decreasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move away from population prevalence trends
	Increased coitus	Increasing number of HIV-infected ANC attendees	ANC HIV prevalence trends move toward population prevalence trends

Table 2.2 Selected factors common to the HIV epidemic in SSA and their expected impact on bias in ANC trends.

With regard to the introduction of ART, it is worth emphasising that these biases in ANC surveillance trends are only hypothesized, as the interaction between ART and fertility use over time is still unknown. With regard to the potential biases in ANC estimates as a result, it is also important to remember that changes in population HIV prevalence will also be occurring as a result of increased survival on ART and reductions in transmission. Consequently, the overall size of the reductions or increases in bias will be relative to whether and by how much population HIV prevalence is increasing or decreasing.

2.4 Adjusting for bias in ANC surveillance estimates and trends

Standardized methods to correct for differences in HIV prevalence estimates and trends between ANC surveillance and the population have been proposed since early on in the epidemic when data on infections in the population overall were scarce [178]. These methods primarily attempted to account for (i) fertility differences between HIV infected and uninfected women, which resulted in lower estimates of HIV prevalence in the female population in some locations; and (ii) inadequate geographic representativeness of ANC surveillance data, which often resulted in an overestimate of prevalence in the population. Controlling for differences due to the distribution of other demographic characteristics associated with uptake of ANC services and HIV infection may also benefit from standardization, although these factors were found to vary by setting [51, 53].

For those adjustment methods that have been proposed relating to fertility differences, the approach, their strengths and weakness, and a description of how others have applied these adjustments are described below in Section 2.4.1 and

Appendix A, Supplemental Table 2.4. To identify relevant articles on the topic of adjusting ANC surveillance data to monitor population prevalence estimates and trends, a search was performed on January 24, 2012 in Google Scholar using the key words *HIV prevalence, population-based surveys, ANC sentinel surveillance, measurement bias,* and *adjustment method.* Of the 87 papers identified, four proposed methods for adjusting for differences between ANC and population survey estimates and an additional five applied or validated these methods in settings in SSA. Articles referenced in papers were also reviewed if they were not originally identified in the search but were considered potentially relevant based on the text.

Articles excluded from the table, but that may be presented in the text, were those that quantified the relative differences of fertility in HIV infected versus unaffected women but did not adjust for these differences in population prevalence estimates. Also, articles that considered adjustment methods unrelated to ANC surveillance data specifically (e.g., adjusting for non-response in population surveys) were excluded. Finally, articles referencing results that use these adjustment methods as routine practice, such as country-specific or global estimates and projections from EPP, were excluded unless they described the process of constructing the adjustment method for the first time. Articles that reference methods for adjusting for geographic biases are described in the text in Section 2.4.2.

2.4.1 Methods to adjust for bias in ANC surveillance estimates and trends relative to HIV prevalence in women of reproductive ages

As mentioned above, various methods have been proposed to correct for the differences observed in HIV prevalence among ANC attendees and women in the general population, which typically result in lower HIV prevalence among ANC attendees due to HIV-related sub-fertility and infertility biases. Prior to the quantification of this bias in the 1990s, it was first thought that female population HIV prevalence estimates could be obtained from surveillance data by direct age standardization alone [178]. As evidence of strong fertility differentials between HIV infected and uninfected women emerged, however, it was recognized that this method could actually lead to a greater underestimate of HIV prevalence in the population because it gives a heavier weight to the older ANC population, where prevalence differences are greatest [42].

Nicoll and colleagues in 1998 proposed one of the first methods to systematically adjust HIV prevalence estimates from pregnant women to account for fertility differentials [179]. Briefly, this method involved the direct comparison of live birth and termination rates among women known to be HIV positive and those in the entire female population. Based on these data, a calculation of the probability that HIV-infected women would be seen at an ANC clinic was made. This value, called the relative inclusion ratio (RIR), could then be used to adjust ANC prevalence estimates.

Validation of this method, which was done by Nicoll and colleagues using data from England and Wales, showed estimates in pregnant women and the female population to be similar. However, outside of London, ANC prevalence estimates would have understated HIV prevalence in the population slightly based on an RIR of

0.80 (CI: 0.71-0.89). As the prevalence in the country was less than 1%, the impact of this underestimate still would have been very small on absolute prevalence, although the relative difference between the crude and adjusted estimate would have reached 28%. No recommendations were provided for standard RIR values as these were seen to depend on the distribution of risk behaviour and fertility patterns specific to the location.

Several concerns with the approach developed by Nicoll were identified when considering the application of this method to adjusting ANC surveillance data from countries in SSA [42]. First, and most importantly, prevalence in the general population was considerably higher than in England, thus the RIR value would be diluted due to the inclusion of a relatively larger proportion of HIV-infected women in the denominator. Second, birth and termination rates separately for HIV-infected women were not well-documented at the time in many countries in SSA. As a result, a second approach was proposed by Zaba and colleagues in 2000 that would allow for a different method to estimate sub-fertility and infertility in the population in countries where prevalence was high [42]. In this method, parity and birth order data collected from ANC surveillance attendees was used to account for differences in fertility in HIV infected and uninfected women. Estimates of the relative risk of HIV prevalence in women giving birth were constructed separately for childless women and for mothers by sexual activity categories. The relative distributions of women in these populations were then obtained from demographic health survey data to apply the adjustment factors. Estimates were developed separately for those countries where contraception use was low (<20%) or high (>20%), as contraceptive use among women can be considered either high-risk (if contraceptive use is low in the population) or low-risk (if contraceptive use is high in the population).

Initial findings from the application of this adjustment method to areas with low contraceptive populations published in the Zaba paper were generally successful. For example, using data from rural Uganda, the adjusted estimate of prevalence in the female population was calculated to be 10.3% (based on a crude ANC surveillance estimate of 7.7%,) which was similar to estimates of adult female HIV prevalence taken from a nearby community-based survey around the same time. A similar outcome was also observed using data from Kisesa, Tanzania where adjusted ANC and female population survey estimates were determined to be very close, and when further standardized to the age structure of the population, the estimates were virtually identical (ANC adjusted prevalence estimate of 7.2% and an observed community prevalence of 7.3%). In Zimbabwe, where contraception was high, it was suggested that ANC prevalence estimates may already be representative of those in the female population, however, population distributions by risk categories using data from DHS suggested that an adjustment factor of 60% would need to be applied to ANC estimates of prevalence among primigravida women and a factor of 110% would need to be applied to estimates of prevalence in multigravida women. In low contraceptive populations, the adjustment factors were estimated to be 80% and 150% respectively.

At about the same time that Zaba and colleagues proposed the method described above, Fabiani and colleagues proposed an alternative approach which adjusted for differences in age-specific fertility risk between HIV infected and uninfected women and then standardized the overall prevalence according to the age structure of the female population generally [57]. Data for age-specific fertility differences among HIV infected and uninfected women were required to be known or estimates based on local data. Using data from the Gulu District in Northern Uganda

and a nearby community, Fabiani and colleagues found that adjusting HIV prevalence estimates among ANC attendees of 26.0% (95% CI: 23.2-29.0%) in 1993 and 16.1% in 1997, would have resulted in population prevalence declines of 25.4% in 1993-1994 and 17.8% in 1996-1997. As no measurements of prevalence in the population were available, however, this adjustment method could not be validated.

Following on the heels of these two proposed methods, and in line with the increasing availability of population and community-based estimates of female prevalence available from longitudinal and cross-sectional surveys, a number of countries undertook studies which used the above methods to adjust, and in some cases, validate adjusted estimates. The most comprehensive of these studies was a comparison of the methods proposed by Fabiani and Zaba using data from Fort Portal in Uganda, Mwanza municipality and a rural area of Mwanza in Tanzania, from Lusaka, Zambia and from a more rural area in Zambia, and finally from Ndola, Zambia [180]. Overall, the validation found that ANC prevalence using either method provided fairly accurate estimates of female population prevalence, although both performed poorly in one instance in Zambia where the unadjusted data was a better representation of underlying female population prevalence. Due to a lack of data on parity in ANC surveillance data in Uganda, the municipality of Tanzania, rural Mposhi, Zambia and for one year in Lusaka, Zambia, Zaba's method could not be validated.

Other subsequent evaluations of Zaba's method in low contracepting populations were conducted elsewhere in rural Malawi [53] and in rural Tanzania [52], and in two high contraceptive locations in Manicaland, Zimbabwe [55] and South Africa [56]. In rural Malawi, applying the proposed adjustment factor for low contraceptive populations resulted in an adjusted ANC prevalence of 15.0%

compared with a community-observed prevalence of 13.9% [53] and a similar result was obtained in rural Mwanza, Tanzania (4.6% versus 4.7%) [52],. In the high contraceptive areas, the methods did not produce similarly robust results however. In Manicaland, HIV prevalence among the female population reporting ANC attendance was 27.0%, and revised estimates of 22.6% and 23.5% with and without adjustment for birth intervals were still slightly lower than the actual estimate of prevalence of 25.5% obtained from the population survey [55]. As the population survey estimate did not take into account refusal bias, which could have potentially been differential with regard to HIV infection, it is possible that unadjusted ANC surveillance data were still the best reflection of the underlying population prevalence among women. In South Africa, similar discrepancies were observed, where the correction factors would have been relatively similar for conversions between primigravida to childless estimates (0.6 in Zaba versus 0.5 in South Africa), however the proposed correction factor for multigravida women of 1.1 was much higher than the 0.7 factor that was actually needed [56].

With regard to the adjustment methods described above, it is worth noting that the increasing availability of DHS survey data with HIV testing may make it more feasible to apply the adjustment method originally suggested by Fabiani, which is also similar to the method used by Nicoll. This method was first applied to ANC-surveillance estimates in SSA in 1998 in Abidjan, Côte d'Ivoire [181], although the study incorrectly calculated an RIR based on data from an ANC clinic thereby underestimating the true level of infertility in the population [182]. More recently, Kongnyuy and colleagues [183] in Cameroon used DHS data to calculate RIRs, finding values similar to those calculated from population surveys in Uganda by Gray [161] and in rural Zimbabwe by Terceira [153] although most countries in SSA now

have population survey data which provide a more robust estimate of population HIV prevalence. Further validation and application of this method as DHS data becomes available should be considered, however, as a means of validating ANC estimates and trends. Also, monitoring changes in fertility patterns in HIV infected and uninfected women from repeated DHS surveys will provide insight into the extent to which bias in ANC estimates may be changing over time.

Along these lines, although many of the authors above identify the potential for the magnitude of bias in ANC data to change over time, none of these have been used to explicitly validate trends. As described in Section 2.3.1, however, Garnett suggests that one potential method for ensuring stability in bias in ANC estimates over time is to adjust for age between the ANC and female population [115]. Although this may exacerbate differences in the overall levels for the reasons mentioned previously, it should prevent much of the change in bias due to changes in the age of infected women as the epidemic progresses. This could be particularly relevant with the introduction of ART, as an example.

2.4.2 Methods to adjust for bias in ANC surveillance HIV prevalence estimates and trends relative to national population HIV prevalence

In addition to adjusting for differences between HIV prevalence estimates among pregnant women and adult women, methods for adjusting ANC surveillance data to estimate national population HIV prevalence have also been proposed and applied. This has been necessary because ANC surveillance clinics selected to participate typically do a poor job at covering rural or more isolated areas. As a result, certain

adjustments may need to be considered for those countries where nationally representative population survey data are not yet available [184].

To compensate for biases with regard to the lack of geographic representation, UNAIDS recommended in 2001 that countries adjust rural population prevalence estimates from ANC surveillance data downwards by 20% [185]. These adjusted rural estimates were then combined with unadjusted urban estimates to produce weighted national estimates of HIV prevalence in the adult population. A major weakness of this approach was that studies comparing ANC and population prevalence in rural areas was truly sparse, thus the appropriateness of a 20% adjustment was unable to be validated for most countries.

Questions about the appropriateness of the 20% adjustment factor were raised when a number of population surveys done in countries in SSA suggested that ANC surveillance data were still overstating population HIV prevalence estimates [12]. In 2008, Gouws and colleagues published a comparison of adult HIV prevalence from national population surveys and ANC clinics from 26 countries, of which 24 were in sub-Saharan Africa [45]. This study, with regard to the overall magnitude and direction of biases in ANC surveillance estimates also was described briefly in Section 2.2.1. The objective of the study was to validate the 20% adjustment factor and to explore if other adjustments to population HIV prevalence estimates from ANC surveillance data might be required also.

Results from the multi-country study showed that the median ratio of population HIV prevalence to ANC prevalence was 0.82 in rural areas, which corresponded closely to the 20% reduction in rural estimates that was already recommended by UNAIDS. However, the study also suggested this bias was equally large in urban areas, and could vary by region. For example, biases in western

Africa, where prevalence was low, were estimated to be 0.73 in urban areas and 0.59 in rural areas. In southern and western Africa where the epidemic was more severe, ANC surveillance was marginally better at representing overall levels of HIV prevalence, although both urban and rural areas still required adjustment of up to 10%.

Following recommendation by the UNAIDS reference group, estimates of population prevalence obtained from EPP were recommended to be adjusted downwards by 20% in those countries without a population survey [17, 65]. Application of the adjustment resulted in a reduction of prevalence in SSA in 2005 from 6.1% to 5.4%. This bias was still assumed to be constant over time, however, so per annum calibrations have remained at 20% for those countries without a population survey. Gouws and colleagues recommended that as additional population survey data becomes available, analyses should be conducted that explore the extent to which this bias might be changing over time [45]. Chapter 3 considers this latter concern regarding bias in trends in more detail.

2.5 Bias in surveillance estimates from PMTCT programme data

Since PMTCT programmes rely on collecting data from pregnant women, it is clear that levels and trends in HIV prevalence will be subject to the same set of biases that have been described in Section 2.2 and 2.3. However, PMTCT-based estimate may also suffer from the additional bias of selective participation to the extent that HIV testing is associated with HIV status. The magnitude and direction of this bias will depend on whether HIV-infected women have access to, are offered and accept HIV testing more than uninfected women. Shifts in how these services

are provided could also differentially bias estimates over time. As briefly discussed in Chapter 1, participation bias may be higher in 'opt-in' than 'opt-out' settings.

To identify relevant published studies assessing the use of PMTCT data for surveillance purposes (including potential biases in these estimates), a comprehensive online literature review was conducted in April 2009 using Google Scholar. Key words included: *Antenatal Care, HIV prevalence, HIV testing determinants, HIV risk factors, pregnant women, prevention of mother-to-child transmission, sentinel surveillance, seroprevalence, and voluntary counselling and testing*. To identify relevant unpublished studies, proceedings from international meetings, conference abstracts, protocols and presentations, colleagues working on HIV surveillance and PMTCT were contacted.

Through these two search strategies, a total of 74 documents were identified and read in full to obtain a broad understanding of the issues around using PMTCT data for surveillance purposes. Subsequent to that, the documents were categorized into broad topic areas (see the following paragraph), in addition to assigning the type of document (e.g., published article, draft paper, conference abstract, presentation, guideline, etc.), its source if published, and, for studies, the geographic location, the period of time, the primary research questions with key results, and a brief critique of the methods and results.

Of the 74 documents reviewed, 19 were determined to have explored issues around bias in PMTCT and ANC surveillance data empirically. Three studies from outside SSA were excluded and a small number of document from the same study presented in multiple formats were consolidated. In the end, nine unique studies from seven countries in SSA were found to have sufficient information and data for further review. Notably, other documents initially reviewed, but not specific to the

topic of bias, were categorized with regard to their primary topic (with the numbers of documents in parentheses) as follows: information on ethics of HIV testing (2), ethics of PMTCT programmes (1), ethics of unlinked anonymous testing (2), predictors of testing and impact of differences in PMTCT delivery strategies on uptake (24), protocols for assessing the use of PMTCT data for surveillance purposes (1), PMTCT programme and CT testing effectiveness (23), and comparisons of VCT versus population prevalence (2).

From the nine remaining studies, studies were further categorized depending on whether they considered 1) the extent to which accepting HIV testing is associated with HIV serostatus (which can be used in turn to measure the impact of non-participation bias on PMTCT-based estimates) or 2) whether PMTCT-based data from clinics were as accurate and of sufficient quality as ANC surveillance data to monitor HIV prevalence in the population. Studies associated with the first category are described in Section 2.5.1. As noted in the initial categorization of the documents identified, although many studies have considered determinants of uptake of PMTCT-based HIV testing with the goal of increasing uptake [80, 83, 91, 92, 186-199], only three have directly linked these determinants to HIV serostatus [91, 92, 192]. Studies in the second category, which are more common, are summarized in Section 2.5.2. Appendix A, Supplemental Table 2.5 and Supplemental Table 2.6 briefly describes key characteristics of all nine studies grouped according to the two topics described above.

2.5.1 Studies of the association between accepting HIV testing and HIV serostatus in PMTCT programmes

The first study of factors associated with HIV testing and serostatus in a PMTCT programme was carried out in a rural North Ugandan hospital from 2001 to 2003. During this period, 13% (1,841/14,040) of ANC attendees were not offered testing, 48% (6,785/14,040) accepted 'opt-in' testing when offered and 39% (5,414/14,040) refused [92]. Women who were not offered testing had similar socio-demographic characteristics to those who were offered testing. Among those who were offered testing, women who lived at their current address for two years or less, were cohabitating but not married, and who had a partner with a non-agricultural occupation accepted HIV testing more often and were also more likely to test HIV-positive, although these associations were found to be only weakly significant. In the end, the authors concluded that PMTCT-based and ANC-based surveillance estimates did not differ greatly (10.9% and 11.1% respectively).

The second study, also in Uganda, followed 4,867 women who attended an urban Entebbe ANC clinic from May 2002 to April 2003 [91]. Similar to the rural Northern Uganda site, 25% (1,239/4,867) of the women were not offered testing, 54% (2,635/4,867) accepted when offered and 20% refused (993/4,867) and were tested anonymously. Among those women who were offered testing, women with no education or only primary education, those who had an HIV-infected partner and those who believed themselves exposed to HIV accepted testing and tested positive more often than others without these characteristics. Women who perceived themselves to be at high risk of HIV were also more likely to accept testing and to test positive. Despite these associations, no differences in prevalence levels were observed between individuals accepting or refusing testing (14% among acceptors

versus 12% among refusers; p-value=0.26). Differences in estimates were observed, however, in the month following introduction of PMTCT services (20% among acceptors vs. 11% among non-acceptors; p-value=0.05) and in months when testing uptake was below 70%, (17% in acceptors vs. 8% among non-acceptors; p-value<0.001). The authors suggested that women who accepted testing when services were initially introduced or when testing uptake was low represented a more motivated group of women who strongly perceived or knew themselves to be HIV-infected.

The third study in Burkina Faso evaluated, among other factors, the extent to which a woman's obstetrical history, age, and risk history were associated with accepting HIV testing and testing positive in an urban ANC clinic [192]. During the study period from 2002 to 2004, only 18% (1,216/6,639) of women accepted testing, and of those, 45% (97/215) of women testing positive reported they already knew their status from a prior test. Excluding these women, factors associated with uptake of testing and testing positive included older age and a history of miscarriage. Unlike the previous study, however, perceived risk of infection was not associated with increased uptake of testing and testing positive. Still, the authors suggested that a higher PMTCT prevalence during the 2002 to 2004 study period, compared to ANC surveillance prevalence estimates at the same clinic in 2002 (10.6% versus 4.0% respectively) could have resulted from attendance at the clinic by HIV-infected women who were more motivated to seek PMTCT services. Since these estimates were taken at different time points, other factors – such as increases in incidence or reductions in HIV-related mortality or changes in the patterns of ANC attendance that were also associated with HIV status - could also explain this disparity.

2.5.2 Studies directly comparing PMTCT programme and ANC surveillance estimates

Thailand was the first country to explore the potential use of PMTCT data for surveillance purposes in a study carried out in the late 1990s [200]. By 2001, 96.7% of women attending clinics where PMTCT services were offered reported accepting to test [200]. Given the near-universal uptake, ANC surveillance and PMTCT estimates differed by just 0.1% in 2001 [88]. A follow-up analysis in 2002 showed similar results. Based on these findings, and since 2003, Thailand has relied on PMTCT data alone to monitor HIV prevalence trends in the country [88].

Using the Thai study as a model, seven studies in five countries in SSA have been conducted to assess the usefulness of PMTCT data for surveillance purposes. Of these, Kenya [89], Cameroon [97], Uganda [94] and Zimbabwe [95] conducted evaluations using data from all clinics where PMTCT services overlapped with ANC surveillance activities. In Botswana, PMTCT-based HIV testing data from two of the most frequently attended clinics per health district were compared to ANC surveillance prevalence estimates from the same clinics [96]. Finally, the remaining two studies [93, 98] occurred at a single hospital in rural Uganda (where the determinants of HIV testing uptake and HIV serostatus were also assessed, as reported in Section 2.4.1).

In Kenya, ANC surveillance and PMTCT programme data from six clinics were used to compare HIV prevalence estimates in 2003 [89]. Acceptance of opt-out testing was 56% (1,258/2,239). Overall median prevalence estimates were similar (PMTCT: 14.4% (range: 7.0%-27.2%) versus ANC: 12.8% (range: 8.1%-26.3%)) as were estimates from those clinics with low (<60%) versus high testing uptake (≥60%). Despite these similarities, the authors found evidence for large relative

differences in HIV prevalence estimates by clinic (-30% to +38%) and problems with accessing PMTCT registers, interpreting nurses' handwriting, a lack of standardization in the format and availability of variables collected across clinic and substantial amounts of missing data. Based on these findings, the authors did not recommend using PMTCT data for surveillance purposes.

Also in 2003, HIV prevalence estimates from ANC surveillance and PMTCT data were compared in Cameroon [97]. Overall uptake was 69%. No information was available from the study authors on whether 'opt-in' or 'opt-out' testing was offered or the number clinics that participated. Findings from the study, however, showed overall prevalence estimates for those clinics that participated to be similar (PMTCT: 7.8% (95% CI: 7.5-7.9) versus ANC 7.3% (95% CI: 6.7-7.9%)). Given these results, the authors concluded that PMTCT data was adequate to monitor the HIV epidemic in Cameroon. Nevertheless, ANC surveillance data are still used in the country to monitor population prevalence trends as of 2011.

In Uganda, PMTCT-based and ANC surveillance prevalence estimates were compared in seven clinics where these activities overlapped in 2003 [94]. Data on HIV testing uptake and the type of testing offered (i.e., 'opt-in' or 'opt-out') was not recorded. While HIV prevalence estimates were determined to be roughly similar (9.8% in PMTCT versus 8.3% in ANC), in two clinics, the estimates were found to differ substantially due to sampling and refusal bias. In Arua clinic, HIV prevalence was approximately 5% among PMTCT acceptors, 23% among PMTCT refusers, and 8% among ANC surveillance participants overall. In Rubaga clinic, prevalence was 7% among PMTCT acceptors, 17% among PMTCT refusers, and 11% among ANC surveillance participants overall. Further investigation into these differences identified confusion around the two protocols which led some women to be sampled twice in

ANC surveillance while others were excluded inappropriately from participating in PMTCT services. Stock-outs in syphilis and HIV test kits also contributed to non-consecutive sampling during ANC surveillance. Substantial inconsistencies in documentation procedures across clinics and incorrect application of testing algorithms applied to discordant test results were also found. Based on these findings, PMTCT data were deemed inadequate for surveillance purposes. Furthermore, the authors cautioned that jointly conducting PMTCT and ANC surveillance in the same clinics could jeopardize both sets of estimates unless staff are well trained on procedures for conducting both activities.

Similar to the Cameroonian, Kenyan and Ugandan experience, the Ministry of Health and Child Welfare (MOHCW) in Zimbabwe evaluated the comparability of HIV prevalence estimates from 19 clinics where overlapping ANC surveillance and opt-in PMTCT data were available in the country in 2004 [95]. Unlike these previous evaluations, however, nationally-reported -- rather than clinic-level -- PMTCT data were used. Median uptake of 'opt-in' testing at the 19 clinics was found to be 42.1% (range: 2.3%-89.4%). Testing was reportedly low due to refusals as well as insufficient availability of test kits and staff to offer testing. Although overall HIV prevalence was observed to be similar (21.8% in PMTCT data versus 21.3% in the ANC clinics), substantial differences in clinic-specific estimates were identified. As national data were used as well, no age or socio-demographic data were available to further interpret trends. Based on these results, the Zimbabwean MOHCW concluded that national-level PMTCT data were unacceptable for surveillance purposes.

At the national level, the most recent and most comprehensive evaluation of ANC and PMTCT data occurred in Botswana during the 2005, 2006 and 2007

surveillance periods using data from two of the most highly attended ANC clinics in each of their 24 health districts [96]. Uptake of 'opt-out' testing exceeded 95% at all clinics during the study period. In general, annual estimates and estimates among rural and urban areas stratified by 5 year age intervals were similar, especially among those aged 15 to 24. Despite these similarities, however, the authors noted that socio-demographic data collected during ANC surveillance were more complete than PMTCT data. Nonetheless, their availability was considered sufficient. In light of this finding, a working group was created to transition from using ANC surveillance data to PMTCT program data for surveillance purposes in Botswana. As of 2011, ANC surveillance data are still used to monitor HIV prevalence trends in the population.

In a final study of the usefulness of PMTCT data for surveillance purposes, estimates of PMTCT prevalence and ANC prevalence were compared in a rural Ugandan clinic for the years 2001 to 2005 in two studies published separately [93, 98]. In the first study, the authors found that despite relatively low but slowly increasing levels of opt-in HIV testing from 2001 to 2003 (45.8% in 2001 to 48.2% in 2003), age-adjusted HIV prevalence from the two data sources were similar (11.1% in ANC and 10.9% in PMTCT) [98]. In the follow-up study from 2004 to 2005, ANC data overestimated PMTCT prevalence in 2004 (10.5% versus 9.0%) but underestimated PMTCT prevalence in 2005 (10.9% versus 11.8%). This shift occurred despite only a marginal increase in uptake (from 49.9% in 2004 to 52.2% in 2005) [93]. Based on these results, further studies were recommended before transitioning to using PMTCT estimates for surveillance purposes.

2.5.3 Summary of bias in PMTCT estimates

As outlined above, evidence from these studies is mixed regarding the usefulness of PMTCT data for surveillance purposes. While most studies found overall crude or adjusted ANC surveillance and PMTCT estimates to be similar, non-participation bias, either at the clinic-level or when services had just commenced or participation was low, affected the accuracy of these data. Unfortunately, factors predicting HIV testing uptake and association with serostatus that could help account for non-participation bias appeared to vary by age and across studies [91, 98, 192] and in the northern Uganda rural study, with time [93]. Potential biases in PMTCT estimates are summarized in the Table 2.3 below:

Type of bias	Factor	PMTCT participation relative to all ANC attendees	Direction of bias in PMTCT data relative to ANC surveillance data
Self-selection	Socio-demographic characteristics associated with being offered testing are positively associated with HIV infection	More HIV-infected PMTCT participants	PMTCT>ANC
	Socio-demographic characteristics associated with being offered testing are negatively associated with HIV infection	Fewer HIV-infected PMTCT participants	PMTCT<ANC
	Socio-demographic characteristics associated with accepting testing are positively associated with HIV infection	More HIV-infected ANC attendees	PMTCT>ANC
	Socio-demographic characteristics associated with accepting testing are negatively associated with HIV infection	Fewer HIV-infected PMTCT participants	PMTCT<ANC

Table 2.3 Expected direction of bias in ANC HIV surveillance estimates due to selective participation in PMTCT programmes.

Specific to the quality and availability of PMTCT data, operational challenges were reported in four of the six studies directly comparing PMTCT and ANC surveillance data (Kenya [89], Uganda [94], Zimbabwe [95], and Botswana [96]. Commonly reported problems included missing and illegible data. In Zimbabwe, age data to stratify results for an UNGASS indicator was not available. In the case of

Botswana, the authors concluded that problems encountered there, primarily missing data, could be addressed with additional resources and staff training when PMTCT data would be collected for surveillance purposes. The other three countries, however, reported problems of a sufficient scale such that they did not recommend PMTCT data be used for surveillance purposes.

While the above conclusions could generate more concern than confidence in using PMTCT data for surveillance purposes, the primary limitation is that all but two of these studies (Kenya and Botswana) were conducted when HIV testing in PMTCT services were offered using 'opt-in' rather than 'opt-out' testing. However, since this time, most countries have moved to 'opt-out' testing, and many of the other challenges such as accessing the data and ensuring adequate standardization of data have been addressed [79, 201]. Given this new context, it is possible that future biases in PMTCT data may be less severe.

2.6 A note on the Manicaland HIV/STD Prevention Project

Data from the Manicaland HIV/STD Prevention Project have been used to assess key questions about the usefulness of ANC surveillance and PMTCT programme data in a number of chapters in this thesis, including those mentioned above. In Chapter 3, the mathematical model constructed to evaluate the usefulness of ANC surveillance data for monitoring trends is parameterized with data from this project. In Chapter 5, ANC surveillance and household population survey data are used to assess the representativeness of prevalence trends among youth. In Chapter 6, ANC surveillance and PMTCT programme data are compared. Therefore, a

summary of the study is provided as background to these chapters, although study details relevant to each analysis are also included in the individual chapters.

The Manicaland Project has collected socio-demographic, behavioural and biomarker data on an open cohort of participants living in 12 communities in three districts in eastern Zimbabwe and ANC attendees at selected clinics in the study's catchment area [20]. The 12 communities can be grouped into four socio-economic geographical areas: (i) towns, (ii) tea, coffee and forestry estates, (iii) subsistence farming areas; and (iv) roadside trading centres.

Data from the Manicaland Project have been collected over four rounds, with the first round beginning in July 1998 and ending in February 2000. Subsequent rounds have been carried out from July 2001 to February 2003 (round 2), July 2003 to August 2005 (round 3) and August 2006 to November 2008 (round 4). At the start of each round, a preliminary household census was conducted through interviews with each dwelling's head of household.

Of the persons enumerated in the household, criteria for inclusion in the individual survey are applied by study staff to select potential participants. Criteria for participant inclusion have changed over the survey rounds. In round 1 and 2 of the household survey, all unmarried men aged 17 to 54 years and women aged 15 to 44 years were eligible to participate. Among married or cohabitating couples, only one person in the partnership meeting the age criteria was chosen to participate. Visitors in the household, defined as those who at the time of the interview did not consider their home to be the household where the interview was occurring or who stayed in the household fewer than four days in the last month, were excluded from participating. New in-migrants in round 2 were included only in communities 5 to 12 given funding limitations [20]. In round 3, the inclusion criteria were expanded to

include all men and women aged 15 to 54 years, regardless of marital status and whether or not a person was a visitor in the household. In round 4, individuals in only two thirds of the households identified during the census were selected at random to participate in the individual household survey.

For those individuals eligible to participate in the household survey, interviews in English and Shona (the primary local language) were conducted for each round in a private setting by trained social science graduates. Questionnaires were designed to minimize changes across the study rounds, although questions are added or modified to promote compatibility with changes in international measures of knowledge and practices. Questionnaires were back-translated from Shona to English to ensure consistency between the languages.

The structure of the individual interviews consisted of a brief description of the study and a request for consent to the participants to answer basic socio-demographic questions. Responses to subsequent questions of a sensitive nature about sexual behaviours were collected using an informal confidential voting interview method by respondents who reported themselves to be literate. A study of this method found that interviews using the voting box method were more likely to report a higher number of sexual partners, signalling that bias due to social desirability may have been reduced [202].

Following questions about the individual's basic socio-demographic background and sexual behaviour, serological samples were collected using dried blood spots. Testing of dried blood spots were done at the Biomedical Research and Training Institute laboratory in Harare, Zimbabwe. At round 1, a highly sensitive and specific (both 99.6%) dipstick-dot ICL-HIV1 & 2 Dipstick EIA was used to detect HIV antibodies [20]. Combaids-HIV-1 & 2 Dipstick was used in subsequent rounds. Apart

from the principal investigators, research staff were blinded to participants' HIV status. In addition to testing for the study, all participants at each round were offered free confidential VCT at a mobile clinic provided by the study along with free STI testing and treatment.

At the conclusion of the interview, all sexually active participants are asked to provide a detailed fertility history, including access to and uptake of ANC services during each pregnancy. For individuals participating in multiple rounds, only fertility-related events occurring since the previous round were collected.

With regard to ANC surveillance carried out by the Manicaland study, participating clinics were selected in the catchment areas of the 12 communities to maximize the number of participants seen during the surveillance period. As a result, not all clinics were continuously sampled. In Rounds 1, 2 and 3, 29 clinics were consistently sampled, with seven additional clinics sampled in some rounds but not others. At round 4, all 36 clinics were included. Of these, four clinics were located in towns, 14 in tea, coffee and forestry estates, 13 in subsistence farming areas and 5 in roadside trading centres.

While the procedures for carrying out ANC-based surveillance in the Manicaland study largely follow WHO's ANC surveillance guidelines [39], two exceptions were made. First, Manicaland participants were considered eligible regardless of whether the visit for prenatal care was their first visit or a subsequent visit. Second, women who were referred to clinics from other health centres were included. These allowances were made to increase the sample size of the women interviewed at the clinic. Where relevant, potential biases introduced as a result of these adaptations are discussed in the individual chapters. The same methods for

collecting and testing dried blood spots for HIV antibodies employed in the household survey were also used in the ANC surveillance round.

Study enrolment for ANC surveillance and in the individual household survey was conditional on participants' written consent at each round, although ANC data were anonymous. The Medical Research Council of Zimbabwe and St Mary's Local Research Ethics Committee, London, provided ethical approval for rounds 1 through 4. All data were entered electronically into custom-designed data entry forms in Zimbabwe by trained data entry staff. In London, data were cleaned and validated by a senior researcher using Access and Stata. Additional quality control checks and data cleaning were made at the time of analysis.

Chapter 3: Comparisons of ANC surveillance and population HIV prevalence estimates and trends in selected countries in sub-Saharan Africa

3.1 Aims and organization of the chapter

The overall aim of this chapter is to explore the extent to which historical ANC-derived HIV prevalence estimates and trends among adults and youth (aged 15 to 24 years) have been representative of household-based population prevalence estimates and trends in rural and urban areas for seven countries in SSA. This chapter begins with a brief review of why these types of comparisons are now possible, primarily due to the increase in the number of repeat DHS and DHS-like household-based population surveys since 2000 in countries in SSA that include HIV testing. This is followed by a brief discussion of three published community-based longitudinal studies (one of which is described in more detail in Chapter 5) that have previously made these types of comparisons within smaller geographic areas. Next, the methods used to compare trends from ANC surveillance and household-based population surveys are described, with results presented for each of the seven countries disaggregated by rural and urban area and gender. Possible reasons for differences in trends for those settings identified as not having representative ANC data are explored.

3.2 Introduction

Monitoring population-level HIV prevalence trends can be a challenge when HIV testing is not universally available and accessed. Data from national household-based population surveys incorporating HIV testing are often considered the best available data source to monitor the impact of the epidemic on the population, although conducting these surveys requires substantial financial contributions and

human resources. As a result, the frequency with which these surveys can be carried out in many sub-Saharan African countries has been limited [18].

To complement national household-based population surveys during the interim time periods, UNAIDS recommends that countries conduct annual or semi-annual HIV surveillance to get repeated estimates of HIV prevalence among ANC attendees over time [39]. These data are then combined with national household-based population survey data to estimate trends and levels of HIV prevalence in most countries with generalized epidemics in SSA. This method assumes, however, that repeated estimates from pregnant women reflect changes in HIV prevalence in the general population over time. In Chapter 2, Section 2.3, reasons why ANC and population survey trends might differ, including (i) variation in the natural dynamics of infection in these groups, (ii) changes with regard to the timeliness of adopting safer sexual behaviours and (iii) more recently, the impact that ART use might have on fertility patterns, were considered in more detail. Changes in methods used to conduct ANC surveillance and population surveys may also contribute to differences in trends over time.

Since 2000, seven countries (Botswana, Lesotho, Kenya, Mali, Niger, Tanzania and Zambia) have conducted two population surveys [203-215] and two countries (Sierra Leone and South Africa) have conducted three [72, 216-219] through 2010. These surveys are most often carried out with technical assistance from MEASURE DHS. Owing to the standard methods adopted by MEASURE DHS, household-based population survey data are typically comparable across countries. When repeated over time, these surveys can be used to validate trends from the more frequently-conducted ANC surveillance, which typically are conducted according to standard WHO guidance [39].

Assessing the representativeness of ANC surveillance data at the national level in SSA has only been possible in the last few years with the addition of these repeated household-based population surveys. Longitudinal analyses considering the extent to which biases in ANC surveillance data have changed over time have been performed previously on a smaller scale, however, using data from two community-based studies among adults in Tanzania [50] and Zambia [116] and one among youth aged 15 to 24 years in Zimbabwe [220] (See Chapter 5). In the Kagera region of Tanzania, ANC trends from 1990 to 1996 were found to be generally reflective of female and male population prevalence trends from 1987 to 1996. In Lusaka, Zambia, ANC estimates from 1994 to 2002 were observed to substantially understate HIV prevalence declines in the population overall from 1995 to 2003, largely due to changing fertility and education patterns of younger women. In Manicaland, Zimbabwe, overall trends among young people were determined to be similar to those among ANC attendees from 1998 to 2005, although more severe declines in population prevalence were observed initially, possibly due to early reductions in risk behaviour in the general population and to changes in the composition of the study participants across rounds also (see Chapter 5).

A limitation of the Tanzanian and Zambian studies, but not the Manicaland study, was that statistical tests to compare trends in ANC and population prevalence relied on separate statistical analyses of the two data sources. In Tanzania and Zambia, trends in HIV prevalence among pregnant women and in the population were considered similar if estimates in both data sources declined and if the declines were linear. In practice, however, declines in one dataset could have outpaced declines in the other, but this difference would have not been detected by the statistical tests which were performed. To correct for this limitation, a Z-score test for

trends was used in the Manicaland study to directly compare the proportional change in HIV prevalence among young pregnant women with that from the population aged 15 to 24 years over the study periods. As indicated, this test permits comparison of the proportional reduction in HIV prevalence over time, rather than relying on odds ratios, which are limited to expressing relative differences only.

In this chapter, a similar method to that which was developed for the Manicaland study evaluation was used to assess whether there is evidence for the representativeness of ANC trends in countries in SSA with two or more nationally-representative household surveys conducted from 2000 to 2010. ANC surveillance trends were compared to household survey estimates among adults aged 15 to 49 years stratified by gender and, where available, by urban and rural residence. Similar comparisons were also made for youth aged 15 to 24 years in Lesotho, South Africa and Zambia, where data were available. For all of these comparisons, an HIV prevalence ratio (PR) of ANC compared to population estimates was constructed to more easily visualize relative changes in bias in ANC HIV prevalence trends over time. Findings from these analyses are a useful measure of the validity of historical ANC-derived trends in SSA. They also provide insight for where additional analyses may be warranted into why differences are occurring in particular settings or within specific groups.

3.3 Methods

3.3.1 Inclusion criteria and data sources

Countries in SSA were considered eligible for inclusion in the analysis if they met the following criteria: (i) had conducted and reported results from two or more ANC surveillance rounds through 2010 and (ii) had published results from a nationally-representative household-based population survey with HIV testing within two years of a corresponding ANC surveillance round. Countries meeting these criteria were: Lesotho, Kenya, Mali, Tanzania and Zambia with two household-based surveys and Sierra Leone and South Africa with three. Countries excluded from analyses were Niger, where three years separated the ANC sentinel surveillance round and the closest household-based population survey, and Botswana, which did not publically make data available from their second household-based survey. Upon further review of the data from countries with three surveys, the first survey in Sierra Leone and the third in South Africa were excluded from analyses because of insufficient published data on HIV prevalence among those aged 15 to 49 years disaggregated by gender. Also, in South Africa, methods for conducting ANC surveillance changed from 2005 and 2008, such that the number of participating clinics quadrupled and it was not possible to ensure the comparability of trends after 2005.

For the ANC surveillance data, national surveillance reports were reviewed to capture relevant information about the methods used to conduct surveillance at each round. To construct ANC surveillance trends for most countries, UNAIDS provided electronic data files that were originally obtained by the organization for other reporting and analyses purposes [personal communication, January 15, 2011].

These files included HIV prevalence estimates and sample sizes per clinic stratified by urban and rural location for each year that ANC surveillance was conducted. In Kenya and Tanzania, data for the 2008-2009 ANC surveillance round and the 2008 round respectively had to be abstracted from national reports that were obtained from in-country staff [221, 222]. In both of these reports, estimates of HIV prevalence from semi-urban clinics were combined with those from rural clinics to permit comparable comparisons of trends over time, as estimates in the first round were disaggregated only by rural and urban clinics.

In addition to the ANC surveillance data files described above, UNAIDS provided clinic-specific HIV prevalence estimates, but not overall sample sizes, for young pregnant women aged 15 to 24 years in South Africa, Tanzania and Zambia. Estimates for those aged 15 to 24 years were not available for the other four countries or for older pregnant women aged 25 to 49 years. In the latter case, HIV prevalence estimates among this age group are not routinely analysed or presented separately in international reports. Also, data disaggregated by regions or geographic divisions other than rural and urban areas were not available in the electronic files, as UNAIDS publishes data stratified by rural and urban residence only.

To avoid constructing trends in HIV prevalence that reflected changes in the clinic selection process over time, only those clinics that participated in both surveillance rounds corresponding to the population survey were included. As previously mentioned, in South Africa, clinic-specific estimates were not available, thus the number of clinics contributing to the trends changed from 396 in 2002 to 336 in 2005. South African ANC surveillance data also are not disaggregated by rural

and urban areas, so only national-level comparisons of median ANC HIV prevalence for all clinics and population survey trends were presented.

For the household population survey estimates, data for most countries were abstracted from published reports on the MEASURE DHS website (http://www.measuredhs.com/). For the 2005 survey in Sierra Leone and for both surveys in South Africa, data were obtained from UNAIDS-supplied electronic reports because these surveys were not supported by MEASURE DHS [72, 216-219]. South African surveys are also available at http://www.wsu.ac.za/hsrc/html/baseline.html (accessed on March 1, 2012). Abstracted data for all countries, unless otherwise noted, included the survey year (or years, if the survey spanned multiple years), the age range of participants by gender, gender-specific participation levels, and testing ratios by gender, residence (urban versus rural) and age (15 to 24 years versus 25 to 49 years).

With regard to the representativeness of the household population survey, participation levels were published in DHS reports as the proportion of eligible individuals, regardless of age, who were located during the survey period and who consented to an HIV test as part of the survey. A secondary analysis of the data specific to HIV testing among accepters aged 15 to 49 years was performed as part of this analysis to determine how the ratio of individuals testing in one group versus another (e.g., female and males) may have changed across survey periods. To provide an indication of the representativeness of the ANC surveillance data, the proportion of women in the survey who reported attending an ANC clinic at their last pregnancy, if that pregnancy was within five years of the survey period, was abstracted from published reports. For the 2005 household-based population survey

in Sierra Leone and for both surveys in South Africa, some of these data were either not collected or not reported in the published findings.

3.3.2 Statistical analyses

Country-specific HIV prevalence estimates and trends stratified by gender and rural/urban areas were constructed based on the abstracted data described above. A secondary analysis was done of ANC surveillance data provided by UNAIDS to obtain national and urban/rural-specific median HIV prevalence for only those clinics that participated consistently in those ANC surveillance rounds for which the household-based population survey data were available. For the population survey data, weighted estimates of HIV prevalence overall (by gender and urban and rural distribution) and estimates stratified by gender and residence were taken from published reports. In both data sets, the HIV prevalence estimate was attributed to the earliest year of data collection if the data were collected over two years. In all countries except Kenya in 2003, South Africa in 2002 and 2005, and Tanzania in 2003-2004, the years in which the ANC surveillance round and the population survey were conducted differed, although none of the comparisons were made using estimates separated by more than two years.

To assess the representativeness of the ANC surveillance data relative to the population survey data, a two-staged approach was used. In the first stage, a PR trend was calculated to visualize the representativeness of the ANC surveillance data over time relative to population HIV prevalence trends. Average PR values were calculated overall, within regions (i.e., southern and eastern Africa, consisting of Kenya, Lesotho, South Africa, Tanzania, and Zambia and western Africa, consisting of Mali and Sierra Leone) and separately by country. The PR within a country was

defined as the median estimate of HIV prevalence among pregnant women divided by the population survey estimate in the same year. PR values for the regions and overall were taken to be the average of the country-specific PRs. As South Africa did not have disaggregated urban and rural data, they only contributed results to national estimates.

Construction of PR trends within countries was limited to the years for which the inter-survey periods and inter-surveillance periods overlapped, meaning HIV prevalence estimates had to be imputed for the start or end data of whichever survey or surveillance period was longer. To do this, a linear change in HIV prevalence between the earlier and later rounds was assumed and an imputed estimate for the corresponding year of the missing estimate was calculated. For example, in Kenya, where the 2010 ANC surveillance round occurred two years after the population survey in 2008-2009, the steady decline of 0.5% in HIV prevalence among ANC attendees from 8.2% in 2003 to 4.8% in 2010 would have meant HIV prevalence among ANC attendees in 2008 was around 5.8%. The impact of this assumption is considered in the discussion.

Where a stable PR trend (regardless of its overall level) was observed, ANC estimates and population HIV prevalence estimates were determined to be similar over time. When the value of the PR changed over time (i.e., increased or decreased), ANC surveillance data were considered less representative. The relationship between the PR trend and the representativeness of ANC surveillance HIV prevalence estimates over time is summarized in Table 3.1.

	PR trend is declining over time	**PR trend is increasing over time**
Population prevalence is declining	ANC surveillance overstates a decline	ANC surveillance understates a decline
Population prevalence is increasing	ANC surveillance understates an increase	ANC surveillance overstates an increase
Population prevalence is moving in opposition to ANC prevalence	ANC surveillance incorrectly signals a decline	ANC surveillance lags in identifying a decline

Table 3.1 Interpreting the prevalence ratio (PR) trend relative to population prevalence.

In the second stage, for those countries where the PR was found to vary over time, ANC and population HIV prevalence trends were compared directly using the Z-score test statistic to determine if those trends differed significantly. For these comparisons, the same imputed estimate of HIV prevalence calculated for the PR trend also was used when the inter-survey and inter-surveillance periods differed. When comparing ANC surveillance and population survey trends, the null hypothesis that there was no difference in trends over the time period considered was rejected when the absolute value of the Z-score was greater than 1.96 (i.e., a p-value<0.05). To calculate the Z–score, the formula:

$$Zscore = \frac{\Delta P12_{ANC} - \Delta P12_{POP}}{\sqrt{\sigma^2\left(\frac{P2-P1}{P1}\right)_{ANC} + \sigma^2\left(\frac{P2-P1}{P1}\right)_{POP}}} \qquad (3.1)$$

was used, where ANC indicated the ANC surveillance data and POP indicated the population survey data. The proportional change in prevalence in each data source (e.g., ANC or POP) was calculated as: (3.2)

$$\Delta_{P12} = \frac{(P2-P1)}{P1},$$

where:

P_1 = HIV prevalence at round 1 in the data source, (3.3)

and

P_2 = HIV prevalence at round 2 in the data source. (3.4)

To approximate the variance in the Z-score formula, which was too complex to calculate directly, the delta method based on the Taylor series expansion was used [223]. The formula for approximate variance around each trend was:

$$\sigma^2\left(\frac{P2-P1}{P1}\right) = \frac{1}{-2(\Delta_{P12})(\sigma^2)(Cov_{P1,P2-P1}) + P1^2\left(\sigma^2_{P2-P1}\right)}\ , \quad (3.5)$$

and the variance of the binomial distribution (σ^2) equal to:

$$\sigma^2 = \frac{P1(1-P1)}{N}\ , \quad (3.6)$$

the variance of the difference in the HIV prevalence at round 1 and round 2 was calculated according to:

$$\sigma^2_{P2-P1} = \sigma^2_{P1} + \sigma^2_{P2} \quad , \tag{3.7}$$

and the covariance:

$$Cov_{P1,P2-P1} = -\sigma^2. \tag{3.8}$$

The assumption that the population survey trend was the “gold standard”, or best representation of true underlying population prevalence in the study area, is considered in more detail in the discussion section.

Calculations for both the PR values and the Z-score tests were done using Excel. A worksheet is available upon request for countries to analyse their own data. An example of the template using data from Kenya for females aged 15 to 49 years is shown in Table 3.2. As the outcome panel illustrates, the proportional decline in median ANC prevalence was 29% compared to just 8% in female population HIV prevalence from 2003 to 2008. The p-value of the Z-score test confirms that the decline in the ANC-based HIV prevalence trend was significantly greater than the decline in population HIV prevalence trend from 2003 to 2008 (p-value=0.009). These declines in prevalence corresponded to a PR trend which fell from 0.9 in 2003 to 0.7 in 2008.

Comparison groups: ANC to Females (aged 15 to 49 years)	ANC surveillance (ANC)		Population survey (POP)	
	Round 1 (2003)	Round 2 (2008*)	Survey 1 (2003)	Survey 2 (2008)
Sample size (N)	10500	12339	3151	3641
HIV Prevalence (P)	8.2%	5.8%	8.7%	8.0%
σ^2	7.2E-06	4.4E-06	2.5E-05	2.0E-05
$\sigma^2_{(P2-P1)}$	1.2E-05		4.5E-05	
$Cov_{(P1,P2-P1)}$	-7.2E-06		-2.5E-05	
$\sigma^2_{((P2-P1)/P1)}$	1.2E-03		5.5E-03	

Outcomes:	
2003-2008 ANC change	**-29.3%**
2003-2008 POP change	**-8.0%**
Z-test value (trends are the same):	**-2.60**
P-value (trends are the same):	**0.009**
2003 ANC:POP PR	**0.9**
2008 ANC: POP PR	**0.7**

* The 2008 ANC surveillance estimate is imputed assuming a linear decline in prevalence between the 2003 and the 2010 rounds

Table 3.2 Excel spreadsheet example for Kenya comparing ANC sentinel surveillance (ANC) and female population prevalence (POP) trends. See the accompanying text for all abbreviations and formulae used to calculate outcomes.

3.4 Results

Characteristics of the ANC surveillance rounds and the household-based population surveys by country and year are summarized in Table 3.3 and Table 3.4 respectively. With regard to the ANC surveillance data, all countries reported using WHO published guidance as the basis for conducting surveillance, although as previously noted, South Africa used different clinic selection procedures than those recommended by WHO and did not report estimates by rural and urban areas [39]. All HIV prevalence estimates were obtained using similar data collection methods based on UAT procedures. Despite this comparability, the number and geographic distribution of the participating ANC clinics varied across countries and over time. For example, in Kenya and Tanzania, the number of rural clinics selected to participate increased from the first to second rounds, but since most of the original

clinics were retained, trends could still be constructed for a large proportion of clinics. In Sierra Leone, Mali and Lesotho, only a few clinics participated, but each contributed data to both rounds. Finally, in Mali and Sierra Leone, the number of urban clinics exceeded the number of rural clinics, despite the fact that two thirds of the countries' populations lived in rural areas throughout the decade [224].

Given that the construction of trends was based on only those clinics that participated consistently, the number of ANC attendees was approximately similar over time within countries. The exception to this was in Kenya, where the target participation level per clinic in urban areas was raised from 300 pregnant women in 2003 to 400 pregnant women in 2010. Target participations levels for rural clinics were also lowered from 300 pregnant women to 250 pregnant women per clinic during the same time periods. Kenya also changed their eligibility criteria between 2003 and 2010 to include women of all reproductive ages as opposed to only those 15 to 49 years of age. This latter change is unlikely to have had a major impact on HIV prevalence trends, however, as those who were under 15 or over 49 years of age were less than one percent of all ANC attendees in the 2010 surveillance round.

			All clinics			Consistent clinics (used in analysis of trends)						
Country	**Year**	**Age range**	**Urban (#)**	**Rural (#)**	**Total (#)**	**Urban (#)**	**Rural (#)**	**Total (#)**	**Urban participants (#)**	**Rural participants (#)**	**Total participants (#)**	**Reported ANC attendance at last pregnancy[¶] (%)**
Kenya	2003	15-49	16	22	38	16	21	37	3993	6507	10500	90
	2010[†]	All women	16	29	43				6325	6014	12339	92
Lesotho	2003	All women	2	4	6	2	4	6	1200	1466	2666	90
	2007	All women	2	4	6				1077	1588	2665	92
Mali	2002	All women	7	2	9	7	2	9	2228	548	2776	58
	2007	All women	7	2	9				2742	641	3383	70
Sierra Leone	2006	All women	9	1	10	9	1	10	2188	265	2453	NC
	2007	All women	9	1	10				2468	300	2768	94
South Africa	2002	15-49	NC*	NC	396	NC	NC	396	NC	NC	16587	97
	2005	15-49	NC	NC	339			339	NC	NC	16510	95
Tanzania	2003-2004	15-49	25	32	57	24	32	56	9846	8129	17975	97
	2008[†]	15-49	46	88	134				9375	7859	17234	97
Zambia	2002	15-44	12	12	24	11	12	23	6827	5299	12126	93
	2006	15-44	12	12	24				7013	5546	12559	97

* Data were either not collected (NC) or reported in the published report

[†] Rural data includes women living in semi-urban and other non-urban areas

¶ As reported among women aged 15 to 49 years who were pregnant in the five years prior in the population survey data

Table 3.3 Characteristics of the ANC surveillance rounds by country and year. Clinics not consistently participating in all surveillance rounds were excluded from the analysis, with the exception of South Africa where median estimates of prevalence were not available separately by clinic or stratified by rural/urban area.

Based on the relatively high and stable proportion of women reporting prenatal attendance during their last pregnancy in most countries as measured in the population surveys, ANC surveillance data should be a reasonably good representation of prevalence trends among females living in the catchment area of these clinics. The exception to this was in Mali, where only about half of pregnant women in 2001 and under three quarters in 2006 reported seeking ANC services at their last pregnancy.

Table 3.4 summarizes selected characteristics of the household surveys by country and year. As most countries partnered with MEASURE DHS to conduct the household surveys, sampling and testing strategies were largely comparable across countries and over time. Exceptions to this, as previously noted, were in Sierra Leone in 2005 and in South Africa in 2002 and 2005. In South Africa, since HSRC oversaw the implementation of both surveys, the results across rounds are more likely to be internally comparable as compared to in Sierra Leone, where the first survey was supported by a private Ghanaian consulting group and the second was supported by MEASURE DHS. In Sierra Leone, both surveys were based on sampling frameworks from national population censuses, thus, coverage is likely to be similar.

With regard to the actual representativeness of the survey estimates, participation levels were generally higher among women as compared to men, except in Kenya in 2003, where approximately the same proportion of men and women participated at round 1. Participation levels also increased from the first to the second survey in all countries other than Sierra Leone and Zambia. The greatest increases were observed in Lesotho, for men and women separately. In Sierra Leone, participation levels in the 2005 survey were atypically high, while the 2008

levels were comparable to those observed in other MEASURE DHS-supported surveys throughout SSA. The decline in participation in the Zambian surveys from 2001-2002 to 2007-2008 was less dramatic than those observed in Sierra Leone, although both Zambian surveys and those from South Africa had the lowest participation levels of any of the countries.

		HIV participation levels					Testing Ratio[§]		
Country	**Year**			*Females*	*Males**	*Total*	**Female to male**	**Urban to rural**	**Youth (15-24 years) to adult (25-49 years)**
Kenya	2003	Eligible	(N)	4303	4183	8486	1.1	0.3	0.7
		Testing	(%)	81	82	81			
	2008-2009	Eligible	(N)	4418	3910[†]	8328	1.2	0.3	0.7
		Testing	(%)	92	84	88			
Lesotho	2004	Eligible	(N)	3758	3305	7063	1.5	0.3	0.9
		Testing	(%)	81	68	75			
	2009	Eligible	(N)	4112	3493	7605	1.4	0.4	0.9
		Testing	(%)	94	88	91			
Mali	2001	Eligible	(N)	4556	4062	8618	1.2	0.4	0.6
		Testing	(%)	85	76	81			
	2006	Eligible	(N)	5157	4643	9800	1.3	0.6	0.7
		Testing	(%)	92	84	88			
Sierra Leone	2005	Eligible	(N)	NR	NR	8450	1.4	0.5	NC**
		Testing	(%)	NR	NR	98			
	2008	Eligible	(N)	3954	3541	7495	1.3	0.6	0.5
		Testing	(%)	86	80	83			
South Africa[‡]	2002	Eligible	(N)	3555	2766	6331	1.5	NC	0.8
		Testing	(%)	67	58	63			
	2005	Eligible	(N)	10204	13923	24127	1.6	NC	0.8
		Testing	(%)	68	62	65			
Tanzania	2003-2004	Eligible	(N)	7154	6196	13350	1.4	0.4	0.7
		Testing	(%)	84	77	81			
	2007	Eligible[†]	(N)	9735	7935[†]	17670	1.3	0.3	0.7
		Testing	(%)	90	80	85			
Zambia	2001-2002	Eligible	(N)	2689	4928	7617	1.2	0.6	0.7
		Testing	(%)	79	77	78			
	2007	Eligible	(N)	7408	7146	14554	1.2	0.8	0.7
		Testing	(%)	77	72	75			

* Unless otherwise specified, the number of eligible men and the testing coverage rate were among those aged 15 to 59 years

† Number of eligible men was available for those aged 15 to 54 years

[§] Testing ratios are calculated using the number tested in the first group divided by the number tested in the second group (e.g., females versus males)

** Data were either not collected (NC) or reported in the published report

[‡] The survey included persons under 15 and over 49 years of age but results on eligibility and testing coverage were available seperately for those aged 15 to 49 years also

Table 3.4 Characteristics of nationally-representative household-based population surveys by country and survey years.

Despite the fact that participation levels in the household surveys changed over time in most countries, the ratio of those testing by gender, urban and rural residence, and age remained relatively constant.

3.4.1 HIV prevalence estimates and trends for those aged 15 to 49 years

Table 3.5 shows the comparison of HIV prevalence estimates from ANC surveillance and household-based data for the seven countries with repeat household based population survey data from 2001 through 2010. Taking into account that the population survey included men and coverage of rural areas was more likely more extensive than ANC surveillance data, HIV infection levels overall were higher among pregnant women than the population of men and women combined for most countries. Relative differences in prevalence were typically greatest between pregnant women and men, especially in Mali, Sierra Leone and South Africa.

For countries in southern and eastern African countries, ANC and population prevalence estimates among women were roughly similar, although urban and rural ANC estimates understated estimates for these countries as a result of the exclusion of data from South Africa, where differences between ANC and female population prevalence were especially large. The greatest understatements of HIV prevalence were observed in the rural areas of southern and eastern African countries, primarily in Kenya and Tanzania. In the second round in Kenya, HIV prevalence among ANC attendees was just over half that of females generally (4.8% versus 8.0% respectively).

	Females						Males						National	
Country/	National		Urban		Rural		National		Urban		Rural			
Data Source/Years	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N
Kenya														
1 ANC (2003)	8.2	10500	10.5	3993	7.0	6507	--	--	--	--	--	--	--	--
POP (2003)	8.7	3151	12.3	779	7.5	2372	4.6	2851	7.5	716	3.6	2135	6.7	6001
2 ANC (2010)	4.8	12339	7.1	6325	4.3	6014	--	--	--	--	--	--	--	--
POP (2008-2009)	8.0	3641	10.4	862	7.2	2779	4.3	3066	3.7	798	4.5	2268	6.3	6707
Lesotho														
1 ANC (2003)	28.5	2666	35.0	1200	25.3	1466	--	--	--	--	--	--	--	--
POP (2004)	26.4	3031	33.0	735	24.3	2295	19.3	2012	22.0	407	18.6	1606	23.5	5043
2 ANC (2007)	28.7	2665	36.7	1077	23.9	1588	--	--	--	--	--	--	--	--
POP (2009)	26.7	2856	31.0	1235	24.6	2543	18.0	2041	21.4	806	16.6	2050	23.0	3778
Mali														
1 ANC (2002)	3.4	2776	3.4	2228	3.5	548	--	--	--	--	--	--	--	--
POP (2001)	2.0	3584	2.5	1009	1.9	2873	1.3	2978	1.9	863	1.1	2206	1.7	6846
2 ANC (2007)	2.6	3383	3.2	2742	1.3	641	--	--	--	--	--	--	--	--
POP (2006)	1.4	4528	1.8	1557	1.2	2971	0.9	3614	1.3	1361	0.6	2253	1.2	8141
Sierra Leone														
1 ANC (2006)	3.5	2453	4.0	2188	1.9	265	--	--	--	--	--	--	--	--
POP (2005)	1.6	4812	2.2	1626	1.3	3186	1.5	3496	1.9	996	1.3	2500	1.5	8308
2 ANC (2007)	4.0	2768	4.7	2468	1.0	300	--	--	--	--	--	--	--	--
POP (2008)	1.7	3448	2.7	1205	1.2	2243	1.2	2726	2.2	1040	0.6	1686	1.5	6174
South Africa														
1 ANC (2002)	26.5	16587	NR*	NR	NR	NR	--	--	--	--	--	--	--	--
POP (2002)	17.7	2372	NR	NR	NR	NR	12.8	1609	NR	NR	NR	NR	15.6	4795
2 ANC (2005)	30.2	16510	NR	NR	NR	NR	--	--	--	--	--	--	--	--
POP (2005)	20.2	5650	NR	NR	NR	NR	11.7	3595	NR	NR	NR	NR	16.2	9245
Tanzania†														
1 ANC (2003-2004)	6.8	17975	9.6	9846	3.6	8129	--	--	--	--	--	--	--	--
POP (2003-2004)	7.7	5755	12.0	1771	5.8	3982	6.5	4994	9.6	1505	4.8	3490	7.0	10747
2 ANC (2008)	5.4	17234	7.1	9375	4.5	7859	--	--	--	--	--	--	--	--
POP (2007-2008)	6.6	8179	10.6	2065	5.3	6114	4.6	6865	6.4	1605	4.0	5260	5.7	15044
Zambia														
1 ANC (2002)	18.9	12126	26.7	6827	9.7	5299	--	--	--	--	--	--	--	--
POP (2001-2002)	17.8	2073	26.3	808	12.4	1265	12.9	1734	19.2	676	8.9	1058	15.6	3807
2 ANC (2006)	16.1	12559	22.5	7013	10.0	5546	--	--	--	--	--	--	--	--
POP (2007-2008)	16.1	5502	23.1	2317	11.0	3185	12.3	4942	15.9	2148	9.4	2795	14.3	10444

* Data were not reported (NR) in the published report

† Rural ANC surveillance data includes women living in semi-urban and other non-urban areas

Table 3.5 Country-specific HIV prevalence estimates among those aged 15 to 49 years using data from national population based surveys and ANC surveillance and stratified by the year of the survey/surveillance round, gender and urban/rural area.

A review of the ANC surveillance and population survey data with regard to trends showed the epidemic overall to be either declining or stable in most countries regardless of the source of the data (See Table 3.6). Among pregnant women, declines in HIV prevalence nationally and separately by urban and rural residences were observed in Kenya and Mali. In Tanzania and Zambia, declines were observed nationally and in urban areas but not in rural areas. In the population survey, among women in South Africa, HIV prevalence increased from 17.7% in 2002 to 20.2% in 2005. Prevalence among men also primarily declined, although increases were observed for men in urban areas of Sierra Leone and in rural areas of Kenya and Zambia.

For those groups for whom HIV prevalence was falling, the steepest proportional declines (as measured for the overlapping inter-survey and inter-surveillance periods) were observed among ANC attendees in the rural areas of Mali (-51%) and Sierra Leone (-47%). The relative reduction in HIV prevalence among females generally in Mali was also large (-33%) but considerably smaller among women in Sierra Leone (-8%). Among men, proportional declines were greatest in the urban areas of Kenya (-51%) and in the rural areas of Mali (-40%) and Sierra Leone (-46%). Proportional increases in either data set were more tempered, with the largest relative gain in prevalence of 25% observed among men in Kenya. More typically, relative increases of HIV prevalence were less than 5%, as they were in both data sets in Lesotho and Sierra Leone.

	ANC change (%)	POP change (%)	Trend difference (p-value)	PR trend (ANC: POP)		Representativeness of ANC surveillance data
Kenya		**2003-2008**		**2003**	**2008**	
Females	-29.3%	-8.0%	0.009	0.9	0.7	**ANC↓ > POP↓***
Urban	-22.9%	-15.4%	0.563	0.9	0.8	ANC↓ > POP↓
Rural	-27.1%	-4.0%	0.038	0.9	0.7	**ANC↓ > POP↓***
Males[†]	--	-6.5%	0.530	1.8	1.3	ANC↓ > POP↓
Urban	--	-50.7%	0.022	1.4	2.2	**ANC↓ < POP↓***
Rural	--	25.0%	0.007	2.0	1.1	**ANC↓ & POP↑***
National	--	-6.0%	0.001	1.2	0.9	ANC↓ > POP↓*

	ANC change (%)	POP change (%)	Trend difference (p-value)	PR trend (ANC: POP)		Representativeness of ANC surveillance data
Sierra Leone		**2006-2007**		**2006**	**2007**	
Females	14.3%	6.3%	0.758	2.2	2.4	ANC↑ > POP↑
Urban	17.5%	12.5%	0.877	1.7	1.9	ANC↑ > POP↑
Rural	-47.4%	-7.7%	0.407	1.5	0.8	ANC↓ > POP↓
Males	--	-14.3%	0.286	2.5	3.1	ANC↑ & POP↓
Urban	--	10.0%	0.845	2.0	2.2	ANC↑ > POP↑
Rural	--	-45.5%	0.967	1.8	1.2	ANC↓ > POP↓
National	--	0.0%	0.536	2.3	2.7	ANC↑& POP=

Lesotho		**2004-2007**		**2004**	**2007**	
Females	3.0%	1.5%	NA	1.1		NA
Urban	3.7%	-8.5%	0.180	1.1	1.2	ANC↑ & POP↓
Rural	-4.4%	1.6%	NA	1.0		NA
Males	--	-9.3%	0.213	1.5	1.6	ANC↑ & POP↓
Urban	--	-3.6%	0.572	1.6	1.7	ANC↑ & POP↓
Rural	--	-15.1%	0.252	1.3	1.5	ANC↓ < POP↓
National	--	-3.0%	0.594	1.2	1.3	ANC↓ > POP↓

Tanzania		**2003-2007**		**2003**	**2007**	
Females	-16.2%	-14.3%	NA	0.9		NA
Urban	-20.8%	-11.7%	0.311	0.8	0.7	ANC↓ > POP↓
Rural	19.4%	-8.6%	0.034	0.5	0.8	**ANC↑ & POP↓***
Males	--	-29.2%	0.841	1.1	1.2	ANC↓ < POP↓
Urban	--	-33.3%	0.178	1.0	1.2	ANC↓ < POP↓
Rural	--	-16.7%	0.008*	0.6	1.1	**ANC↑ & POP↓***
National	--	-18.6%	NA	1.0		ANC↓ < POP↓

Mali		**2002-2006**		**2002**	**2006**	
Females	-17.6%	-26.3%	0.640	1.8	2.0	ANC↓ < POP↓
Urban	-5.9%	-21.7%	0.563	1.5	1.8	ANC↓ < POP↓
Rural	-51.4%	-33.0%	0.464	2.0	1.5	ANC↓ > POP↓
Males	--	-25.0%	0.744	2.8	3.1	ANC↓ < POP↓
Urban	--	-27.8%	0.465	1.9	2.5	ANC↓ < POP↓
Rural	--	-40.0%	0.691	3.5	2.9	ANC↓ > POP↓
National	--	-25.0%	0.665	2.1	2.3	ANC↓ > POP↓

Zambia		**2002-2006**		**2002**	**2006**	
Females	-14.8%	-6.3%	0.151	1.1	1.0	ANC↓ > POP↓
Urban	-15.7%	-8.5%	NA	1.0		NA
Rural	3.1%	-8.2%	NA	0.8		NA
Males	--	-3.1%	0.123	1.5	1.3	ANC↓ > POP↓
Urban	--	-11.8%	NA	1.4		NA
Rural	--	3.3%	NA	1.1		NA
National	--	-5.8%	0.720	1.2	1.1	ANC↓ > POP↓

South Africa		**2002-2005**		**2002**	**2005**	
Females	14.0	14.1	NA	1.5		NA
Males	--	-8.6	0.003	2.1	2.6	**ANC↑ & POP↓***
National	--	3.8	0.037	1.7	1.9	**ANC↑ > POP↑***

* Z-score values indicate that differences in the ANC and population survey trends are significant (p-value<0.05)

[†] Comparisons are made relative to the closest ANC estimate (e.g., ANC change (%) among rural females compared to POP change (%) in rural males; national compared to ANC females)

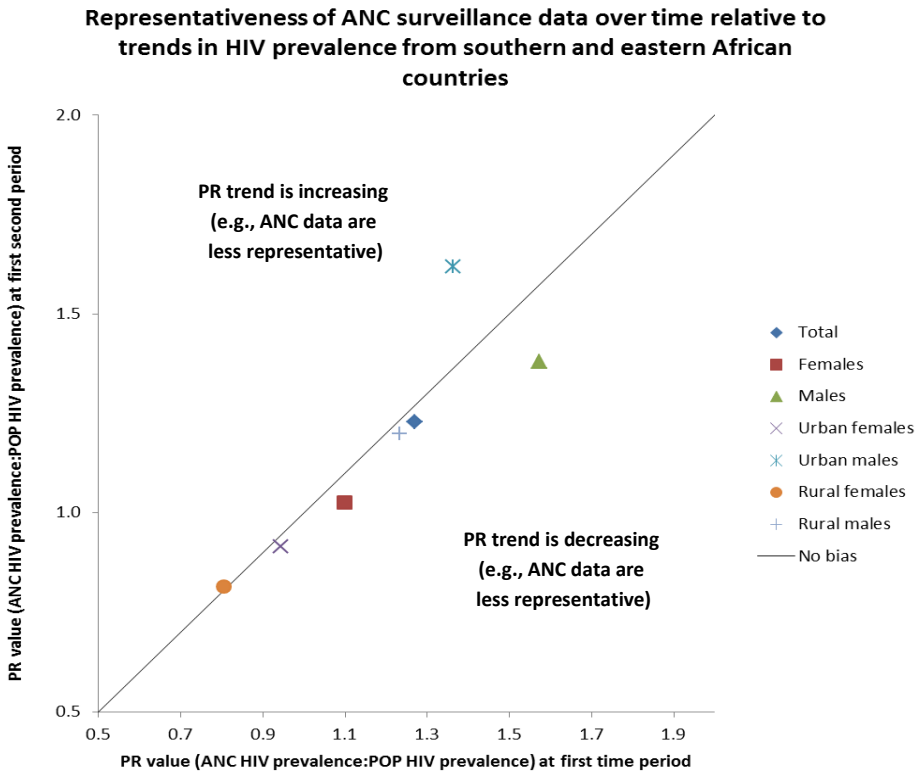
Table 3.6 Comparison of proportional changes in HIV prevalence during the overlapping inter-survey and inter-surveillance periods for adults aged 15 to 49 years using data from ANC surveillance (ANC) and population-based surveys (POP). Prevalence ratios (PR) represent HIV prevalence among ANC attendees versus HIV prevalence in the population. Cell colours show similarity with regard to the representativeness of the ANC surveillance data (e.g., orange cells show ANC declines were greater than population prevalence declines). Prevalence ratio values for which only one number is presented indicate that the value did not change over time.

With regard to the representativeness of ANC surveillance data for monitoring population HIV prevalence trends as measured by changes in the PR values over time, the overall ratio of HIV prevalence among ANC attendees versus population HIV prevalence was observed to be remarkably stable over time in southern and eastern Africa as illustrated in Table 3.7. Temporal bias was less stable for the two countries in western Africa, however, especially when stratified by gender in the rural areas (see Figures' 3.1a-b).

	All		**Southern and Eastern Africa**		**Western Africa**	
	PR trend (ANC: POP)		**PR trend (ANC: POP)**		**PR trend (ANC: POP)**	
Females	1.4		1.1	1.0	2.0	2.2
Urban females	1.2		0.9		1.6	1.8
Rural females	1.1	0.9	0.8		1.7	1.1
Males	1.9	2.0	1.6	1.4	2.6	3.1
Urban males	1.6	1.9	1.4	1.6	2.0	2.4
Rural males	1.7	1.5	1.2		2.6	2.1
Total	1.5	1.6	1.3	1.2	2.2	2.5

Table 3.7 Comparison of regional HIV prevalence ratio (PR) trends for adults aged 15 to 49 years stratified by gender and rural/urban area from ANC surveillance (ANC) and population (POP) prevalence data. Urban and rural southern and eastern Africa comparisons exclude South Africa, for which no disaggregated estimates were available. Prevalence ratio values for which only one number is presented indicate that this value did not change over time.

a)



b)

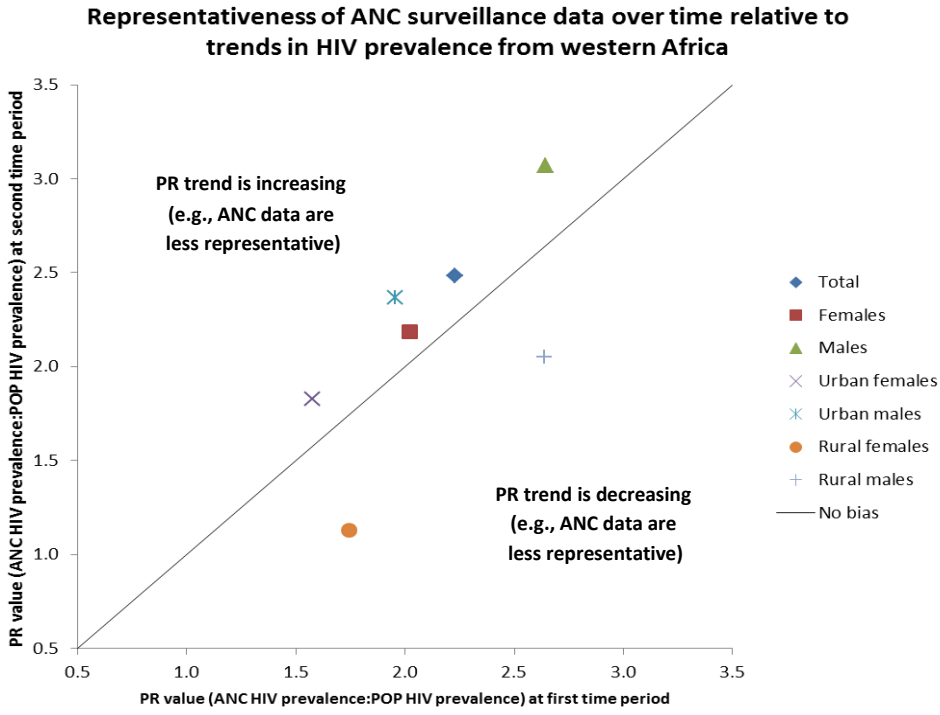
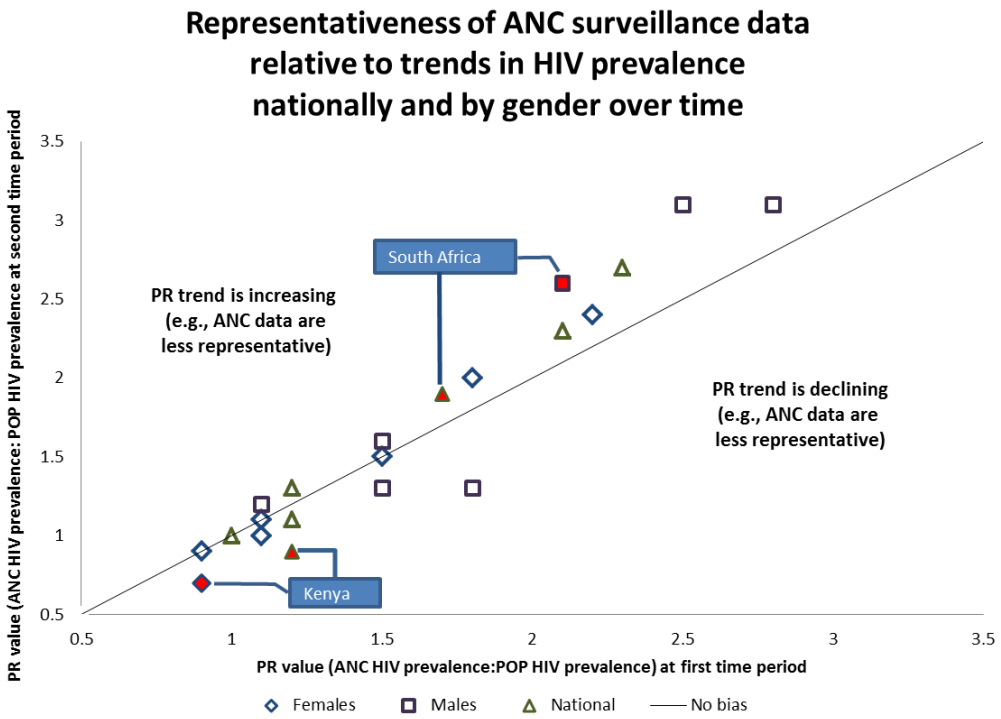


Figure 3.1 Comparison of adult prevalence ratios (PR) values from the two time periods in a) five southern and eastern African countries (Kenya, Lesotho, South Africa, Tanzania and Zambia) and b) two countries in western Africa (Mali and Sierra Leone). Urban and rural southern and eastern Africa comparisons exclude South Africa, for which no urban or rural estimates were available. Prevalence ratio values are calculated as the HIV prevalence among ANC surveillance attendees relative to population prevalence HIV estimates for the inter-survey and inter-surveillance period.

As the country-specific PR trends from Table 3.6 show, however, these regional aggregations masked considerable country-specific variation. For example, among all seven countries, only 8 of the 45 comparison groups had PRs that agreed over time (see national and gender-specific comparisons in Figure 3.2a and gender-specific comparisons disaggregated by urban/rural residence in Figure 3.2b). At the national level, this included comparisons between ANC and household-based data for Tanzania, and among females, also for Tanzania and for Lesotho and South Africa. Comparisons of trends between ANC attendees and men typically showed less steady PRs across all seven countries; however, when stratified by rural and urban residence, ANC data performed extremely well in Zambia for men (as they did for women). Trends in HIV prevalence in rural areas of Lesotho among women were also comparable over time, although not for females generally.

Of the 37 country-specific groupings where some variation over time in the PR values was observed, ANC surveillance data could still be considered generally representative of underlying population HIV prevalence trends in 29 of the comparisons (as measured by a p-value≥0.05 from the Z-score test for trend). In eight instances, however, ANC surveillance and population survey trends were found to differ significantly (i.e., p-value<0.05). For those 29 comparisons where the trends were not found to differ according to the Z-score test, ANC data were still relatively less representative of HIV prevalence trends among men as opposed to women.

a)



b)

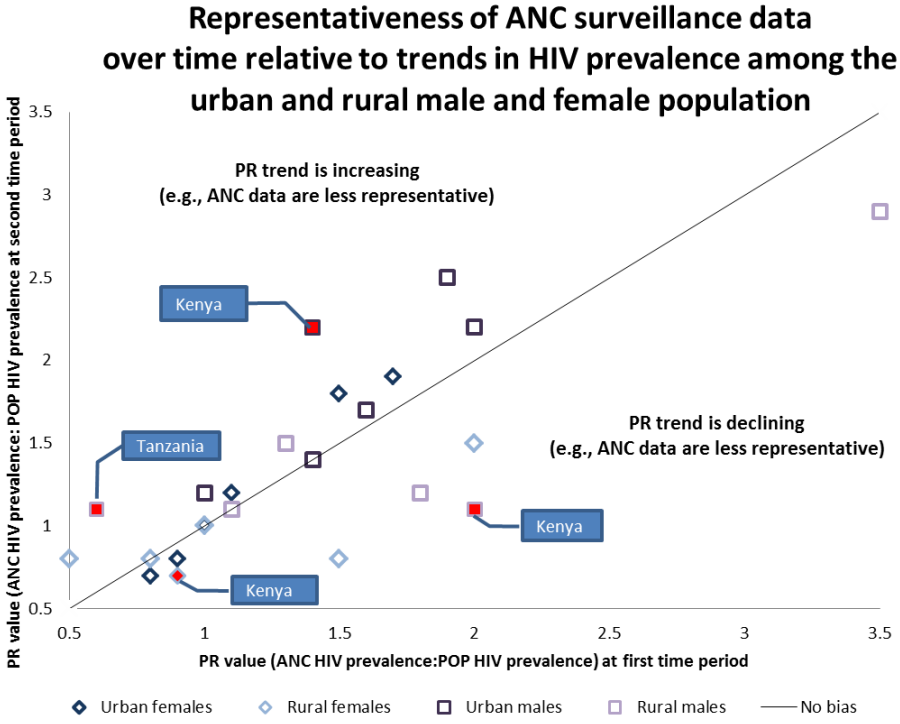
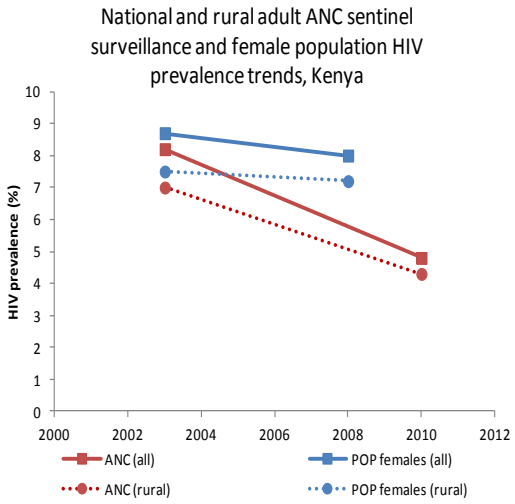


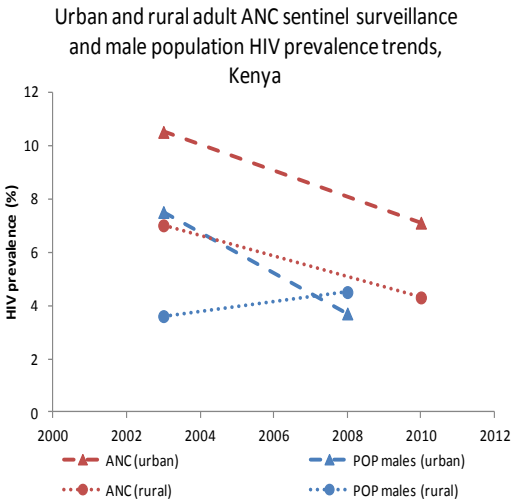
Figure 3.2 Comparison of prevalence ratios (PR) using data from national population-based surveys and ANC surveillance for adults aged 15 to 49 years, stratified by a) gender and b) gender and urban/ rural area. Markers in red indicate significant differences in trends over time as determined by the Z-score test. Prevalence ratio values are calculated as the HIV prevalence among ANC surveillance attendees relative to population prevalence HIV estimates for the inter-survey and inter-surveillance period.

In the eight instances where trends differed significantly, the poorest performance by ANC data occurred in three countries, Kenya, South Africa and Tanzania, and primarily involved comparisons with men or with those who lived in rural areas. In Kenya, Figure 3.3a shows the proportional declines among ANC attendees nationally and in rural areas, which were found to be significantly steeper than those occurring among females in the population generally. In the case of comparisons of ANC surveillance data to men, however, trends in HIV prevalence among pregnant women in urban areas understated declines in prevalence in the surrounding populations by about half as much. ANC surveillance data also failed to reflect an increase in HIV prevalence that was occurring in rural areas as well (see Figure 3.3b). The combination of differences in urban and rural trends and those between females and males resulted in a misrepresentation by the ANC surveillance data of population prevalence at the national data (see Figure 3.3c). Similar to the patterns among women as compared to ANC attendees overall and in rural areas, relative declines in HIV prevalence among pregnant women were nearly five times greater than that which was occurring in the population generally.

a)



b)



c)

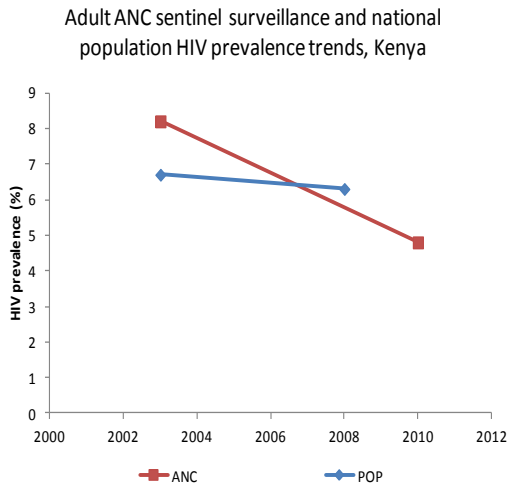
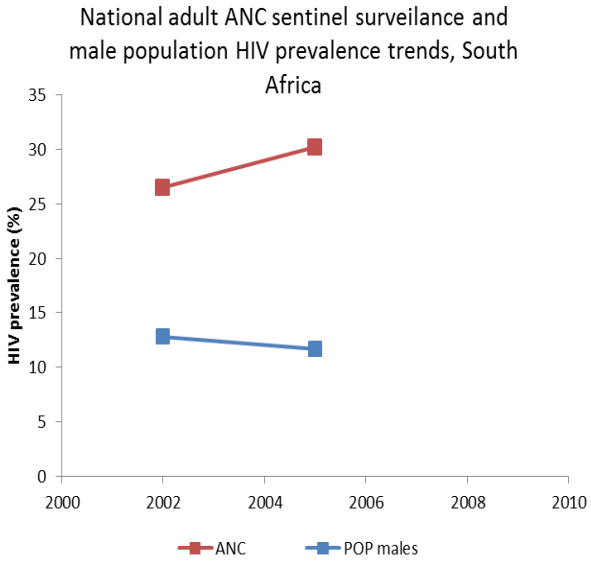


Figure 3.3 Comparison of HIV prevalence trends for those aged 15 to 49 years from ANC surveillance and household surveys in Kenyan a) females nationally and in rural areas; b) males in urban and rural areas; and c) nationally, among females and males combined from 2003 to 2008.

In South Africa, as was the case in Kenya, differences in patterns of HIV prevalence among female ANC attendees and men generally were also observed (see Figure 3.4a). As a result of these differences, national HIV prevalence trends were found to differ (as shown in Figure 3.4b), even though ANC surveillance data were very representative of patterns of infection among females over time.

a)



b)

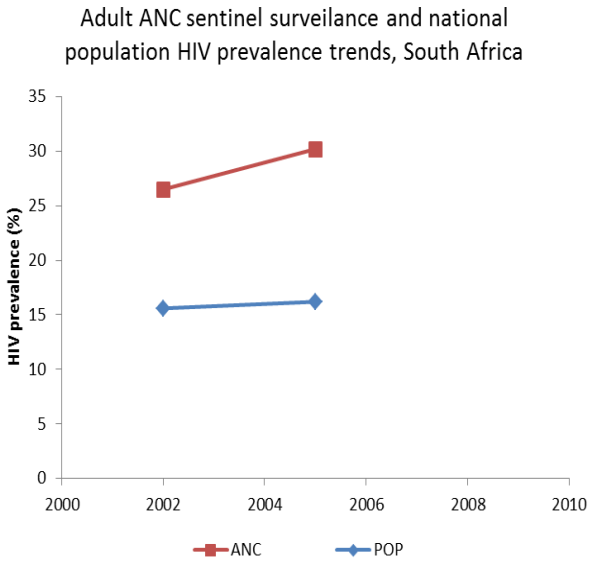


Figure 3.4 Comparison of HIV prevalence trends from ANC surveillance and household surveys in South Africa among adults aged 15 to 49 years a) nationally; and b) among males from 2002 to 2005.

Finally, in Tanzania, ANC surveillance data in rural areas showed an increase in HIV prevalence that contrasted significantly with a decline in HIV prevalence among men in rural areas (see Figure 3.5).

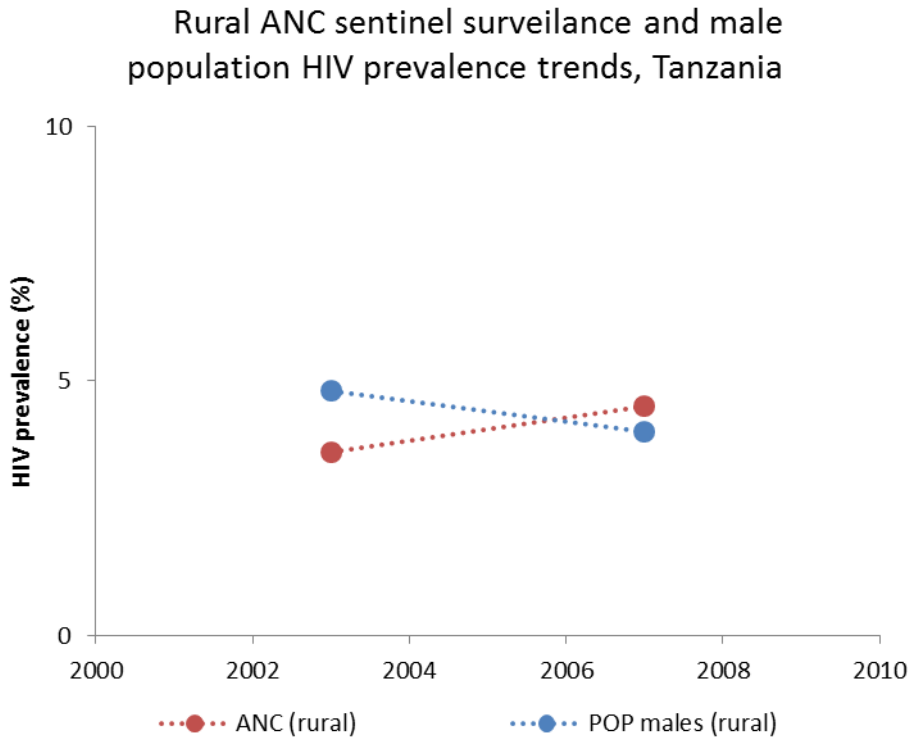


Figure 3.5 HIV prevalence trends among males aged 15 to 49 years from national population based surveys and ANC surveillance in Tanzania from 2003 to 2007.

In the urban areas and for men nationally, however, ANC surveillance trends tended to understate these declines, albeit not at a statistically significant level.

As can be observed from the above comparison of trends found to differ significantly, very few common patterns with regard to the overall representatives of ANC surveillance data were evident (see Table 3.6). In general, the tendency across countries was for ANC surveillance data to signal that the epidemic in the general population was declining faster than it actually was in the majority of comparisons; however, the data also frequently understated population prevalence declines or

showed increasing HIV prevalence for some groups, even as the underlying population prevalence trend among the comparison group had already begun to fall. In part, this may be explained by the poor representativeness of ANC clinics in rural areas and the differences in the rates of decline in median HIV prevalence in urban areas versus rural areas. However, no patterns were noticeably apparent when stratified by gender and according to urban or rural areas either.

3.4.2 HIV prevalence estimates and trends for those aged 15 to 24 years

Median ANC surveillance and population survey HIV prevalence estimates and trends for those aged 15 to 24 years for three countries, Lesotho, South Africa, and Zambia, are presented in Table 3.8.

		Females						Males						National	
		National		Urban		Rural		National		Urban		Rural			
Country/Data Source		(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	N
Lesotho															
1	ANC (2003)	24.7	NR	25.9	NR	24.0	NR	--	--	--	--	--	--	--	--
	POP (2004)	15.4	1342	21.4	273	13.9	1069	6.0	1026	4.7	160	6.2	866	11.3	2368
2	ANC (2007)	20.3	NR	24.8	NR	16.0	NR	--	--	--	--	--	--	--	--
	POP (2009)	13.6	1674	17.9	482	11.9	1192	4.2	1411	5.8	356	3.6	1055	9.3	3084
South Africa															
1	ANC (2002)	23.5	8263	NR	NR	NR	NR	--	--	--	--	--	--	--	--
	POP (2002)	12.0	1123	NR	NR	NR	NR	6.1	976	NR	NR	NR	NR	9.3	2099
2	ANC (2005)	28.6	5402	NR	NR	NR	NR	--	--	--	--	--	--	--	--
	POP (2005)	16.9	2335	NR	NR	NR	NR	4.4	1785	NR	NR	NR	NR	10.3	4120
Zambia															
1	ANC (2002)	18.6	NR	26.7	NR	9.5	NR	--	--	--	--	--	--	--	--
	POP (2001-2002)	11.0	855	15.2	394	7.5	461	3.0	675	3.7	276	2.6	399	7.5	1530
2	ANC (2006)	16.7	NR	22.5	NR	8.7	NR	--	--	--	--	--	--	--	--
	POP (2007-2008)	8.5	2225	11.1	1032	6.2	1193	4.3	2028	5.7	990	2.9	1038	6.5	4253

* Data were not reported (NR) to UNAIDS

Table 3.8 HIV prevalence estimates and trends among youth aged 15 to 24 years by gender and urban rural area using data from national population based surveys and ANC surveillance.

The relationship between HIV prevalence estimates among young ANC surveillance attendees and population survey participants was remarkably consistent across the three countries. The most extreme differences in HIV prevalence levels by gender and data source were observed between ANC attendees and young men. These differences reflect the higher risk of HIV infection among women at younger ages as compared to young men in SSA, the relatively older ages of pregnant women attending ANCs as compared to their peers in the general population, and the selection for risky sexual behaviour among women which differentially exposes them to HIV infection and to pregnancy [117]. Among young ANC attendees in the three countries, HIV prevalence was very high, and in some countries including South Africa and Zambia, higher than HIV prevalence among all ANC attendees, regardless of age.

With regard to trends among youth, ANC prevalence data generally reflected the underlying trend in the female population in Lesotho and South Africa, although differences were larger in Zambia than might have been expected given the relatively good agreement among adult female and ANC estimates (see Table 3.9). The largest proportional declines in HIV prevalence were observed among ANC attendees in rural Lesotho (-27.3%), although this was small compared to declines in the population among men in rural areas (-58.1%) and overall (-41.7%). Substantial increases in proportional HIV prevalence were also observed in all three of the countries, primarily among urban men in Lesotho and Zambia. In South Africa, prevalence appeared to be rising among women aged 15 to 24 years, regardless of the source of the data.

		ANC change (%)	POP change (%)	Trend difference (p-value)	PR trend (ANC: POP)		Representativeness of ANC surveillance data
Lesotho			**2004-2007**		**2004**	**2007**	
	Females	-14.0%	-16.2%	NA*	1.5	1.6	ANC↓ < POP↓
	Urban	-3.1%	-22.9%	NA	1.2	1.5	ANC↓ < POP↓
	Rural	-27.3%	-20.1%	NA	1.6	1.4	ANC↓ > POP↓
	Males†	--	-41.7%	NA	3.9	5.8	ANC↓ > POP↓
	Urban	--	31.9%	NA	5.5	4.0	ANC↓ & POP↑
	Rural	--	-58.1%	NA	3.4	6.3	ANC↓ < POP↓
	National	--	-24.8%	NA	2.1	2.4	ANC↓ < POP↓
South Africa			**2002-2005**		**2002**	**2005**	
	Females	21.7%	40.8%	0.162	2.0	1.7	ANC↑ < POP↑
	Males	--	-27.9%	<0.001	3.9	6.5	**ANC ↑ & POP↓***
	National	--	10.8%	0.271	2.9	2.8	ANC↑ > POP↑
Zambia			**2002-2006**		**2002**	**2006**	
	Females	7.7%	-16.0%	NA	1.5	1.9	ANC ↑ & POP↓
	Urban	-18.8%	-18.6%	NA	1.9		NA
	Rural	-8.4%	-12.3%	NA	1.3	1.4	ANC↓ < POP↓
	Males	--	28.1%	NA	4.8	4.1	ANC↑ < POP↑
	Urban	--	35.0%	NA	6.2	4.2	ANC↓ & POP↑
	Rural	--	7.4%	NA	3.2	3.1	ANC↓ & POP↑
	National	--	-8.2%	NA	2.1	2.5	ANC↓ > POP↓

* Z-score values indicate that differences in the ANC and population survey trends are significant (p-value<0.05). Tests could not be done for Lesotho and Zambia because the ANC sample sizes were not available (NA).

† Comparisons are made relative to the closest ANC estimate (e.g., ANC change (%) among rural females compared to POP change (%) in rural males; national compared to ANC females)

Table 3.9 Comparison of HIV prevalence trends among youth aged 15 to 24 years by gender and urban rural area using data from national population based surveys and ANC surveillance. Prevalence ratio (PR) values are calculated as the HIV prevalence among ANC surveillance attendees relative to population prevalence HIV estimates for the same year. Z-score tests for the significance of trends could not be done for Lesotho and Zambia because the sample sizes of the ANC populations were not available. Trends differences for these comparisons are indicated as not available (NA)

In terms of the representativeness of the data, comparison of PR values over time showed only those from women in the urban areas in Zambia to be the same (See Figure 3.6). Generally, however, bias in ANC data was relatively stable over time in all comparisons to young females. As was true of comparisons of adult trends, ANC data appeared to be less representative of trends among young men. In rural areas of Lesotho, for example, among young men, the PR ratio increased from 3.4 in 2004

to 6.3 in 2007 while the change in women was from 1.6 to 1.4. The same was true for young men and young women in urban areas in Zambia.

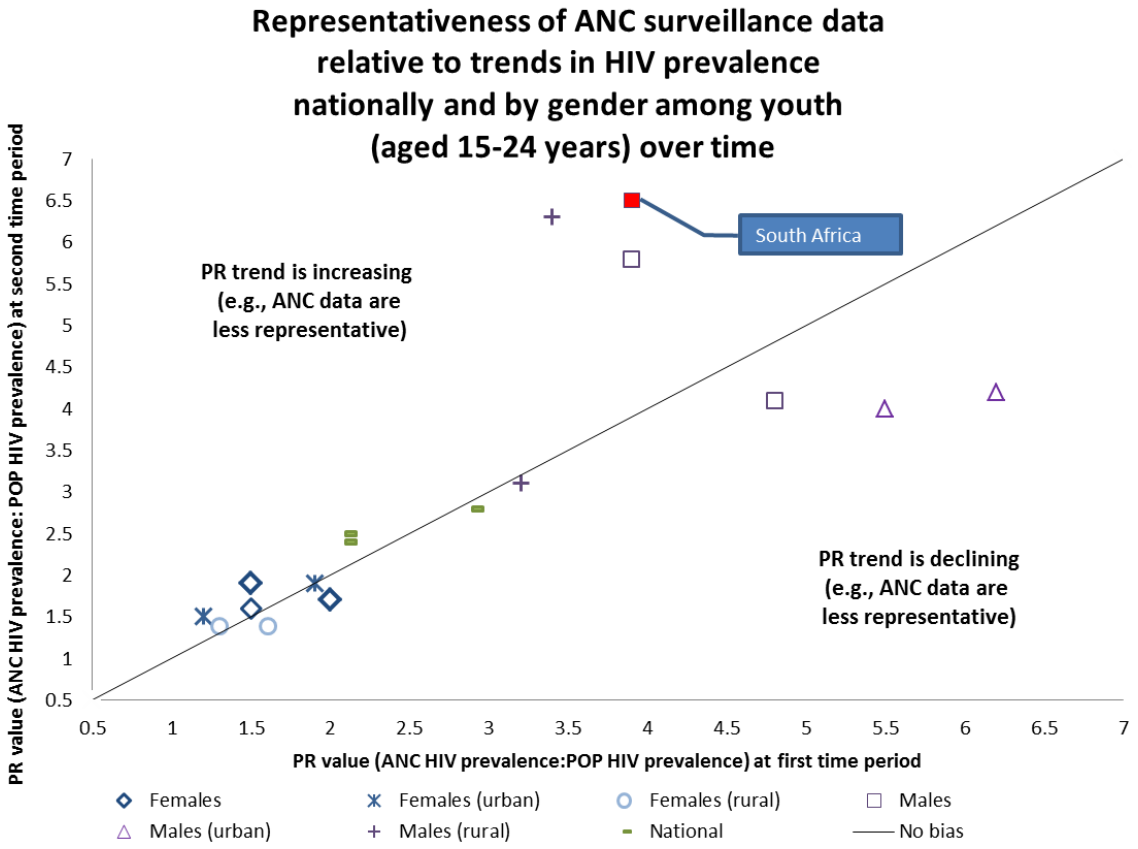


Figure 3.6 Comparison of HIV prevalence ratios (PR) among youth aged 15 to 24 years using data from national population-based surveys and ANC surveillance nationally, by gender and within urban or rural area. The marker in red for South African men indicates a significant difference in trends over time as determined by the Z-score. Prevalence ratio (PR) values are calculated as the HIV prevalence among ANC surveillance attendees relative to population prevalence HIV estimates for the same year.

In South Africa, where the difference in trends could be compared directly, Figure 3.7 shows that ANC and male population HIV prevalence trends differed significantly (p-value<0.001).

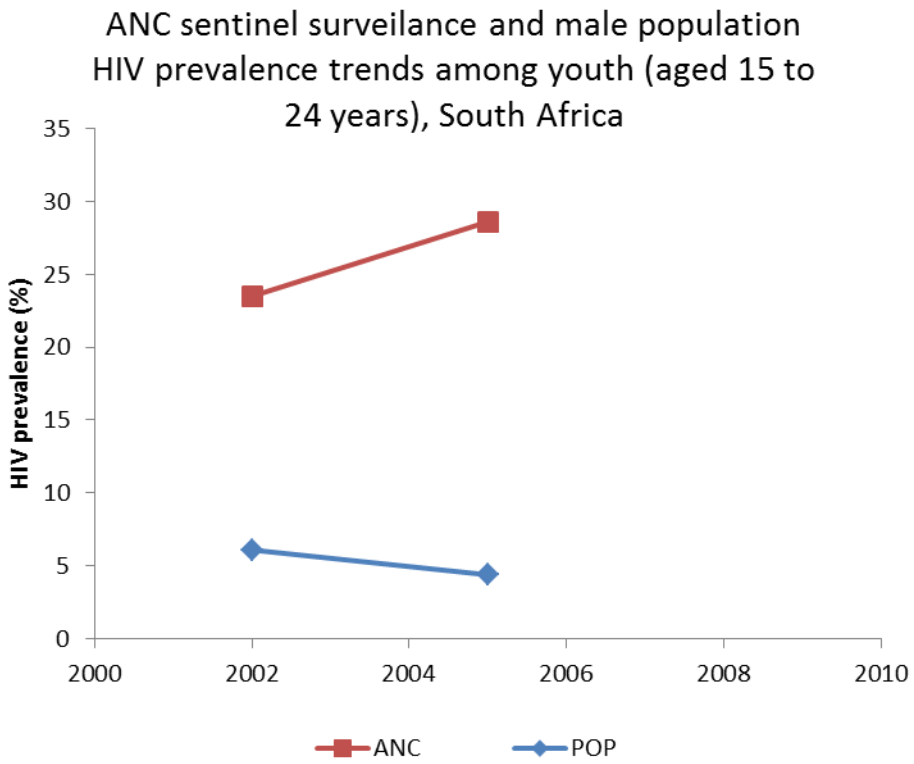


Figure 3.7 HIV prevalence trends from national population based surveys and ANC surveillance among youth aged 15 to 24 years in South Africa from 2002 to 2005.

In this case, HIV prevalence among young ANC attendees was observed to be rising while HIV prevalence trends among young men over the same time period had fallen.

3.5 Discussion

Comparisons of ANC surveillance and population prevalence trends among adults showed that ANC surveillance data generally performed better as a means of monitoring population prevalence trends in countries in southern and eastern SSA as opposed to in the two countries in western SSA. ANC surveillance data were also observed in these comparisons to be more representative of adult female population prevalence trends, as opposed to trends among men, and of urban areas, as

opposed to rural areas. For countries with data for youth aged 15 to 24 years, similar conclusions about the representativeness of ANC surveillance data among females and in urban areas can be drawn, although these conclusions are based on data from three countries only. Comparisons of estimates in ANC surveillance data in particular may be influenced by differences in rates of declines in urban and rural areas, thus results stratified by gender and rural and urban areas may provide the best indication of the representativeness of these data.

The patterns described above are useful when assessing the general representativeness of ANC surveillance data to monitor population prevalence trends regionally and globally; however, these generalizations masque a variety of experiences at the individual country level. For example, ANC surveillance seemingly performed best in Zambia for monitoring adult population prevalence trends in particular; however, they also performed very poorly in Kenya in almost every instance. In Sierra Leone, bias in national estimates increased between survey rounds at a pace that was even greater than that which was observed in Mali.

Notably, the conclusion that ANC surveillance data were especially representative of population prevalence trends in Zambia contrasts with a previous, smaller study by Michelo and colleagues, where estimates from an urban ANC clinic in Lusaka from 1995 to 2002 were found to significantly understate HIV prevalence declines in the surrounding catchment population over the same time period [116]. Increasing levels of education associated with a later age at first marriage and first pregnancy among young women were thought to explain the temporal bias in ANC trends. Results presented here for Zambia similarly showed that ANC surveillance data understated declines in HIV prevalence among young urban woman, although this difference was not found to be significant. Differences in methods used to

quantify the comparisons and the geographical scope of the comparisons (e.g., in Lusaka versus national) can explain these contrasting conclusions, although differences in the timing of the two studies are the most likely explanation. In the Lusaka study, the proportion of females and males aged 16 to 24 years attending school in Zambia rose between 1992 and 2002, however, from 2002 to 2007 this proportion remained unchanged [214, 215, 225, 226]. This suggests that temporal changes in bias due to changing educational and fertility patterns among young women would have been relatively smaller in the 2000s, as is apparent from the results presented here.

In Kenya, where ANC surveillance data were found to be particularly poor at monitoring population prevalence trends, significant differences in trends were observed among a variety of groups, including for comparisons at the national level, among females generally and those living in rural areas, and separately among men and for those men living in either urban or rural areas. For the majority of these comparisons, HIV prevalence among pregnant women appeared to be declining more steeply than in the population. Importantly, these trends have been reported separately in national reports [206, 222] but a more thorough exploration of the differences has not yet been published. One possible explanation for the poor performance of ANC estimates (although not the only one) is that the geographic coverage of participating clinics is insufficient. Using data from the 2003 DHS survey in Kenya, Montana and colleagues found unusually large sub-regional differences in prevalence of the country by gender and rural and urban residence which suggest that the epidemic is highly heterogenic [119]. When taken together with the results presented here, there is strong evidence for a need to increase the number and

geographical representativeness of ANC clinics in the country or to move away from ANC surveillance in Kenya if the number and diversity of clinics cannot be improved.

One of the key findings to emerge from this analysis, as highlighted by the results in Kenya, is that very few similarities were evident with regard to the ways in which ANC surveillance data mis-represented underlying population HIV prevalence trends. Strictly speaking, ANC surveillance data among adults more frequently overstated population prevalence declines, although other patterns were apparent in South Africa, Sierra Leone and Tanzania. In a previous study, Gouws and colleagues recommended that ANC estimates used to construct national HIV prevalence estimates in EPP should be adjusted downwards by 20% for those countries without a population survey [45]. Application of this adjustment method here across the southern and eastern region of SSA where prevalence is highest would appear to be appropriate, however, at the individual country level, the application of a constant standard could distort population prevalence trends.

With regard to the reasons why trends were observed to differ in some countries, three explanations are possible. First, ANC and population survey trends could be observed to differ due to changes in sexual behaviour over time. For example, some studies have shown that ANC data will understate population prevalence declines among women due to a rapid increase in the age of sexual debut [117, 227] or successful condom prevention programmes [113]. The increasing availability of repeat DHS data should permit a greater understanding of the impact of changes in sexual risk behaviour on HIV prevalence trends.

A second possible explanation for differences could be that fertility and age patterns of HIV infection in the country are changing over time, which results in the differential inclusion or exclusion of HIV-infected women in the ANC sample over

time. For example, HIV prevalence among ANC attendees may decline more steeply relative to population prevalence as the epidemic matures because the median age of HIV-infected women in the population increases and these women are increasingly excluded from the ANC sample due to age and HIV-related sub-fertility [115]. HIV prevalence among ANC attendees could also rise more quickly relative to the general population, and when compared to women specifically, if new infections are increasing among younger women at peak fertility ages or if fertility of HIV infected women is restored after introducing ART. In the countries included here, neither of these explanations is particularly likely as bias in ANC estimates due to changes in age are thought to be stable in mature epidemics [115] and ART access was generally limited in the years in which these surveys were conducted [228]. Chapter 4 explores in more detail factors related to changing fertility patterns, age, and ART use on bias in ANC surveillance estimates over time.

A third possible reason for differences between trends from these two datasets is that characteristics inherent to the surveys and its participants have changed over time. In this analysis, for example, repeated population surveys are assumed to be the “gold standard“ indication of population-level HIV prevalence trends. In practice, however, participation levels in the population surveys in all countries (except Zambia where representativeness of ANC surveillance data were generally better than in other countries) were shown to vary across surveys periods, thus these data may not be the best measure of true prevalence trends if participation is conditioned on HIV status. As discussed in Chapter 1, however, a large study by Mishra and colleagues using DHS and DHS-like data from 14 countries (including much of the data from countries reported here) suggested that the effect of non-participation bias on population estimates was likely to be minimal,

especially in countries where HIV prevalence was relatively higher [74]. One key limitation to that study's conclusions, however, was that the accuracy of population prevalence estimates adjusted for non-participation depended on the extent to which socio-demographic and behavioural characteristics correlated with risk of HIV infection. Further analysis suggested that these characteristics were not especially predictive of HIV prevalence among testers in the countries considered, thus it is possible that the impact of non-participation bias on population survey estimates was discounted. A second limitation of that study was that it did not consider the extent to which changing levels of refusal bias over time could influence the validity of the data to monitor true population prevalence trends, as analyses were limited to a single study only. So long as the impact of bias on population estimates at any one survey period is negligible, however, temporal bias due to non-participation is unlikely to explain the differences in trends.

ANC surveillance data also suffer from methodological changes that could themselves contribute to bias in estimates over time. For example, among ANC attendees, socio-demographic factors or behaviour risk associated with HIV infection and ANC uptake at a particular clinic could have shifted over time, and these factors are seldom described in regard to their potential for contributing to bias in estimates. Another potential source of bias can be introduced when ANC uptake is changing over time, although uptake for most countries apart from Mali was reasonably high, and unchanging over time. Changes in HIV testing algorithms can also play a role in introducing bias in estimates over time, although this was not explored in detail here as most countries take precautions to validate new testing procedures as they are introduced.

The methods that were used to compare trends over time were selected so as to frame these results in terms of commonly used measurements of proportional reductions typically cited by UNAIDS. These methods suffer from a number of limitations, however, with the most important one being that the Z-score test takes into account the number of ANC participants while in practice, HIV prevalence is based on the median clinic HIV prevalence. This is unlikely to have a large influence on the validity of the comparisons, however, as overall samples sizes were relatively stable over time due to the inclusion of consistently participating clinics. The exception to this was in South Africa, where those clinics not consistently participating were unable to be removed and in Kenya, where sample size targets changed over time in the rural and urban areas. With regard to the latter finding, even if sample sizes in Kenya had remained the same at both rounds, findings regarding the number and type of significant differences in trends would have remained, although the variance around the estimates would have been larger. Still, differences with regard to clinic participation in South Africa and lack of rural and urban estimates can introduce a substantial challenge when interpreting the representativeness of ANC surveillance data in the country.

Another limitation, though not necessarily of this study specifically, was that for many of the countries included here, surveillance rounds and population surveys were conducted in different years. As a result, estimates from one survey or surveillance round had to be imputed. To address this problem, other studies comparing ANC and DHS estimates (rather than trends) have used EPP to construct fitted urban and rural HIV prevalence curves from ANC surveillance data (and not calibrated to population survey data) and then selected the estimate for the appropriate year [45, 46]. As the primary purpose of the analysis here was to

compare trends rather than levels, fitted estimates may be less important. Notably, the methods used here are similar to those in another analysis of trends using ANC surveillance data by Gouws and colleagues, although that analysis did not take into account the differences in the time periods compared [21].

Other limitations of this study in terms of the ability to draw conclusions about the usefulness of ANC surveillance data to monitor population prevalence trends is that the data presented here are drawn from only two data points (which span less than 10 years in time). Also, the number of countries with repeat population survey data is limited; thus, these results are extremely limited in their generalizability to the region and to SSA as a whole. Furthermore, extreme differences in Sierra Leone's participation levels between survey rounds and the low and changing level of uptake of ANC services in Mali suggest that results for these countries in particular are susceptible to mis-representation of true population prevalence population and ANC trends, respectively. As additional surveys and ANC surveillance data become available in the future, it will be important to extend these analyses, especially to assess whether patterns in bias become clearer such that an adjustment factor could be proposed to compensate for any temporal bias in ANC surveillance data during those years in which population survey data are not available. More importantly, additional data points can be used to determine the extent to which bias is likely to remain stable over time in a country, thus providing reassurances to countries that ANC surveillance data are a good indicator of the impact of targeted HIV prevention interventions.

In summary, while the results here do not test specific hypotheses for why ANC surveillance trends might differ from those in the underlying population, they do provide an easy method for countries with repeat population-based surveys to

quickly assess whether or not ANC data are representative of underlying population prevalence trends and where differences may be most apparent. They also illustrate that for women of all ages and among young women in particular, ANC surveillance data do appear to do reasonably well at monitoring population HIV prevalence trends, particularly in southern and eastern Africa; although for other groups, caution may be required when relying on these data. Finally, the results provide insight into where additional investigations may be warranted within these countries to explore why interventions in one population group versus another may not be producing an expected impact or ways in which ANC surveillance can be improved. In Chapter's 4 and 5, further investigations into specific causes of differences in ANC and population prevalence trends in selected countries in SSA and among youth in Manicaland, Zimbabwe, in particular, are considered.

Chapter 4: Mathematical modelling of bias in HIV prevalence trends among ANC attendees

4.1 Aims and organization of the chapter

The overall aims of this chapter are to (i) validate historical trends in ANC prevalence in declining epidemics typical of three countries in SSA (Botswana, Côte d'Ivoire, and rural Zimbabwe) and (ii) explore how different scenarios of ART expansion associated with changing fertility patterns among women in these countries might influence trends in ANC and female population prevalence among adults aged 15 to 49 years. These scenarios are considered for the pre-ART era from 1985 to 2002, and, after introducing ART, from 2003 to 2030 using mathematical modelling for each setting.

The chapter begins briefly by reviewing the reasons why HIV prevalence trends might differ between ANC and population data, with a focus on the implication for bias given changes in the age and fertility patterns of women in the population and the introduction of ART in declining epidemics. In the next section, a description of the mathematical model and its parameters is provided. Results from the model are presented first for the pre-ART era in the three settings and secondly in the ART era (assuming faster and higher levels of ART coverage area in Botswana and slower and lower levels of ART coverage in Côte d'Ivoire and rural Zimbabwe). The chapter concludes by comparing these results to previous work and highlights the potential areas for concern when using ANC surveillance data to monitor the HIV epidemic.

4.2 Introduction

As Chapters' 1 and 2 illustrated, ANC surveillance data have historically been used as the foundation for monitoring the HIV epidemic in SSA. However, these data have been, and continue to be, subject to multiple sources of selection and structural bias.

Briefly, these biases are (i) the lack of geographic representativeness in the selection of participating ANC clinics [65]; (ii) the self-selection of women who have access to and who use ANC services [51]; and (iii) the limitation of testing only those women who become pregnant [42, 47, 55, 56, 112]. As has been illustrated, these biases can have varying influence on the accuracy of ANC-based estimates and trends.

As the previous chapter also showed, bias in ANC estimates relative to population survey data does appear to be changing over time in some countries. However, because the period of time over which these comparisons can be made is relatively short, it is ultimately difficult to draw conclusions about the representativeness of ANC surveillance data. Also, little can be said about the historical representativeness of ANC surveillance data before the 2000s, or the representativeness of ANC data beyond 2012, and most importantly during the ART era. One of the biggest concerns, historically, has been whether age-specific fertility patterns and HIV-associated morbidity, in addition to changes in the average age of women who are infected, will affect the reliability of ANC surveillance trends, especially as incidence declines due to changes in behaviour [41, 115]. More recently, the influence of a recent and rapid expansion of ART on the validity of ANC trends in SSA also has the potential to bias estimates. As of 2008, nearly 3 million people were receiving ART in SSA, representing a 30-fold increase in coverage since 2003 [229]. Based on this expansion, it is predicted that HIV estimates in the population may begin to decline more slowly or even rise due to extended survival. Whether HIV prevalence among ANC attendees, who are younger and likely more recently infected, will accurately capture these changes in prevalence in the ART era is unknown. Finally, it has been hypothesised that women on ART could experience different fertility levels due to improved health or behaviour change. If ART use

results in a decline in fertility, possibly due to increased contraceptive use, differences in trends could be exacerbated over time as HIV-positive women are increasingly excluded from the ANC sample. If, however, ART use results in an increase in fertility, which is most biologically plausible [165], differences in trends over time may dissipate gradually. Predicting the magnitude and direction of these changes will be critical in future years if ANC surveillance data continue to be the primary source for monitoring population prevalence trends.

To explore how ART expansion might influence trends in ANC and population prevalence, and to validate historical trends in ANC prevalence in a declining epidemic, a mathematical model that quantifies bias in ANC trends was developed. These patterns are assessed during the pre-ART era from 1985 to 2002, and, after introducing ART from 2003 to 2030. A range of potential fertility patterns among ART users as compared to uninfected women is explored. Model parameters and methods for measuring temporal biases are described further below.

4.3 Methods

An individual-based stochastic cohort model written in C++ was developed by Dr. Tim Hallett of Imperial College London to study the relationship between HIV prevalence trends in pregnant women and women of all reproductive ages (defined as aged 15 to 49 years) from 1985 to 2030. Under his guidance, model parameters were selected to reflect HIV epidemics typical of sub-Saharan Africa over a forty-five year period, namely: (i) high and declining HIV incidence, as in Botswana [20] and rural Manicaland, Zimbabwe [26, 230]; and (ii) low and declining HIV incidence, characteristic of Western African countries such as Côte d'Ivoire [22]. The effect of

naturally declining fertility rates in rural Zimbabwe, for which there is some evidence in the late 1980s through the early 2000s [153], is also investigated. A brief description of the stochastic cohort model follows. A full description of the original model by Hallett and colleagues is described in a previous publication [231, 232].

4.3.1 Model description

As previously noted, this model is based on an earlier approach to explore the impact of treatment on health outcomes and the potential for bias in child mortality statistics in countries in SSA with generalized HIV epidemics [231, 232]. Detailed specifications on the construction of the birth cohorts, probability of death without HIV, and the iterative nature of that model are provided in the online appendix [232]. Briefly, model is individual-based stochastic micro-simulation model that probabilistically calculates the time to the next event (e.g., pregnancy, HIV infection, death) for each individual according to specified parametric distributions. This process then repeated until the individual dies. With regard to the simulation within the broader population, the model is run 50 times, with the same set of model parameters so that the only variability is the stochastic variability. Results are then averaged across the 50 runs to produce a single set of estimates of trends in HIV prevalence among pregnant women and the general population. To reduce computation time in the model, one woman in the simulation represents 100 women in the population. Appendix B summarizes the model's key parameter values.

Briefly, to model bias in estimates, a series of birth cohorts representing women born between 1955 and 2015 is created. Yearly population size is determined by country-specific census data estimates and projections published by

the UN Population Division [224]. Women in each birth cohort form the adult female population who are then tracked over their life during the years between 1980 and 2030. An illustration of a woman's life course (Figure 4.1a) and fertility cycle (Figure 4.1b) as modelled in the simulation is shown below.

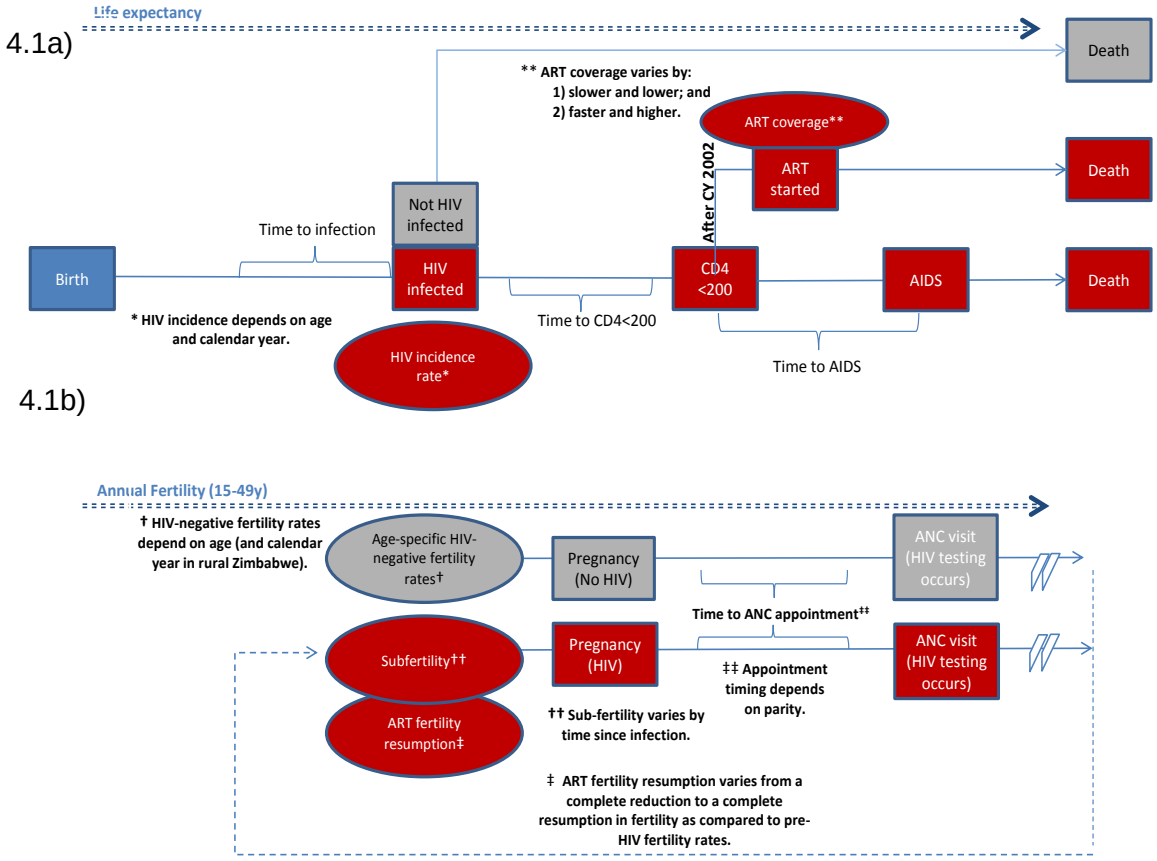


Figure 4.1 Illustrated depiction of the a) life expectancy and b) annual fertility cycle of a woman in the stochastic cohort model. Gray rectangles indicate an event of interest in the model for an HIV-negative woman. Red rectangles indicate an event of interest in the model for an HIV-infected woman. Ovals represent parameters determining the outcome of the event (e.g., HIV-infected or not, pregnant or not, on ART or not). Parameter ovals applicable to only HIV-positive women are shown in red. ART is introduced only after the 2002 calendar year (CY).

In the model, a woman's exposure to four events is tracked: (i) HIV infection; (ii) pregnancy (and an ANC visit at three months when she is tested); (iii) ART use; and (iv) death. Beginning at age 15, women are subjected to a per annum and age-specific HIV infection hazard which is used to determine probabilistically the timing of

the infection or whether the women is never infected. Calculations of hazards are based on estimates of annual incidence in women from ANC and population survey HIV prevalence data provided by UNAIDS (personal communication 18/01/2011). For Zimbabwe, because the focus of the simulations was on trends in rural areas rather than nationally, estimated incidence rates were available in rural areas for both sexes combined only. HIV incidence data used to parameterize the simulations in Botswana, Côte d'Ivoire and rural Zimbabwe are for illustrative purposes only. Figure 4.2 shows the trends in HIV incidence through 2010 provided by UNAIDS.

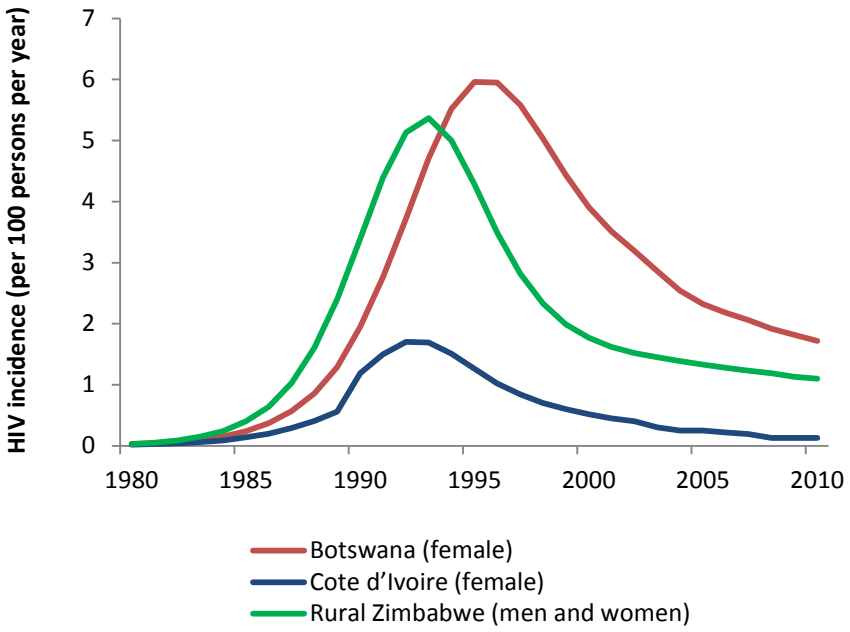


Figure 4.2 Assumed calendar year trends in HIV incidence per 100 persons aged 15 to 49 years per year in Botswana (red line), Côte d'Ivoire (blue line) and rural Zimbabwe (green line), 1980-2010. In Botswana and Côte d'Ivoire, incidence is for women only. In rural Zimbabwe, trends are for men and women combined. Beyond 2010, incidence is assumed to decline through 2030 based on the average decline from 2005 to 2010.

Beyond 2010, HIV incidence in all three settings is assumed to decline through 2030 based on a moving average of the decline over the previous 5 years.

Age-specific relative HIV incidence patterns were constructed by Hallett using prevalence data from repeated national population surveys [75]. These estimates are

shown in Figure 4.3, and describe incidence patterns per 100 person years by age relative to the average incidence in the country. For Botswana, because not all required data were publically available to construct these estimates, national Zimbabwe population survey data were used instead [233, 234]. For rural Zimbabwe simulations, direct measurement was made from rural Manicaland cohort data [235]. Estimates of incidence in Côte d'Ivoire were based on estimates of HIV prevalence from the 2005 DHS survey. Constant prevalence was assumed to produce the age-specific estimates of incidence for the model. This resulted in an estimate of HIV incidence for those aged 40 to 49 years that is well above what might be expected in sub-Saharan Africa. Additional investigation is needed to understand whether these rates truly reflect higher incidence or are more likely the result of peculiarities in migration or mortality patterns in the population, differences in the representativeness of the population survey data over time, or random statistical error. In the latter case, for example, CIs around the estimates for those aged 40 to 49 are extremely wide (not shown).

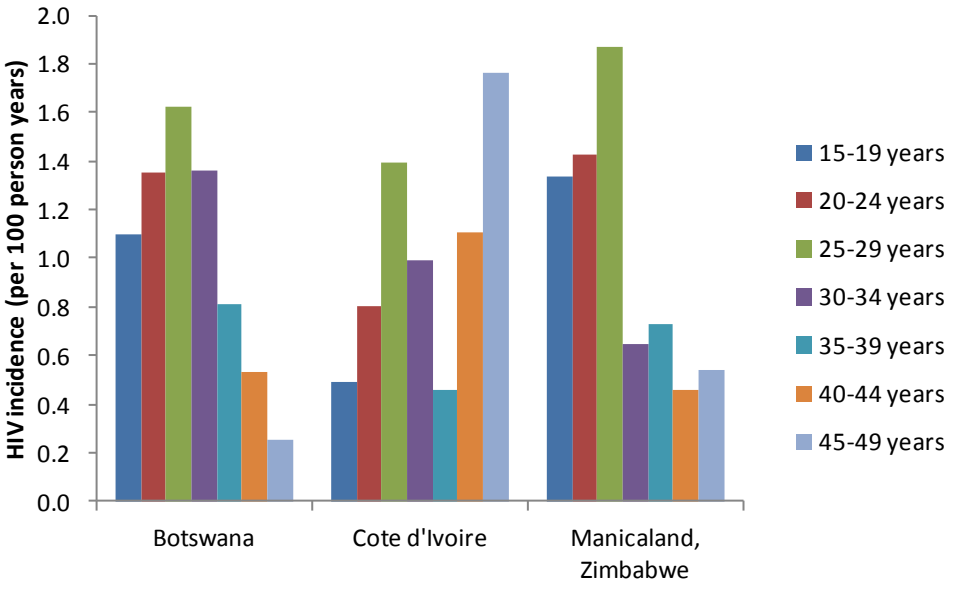


Figure 4.3 Patterns of HIV incidence among women by five year age groups in Botswana, Côte d'Ivoire and rural Zimbabwe, calculated from repeated national population surveys. For Botswana, because not all required data were available to construct these values, national Zimbabwe population survey data were used instead [233, 234]. For rural Zimbabwe, direct measurement was made using previously published data from the Manicaland cohort [235].

In the model, for each year of a woman's life, the hazard of pregnancy is used to determine probabilistically the timing of pregnancy. A woman's likelihood of becoming pregnant is determined by age-specific fertility rates and her HIV status. For HIV-negative women in Botswana and Côte d'Ivoire, DHS data from the mid-1980s and early 1990s (prior to when HIV might have negatively influenced fertility rates) were used (See Figure 4.4) [236, 237].

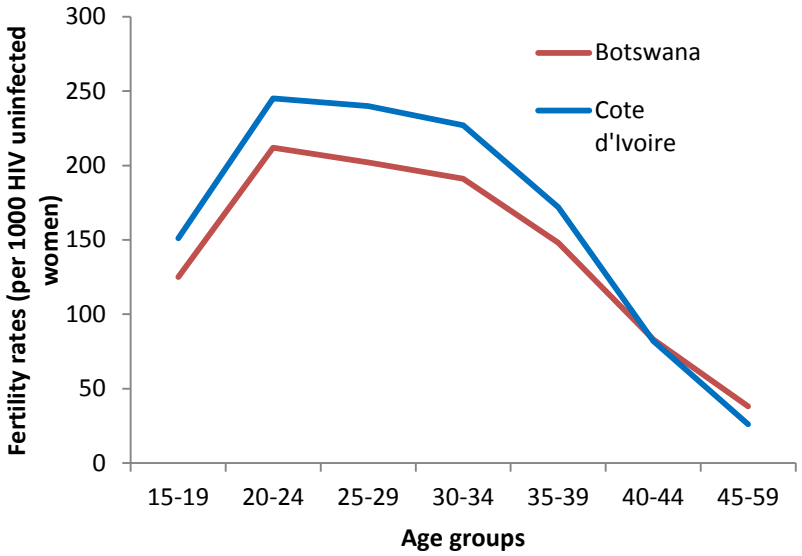


Figure 4.4 Age-specific fertility rates (per 1000 HIV-negative women) in Botswana (red line) and in Côte d'Ivoire (blue line) [236, 237].

In rural Zimbabwe, scenarios where fertility rates are either (i) stable or (ii) declining over time (and independent of the HIV epidemic) are explored. Stable age-specific fertility rates from rural Zimbabwe are taken from the 1988 DHS [238]. Fertility rate declines are calculated as a linear decrease between the 1988 estimates and age-specific estimates from the Manicaland HIV-negative cohort in 2005 (See Figure 4.5). Women can become pregnant any number of times through her lifetime subject to her age, HIV status and, in the case of Zimbabwe, the year.

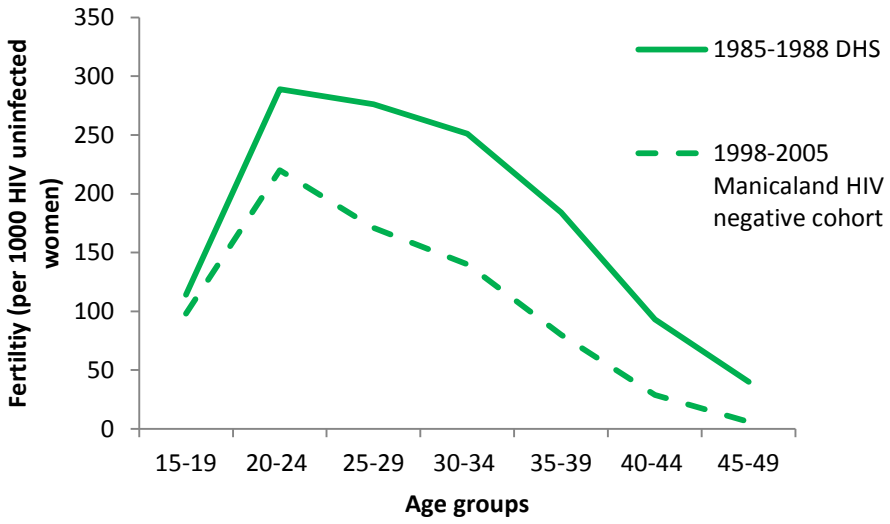


Figure 4.5 Calendar-year fertility rates (per 1000) among HIV-negative women in rural Zimbabwe (1985-1988) [238] (solid green line) and Manicaland, Zimbabwe (1998-2005) (dotted green line).

For HIV-positive women, the hazard of pregnancy is restricted from the original HIV-negative age-specific fertility rates by a 35% reduction within four years and a 60% reduction after four years of infection to account for HIV-related sub-fertility [158]. The model assumes that all women who become pregnant regardless of HIV status attend an ANC and are tested for HIV three months after conception, whereas in SSA, some women may not

Life expectancy in the absence of HIV is calculated at birth using cohort data from Manicaland, Zimbabwe [239]. Estimates are typical of non-HIV-related child and adult survival times for SSA. Net survival of HIV-infected women is modelled on combined age-stratified estimates taken from observational cohort studies in Africa [240]. HIV-infected women not on ART survive a median of 10 years, with CD4 counts reaching <200 two to seven years after infection.

If the calendar year is after 2003 in the ART era simulations, women with CD4 counts<200 will access ART with the probability of coverage as determined within two scenarios: (i) slower and lower levels of coverage, where coverage increases

linearly from 0% to 75% from 2003 to 2020 and (ii) faster and higher levels of coverage, where coverage increases linearly from 0% to 95% from 2003 to 2013. The slower and lower levels of coverage are characteristic of Côte d'Ivoire and rural Zimbabwe, while the faster and higher coverage levels are characteristic of Botswana. Survival after initiating ART is approximately 10 years [25].

The primary question of interest is the extent to which trends among pregnant women mirror true HIV prevalence in the population as age-specific and HIV-related fertility patterns change over time. In the era of ART, changes in fertility levels of users are explored for a range of values from a complete reduction in fertility (i.e., -100% or no further births) to a complete rebound (i.e., +100% or fertility at the same level as an HIV-negative women of the same age). Figure 4.6 summarizes the range of fertility levels which may be experienced by women on ART in the model.

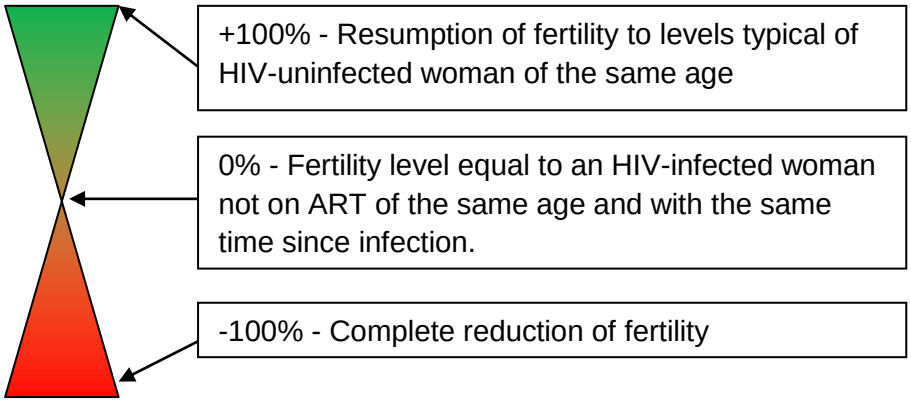


Figure 4.6 Fertility resumption and reduction scenarios for an HIV-infected woman on ART compared to an uninfected woman of similar age. Females on ART are subject to the new fertility rate immediately after initiating ART. This rate is unchanged over time.

4.3.2 Outcomes

Two measures of HIV prevalence are calculated in the model. The first, prevalence among ANC attendees in the model, serves as a proxy for ANC surveillance estimates and is calculated as the number of pregnant women testing positive at ANC in a particular year divided by the number of women attending ANC that year. Factors influencing overall HIV prevalence in ANC surveillance include (i) HIV incidence; (ii) fertility rates in HIV-negative women; (iii) fertility rates in HIV-positive women; (iv) HIV-related mortality; and (v) non-HIV-related mortality. Selection bias related to the timing and profile of women's attendance and the clinics selected to participate in ANC surveillance are not accounted for in the model. The second measure is true annual population HIV prevalence among women in the general population, which is calculated as the prevalence (women infected and alive divided by women alive) at the year mid-point. Population prevalence is influenced by (i) HIV incidence; (ii) HIV-related mortality; (iii) non-HIV-related mortality; and (iv) survival beyond the upper age bracket of 49 years when a woman no longer contributes to population prevalence estimates.

The overall outcome of interest is the extent to which the trend in HIV prevalence from ANC surveillance mirrors the true population HIV prevalence trend. Similar to Chapter 3, representativeness, or lack thereof defined as "bias", is measured as the ratio of HIV prevalence among pregnant women to that of the true female population. The PR -- rather than the absolute difference between the point estimates from the two data sources -- is used to emphasise how estimates move relative to one another.

To remove noise from the stochastic simulation, the final PR trend is shown as a five-year moving average through time of the results from the 50 runs per

simulation. Shown below is an example of typical stochastic variation around the mean PR trend during the pre-ART era from 1985 to 2002 in Botswana (See Figure 4.7a) and Côte d'Ivoire (Figure 4.7b). Results for the post-ART era from 2003 to 2030, are also displayed, assuming 100% rebound fertility in Botswana, with faster and higher ART coverage (Figure 4.7c), and Côte d'Ivoire, with slower and lower levels of coverage (Figure 4.7d).

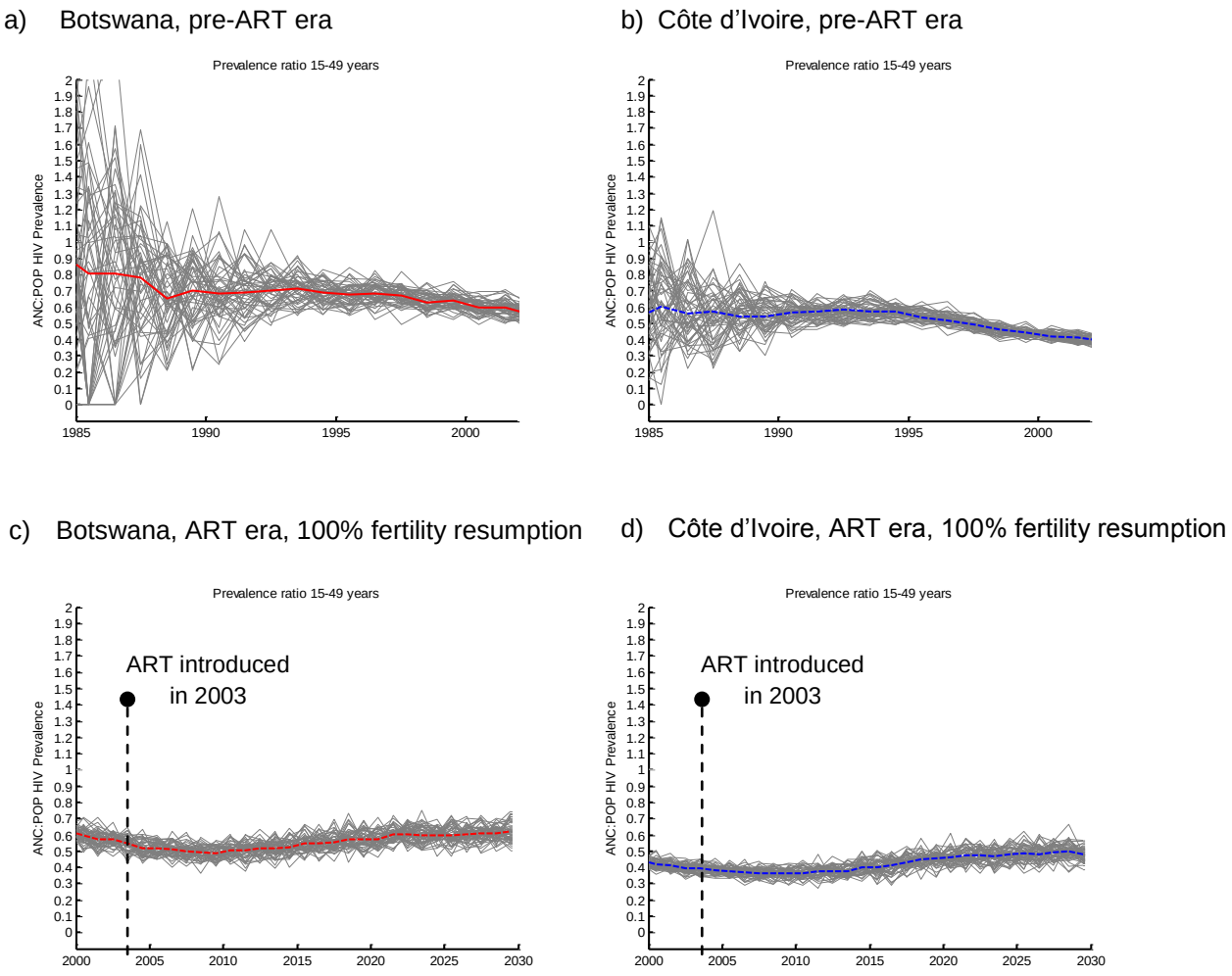


Figure 4.7 An example of typical stochastic variation around the mean PR from the 50 simulations for the pre-ART era (1985-2002) in a) Botswana (solid red line) and b) Côte d'Ivoire (solid blue line). Also results from the 50 runs are shown in the post-ART era (2003-2030) assuming 100% rebound fertility in c) Botswana (dashed red lines) and d) Côte d'Ivoire (dashed blue line).

As expected, stochasticity in the simulations is greatest in the largest epidemic (e.g., Botswana versus Côte d'Ivoire) and just as the epidemic takes off (1985-1990 versus 1995-2030). As time passes, however, infections relative to population size increase and a narrower (i.e. more stable) variability in potential PR trends result. Because patterns of variance were similar to those above for Zimbabwe and with regard to the remaining ranges of positive, no and negative associations between fertility and ART, the remaining graphs are not shown.

When assessing the representativeness of ANC trends, the data are considered to mirror true population prevalence trends if the PR trend is stable over time. When the trend in the PR is declining or increasing, ANC surveillance data are considered less reliable and will either understate or overstate true population prevalence trends. Table 3.1 from Chapter 3 summarizes this relationship. To isolate possible causes for trend differences, selected analyses are presented separately for women aged 15 to 24 and 25 to 49 years old. Results from the pre-ART era span from 1985 to 2002. The impact of introducing ART in 2003 through 2030 is then considered in Section 4.4.2.

4.4 Results

4.4.1 The pre-ART era (1985-2002)

If the fertility rates of uninfected women in Botswana, Côte d'Ivoire and rural Zimbabwe were stable over time, then results from the simulation indicate that ANC sentinel surveillance would have generally represented true population trends among women aged 15 to 49 years through the first 10 years or so of the epidemic.

However, these estimates would have been less representative in subsequent years as the epidemic progressed (See Figure 4.8a).

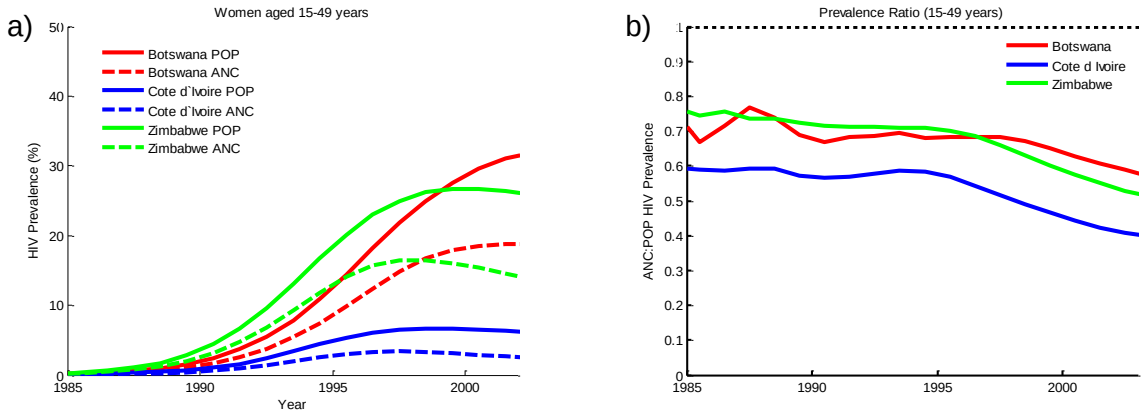


Figure 4.8 Measures of a) trends in HIV prevalence among ANC attendees (dashed lines) compared to women of reproductive age (15 to 49 years) (solid lines) in Botswana (red lines), Côte d'Ivoire (blue lines) and rural Zimbabwe (green lines) and b) the predicted HIV prevalence ratio (PR – i.e. annual ANC HIV prevalence compared to female HIV prevalence) assuming stable fertility rates among HIV-negative women.

In the early years, which were marked by increases in HIV incidence, bias in ANC trends would have been reasonably stable (as shown in Figure 4.8b). This is because the average age of HIV-infected women in the population remained relatively stable over time and women with more recently-acquired HIV infections would have experienced less HIV-related sub-fertility. As a result, fewer HIV-infected women would have been excluded from the ANC sample initially.

As the epidemic progressed and incidence began to decline, however, ANC trends in prevalence would have become less representative of underlying population estimates for two reasons. First, HIV-related sub-fertility would have excluded women from the ANC sample as the average time since HIV infection in the population grew. Second and more importantly, the rise in the average age of the

HIV-infected population beyond their most fertile years would have excluded an increasing number of HIV-positive women from the ANC sample. As a consequence of these dynamics, HIV prevalence among ANC attendees would have risen less steeply, peaked earlier, and declined more rapidly than female population prevalence overall.

Using data from the Botswana simulation, the shifts described above in the average age of HIV-infected women and the average number of years since infection can be observed in Figure 4.9.

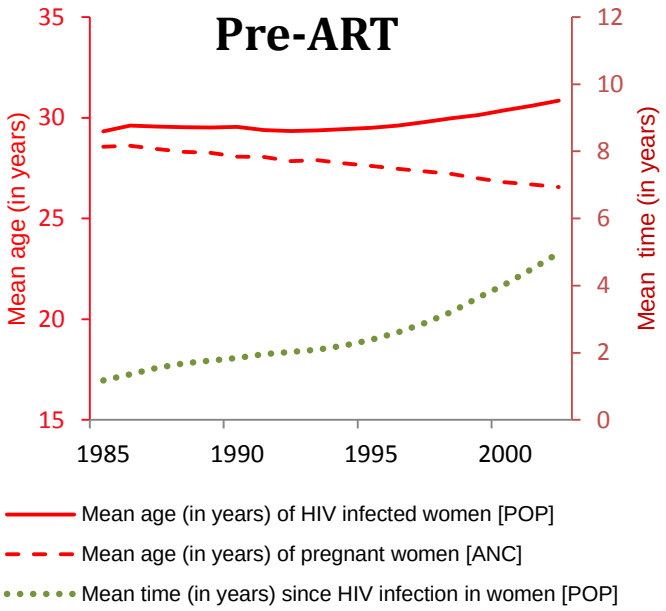


Figure 4.9 Increases in the mean age (in years on the left y-axis) of HIV-infected women (solid red line) and the mean time (in years on the right y-axis) since infection among women (dotted green line) in the population result in increasing sub-fertility among HIV-infected women. The consequence of these shifts over time can be seen in the decline in the mean age (in years) of pregnant women (dashed red line) in Botswana, 1985-2002.

In the graph, the decline in the mean age of pregnant women over time is a consequence of the fact that older HIV-infected women are increasingly excluded from the ANC sample. This shift, in turn, introduces a greater bias in the ANC estimates as the epidemic progresses.

Given the relationship between age, HIV infection, and fertility patterns in Botswana, it might be expected that the representativeness of ANC-based trends would differ by age. Stratification of results by women aged 15 to 24 years and those aged 25 to 49 years shows that ANC prevalence trends for younger ages do more accurately capture underlying population trends among young women in the population (see Figure 4.10a and Figure 4.10c) as compared to a similar scenario for older women (see Figure 4.10b and Figure 4.10d).

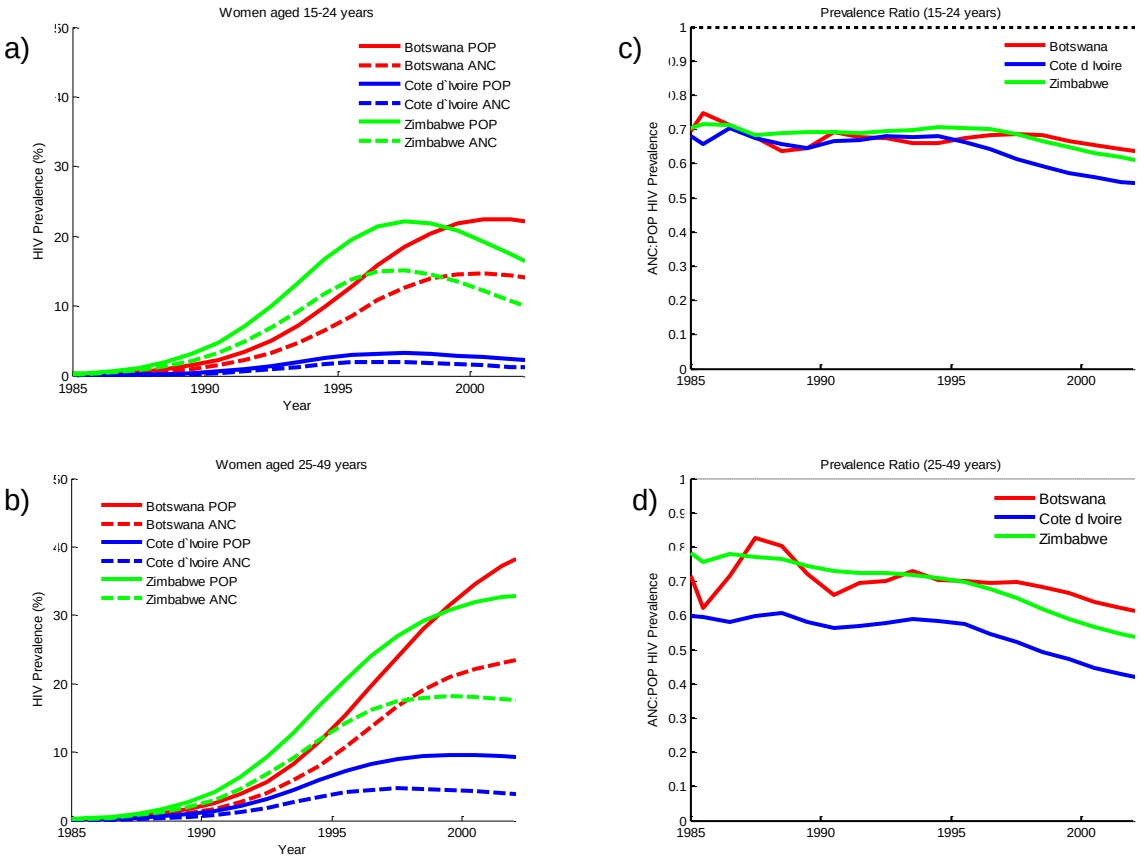


Figure 4.10 Measures of trends in HIV prevalence among ANC attendees compared to women in Botswana (red lines), Côte d'Ivoire (blue lines) and rural Zimbabwe (green lines) for those aged a) 15 to 24 years and b) aged 25 to 49 years and the predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence), also for those aged c) 15 to 24 years and d) 25 to 49 years.

The reason why ANC surveillance trends in younger women are more representative than when compared to older ages is that younger HIV-infected women will be less frequently excluded from the ANC sample because sero-conversion is more recent and HIV-related sub-fertility is less severe. Furthermore, for many younger women, natural fertility levels will increase, rather than decline, as they age. Among older HIV-infected women, however, natural declines in fertility with age will lead to greater exclusion from the ANC sample as the average age of infected women increases beyond peak reproductive years. Also, because women in these age groups are less likely to be recently infected, the influence of HIV-related sub-fertility will be greater initially, although as mean time since infection in the group increases as the epidemic progresses, the effect of this bias will become less severe because older women will already be subjected to the maximum sub-fertility level.

Again in Botswana, the magnitude of the bias resulting from HIV-related sub-fertility and natural aging of the HIV-infected population by age group can be observed from the simulation. As shown in Figure 4.11a, if younger women experienced no HIV-related sub-fertility, HIV prevalence in the ANC sample would have risen more quickly, peaked later and fallen slightly faster than prevalence in the general population. This is because the age distribution of the ANC sample is older than the age distribution in the general population.

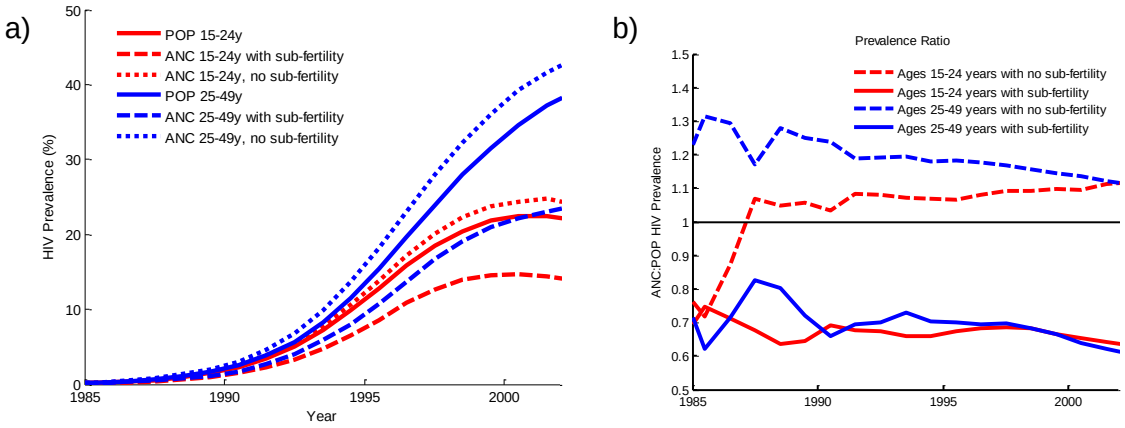


Figure 4.11 Measures of a) ANC-based and population HIV prevalence trends and b) the predicted HIV prevalence ratio (PR – i.e. annual ANC HIV prevalence compared to female HIV prevalence) for women in Botswana, aged 15 to 24 years (in red) and 25 to 49 years (in blue) assuming the effects of sub-fertility (indicated by dashed lines) and no sub-fertility (indicated by dotted lines).

If HIV-related sub-fertility was included, however, some HIV-infected women would have been selectively removed from the ANC sample over time as their infections progressed, resulting in a reduction in the overall numbers of HIV-infected pregnant women relative to the population and, as a consequence, a sharp decline in the trend in the PR over time as ANC surveillance estimates increasingly overstated population prevalence declines (see Figure 4.11b). The situation for those aged 25 to 49 years is similar, although the primary reason for the more severe decline in the PR trend (as shown in 4.11b) is not the inclusion of HIV-related sub-fertility but rather the increase in the average age of infected women which subjects them to lower natural fertility levels. Accordingly, the slope of the PR trend is only slightly steeper with respect to the effect of sub-fertility as compared to without it in the later years.

Since fertility patterns in Côte d'Ivoire and rural Zimbabwe are similar to those in Botswana, bias in ANC-based trends within the age groups and among females overall would be expected to be similar. However, in Côte d'Ivoire, the higher relative

level of HIV incidence among older women (as indicated in Figure 4.3) would result in about a 5% relative increase in the magnitude of bias in the PR over time, since natural fertility levels would already be lower among these older HIV-infected women. As hypothesized, in rural Zimbabwe, similar patterns of bias in ANC trends to Botswana were evident because age-specific fertility and incidence patterns in the two settings were similar.

If age-specific fertility levels instead declined with time and independent of the influence of HIV, as was most likely occurring in rural Zimbabwe from the late 1980s through the early 1990s [241], however, the patterns of bias could have differed. Surprisingly, the temporal bias from non-HIV-related fertility rates declining was minimal (See Figure 4.12).

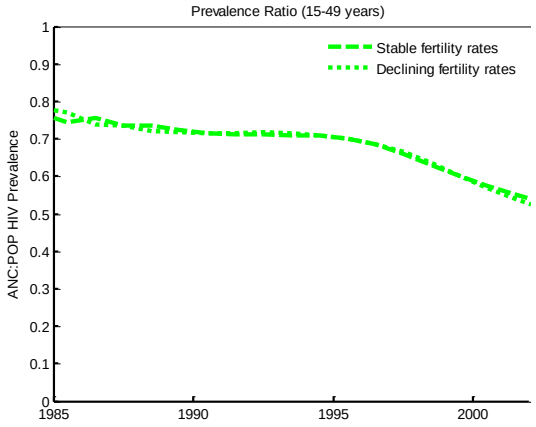


Figure 4.12 The predicted HIV prevalence ratio for those aged 15 to 49 years assuming stable (dashed green line) versus declining (dotted green line) background fertility patterns in rural Zimbabwe.

The reason for this very small difference when assuming an overall decline in the natural fertility rate is because the decline is of a similar magnitude for age groups with the highest fertility levels. However, if fertility reductions had occurred over a short period of time in one group as opposed to others in Zimbabwe (e.g., a rapid rise in the age of sexual debut from the teens to twenties), then the ANC sample

eventually would have exaggerated the declines in population prevalence more severely.

4.4.2 The ART era (2003-2030)

4.4.2.1 Modelling bias in ANC prevalence trends given no association between ART use and fertility

If it is first assumed in the simulations for each of the three settings that there is no relationship between ART use and fertility, then the representativeness of ANC trends will be primarily influenced by the changing age-profile of HIV-infected women due to increased survival on ART. In the earliest years after the introduction of ART, for example, ANC-based estimates of prevalence will overstate declines in true population prevalence (as it did in the pre-ART era) because any gains from extended survival in either the ANC sample or the population will be negligible still.

As ART coverage expands, however, the trend in HIV prevalence among pregnant women will eventually begin to diverge from true population prevalence. Among pregnant women, the sub-set of ART users will benefit from a longer reproductive lifespan (even though they are still constrained by pre-ART sub-fertility levels), and ANC prevalence will begin to stabilize. In contrast, true population HIV prevalence trends will continue to fall, in part because an increasing number of HIV-infected women will now survive beyond age 49 years and thus be excluded from contributing to estimates of true population prevalence.

The consequences of the changes described above, as measured by prevalence trends and the trend in the PR, are shown in Figure 4.13a and Figure

4.13b, respectively, for Botswana. For comparison, a measure for a scenario in which ART is not available has also been included

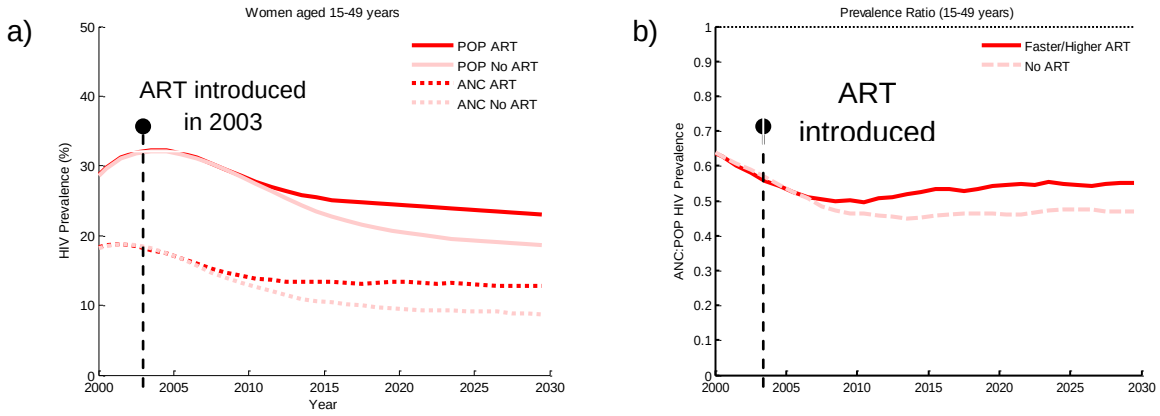


Figure 4.13 Measures of a) ANC-based and population HIV prevalence trends and b) the predicted HIV prevalence ratio (PR – i.e. annual ANC HIV prevalence compared to female HIV prevalence) for women aged 15 to 49 years (dashed line) versus pregnant women (dotted lines) assuming rapid ART scale-up (red lines) in 2003 or no ART (pink lines) in Botswana, 2000-2030.

As expected, the overall PR trend rises for women aged 15 to 49 years as compared to a scenario in which ART was never introduced. This is because ANC prevalence fails to capture the slight decline in true population prevalence among women. Results from simulations for those aged 15 to 24 years and 25 to 49 years (see Figure 4.14a and Figure 4.14b) underscore the contributions to bias by older HIV-infected women who are benefitting the most from a longer reproductive lifespan in the ANC sample, but who are also aging out of the population sample at the same time.

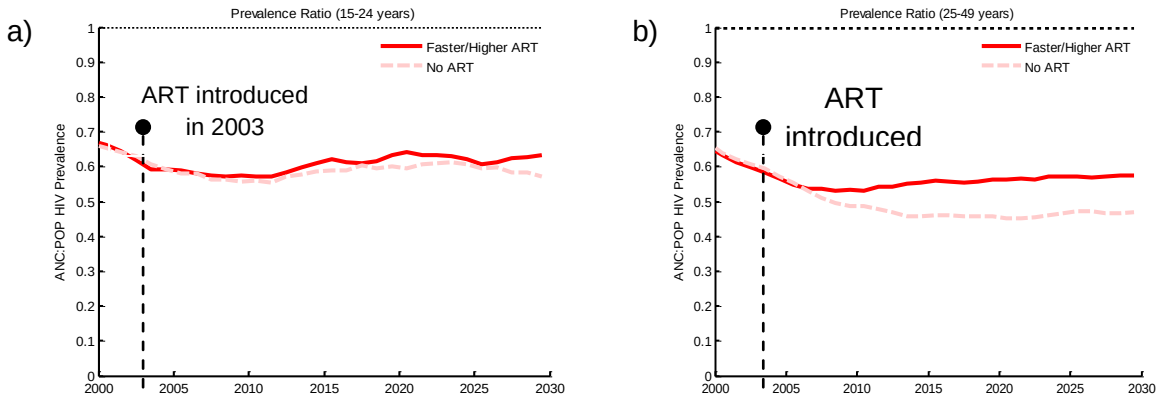


Figure 4.14 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged a) 15 to 24 years and b) 25 to 49 years after the introduction in 2003 of ART (red line) as compared to if ART had never been introduced (dashed pink line) in Botswana.

The dynamics discussed above for the age-stratified groups also operate similarly for women of all ages in Côte d'Ivoire (See Figure 4.15a) and Zimbabwe (see Figure 4.15b). In both settings, ANC prevalence initially declines faster than true population prevalence and similar to a scenario in which ART had never been introduced. In later years as ART scale-up expands, however, ANC prevalence eventually stabilizes while population prevalence continues to decline – as it did in Botswana. Because the scale up of ART coverage is less rapid and reaches fewer people, however, the rise in the trend of the PR is somewhat less severe than if the scale-up was faster and reached more women. A faster implementation of ART, which is also shown in Figure 4.15a and Figure 4.15b for Côte d'Ivoire and rural Zimbabwe would result in a more severe bias initially, although trends would then stabilize more quickly.

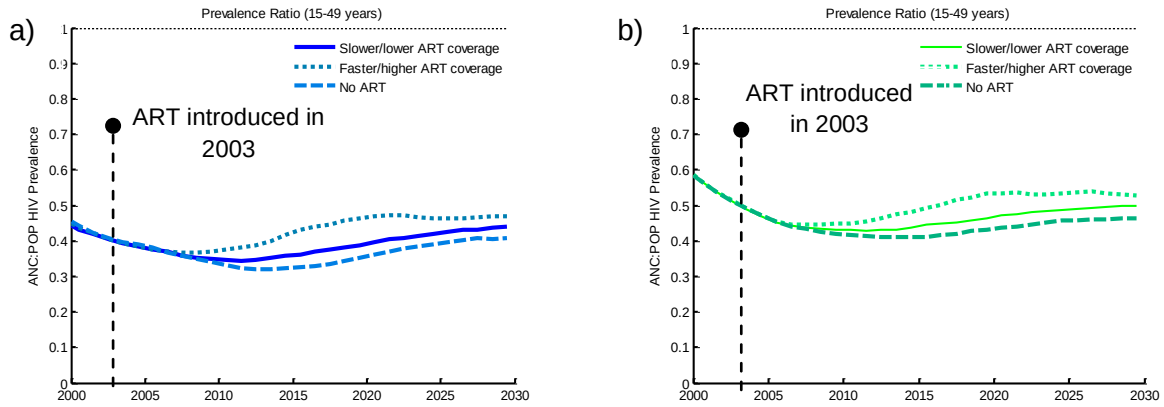
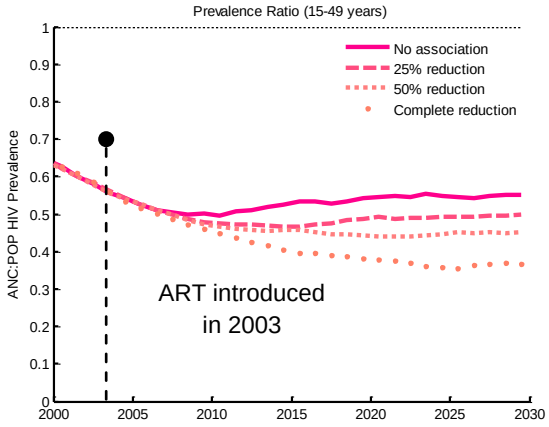


Figure 4.15 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged 15 to 49 years in a) Côte d'Ivoire (blue lines) and b) rural Zimbabwe (green lines) after the slower and lower levels of ART introduction in 2003 (solid lines) and as compared to if ART had never been introduced (dashed line) or with faster and higher coverage (dotted lines).

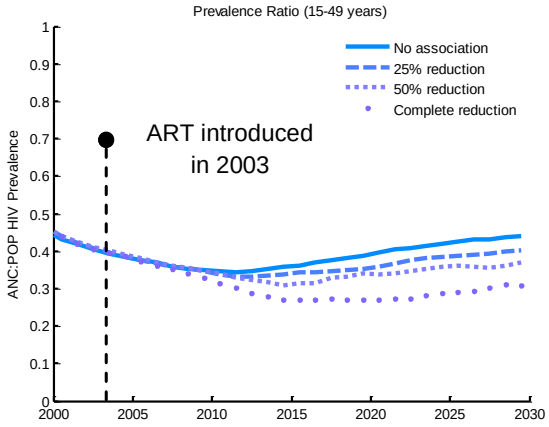
4.4.2.2 Modelling bias in ANC prevalence trends given a negative relationship between ART use and fertility

If instead of assuming there was no relation between ART use and fertility, a negative relationship (i.e., women on ART are less fertile than uninfected women of the same age) was assumed, then the representativeness of ANC trends would still be influenced by the changing age-profile of HIV-infected women. This is due to increased survivorship in the population due to ART. However, the additional bias from HIV-infected women self-selecting out of the ANC sample would also need to be considered. As Figures' 4.16a – c, a negative association would initially draw the trend in the PR lower for each location as compared to if there was no association.

a) Botswana



b) Côte d'Ivoire



c) Rural Zimbabwe

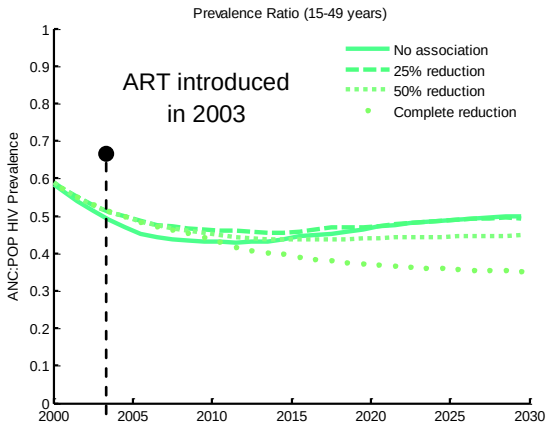


Figure 4.16 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged 15 to 49 years as ART has either no association (solid line), a 25% reduction (dashed line), a 50% reduction (dotted lines), or a complete reduction (diamond markers) in fertility for a) Botswana, b) Côte d'Ivoire and c) Zimbabwe.

The reason for the more severe decline is because, as fertility among ART users is reduced, they appear less frequently in the ANC sample. Not unexpectedly, the magnitude of bias when fertility of users is 25% to 50% less than uninfected women is relatively smaller and occurs over a shorter period of time as compared to when fertility among users is completely reduced (i.e., -100% or no further births). Among women aged 15 to 24 years in Botswana, for example, trends still appear reasonably representative of true population prevalence trends among their peers regardless of the new level of reduced fertility (Figure 4.17a). Among older women aged 25 to 49 years in Botswana, however, the increasing influence of reductions in fertility among those who otherwise would have had the highest levels of fertility is more apparent (Figure 4.17b)

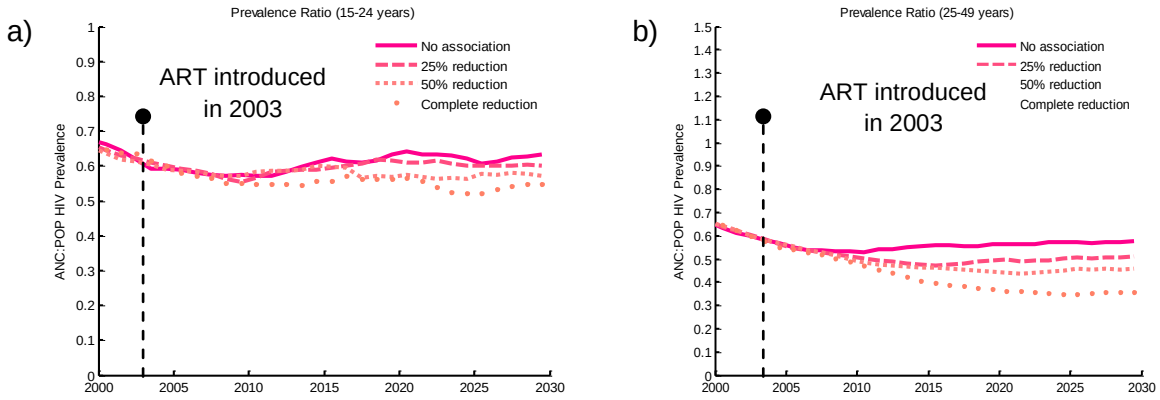


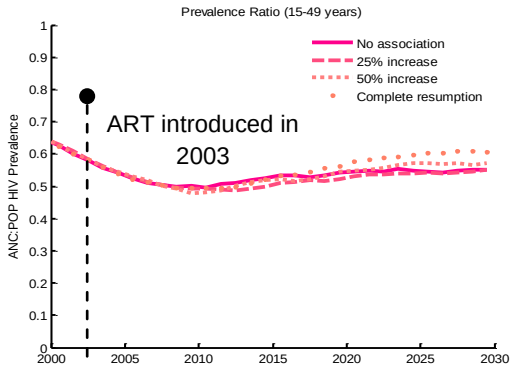
Figure 4.17 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged a) 15 to 24 years and b) 25 to 49 years as ART has either no association (solid line), a 25% reduction (dashed line), a 50% reduction (dotted lines), or a complete reduction (diamond markers) in fertility in Botswana.

Similar results by age groups were also found for Côte d'Ivoire and Zimbabwe.

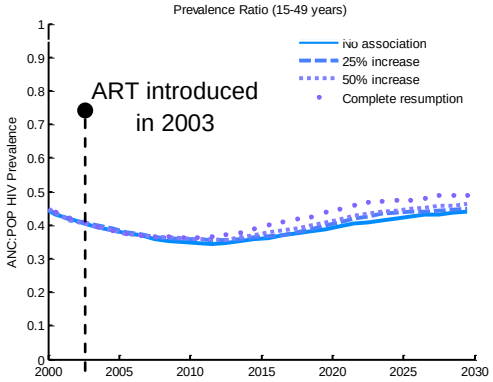
4.4.2.3 Modelling bias in ANC prevalence trends given a positive relationship between ART use and fertility

If, in a third and final scenario, where ART is assumed to lead to some immediate increase in fertility relative to age-matched uninfected women, then the trend in the PR would be expected to rise commensurate with the strength of the association. This rise would result from the addition of previously sub-fertile HIV-infected women back into the ANC sample. Figures' 4.18a, 4.18b and 4.18c demonstrate the shift in the PRs for Botswana, Côte d'Ivoire and rural Zimbabwe respectively.

a) Botswana



b) Côte d'Ivoire



c) Rural Zimbabwe

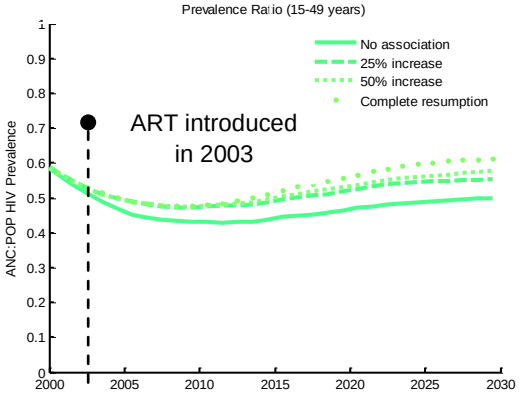


Figure 4.18 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged 15 to 49 years as ART has either no association (solid line), a 25% increase (dashed line), a 50% increase (dotted lines), or a complete resumption (diamond markers) in fertility for a) Botswana, b) Côte d'Ivoire and c) rural Zimbabwe.

When stratified by age groups, as is the case below in Figure 4.19a and 4.19b in Botswana, trends are less severely biased. In the case of the younger women aged 15 to 24 years, the addition of women back into the sample has a relatively modest impact on the younger age groups as does increased survival since these women are most likely to have been relatively recently infected and not yet eligible for ART. Among the older women, however, the addition of HIV-infected women back into the ANC sample still pulls the PR up but it is less dramatic because natural fertility declines associated with age and time since infection limit the rise.

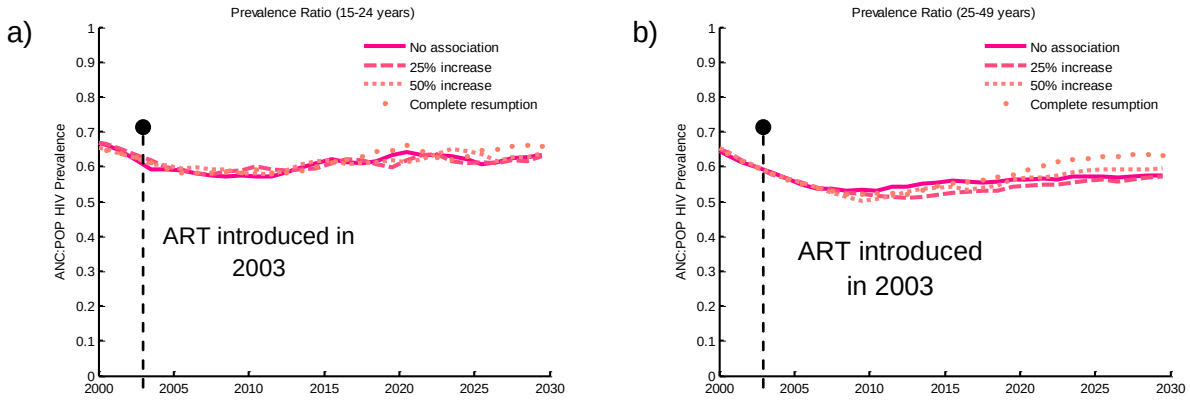


Figure 4.19 The predicted HIV prevalence ratio (PR: i.e., annual ANC HIV prevalence compared to female HIV prevalence) for those aged a) 15 to 24 years and b) 25 to 49 years as ART, which was introduced in 2003, has either no association (solid line), a 25% increase (dashed line), a 50% increase (dotted lines), or a complete resumption (diamond markers) in fertility in Botswana.

Results by age group for Côte d'Ivoire and Zimbabwe were largely similar, although in Zimbabwe, the PRs for the range of positive fertility associations among those aged 25 to 49 years span a slightly wider range than in Botswana and Côte d'Ivoire over time because natural fertility rates are also declining.

4.5 Discussion

By simulating HIV-prevalence trends among pregnant women and women in the population of reproductive ages, it has been possible to explore and describe the magnitude and direction of bias that might be present in ANC surveillance trends as the epidemic progresses in Botswana, Côte d'Ivoire and rural Zimbabwe. The most important finding from these simulations is that primarily relying upon ANC data to monitor true population prevalence trends for women of reproductive aged 15 to 49 years in the pre-ART era may have been problematic. During this time, ANC prevalence would have misrepresented changes in true population HIV prevalence in all three locations. In the case of Botswana, as an example, this bias would have led to a gradual understatement of the relative increase in population prevalence trends by 10% from 1997 to 2002. As overall prevalence is quite high in Botswana, a 10% understatement would have corresponded to an absolute difference in prevalence in the two datasets of 8% in 1997 and 12% in 2002, which is a relatively large change. Conversely, in Côte d'Ivoire and rural Zimbabwe, declines in population prevalence would have been overestimated by ANC surveillance data by a similar magnitude.

As noted previously, the primary causes of temporal bias in pre-ART era ANC-based trends would have been the initial progressive effect of HIV-related sub-fertility

and the later increase in the average age of HIV-infected women beyond the their most fertile years. As the simulations showed, this second cause would have had an especially strong negative influence on the representativeness of trends for older women aged 25 to 49 years. Among these older women, ANC prevalence would have clearly overstated declines in true population prevalence. Fortunately, trends in ANC prevalence among younger women 15 to 24 years of age, which are also used by most countries in SSA to measure changes in incidence among youth [64], would have been a better indicator of true population prevalence declines among young women. Even for this younger age group, however, the model suggests that some modest over-estimation of reported declines in true population prevalence still could have occurred from the mid-1990s to the early 2000s. This bias should be taken into account when assessing the effectiveness of the country's response to the HIV epidemic in SSA among youth.

With regard to simulations conducted for the ART era, under our model assumption, results suggest that the introduction of ART would not be expected to greatly influence the representativeness of ANC surveillance data with respect to underlying population HIV prevalence trends even if fertility among HIV-infected women of all ages or among youth rebounded fully to pre-HIV infection rates. However, if ART reduced fertility by 50% or more, as shown in the model results for Botswana, an increasing bias of more than 25% between ANC and population survey estimates will be observed for around the next twenty years, and mostly among adults and those aged 25 to 49 years. Smaller fertility reductions up to a quarter of overall age-specific fertility levels resulted in less bias, although comparatively more than when fertility on ART

increased. The reason for this is because fertility reductions can result in no further pregnancies, while the limit of any increase depends on the length of a woman's remaining reproductive span in addition to the relative level of rebound actually explored. Across all scenarios, prevalence trends at ANC among 15-24 year-olds closely matched those among the wider population of women aged 15-24, indicating that a focus on young women may be the safest way to guard against biases introduced by these factors

The above results highlight two issues that are important when considering the representativeness of ANC surveillance trends in the ART era. First, knowing the strength and direction of the association between ART use and fertility (when compared to fertility in uninfected women) as well as the pace of the scale-up of ART services in a country will be critical. Although a negative association between fertility and ART use typically resulted in a lower PR than if there was no or a lesser association -- and the inverse was true for a positive association – patterns of bias could vary across countries or over time. As a result, it would be difficult to develop a systematic approach to adjusting for this bias for women that could be uniformly applied to ANC estimates from across all countries in SSA in the future.

Second, and as was true in the pre-ART era, HIV prevalence trends from the ANC surveillance data by age group were generally more robust for younger ages (i.e., 15 to 24 years) compared to older ages (i.e. 25 to 49 years) and this was also true for the younger groups regardless of the association between ART and fertility or the level of scale-up of treatment services. As a result, ANC prevalence should still remain a

reasonably good indicator of underlying population prevalence trends for young women in the ART era.

The findings from these simulations are similar to previous evidence supporting the use of ANC-based trends among young women aged 15 to 24 years to monitor prevalence trends among youth [50, 116, 117, 220]. Results from the model appear to conflict, however, with the original assumption that ANC estimates were stable enough over time to permit their use when monitoring true population prevalence trends for women of all reproductive ages. In the case of the previous modelling efforts by Garnett and Gregson in 2000, the main difference between their model and the model here is that, with the benefit of hindsight, the newer model more accurately captures transmission dynamics over the last 30 years in SSA. It is possible that using parameter values for incidence similar to those used here, the original model might produce patterns of bias that are consistent with our results, however, additional testing would be required to validate this assumption.

With regard to the empirical study in rural Tanzania [50], which also found evidence to support the representativeness of ANC-based trends, several possible factors could explain the discordance between this model and their study results. First, changes in behavioural risk and mortality, which are not explicitly measured and reported in the study, could have contributed in an equal but offsetting way to the declines in population and ANC-based prevalence and these patterns might have differed from the parameters used here. A second possible explanation is that trends in the Tanzanian study were measured and compared over a nine year period only, which may have been too short of a time frame to detect the gradual shifts in the magnitude of

bias which were observed in the model. Third, and finally, the model is simpler in its consideration of bias than that which will operate on trends in a real-world setting. In practice, empirical trends will be influenced by the quality of data collection and HIV testing across surveys, shifts in non-responder bias with time, and changes in access to and uptake of ANC surveillance that may be associated with HIV-status. As a result, these changes could explain the discordance in the findings between the Tanzanian study and those results presented here.

A final source of evidence with regard to the similarity or differences in trends and validation of this model's results is the unpublished findings reported in Chapter 3. Although the statistical analyses of these trends generally indicate that ANC data are reasonably representative for most countries in SSA, the PR in each of the settings was observed to vary for males and in rural areas in particular. Because those comparisons also covered shorter time periods and were influenced by the sources of bias described in the Tanzanian study, it is not possible to definitively conclude that the results in Chapter 3 differ from the simulations here. Countries using historical ANC trend data to measure the effectiveness of previous prevention efforts in particular should consider the real possibility that, aside from younger women, ANC prevalence trends may have overstated historical declines in true population prevalence in the pre-ART era.

While the reliability of ANC prevalence trends in the pre-ART era can be reasonably assessed through the model, it is considerably more difficult to validate output from the ART era, where scale-up in many countries in SSA is on-going. To do this in the future, additional data on the relationship between ART initiation (assuming a current initiation when a woman's CD4 counts reaches 200 as explored here -- or other

starting values based on new WHO recommendations) and subsequent fertility patterns among users compared to non-HIV-infected women in SSA is required. For example, in the simulations, the upper range of the positive association between ART and fertility was 100%, although ART users who may have taken steps to avoid pregnancy prior to initiating ART may also change their behaviour in such a way in the future that fertility on ART exceeds that of uninfected women. Also, this model assumes that fertility changes for ART users are immediate rather than gradual and do not differ by location. In reality, however, several studies have already indicated that fertility outcomes could change with time and according to age [167-169] and no study has looked at the extent to which ART users in more urban areas, for example, might respond differently to those in rural areas with regard to their fertility choices.

A final limitation in this model, which merits further consideration in subsequent studies of the representativeness of ANC surveillance data over time, is the extent to which risk of HIV infection is associated with pregnancy or contraceptive use. Although there is also some evidence that pregnant women are at higher risk of HIV infection during their pregnancy, either due to behavioural or biological changes [163], the influence of this latter bias on ANC trends is likely to be minimal, provided the infection is detectable at a woman's first ANC surveillance visit. If infection does occur within the first few months of becoming pregnant, ANC surveillance estimates may under-represent HIV prevalence among pregnant women because tests used for surveillance purposes may not be sensitive enough to detect a recent infection, but this infection would be detected in the general population in the model. However, even to the extent that this is occurring, the implication for changes in bias would be small unless fertility

patterns in the population are also shifting over time for other reasons not related to HIV infection. With regard to hormonal contraception, the extent to which hormonal contraceptive use may place women at a greater risk of either acquiring HIV or experiencing more rapid disease progression [154] could reduce bias in ANC estimates over time if prevention programmes recommend additional prevention measures, such as condom use, or other contraceptive methods for those at highest risk. This once again highlights the importance of having detailed data in countries in SSA on whether and how fertility patterns are changing over time.

In summary, this model has highlighted some of the historical and potential challenges of using ANC data to monitor true population prevalence trends among women of reproductive ages based on a current understanding of the HIV epidemic in selected SSA settings. Moving forward, while additional, more rigorous studies on associations between fertility and ART use are being carried out, steps to identify whether ANC-based trend data are subject to bias in the ART era can still be taken now in many countries in SSA. For example, collecting data at the time of the ANC surveillance round on whether ANC attendees are or have been on ART, the date when ART was initiated, and a brief pregnancy history could be used to identify HIV-infected women who are returning to the clinic after long periods of sub-fertility. In the course of providing PMTCT counselling, these questions are likely to be routinely discussed and thus would not violate the ethical principles associated with unlinked anonymous surveillance [242]. As it is difficult to identify the extent to which HIV-infected women on ART are not appearing in ANC clinics, however, other methods for measuring trends, particularly for older women and women of all reproductive ages might need to be

considered. Using interpolations of prevalence – and incidence – from repeated population surveys [75] or estimates arising from the application of incidence assays (should they become available) [243] may also be preferred until such a time when bias in ANC surveillance trends in the ART era is more easily quantifiable. Along these lines, this model could be modified in future revisions to explore the extent to which HIV prevalence trends among young pregnant women are representative of HIV incidence trends among youth, which is often assumed. These issues are discussed in greater detail in the concluding chapter.

Chapter 5: Monitoring trends in HIV prevalence among young people, aged 15 to 24 years, in Manicaland, Zimbabwe

5.1 Aims and organization of the chapter

The aims of this chapter are twofold. First, it is to assess progress toward the United Nations General Assembly Special Session (UNGASS) target of reducing HIV prevalence among young women and men, aged 15 to 24 years, by 25% in the worst-affected countries by 2005 using repeated household-based population serosurvey data in Manicaland, Zimbabwe. Second, it is to validate the representativeness of surveillance data from young pregnant women, aged 15 to 24 years, attending antenatal care (ANC) clinics, which UNAIDS recommends for monitoring population HIV prevalence trends in this age group. Changes in socio-demographic characteristics and reported sexual behaviour of participants were also investigated to identify possible causes for any disparities.

The chapter begins by summarizing why monitoring trends among young people is important and what factors might contribute to differences between ANC and population HIV prevalence over time. Following that, background is provided on the Manicaland HIV/STD Prevention Project specific to the analyses performed here. A discussion on the statistical methods used to make comparisons is also included. Finally, results and a discussion of the main findings are provided.

5.2 Introduction

As mentioned in Chapter 1, in June 2001, the United Nations General Assembly Special Session (UNGASS) set a target of reducing HIV prevalence among youth, aged 15 to 24 years, by 25% in the worst-affected countries by 2005, and by 25% globally by 2010 [244]. Recently infected youth experience low HIV-related mortality [245, 246].

Accordingly, changes in prevalence over time among young people should signal underlying changes in incidence. Changes in incidence are useful when gauging the effectiveness of prevention and treatment efforts [41, 49].

Chapters' 3 and 4 have shown that monitoring HIV prevalence trends in the general population using ANC surveillance data can be challenging; however, repeated national population surveys, which are believed to be a better source of data for monitoring the epidemic, are often too costly and complex to conduct more frequently [39]. Also, laboratory assays to detect recent infections have so far proven unreliable in sub-Saharan Africa [65, 247]. As a result, the Joint United Nations Programme on HIV/AIDS (UNAIDS) continues to recommend that countries in SSA use data from surveillance among pregnant women, also aged 15 to 24 years, attending antenatal care (ANC) clinics, to monitor progress toward the UNGASS target [64].

Implicit in the UNAIDS recommendation is an assumption that ANC prevalence trends will mirror those among male and female youth in the general population. However, as the previous chapters have also shown, changes in sexual behaviour could cause ANC estimates to misrepresent general population trends. For example, prevention interventions promoting delays in initiating sex and/or consistent condom use could lead to general population HIV prevalence declines from reduced risk behaviour, even as prevalence at ANC clinics remains steady since, by definition, attendees are having unprotected sex. Conversely, if interventions, such as consistent condom use following HIV testing, successfully target infected individuals, a sudden drop in the ANC estimate of HIV prevalence could be observed (due to a fall in pregnancy rates in HIV-positive women) that would not be representative of the general population.

Beyond these sources of bias, ANC surveillance data are also subject to other biases that could change with time, including: (i) ANC attendance varying with regard to availability and uptake and (ii) HIV-infected women having different levels of contraceptive use and lower fertility rates [42, 45, 47, 51, 55]. To address these potential biases in ANC data, UNAIDS recommends using population survey data to validate ANC estimates wherever possible, and analysing sexual behaviour data and characteristics of the testing populations to provide context to observed changes in prevalence [39, 64].

In this chapter, data from the open-cohort, population-based household survey in Manicaland, Zimbabwe, conducted at three time intervals from 1998 to 2005 is used to assess directly whether the UNGASS indicator for prevalence reductions of 25% by 2005 was met among youth aged 15 to 24 years. Also, the extent to which HIV prevalence trends in the general population mirror those among ANC attendees is considered, as many countries, including Zimbabwe, will not have access to repeated population survey data spanning the period covered by the UNGASS target. To validate the ANC surveillance data, the proportional changes in HIV prevalence are compared over the three rounds among pregnant women attending ANC clinics with those from the three parallel rounds of the general population survey in the same geographic areas. Finally, changes in participation, HIV prevalence by socio-demographic characteristics, such as educational status, and trends in sexual behaviour that could explain differences in the patterns of HIV estimates observed between the two datasets over time are explored. Previous assessments in this population using data from 1998 to 2003 have shown substantial declines in population and ANC-derived HIV prevalence

estimates for men and women aged 15 to 49 years in this mature epidemic, primarily linked to behaviour change [26, 27].

5.3 Methods

5.3.1 Study population and data collection procedures

Data for the open-cohort, household-based population survey were collected in 12 communities in Manicaland Province, representing four geographic strata (two small rural towns, two roadside trading centres, four tea, coffee and forestry estates, and four subsistence farming areas). For the ANC surveillance, clinics offering services to pregnant women in the population survey catchment areas were selected.

Prior to each population survey round, all households and their residents in the study area were enumerated by local census. At round 1 and round 2, males aged 17 to 54 years and females aged 15 to 44 years resident in the study households were considered eligible, except that only one eligible household member of each cohabitating or marital union was selected (at random) to participate. To be considered resident in a household, an individual must have slept in that house for at least four nights in the past month and also been present in the household at the same time one year previously.

At round 2, residency requirements were dropped to include household visitors. Due to funding constraints, however, new in-migrants (i.e., individuals from existing and new households moving from outside the study area into the study area between round 1 and round 2) were only included in communities 5 to 12. Starting at round 3, eligibility was further expanded to include in-migrants in all 12 communities and those aged 15 to

54 years for both sexes, regardless of marital status. Participants excluded in a prior round but joining the study in round 2 or round 3 were classified by their previous status (e.g. in-migrant, spouse) for that subsequent round. For consistency in exploring trends, individuals reporting having moved into a community where they were interviewed at round 1 within two years of the study date were identified as in-migrants for that round, although this likely represents an overestimate of the in-migrant population at round 1 as some individuals may have reported a move that was internal to the study area. With regard to the change in inclusions criteria related to exclusion of spouses at round 1 and round 2, spouses were considered to be routine participants, since in this younger age group, they represented less than 2% of the total population aged 15 to 54 years at round 3.

In the parallel ANC surveillance, all women seeking prenatal care at participating clinics (22 in all three rounds and seven additional clinics in one or two rounds only) during the population survey period were considered eligible. Surveillance was typically conducted over a six to eight week period in each community. In round 2 and round 3, women attending ANC clinics that were not their local clinic were considered eligible, but also identified as non-local attendees. In round 1, information on the number of non-local attendees was not collected; however it was hypothesized that attendance by women from more rural communities outside the study and clinic catchment areas may have biased ANC surveillance estimates downward [55]. In round 2, 15.6% of women reported non-local clinic attendance. In round 3, that proportion was 14.4%.

Study enrolment and eligibility for both the population survey and ANC surveillance was conditional on participants' written consent at each round, although

ANC data were anonymised at data entry. The Medical Research Council of Zimbabwe and St Mary's Local Research Ethics Committee, London, provided ethical approval. Round 1 was completed from July 1998 to February 2000; round 2 began in July 2001; and round 3 began in July 2003. Further details on study methods were summarized in Chapter 2, Section 2.6 and have been published previously [26].

5.3.2 HIV diagnostics

The Biomedical Research and Training Institute laboratory in Harare, Zimbabwe, performed all HIV testing. At round 1, a highly sensitive and specific (both 99.6%) dipstick-dot ICL-HIV1 & 2 Dipstick EIA was used to detect HIV antibodies [26, 248]. Combaids-HIV-1 & 2 Dipstick was used in subsequent rounds, which was also determined in laboratory conditions to have high sensitivity and specificity (>99.9%). A small in-house comparison of these two dipstick tests showed 100% agreement between testing results from 160 positive and negative samples. For each round, all positive test results and a 10% sample of negatives were confirmed using a Plate EIA (Abbott 3rd Generation HIV 1 & 2 EIA, USA or Genelavia MIXT HIV1&2, Sanofi Diagnostics Pasteur S.A., France). [248] . Research staff were blinded to participants' HIV status.

5.3.3 Data analysis

5.3.3.1 Inclusion criteria

In the population survey, all women aged 15 to 24 years and men aged 17 to 24 years resident in the study area at each round were included in the analysis. This led to the exclusion of 251 visitors (135 in round 2 and 116 in round 3) and 567 men aged 15 to 16 years in round 3 from the analysis. Excluding these individuals permitted a more accurate description of changes in underlying HIV prevalence among individuals living in the study area over all three rounds. The total number of remaining individuals was 4366 in round 1, 3289 in round 2 and 6371 in round 3.

In the ANC surveillance, women aged 15 to 24 years seen at the 22 ANC clinics participating in all three surveillance rounds were included (i.e., data from seven clinics participating in one or two rounds were not used as recommended by UNAIDS and the World Health Organization to construct trends) [39]. The total number of participants was 676 in round 1, 667 in round 2 and 700 in round 3.

5.3.3.2 Statistical analyses

To describe HIV prevalence by data source (e.g., the population survey and ANC surveillance), crude HIV prevalence was calculated as the number of individuals testing positive divided by the number of individuals tested in the survey or surveillance round. To account for differences in population survey estimates across rounds due to shifts in the demographic composition of the population, crude estimates were adjusted by five year age groups and marital status (and sex, in the case of overall population survey estimates). Adjustments were made using a simple direct standardization method [249],

where the reference population was the distribution of all individuals at round 3. To account for the change in the inclusion of in-migrants in the study, demographic-standardized estimates were similarly adjusted. Other methods to account for changes in migration were also explored, including (i) imputing missing HIV prevalence estimates by age and marital status for in-migrants in communities 1 through 4 (based on the round 3 distributions) and then standardizing estimates for demographic differences, and (ii) excluding in-migrants. In the ANC surveillance, crude and age-marital standardized estimates were calculated, also using the round 3 ANC surveillance participants as the standard population.

To quantify uncertainty in population survey and ANC surveillance HIV prevalence estimates, 95% binomial confidence intervals (CIs) were calculated. Confidence intervals for round 1 and round 3 ANC-based surveillance estimates were widened to account for over-dispersion, which was detected by comparing the sum of the saturated log likelihood across clinics to the sum of the log likelihood assuming constant (e.g., average) prevalence within the clinics using the chi-square test (DF=21) [223]. The null hypothesis (e.g., no over- dispersion) was rejected when the resulting p-value for the chi-square value was <0.05. The adjustment factor to the 95% CI was 1.26 times the standard error in round 1 and 1.14 times the standard error in round 2.

To calculate the relative proportional change in prevalence across rounds (round 1 to round 3) and between rounds (round 1 to round 2; round 2 to round 3) as described in the UNGASS indicator, the difference between the earlier and the later round estimates was divided by the earlier estimate. When validating ANC surveillance trends relative to those in the population survey, proportional differences in HIV prevalence

across (round 1 to round 3) and between rounds (round 1 to round 2; round 2 to round 3), the Z-score test-statistic was used. To approximate variance in these proportional differences, which was too complex to obtain analytically, the delta method based on the Taylor series expansion of the variance was used [223]. The null hypothesis for trend similarity was rejected where $|Z| > 1.96$ (i.e., p-value < 0.05). This approach was adopted, rather than an odds ratio regression analysis, to permit comparison of the proportional change in HIV prevalence. A limitation of this approach, however, is that the Z-score test assumes independence in the samples across rounds, whereas in the population survey, the same individual may be tested across multiple rounds. The influence of this limitation on study findings is considered further in the discussion.

For the purposes of these analyses, general population survey trends were assumed to be the "gold standard" or the best representation of true underlying population prevalence in the study area; hence, the representativeness of ANC data was considered relative to that of the general population survey. Due to the rolling nature of the survey start date, the UNGASS indicator baseline measurement against which proportional prevalence change by 2005 was measured was assumed to be round 1, which spanned the period from 1998 to 2000.

Changes in behaviour between rounds in the sample dataset, including the proportion of non-sexually active youth, new partnership formation in the past year, consistent condom use among unmarried persons and partner's age for individuals reporting sex in the past two weeks were compared using two-tailed Z-scores and Student's t-tests. Behavioural data were collected using informal confidential voting

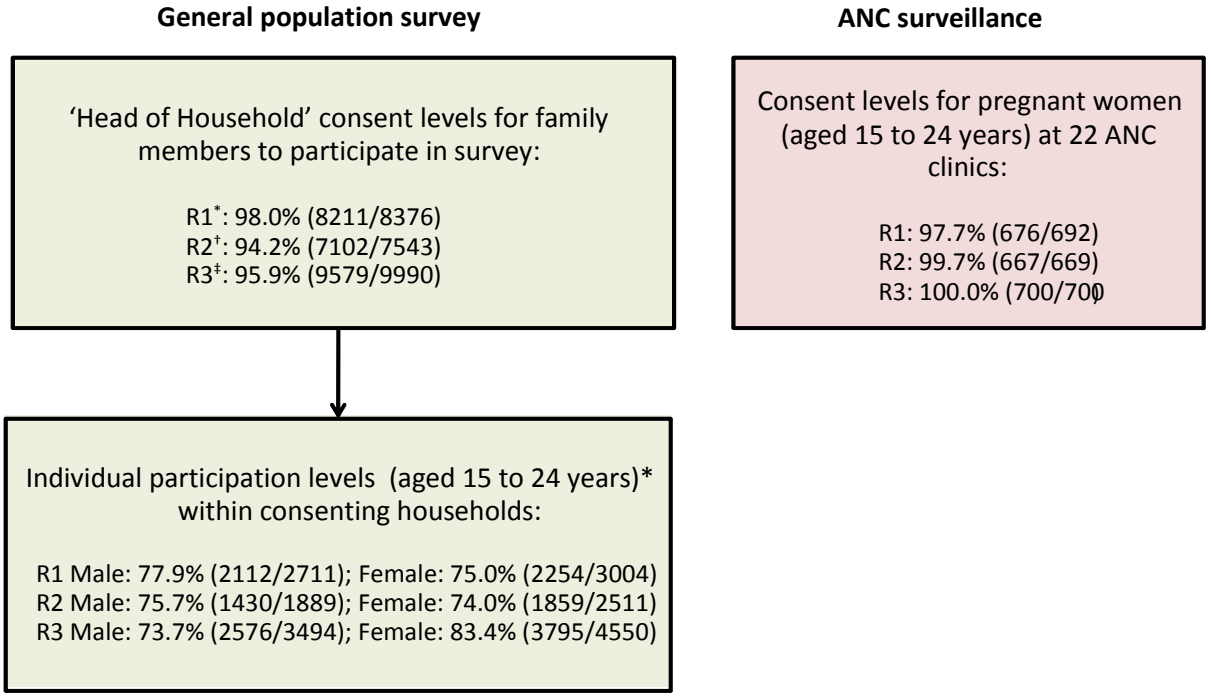
interviews, which have been associated with less reported “social desirability bias” than conventional face-to-face interviewing methods in the study population [202].

The first three behavioural indicators from the survey data most closely approximate UNAIDS recommendations for monitoring behaviour change among youth as part of the 2001 UNGASS targets [64]. The fourth indicator, partner age, has been shown previously to be an important factor in HIV transmission in this population [250]. Other key factors, such as changes in sexually transmitted infections (STIs), were not investigated: STI biomarkers were not included in the survey, self-reported symptoms can be unreliable, and prevalence of STIs are thought to be low in this population [248].

5.4 Results

5.4.1 Study participant characteristics

Figure 5.1 shows the results of household- and individual-level participation levels in the population survey and ANC surveillance datasets by round among eligible individuals. Enrolment in the population survey was high, with more than 94% of households agreeing to participate in each round. Among youth in the participating households, participation levels were similar for males and females, except that fewer males (73.7%) compared to females (83.4%) participated in round 3 (p-value <0.001). Absenteeism, as opposed to refusals, primarily explained lower individual participation levels. In the ANC surveillance, agreement to participate was nearly universal (97.7%-100%).



* Men aged 17 to 24 years only.

Figure 5.1 Round-specific household and individual participation levels for the Manicaland project general population survey (green-shaded boxes) and ANC surveillance (red-shaded box). Round 1 (R1): 1998-2000; Round 2 (R2): 2001-2003; Round 3 (R3): 2003-2005

Specific to the socio-demographic characteristics in each data set, the sex ratio (males/females) fluctuated over time in the population survey from 0.94 in round 1 to 0.77 in round 2 and 0.68 in round 3. Across rounds, the mean age of individuals in the population survey was younger (19.6 years) than that in the ANC surveillance (20.3 years) ($p < 0.001$). The proportion of men aged 17 to 19 years was approximately 47% in all three rounds. The proportion of women in the population survey aged 15 to 19 years was roughly the same at round 1 and round 3 (55.2% and 53.5%), but was significantly higher at round 2 (62.8%) (p-value <0.001).

Reflecting their younger ages and the inclusion of men, fewer individuals in the population survey were married (24.9% versus 87.2% in ANC surveillance, p-value <0.001), but more had secondary or higher education (81.8% versus 64.5% in ANC surveillance, p <0.001). With regard to marital status in the population survey, in round 1, men were slightly less likely to be married (9.5%) as compared to in round 2 (12.5%) and round 3 (11.5%). Women, on the other hand, were less likely to be married (29.3%) in round 2 as compared to in round 1 (37.3%) and in round 3 (37.9%). This latter distribution coincides with the younger ages of the population at round 2.

The residence of participants in the population survey distribution reflected the number of study sites, with 36.1% living in subsistence farming areas, 29.4% in estates, 19.2% in roadside trading centres, and 15.8% in towns aggregated across all rounds. Estimates did not vary greatly across rounds. The proportion of in-migrants was highest in towns and estates at all rounds. Relative to the population overall, 31.1% of the population reported moving to their community within two years of round 1 (see Figure 5. 2). At round 2, reflecting in part the exclusion of in-migrants in communities 1 through 4, the proportion of in-migrants was just 14.2%. In round 3, in-migrants comprised 19.6% of the total population.

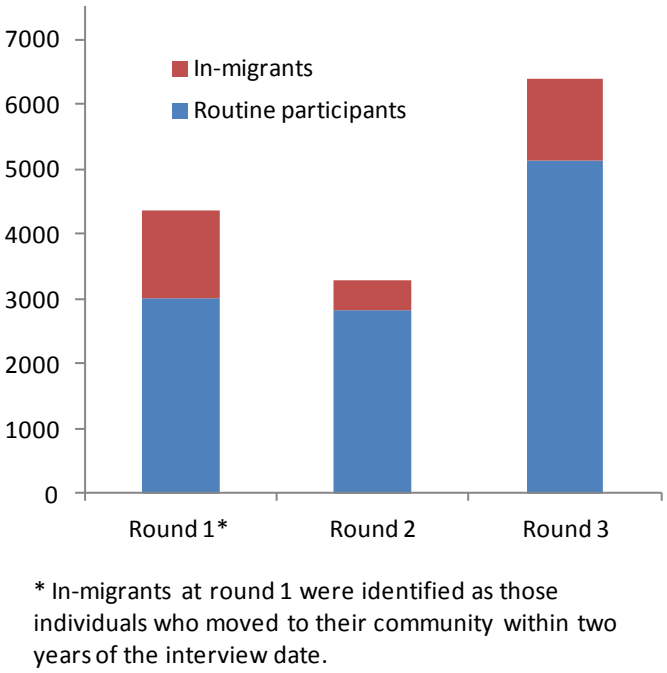


Figure 5.2 Routine participants and in-migrants in the population survey in Manicaland, Zimbabwe, 1998-2005. In-migrants at round 1 were identified as those individuals who moved to their community with two years of the first interview date.

In the ANC surveillance, 32.9% of participants attended clinics in subsistence farming areas, 33.7% in estates, 15.8% in roadside trading centres, and 18.6% in towns, and this also did not vary across rounds.

Considering the potential representativeness of ANC surveillance data, in the population survey, 21.8% of sexually active women at round 1, 20.6% at round 2 and 25.4% at round 3 identified themselves as being either currently pregnant or having completed a pregnancy in the six months prior to the interview date. Clinic attendance among these women was 81.9% in round 1, 82.4% in round 2 and 84.6% in round 3. Of those seeking ANC services, approximately 80% at each round reported attending their local clinic. Similar levels of local clinic attendance at round 2 and round 3 were also reported in the ANC surveillance.

5.4.2 Population-based and ANC HIV prevalence among youth

Table 5.1 summarizes crude and adjusted HIV prevalence levels and trends among youth (women aged 15 to 24 years and men aged 17 to 24 years separately, and combined) in the general population survey and among ANC attendees at each survey round between 1998 and 2005. In the columns following each set of estimates, the proportional changes in HIV prevalence across and between rounds, along with the accompanying 95% confidence intervals, are provided.

In general, crude HIV population prevalence separately by sex, and among men and women combined, was lower than ANC prevalence at each round (see Table 5.1 and Figure 5.3a. The higher levels of HIV prevalence among all ANC attendees reflected the older average age of pregnant women as compared to the general population and the selection for high-risk sexual activity that exposes women to pregnancy and HIV infection. In the population survey, women, in comparison to men, also had higher HIV prevalence levels, suggesting that females compared to males are at a higher risk of HIV infection generally at young ages in the study area.

	Round 1 (1998 - 2000)				Round 2 (2001-2003)				Round 3 (2003-2005)				Round 1 to 3		Round 1 to 2		Round 2 to 3	
	N (#)	HIV+ (n)	HIV+ (%)	95% CI	N (#)	HIV+ (n)	HIV+ (%)	95% CI	N (#)	HIV+ (n)	HIV+ (%)	95% CI	Proportional Change (95% CI)		Proportional Change (95% CI)		Proportional Change (95% CI)	
Population survey																		
Women																		
Crude	2254	349	15.5	(14.0 - 17.0)	1859	149	8.0	(6.8 - 9.3)	3795	311	8.2	(7.3 - 9.1)	-47.1%	(-54.7, -39.5)	-48.2%	(-57.6, -38.8)	2.2%	(-16.9, 21.4)
Standardized (demographics)*			15.6	(14.1 - 17.0)			9.3	(7.9 - 10.8)			8.2	(7.3 - 9.1)	-47.4%	(-54.9, -39.8)	-39.9%	(-50.5, -29.6)	-12.4%	(-27.9, 3.1)
Standardized (migration & demographics)†			15.4	(13.9 - 16.8)			9.1	(7.7 - 10.5)			8.2	(7.3 - 9.1)	-46.7%	(-54.4, -39.1)	-40.6%	(-50.9, -30.4)	-10.3%	(-26.3, 5.7)
Men																		
Crude	2112	100	4.7	(3.9 - 5.7)	1430	44	3.1	(2.2 - 4.1)	2576	74	2.9	(2.2 - 3.5)	-39.3%	(-57.6, -12.4)	-35.0%	(-57.6, -12.4)	-6.6%	(-40.9, 27.7)
Standardized (demographics)*			5.0	(4.0 - 5.9)			2.9	(2.1 - 3.8)			2.9	(2.2 - 3.5)	-41.0%	(-61.7, -20.2)	-41.0%	(-61.7, -20.2)	-2.2%	(-38.7, 34.3)
Standardized (migration & demographics)†			4.6	(3.7 - 5.6)			2.9	(2.1 - 3.8)			2.9	(2.2 - 3.5)	-40.6%	(-50.9, -30.4)	-36.3%	(-59.0, -13.7)	-2.2%	(-38.7, 34.3)
Men and women combined																		
Crude	4366	449	10.3	(9.4 - 11.2)	3289	193	5.9	(5.1 - 6.7)	6371	385	6.0	(5.5 - 6.6)	-41.2%	(-48.9, -33.7)	-42.9%	(-55.2, -33.7)	3.0%	(-14.3, 20.2)
Standardized (demographics)*			11.3	(10.3 - 12.2)			6.7	(5.9 - 7.7)			6.0	(5.5 - 6.6)	-46.4%	(-53.2, -39.5)	-40.1%	(-49.2, -31.0)	-10.6%	(-24.8, 3.7)
Standardized (migration & demographics)†			10.5	(9.6 - 11.4)			6.6	(5.7 - 7.5)			6.0	(5.5 - 6.6)	-42.6%	(-50.0, -35.1)	-41.2%	(-46.8, -27.3)	-8.7%	(-23.4, 5.5)
ANC surveillance data																		
Crude	676	125	18.5	(15.6 - 21.6)	667	88	13.2	(10.7 - 15.8)	700	69	9.9	(7.8 - 12.3)	-46.7%	(-64.0, -29.4)	-28.7%	(-48.6, -8.7)	-25.3%	(-49.3, -1.3)
Standardized (demographics)*			18.4	(15.5 - 21.3)			13.2	(10.7 - 15.8)			9.9	(7.8 - 12.3)	-46.6%	(-63.9, -29.3)	-28.1%	(-48.1, -8.1)	-25.7%	(-49.5, -1.8)

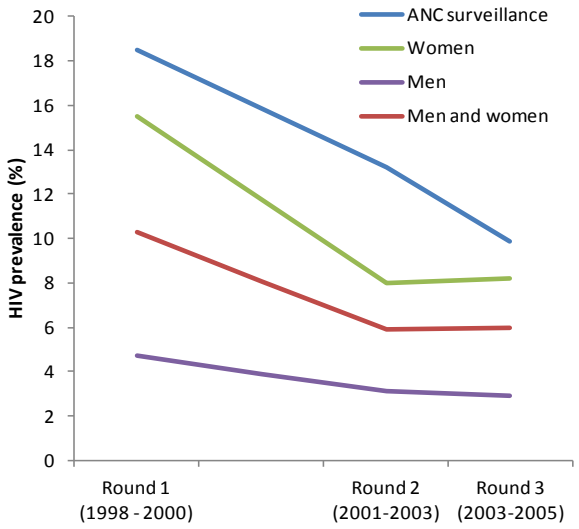
* Estimates adjusted (i.e. standardized) across rounds for changes in participation by 5 year age groups, marital status, and sex (for women and men combined) using the population stratum totals in round 3 as the standard.

† Estimates adjusted (i.e., standardized) across rounds for changes in participation by 5 year age groups, marital status , and sex (for men and women combined) and for in-migration using the population stratum totals in round 3 as the standard.

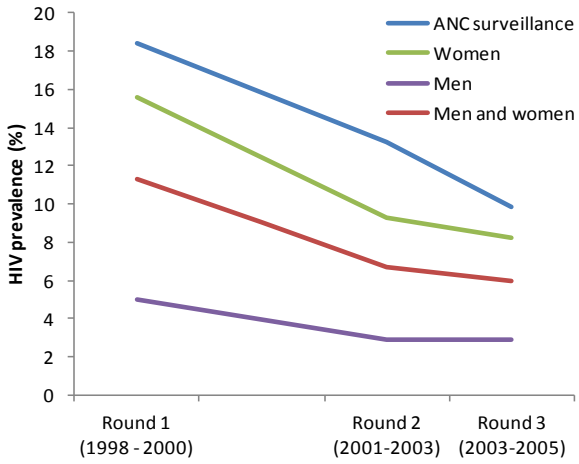
Table 5.1 Crude and adjusted (i.e., standardized) HIV prevalence and proportional reductions in the general population survey and ANC surveillance in Manicaland, Zimbabwe, 1998-2005.

With regard to the UNGASS indicator in the population survey, larger crude proportional reductions in HIV prevalence during the study period were observed among women (-47.1%; 95% CI: -54.7%, -39.5%) than men (-39.3%; 95% CI: -57.6%, -12.4%). The increasing ratio of women to men between round 1 and round 3, however, reduced the overall magnitude of the decline for men and women combined (-41.2%; 95% CI: -48.9%, -33.7%). Not surprisingly, the proportional reduction in HIV prevalence among women from round 1 to round 3 was most similar to that observed among ANC attendees (-46.7%; 95% CI: -64.0%, -29.4%). Regardless of the data source or sub-population considered, however, crude round 1 to round 3 reductions in HIV prevalence comfortably exceeded the UNGASS target of 25% by 2005. Also, no statistically significant differences were identified in the comparison of round 1 to round 3 trends, indicating that crude ANC estimates reasonably reflected the proportional reduction overall in HIV prevalence in the population without adjusting estimates.

a) Crude estimates



b) Standardized (demographics)



c) Standardized (demographics and migration)

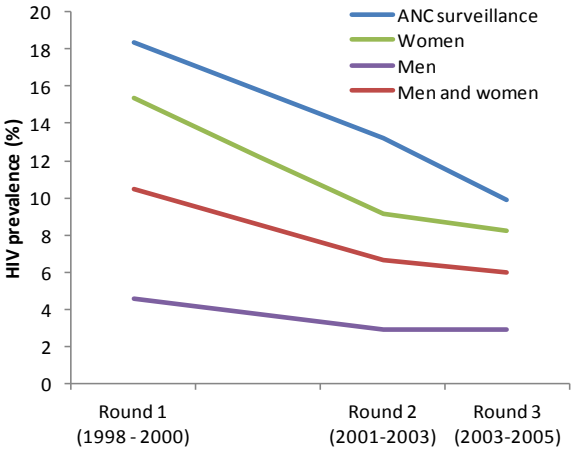


Figure 5.3 Estimates of HIV prevalence in the general population and ANC surveillance a) unadjusted and b) adjusted for demographic shifts in the composition of the population only and c) also for migration patterns in Manicaland, Zimbabwe, 1998-2005. Round 3 is the reference population for all adjustments.

Despite this latter finding, as Figure 5.3a shows, intermediary trends in the two data sources were less comparable. From round 1 to round 2, which covered about five of the eight years of the study, the tendency was for the proportional reduction in the ANC crude prevalence estimate to greatly understate that in the population survey. In the case of men and women combined, the general population decline between 1998 and 2001 was 42.9% (95% CI: -55.2%, -33.7%) as compared to 28.7% (95% CI: -48.6%, -8.7%) in the ANC surveillance over the same time period. In the period covering the last three years approximately, from round 2 to round 3, the reduction in the ANC estimate (-25.3%; 95% CI: -49.3%, -1.3%) contrasted with an increase in the population survey estimate (3.0%; 95% CI: -14.3%, 20.2%). This rise was driven by the higher proportion of women, relative to men, at round 2 and round 3, and the larger proportion of female in-migrants at round 3 with disproportionately high HIV prevalence in comparison to the routine female participants (see Figure 5.4a).

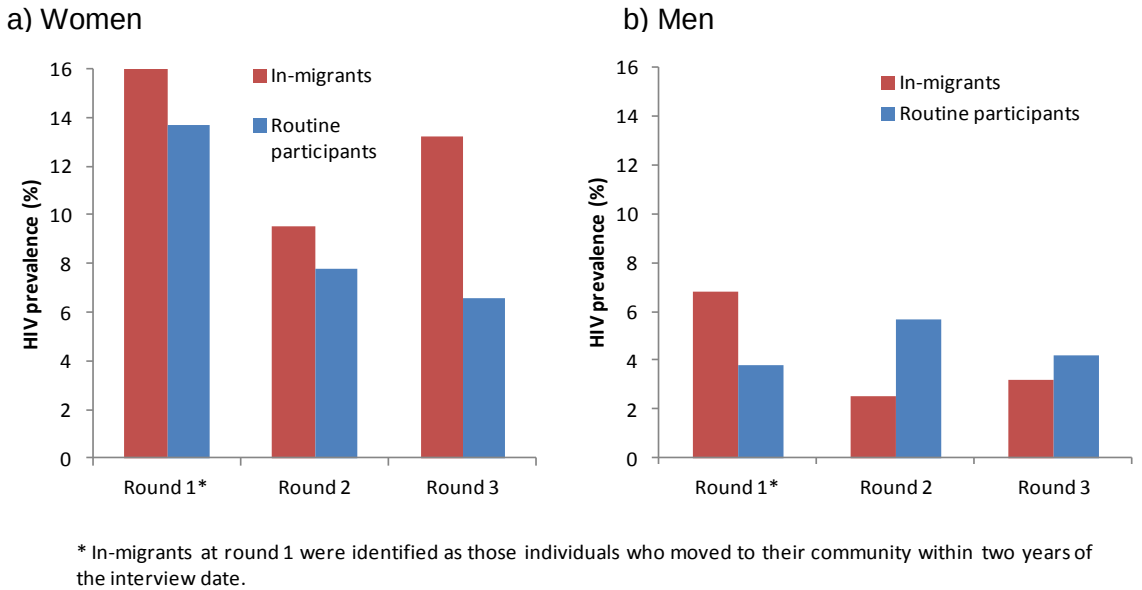


Figure 5.4 HIV prevalence of a) women aged 15 to 24 years and b) men aged 17 to 19 years by participant status (e.g., routine and in-migrant).

Although none of the differences in intermediary trends reached a level of statistical significance at the 95% level (p-value<0.05), comparison of ANC surveillance trends with those among females, and females and males combined between round 1 and round 2 produced p-values that were less than 0.10.

Standardization of ANC and population survey data to account for changes in the demographic composition of participants over time did not dramatically influence intermediary trends, although the proportional increase in the prevalence among women only, and men and women combined, from round 2 to round 3 was reversed in the standardized estimates (See Table 5.1 and Figure 5.3b). This reversal resulted from increasing the relative weight of HIV prevalence among married women at round 2, consistent with that of round 3, and among men and women combined, accounting for the shifting ratio of male to female participants. Even after adjusting for demographic differences, however, ANC estimates still declined less steeply from round 1 to round 2 and more steeply from round 2 to round 3 as compared to the population survey trends, in part due to the higher HIV prevalence among in-migrant females at round 3. Notably, however, the overall decline among men and women combined (-46.4%; 95% CI: -53.2%, -39.5%) more closely resembled the proportionate reduction in ANC estimates from round 1 to round 3, reflecting the standard distribution of females compared to males.

Further standardization of these estimates to account for changing migration patterns also did not alter overall or intermediary trends substantially (see Table 5.1 and Figure 5.3c), although the lower HIV prevalence at round 2 among women (relative to the demographic-standardized estimate) highlighted the unusual finding that the higher

HIV prevalence among in-migrants was concentrated in unmarried women aged 15 to 19 years only. In round 1 and round 3, all female in-migrants regardless of age or marital status had higher HIV prevalence than the general population. Imputing HIV prevalence estimates for missing in-migrants in communities 1 through 4 and then standardizing them for demographic and in-migrant differences also resulted in no change. This was true because even though the potential HIV prevalence among missing in-migrants in communities 1 through 4 by sex would likely have been higher than the estimates among in-migrants in communities 5 through 12 (females: 11.0% versus 9.5% and males: 10.1% versus 4.8%), the proportion of missing in-migrants relative to the overall population size was very small.

One final consideration with regard to in-migrants was whether ANC surveillance data would be more representative of persons living in the study area for at least two years (i.e., excluding in-migrants). In this case, proportional changes in crude and standardized estimates would have slightly outpaced those observed among ANC attendees as compared to when in-migrants were included, although overall reductions were in both data sets were similar (see Table 5.2). More importantly, however, exclusion of in-migrant females generated more consistent reductions between rounds, after standardization for demographic changes in the population, than when in-migrants were included. Among men, exclusion of in-migrant participants did not appear to improve the representativeness of ANC surveillance data either.

	Round 1 (1998 - 2000)				Round 2 (2001-2003)				Round 3 (2003-2005)				Round 1 to 3	Round 1 to 2	Round 2 to 3
	N (#)	HIV+ (n)	HIV+ (%)	95% CI	N (#)	HIV+ (n)	HIV+ (%)	95% CI	N (#)	HIV+ (n)	HIV+ (%)	95% CI	Proportional Change (95% CI)	Proportional Change (95% CI)	Proportional Change (95% CI)
Population survey (excluding in-migrants)															
Women															
Crude	1559	214	13.7	(12.1 - 15.5)	1587	123	7.8	(6.5 - 9.2)	2919	195	6.7	(5.8 - 7.6)	-51.3% (-60.3, -42.4)	-43.5% (-55.4, -31.7)	-13.8% (-32.5, 4.9)
Standardized (demographics)*			13.4	(11.8 - 15.0)			8.6	(7.2 - 10.0)			6.7	(5.8 - 7.6)	-50.2% (-59.4, -40.9)	-35.8% (-48.9, -22.7)	-22.4% (-38.7, -6.1)
Men															
Crude	1448	55	3.8	(2.9 - 4.9)	1234	39	3.2	(2.3 - 4.3)	2201	62	2.8	(2.2 - 3.6)	-25.8% (-52.3, 0.6)	-16.8% (-50.3, 16.8)	-10.9% (-46.0, 24.3)
Standardized (demographics)*			4.6	(3.1 - 5.2)			2.9	(2.1 - 4.0)			2.8	(2.1 - 3.5)	-31.9% (-55.7, -8.2)	-26.7% (-56.1, 2.7)	-7.1% (-44.2, 30.1)
Men and women combined															
Crude	3007	269	8.9	(7.9 - 10.0)	2821	162	5.7	(4.9 - 6.7)	5120	257	5.0	(4.4 - 5.7)	-43.9% (-53.1, -34.6)	-35.8% (-47.9, -23.7)	-12.6% (-29.3, 4.1)
Standardized (demographics)*			9.2	(8.2 - 10.2)			6.1	(5.2 - 7.0)			4.9	(4.4 - 5.6)	-45.2% (-54.2, -36.3)	-33.5% (-45.7, -21.3)	-17.7% (-33.1, -2.2)
ANC surveillance data															
Crude	676	125	18.5	(15.6 - 21.6)	667	88	13.2	(10.7 - 15.8)	700	69	9.9	(7.8 - 12.3)	-46.7% (-64.0, -29.4)	-28.7% (-48.6, -8.7)	-25.3% (-49.3, -1.3)
Standardized (demographics)*			18.4	(15.5 - 21.3)			13.2	(10.7 - 15.8)			9.9	(7.8 - 12.3)	-46.6% (-63.9, -29.3)	-28.1% (-48.1, -8.1)	-25.7% (-49.5, -1.8)

* Estimates adjusted (i.e. standardized) across rounds for changes in participation by 5 year age groups, marital status, and sex (for women and men combined) using the population stratum totals in round 3 as the standard.

Table 5.2 Crude and adjusted (i.e., standardized) HIV prevalence and proportional reductions among non-in-migrants in the general population survey and ANC surveillance attendees in Manicaland, Zimbabwe, 1998-2005.

5.4.3 Socio-demographic predictors of trend differences

Using the Z-score test statistic to compare gender-specific proportional changes in overall and intermediary adjusted HIV prevalence trends (e.g., round 1 to round 2 and round 2 to round 3) by socio-demographic strata (e.g., 15 to 19 year olds versus 20 to 24 year olds), no stratum-specific differences in trends between the two data sources were identified (see Table 5.3). Nevertheless, from these stratum-specific comparisons, it was evident that ANC surveillance data did not reflect changes in HIV prevalence trends among men as well as they did among women. In particular, among men aged 17 to 19 years and those who were single, estimates were observed to fluctuate between rounds, whereas among ANC attendees, they declined sharply. Equally, reductions in adjusted HIV prevalence among men who were single or who resided in towns declined considerably less steeply than those among ANC attendees in similar stratum.

Socio-demographic characteristics		Population survey						ANC surveillance					
		Round 1 (1998-2000)		Round 2 (2001-2003)		Round 3 (2003-2005)		Round 1 (1998-2000)		Round 2 (2001-2003)		Round 3 (2003-2005)	
		Adjusted HIV (%)	95% CI (adjusted)	Adjusted HIV (%)	95% CI (adjusted)	Adjusted HIV (%)	95% CI (adjusted)	HIV (%)	95% CI	HIV (%)	95% CI	HIV (%)	95% CI
Women													
Age*	15-19 years	6.3	(5.0 - 7.7)	3.2	(2.2 - 4.3)	3.0	(2.2 - 3.7)	13.2	(9.4 - 18.0)	7.7	(4.8 - 11.6)	5.0	(2.8 - 8.2)
	20-24 years	25.8	(23.1 - 28.6)	15.9	(13.1 - 18.8)	14.2	(12.6 - 15.9)	22.0	(17.9 - 26.2)	16.7	(13.2 - 20.7)	13.1	(10.0 - 16.7)
Marital status†	Single	10.4	(8.9 - 11.9)	6.2	(4.8 - 7.6)	5.4	(4.5 - 6.3)	20.0	(10.8 - 32.3)	10.0	(5.3 - 16.8)	7.3	(2.7 - 15.2)
	Married	23.6	(20.7 - 26.5)	14.0	(10.9 - 17.0)	12.8	(11.1 - 14.5)	18.3	(15.4 - 21.6)	13.9	(11.1 - 17.1)	7.6	(7.9 - 12.9)
Education‡	None/primary	24.9	(21.4 - 28.4)	17.6	(13.3 - 22.0)	14.7	(12.1 - 17.2)	18.9	(14.4 - 24.1)	11.4	(7.6 - 16.3)	11.0	(7.2 - 15.8)
	Secondary/higher	12.3	(10.8 - 13.8)	7.1	(5.6 - 8.5)	6.6	(5.7 - 7.4)	18.2	(14.6 - 22.3)	14.1	(11.0 - 17.8)	9.3	(6.9 - 12.3)
Residence‡§	Town	26.0	(20.2 - 30.0)	16.4	(11.6 - 21.1)	13.5	(10.9 - 16.2)	19.8	(13.0 - 28.3)	12.3	(6.9 - 19.7)	9.3	(4.9 - 15.7)
	Commercial estate	19.0	(15.9 - 22.1)	10.0	(7.3 - 12.8)	8.8	(7.0 - 10.47)	20.8	(15.7 - 26.7)	14.3	(10.0 - 19.5)	11.2	(7.5 - 16.0)
	Subsistence farm	10.1	(8.2 - 12.0)	7.1	(4.3 - 10.0)	6.1	(4.9 - 7.3)	18.4	(13.5 - 24.2)	11.8	(7.9 - 16.8)	11.1	(7.4 - 15.8)
	Roadside trading	12.1	(9.1 - 15.1)	6.7	(4.0 - 9.4)	7.1	(5.4 - 8.9)	12.8	(7.4 - 20.3)	14.7	(8.5 - 23.1)	4.8	(15.8 - 10.9)
Men													
Age*	17-19 years	0.8	(0.3 - 1.4)	0.6	(0.10 - 1.3)	1.5	(0.8 - 2.2)	See above for estimates among female ANC attendees					
	20-24 years	7.9	(6.2 - 9.7)	4.9	(3.4 - 6.4)	4.1	(3.0 - 5.1)						
Marital status†	Single	3.4	(2.6 - 4.3)	2.0	(1.2 - 2.8)	2.2	(1.6 - 2.8)						
	Married	13.6	(8.5 - 18.8)	10.0	(5.8 - 14.4)	8.1	(5.0 - 11.2)						
Education‡	None/primary	5.9	(3.4 - 8.4)	5.7	(2.7 - 8.8)	3.2	(12.6 - 5.1)						
	Secondary/higher	4.5	(3.6 - 5.6)	2.4	(0.14 - 5.9)	2.8	(2.2 - 3.5)						
Residence‡§	Town	6.6	(3.1 - 7.9)	5.6	(2.4 - 8.7)	5.3	(2.3 - 7.5)						
	Commercial estate	6.0	(4.5 - 8.2)	3.6	(0.80- 7.4)	3.7	(2.4 - 5.1)						
	Subsistence farm	3.3	(1.8 - 4.8)	1.8	(0.74 - 2.8)	1.8	(0.9 - 2.6)						
	Roadside trading	5.5	(2.4 - 6.5)	2.0	(0.2 - 3.8)	1.7	(0.6 -2.7)						

* Estimates adjusted across rounds for changes in participation by marital status across all rounds and in-migration using the population stratum totals in round 3 as the standard

† Estimates adjusted across rounds for changes in participation by 5 year age group across all rounds, and in-migration using the population stratum totals in round 3 as the standard

‡ Estimates adjusted across rounds for changes in participation by 5 year age group and marital status across all rounds and in-migration using the population stratum totals in round 3 as the standard

¶ The residence of ANC attendees is defined as where the woman attended the ANC and not her actual household residence.

Table 5.3 HIV prevalence estimates by socio-demographic characteristics among young women and men aged 15 to 24 years in the general population survey and ANC surveillance in Manicaland, Zimbabwe, 1998-2005.

5.4.4 Behavioural risk factors

Table 5.4 shows trends in selected behavioural indicators reported in the general population dataset that could explain observed intermediary differences. For both sexes and age groups, the proportion of those not yet initiating sex increased significantly from round 1 to round 2. From round 2 to round 3, evidence of a continued and significant increase was limited to men only. Among younger women (aged 15 to 19 years), the proportion not yet initiating sex declined slightly (from 79.5% to 78.4%) while the decline among older women aged 20 to 24 years was significant (17.6% to 14.1%; p-value=0.029).

For those who had sex within the past year, the proportion of women reporting none, 1 or 2 or more partners did not change from round 1 to round 2. From round 2 to round 3, however, a significant decline in the number of women reporting one partner and an increase in the proportion reporting no new partners was observed. Among men reporting of one new partner in the previous year increased from round 1 to round 2 (34.1% to 40.1%; p-value=0.006), but then remained relatively unchanged from round 2 to round 3.

Estimates of mean partner age of persons having sex in the past two weeks and consistent condom use among unmarried women and men generally tended toward less risky behaviour, although among women, mean partner age did not change greatly. With regard to the partner's mean age among men, the overall significant increase from round 1 to round 2 likely reflected the increasing proportion of men delaying initiation of sex. From round 2 to round 3, however, a significant decrease in mean partner age, was observed, from 19.2 years to 18.6 years (p-value=0.001).

Finally, with regard to the behavioural indicators, among unmarried women and men, steady increases were observed in consistent condom use. From round 2 to round 3, this increase was significant for both sexes ($p<0.001$) and reflect the relative emphasis in the study area on interventions promoting safe sex in this age group.

	Round 1 (1998-2000)			Round 2* (2001-2003)			Round 3 (2003-2005)			Round 1 to 2 p-values	Round 2 to 3 p-values
Individuals not yet initiating sex (n, N, %)											
Female											
15-19 years of age	829	1243	66.7	928	1167	79.5	1593	2032	78.4	**<0.001**	0.454
20-24 years of age	108	1011	10.7	122	692	17.6	249	1763	14.1	**<0.001**	**0.029**
Male											
17-19 years of age	512	1013	50.5	475	664	71.5	1045	1204	76.2	**<0.001**	**0.020**
20-24 years of age	152	1100	13.8	153	766	20.0	327	1372	23.8	**<0.001**	**0.040**
Number of new partners among those having sex in the last year (n, N, %)											
Female											
0 new partners	773	1104	70.0	401	571	70.2	1051	1328	79.1	0.929	**<0.001**
1 new partner	302	1104	27.4	151	571	26.4	249	1328	18.8	0.691	**<0.001**
2+ new partners	29	1104	2.6	19	571	3.3	28	1328	2.1	0.415	0.117
Male											
0 new partners	446	1127	39.6	231	604	38.3	202	555	36.4	0.589	0.413
1 new partner	384	1127	34.1	242	604	40.1	218	555	39.3	**0.013**	0.883
2+ new partners	297	1127	26.4	131	604	21.7	135	555	24.3	**0.032**	0.2865
Partner's mean age and 95% CIs (in years) for those reporting sexual intercourse in the past two weeks											
Female	27.9	(27.5 - 28.4)		27.7	(17.1 - 28.2)		27.2	(26.9 - 27.4)		0.455	0.0849
Male	18.4	(18.1 - 18.7)		19.2	(18.7 - 19.8)		18.6	(18.4 - 18.8)		0.070	**0.001**
Consistent condom use with the last partner in the previous two weeks among unmarried individuals (n, N, %)											
Female	61	113	54.0	48	74	64.9	297	336	88.4	0.141	**<0.001**
Male	263	373	70.5	97	145	66.9	584	655	89.2	0.423	**<0.001**

***Inclusion criteria changed to include in-migrants in communities 5-12 at round 2 and all in-migrants at round 3.**

Men aged 15 to 16 years were excluded in round 3 and data were not collected for these ages at round 1 and round 2.

Table 5.4 Selected behavioural indicators among young women aged 15 to 24 years and men (aged 17 to 24) in the general population survey in Manicaland, Zimbabwe, 1998-2005.

5.5 Discussion

Data from the three large population surveys conducted from 1998 to 2005 in Manicaland, Zimbabwe have shown that the UNGASS target of a reduction of 25% in HIV prevalence by 2005 among young women aged 15 to 24 years and young men aged 17 to 24 years was most likely achieved, and possibly substantially exceeded, in the study area. Among women, the proportional reduction in HIV prevalence over the three study rounds (from 1998 to 2005) was about 47%. Among men, as compared to women alone, reductions in crude and standardized estimates were modestly smaller, at around 40%, but still above the 25% UNGASS target. Considering the study population as a whole, HIV prevalence fell by 46.4%, after accounting for changes in the demographic composition and shifts in in-migration patterns over the study rounds. Similar proportional declines of approximately 46% were observed among ANC attendees at clinics over the same time period, suggesting that these data were generally representative of population HIV prevalence trends. The 95% confidence intervals for all proportional HIV prevalence reductions comfortably exceeded 25%, except among men where the reduction could have been less.

Despite these results, which are broadly encouraging of HIV prevention interventions in the study area and the use of ANC surveillance data to monitor population prevalence trends among youth, there were some findings which merit further consideration. Most importantly, with regard to the usefulness of ANC surveillance data, although proportional reductions were similar between the two data sources, intermediary trends were observed to differ. In particular, crude population-level HIV prevalence reductions were considerably greater than those observed among ANC attendees from round 1 to round 2, but substantially smaller

than – and in the case of women, even in opposition to – the reductions observed in the ANC estimates from round 2 to round 3.

Before exploring whether these intermediary differences reflect changes in behaviour between ANC and general population participants, it is first important to account for possible participation biases in the data sources as these may change in magnitude over time. In the population survey, one of the biggest sources of participation bias that could be quantified and accounted for using adjustment methods arose from the changing distribution of the socio-demographic profile of survey participants at each round. For example, at round 2, as compared to round 1 or round 3, the proportion of females who were younger and unmarried with low HIV prevalence was much larger than the proportion of those who were older and married with higher HIV prevalence. Adjusting for these differences reduced the bias in estimates at round 2 such that population prevalence among women no longer increased over the last two survey rounds. Among men, however, the proportional distribution of age categories and marital status was more consistent across the rounds, thus adjusting estimates made only a modest difference to the intermediary trends. In the population survey, the adjusted estimates would be a better reflection than the crude estimates for changes in the intermediary population HIV prevalence trends.

The other source of participation bias that could be directly measured and accounted for in the population survey estimates was that resulting from changes in the ratio of men to women across the population survey rounds. As a consequence of women becoming increasingly over-represented in the survey at each round, crude reductions among men and women combined would have been smaller as time progressed since women were at higher risk of HIV generally when compared

to men. Standardization of estimates by sex for men and women combined across rounds thus permitted a less biased indicator of changes in population trends.

A third source of bias in the population survey estimates resulted from the changes more generally in the distribution of in-migrants across the survey rounds, and the exclusion of in-migrants in four of the 12 communities at round 2 specifically. Adjusting for in-migration, however, did not considerably change the large intermediary differences in trends that were also present in the demographically-adjusted estimates. Attempting to impute values for in-migrants excluded from round 2 also resulted in no appreciable difference in the intermediary trends. The limitation to both of these analyses, however, is that data on HIV prevalence among in-migrants at round 2 for the four communities was ultimately unknown and associations between HIV infection and in-migration was different at round 2 when compared to round 1 and round 3, especially among women. Excluding in-migrants from the population study completely resulted in the best representation of intermediary reductions in trends as represented by the ANC surveillance data.

With regard to the choice of the standard population for adjusting estimates for changes in the demographic composition in the population survey, it should be noted that using either round 1, round 3 or the average across the rounds produced similar estimates, given that round 1 and round 3 shared similar distributions of age and marital status. Round 3 was selected as the standard population, however, as it had the fewest restrictions on participation, included the largest number of participants in any round, and had the most reliable information on in-migrants in the study area. In terms of the previously discussed limitation of using the Z-score test in non-independent groups to evaluate differences in trends, taking into account that the repeated measures would have only widened confidence intervals further, this source of bias would not be a factor in interpreting the results presented here.

In addition to the biases discussed above, a final source of bias in the population survey that must also be considered is that related to refusal and absentee levels. Among men, participation was found only marginally lower at each progressive survey round. Among women, participation at round 3 was higher compared to the other rounds. To the extent that men who knew or suspected themselves to be HIV positive refused or were absent with greater frequency over time, the intermediary estimates of HIV prevalence in this group could have increasingly understated true underlying prevalence in the area. Conversely, among women, the higher levels of consent at round 3 may have presented a more accurate estimate of underlying HIV prevalence as opposed to the estimates at round 1 or round 2, where participation levels were lower and HIV prevalence also could have been understated. In this case, the differential exclusion of HIV infected women at round 1 and round 2 would not have likely explained the steep reductions observed from round 1 to round 2, but could have contributed to the slower decline from round 2 to round 3.

Even considering this possibility, however, it is unlikely that the magnitude of any participation bias due to selective absenteeism or refusal among HIV infected individuals would have been greater at any one study round. Overall participation levels observed in the survey among both men and women were consistent with those achieved in other HIV population surveys in SSA [67], and which have been shown to produce minimally biased HIV prevalence estimates [74]. Also, knowledge of serostatus at all ages in the study area was low, with only 11% in round 2 [251] and 8.6% in round 3 [252] reported having ever been tested and received their test result. Accordingly, few people would have avoided participation based on a confirmed HIV diagnosis. Finally, a study of individuals participating at round 1 who later migrated to more urban areas did not show out-migrants to have higher levels

of HIV prevalence [253], thus even relatively high levels of male absenteeism at round 3 would have a limited influence on trends. Mobility, and therefore absenteeism, is likely to be high in this population since many individuals will move out of the study area for educational or employment opportunities elsewhere, independent of their HIV status. Recently married women will also be more likely to leave their village to move to the village of their husband. Still, because HIV prevalence was not able to be measured among non-participants, and previous studies showing the magnitude of bias due to non-response are limited by the assumption that testers and non-testers have similar demographic and risk profiles, it is important to consider the potential for this type of bias when interpreting prevalence trends in these types of longitudinal cohort surveys.

Although biases were more likely to have been present in the population survey, ANC surveillance data can also be biased differentially with time and this could have affected the results described here. Although participation in ANC surveillance was nearly universal at each round, it is still possible that changes in the profile of women who became pregnant and who sought ANC services might have influenced ANC trends differentially over time. With regard to fertility levels in the area, the proportion of women pregnant in the population survey did not change over time, indicating that ANC data should be, at minimum, representative of pregnant women in the surrounding communities. With regard to differences in those who sought ANC services, the profile of women by age and marital status also did not change greatly over time, as evidenced by the very small adjustments in the standardized estimates. As a result, it is unlikely that these shifts would have contributed to the differences between the ANC and population survey intermediary trends. Also, although data was not collected to identify those from outside the clinic catchment area at round 1, the proportion of non-local ANC attendees was similar,

as were their respective levels of HIV prevalence, at round 2 and round 3. As a result, the inclusion of non-local ANC attendees would have not been a great source of bias in the trends, even if the overall levels of HIV prevalence differed from those in the surrounding communities.

A more recent consideration with regard to possible biases in the ANC surveillance data is the extent to which the scale-up of HIV testing and prophylaxis services for pregnant women also could have introduced a differential upwards bias over time in estimates, especially at round 3; however, in Mwanza, Tanzania, while the quality and type of ANC services influenced where women sought prenatal care, these preferences were not differentially associated with a woman's HIV status [123]. Furthermore, this study occurred during a period when HIV testing and prophylaxis services for pregnant women in Zimbabwe were still limited; thus, a selective increase in uptake of ANC services by HIV-positive women over time, leading to less steep reductions from round 2 to round 3, is unlikely.

While it is possible that any number of the biases described above could have influenced the observed patterns of intermediary change in the ANC and the population survey data, it is also possible that these differences are real. From round 1 to round 2, steeper reductions could have reflected the rapid expansion and impact of HIV prevention campaigns in the early 2000s that were occurring throughout the country [254, 255]. The impact of these campaigns may be evident in the early increases in the proportion of women and men at all ages delaying initiating sex. Also, and as was the case in Uganda, another sub-Saharan Africa country with high prevalence early on in the epidemic, a visible increase in HIV-related mortality in the late 1990s among the participating communities may have accelerated very earlier behaviour change among youth, the impact of which would be captured from round 1 to round 2 [254]. Similar declines in HIV prevalence were observed among young

women and ANC attendees nationally in Zimbabwe, although the time frame for that comparison was from 2001 to 2007 [21].

A similar study from Lusaka, Zambia, also comparing trends in the general population and among ANC attendees found that HIV prevalence among youth between 1995 and 2003 declined more rapidly than among ANC attendees due to increases in educational attainment leading to postponement in ages at first sex and first pregnancy [116]. As was the case in Lusaka, one possible explanation for these divergences in Manicaland is that changes in sexual behaviour in the general population were not reflected initially among ANC attendees. Primarily, the postponement of sexual debut and, to a lesser extent, reductions in the number of new partners and the age of partners, and increases in consistent condom use among youth generally from round 1 to round 2 could have rapidly reduced HIV transmission in this population while having a more limited impact on the declining fraction who continued to become pregnant by practicing unprotected sex. Mathematical modelling by Zaba and colleagues supports this hypothesis, showing how young pregnant women become increasingly less representative of the general population with regard to their sexual behaviour as the age of sexual debut increases and risk of HIV transmission declines, although these biases eventually will stabilize [117].

With regard to the round 2 to round 3 changes, the relatively slower declines in prevalence could indicate that prevention efforts in later years may have been less effective in reaching high-risk individuals. This is supported by the significant increase in the proportion of women aged 20 to 24 years initiating sex from round 2 to round 3 and the lack of further increases among women aged 15 to 19 years. At the same time, reports of consistent condom use did increase steadily over all three

rounds among men and women, suggesting that some prevention messages may have been more effective than others at reaching young men and women.

One of the issues highlighted throughout is the profile of in-migrants into the study area and the differences in their underlying risk of HIV infection. ANC estimates in the area should reflect changes in migration so long as those individuals have similar fertility patterns as the populations into which they move. At round 2, however, in-migrants were more likely to be younger, not yet married, and more likely to be HIV infected than other in-migrant groups. At round 3, migrants were equally likely as non-migrants to have been recently pregnant, but it is possible that those pregnancies occurred before they moved into the study area, suggesting yet another reason why ANC estimates might differ from those in the surrounding population. Removing in-migrants from the rounds highlighted the fact that ANC estimates may best reflect those women living in the study area the longest and that factors related to in-migration should be carefully considered when assessing the representativeness of trends in small geographic areas, such as was done here.

A remaining, albeit important concern, apart from the issue of the validity of ANC data to monitor population trends generally, is their usefulness in monitoring trends among men specifically. Although the UNGASS indicator assumes that ANC surveillance data accurately reflects changes in prevalence among men and women, results here highlighted some challenges. In particular, the overall round 1 to round 3 changes in HIV prevalence among men was less than those observed among women, and relying on ANC surveillance data to monitor trends among men could significantly understate prevention gains. Also, estimates of HIV prevalence by socio-demographic characteristics in the two data source indicated further inconsistencies in trends. It may be better for countries to find alternative measures of trends in HIV prevalence among men or to explore methods for adjusting ANC

surveillance data to overcome these limitations. The analyses here were also limited by incomplete data available on men aged 15 to 16 years. As HIV prevalence in this population is extremely low though, it is unlikely that their inclusion across the rounds would have changed these findings.

As most countries will not have access to repeated population survey data, the results of this comparison between ANC and population survey data, showing that ANC-based surveillance data broadly reflected the overall change in HIV prevalence among young men and women in the general population between 1998 and 2005, are still encouraging. Nevertheless, the ANC estimates appeared to be less sensitive to intermediary changes in prevalence occurring in the general population. This was either because of differences in the speed with which less risky behaviour was adopted by pregnant women or because the population survey data produced an unreliable measure of trends in this population. This issue will be important to explore over subsequent rounds in Manicaland, Zimbabwe to ensure that ANC surveillance data are a reliable indicator of more recent changes HIV prevalence, and by extension, incidence among youth in the study area. Additional studies in other countries with longitudinal or repeated cross-sectional surveys would also be useful to further validate comparisons such as these.

Chapter 6: Using HIV testing data from PMTCT programmes for HIV surveillance, in Manicaland, Zimbabwe

6.1 Aims and organization of the chapter

The primary aim of this chapter is to determine whether HIV prevalence estimates from PMTCT programme data are an accurate measure of prevalence among pregnant women attending ANCs in Manicaland, Zimbabwe between 2006 and 2008. HIV prevalence estimates among ANC attendees who were offered testing, versus not, and among those who accepted testing, versus refused, are compared using data from round 4 of the ANC surveillance and the household population survey (which spanned the years' 2006 to 2008). In the ANC surveillance data, HIV prevalence estimates are compared in non-PMTCT and PMTCT clinics, and in PMTCT clinics grouped according to similar levels of the proportion of women who were tested. Additionally, individual-level socio-demographic and behavioural risk factors were assessed for their potential to explain differences in prevalence between those women testing and not testing as part of the PMTCT programme. The concluding section identifies the strengths and limitations of using PMTCT data for surveillance purposes from the Manicaland Project study.

6.2 Introduction

As discussed in previous chapters, in resource-limited settings in SSA, annual or bi-annual anonymous HIV surveillance among pregnant women routinely seeking ANC has been conducted to monitor HIV population prevalence trends [39]. In recent years, whether PMTCT programme data can be used to complement, or even replace, ANC surveillance to monitor population prevalence trends, has been increasingly debated [256]. Although HIV testing rates among pregnant women in many countries in SSA have typically been very low, the introduction of 'opt-out' testing policies and greater availability of nevirapine and other efficacious ART

regimens have pushed up HIV testing rates to greater than 80% in a few countries, including Botswana, Namibia, South Africa, and Zambia [257].

Using PMTCT data for surveillance purposes offers certain advantages over ANC surveillance alone. Most importantly, since data on the number of women testing and their HIV status are routinely collected as part of PMTCT programme monitoring activities, estimates of HIV prevalence among pregnant women should be easier to obtain from clinics. Additionally, ethical concerns of using leftover blood to test women for HIV without consent for ANC surveillance purposes could be avoided [128, 242]. Finally, using PMTCT data from ANC clinics could improve the geographic representativeness of trends since many more ANC clinics offer PMTCT-based HIV testing than participate in ANC surveillance.

Despite the considerable financial and epidemiologic advantages associated with using PMTCT data for surveillance purposes, some possible disadvantages have been identified also. Of greatest concern has been that estimates of HIV prevalence among PMTCT attendees may be distorted by biases in participation [88, 91, 98, 192]. For example, if HIV-infected women, due to stigma or inaccessibility of treatment or prophylaxis are not offered or choose not to test, estimates derived from the PMTCT programme will understate HIV prevalence among ANC surveillance attendees. If the opposite is true, and HIV-infected women have access to, are offered, and accept testing more often than uninfected women, PMTCT-based estimates will overstate HIV prevalence among all ANC attendees [88, 91]. Equally concerning, any change in participation biases over time could distort the validity of trends in HIV prevalence constructed from PMTCT data [93]

Previous studies in SSA have identified many of the advantages and disadvantages described above, with studies in Cameroon [97], Uganda [93], and Botswana [96] concluding that PMTCT programme data should be used to monitor

HIV prevalence in pregnant women while others, also from Uganda [91, 94], as well as Kenya [89], and Zimbabwe [95], suggesting that the data are still of limited use due to biases in who is tested. One of the primary drawbacks in all but two of the studies (Kenya and Botswana) was that they occurred at a time when geographic coverage was limited and strategies for delivering PMTCT services relied on an 'opt-in' testing strategy, which has been shown to result in much lower rates of testing [80, 83].

This was the situation in 2004 in Zimbabwe when the Ministry of Health and Child Welfare (MOHCW) investigated and determined that estimates of HIV prevalence from PMTCT data did not accurately reflect HIV prevalence estimates among pregnant women in 19 ANC surveillance clinics where both activities were occurring. During the time of the study, national policy specified the provision of 'opt-in' client-initiated testing programmes [95]. In practice, this meant that women would have had to have requested HIV testing during their prenatal visit, although the importance of testing for the mother and baby would have been communicated during group or individual pre-test counselling at the start of the visit.

Using data from the national PMTCT reporting system, the proportion of women who were reported to have been tested during the study period at the 19 clinics was 42.1%. The MOHCW cited refusals by clients, stock-outs of test kits, and insufficient availability of trained staff as reasons for the low testing level. Comparison of ANC and PMTCT data showed that, although HIV prevalence among pregnant women was similar at the national level (21.3% in ANC surveillance data and 21.8% in PMTCT data), very large clinic-specific discrepancies were observed. As a result, MOHCW staff concluded that PMTCT data, at least as reported to the national level, were ultimately not suited for surveillance purposes in Zimbabwe.

In the year following the 2004 study, the MOHCW adopted an overall objective to increase uptake of PMTCT services by moving to an 'opt-out' provider-initiated testing approach, strengthening pre-test counselling, and augmenting the number of staff trained to provide testing with lay counsellors [95]. Also, the number of clinics where PMTCT services were offered was expanded greatly, such that, by 2008, 55% of ANC clinics offered HIV testing integrated into a woman's prenatal care visit [258]. Due to the economic and political turmoil in Zimbabwe during 2007 and 2008, however, many women continued to experience problems accessing ANC and PMTCT services [259].

Despite the economic and political pressures which severely disrupted the provision of health care services in Zimbabwe, the results of the MOHCW PMTCT policy shift and programme expansion in 2005 were still notable in the Manicaland Project study area. From 2003 to 2005, which corresponded to round 3 of the survey, only 6 of the 29 clinics participating in ANC surveillance offered testing. In the follow-up survey, carried out between 2006 and 2008, which corresponded to round 4, 20 of the 36 participating clinics were reported to offer PMTCT services. These data on uptake of PMTCT services provide a unique opportunity to assess whether estimates of HIV prevalence from them are similar to or differ from those collected through ANC surveillance. Additionally, determining what factors influence the validity of PMTCT estimates can provide insight into mechanisms for possibly adjusting for these biases in the future.

6.3 Methods

6.3.1 ANC surveillance

In the study catchment area, ANC surveillance was conducted on a sequential (i.e., rolling) basis at 36 clinics from August 2006 to November 2008. At 20 of the clinics, PMTCT-based HIV testing was reported to be available during at least some of the time when ANC surveillance was on-going. In 2006, two of the eight clinics surveyed reported offering PMTCT services. In 2007, seven of the 16 clinics did. In 2008, all but one of the 12 clinics reported the availability of PMTCT services.

Information obtained during the surveillance interview was used to determine whether PMTCT-based HIV testing had been offered to an attendee during her prenatal care visit, and if so, whether she accepted testing. Women attending follow-up visits were also asked about testing at their first visit, since MOHCW policy is to provide HIV testing to all women on their first visit. More detailed information regarding methods for conducting surveillance and the questionnaire were provided in Chapter 2.

6.3.2 Household survey data

Information on access to and acceptance of HIV testing through PMTCT services was obtained from women aged 15 to 49 years participating in the round 4 household survey. Individual interviews were conducted over approximately the same time period as the ANC surveillance in the 12 study sites. Serological samples were collected for all women at the time of the interview.

In the household survey interview, women who attended an ANC clinic at their last pregnancy were asked if PMTCT services, including HIV testing, were offered at the clinic they attended, and whether they accepted or refused testing. Information

about which clinic a woman attended was not collected to verify whether PMTCT services were actually available during the pregnancy. Further information on the Manicaland Project study methods, laboratory testing procedures, and the individual questionnaire are provided in Chapter 2 of this thesis and a previous publication [26].

6.3.3 Statistical Analysis

Analyses to assess the usefulness of PMTCT data for surveillance purposes were performed separately for each data source (i.e., ANC surveillance and the household survey) given differences between data collection methods and the populations included. For both the surveillance and the household survey, the primary outcome of interest was HIV prevalence among PMTCT participants (e.g., those pregnant women tested as part of the provision of PMTCT programme services) compared to HIV prevalence among all ANC attendees as determined by testing through the study. Women in the household survey who provided information about pregnancies prior to 2006 were excluded from the analysis since PMTCT services in the study area were not routinely offered at the time, and, when they were, they were most likely provided using an 'opt-in' testing approach.

Bias in the PMTCT HIV prevalence estimate was calculated as the relative difference between the PMTCT and ANC surveillance estimates. HIV prevalence was also calculated separately for women who were offered (as opposed to not offered) testing and for those who accepted (as opposed to refused) testing for each data source. Where comparisons of HIV prevalence estimates involved two separate groups of individuals (e.g., those offered versus those not offered HIV testing), statistical testing for significant differences in HIV prevalence was done using a chi square test with one degree of freedom. P-values of <0.05 were considered

statistically significant. For those comparisons where the same women were included in both the PMTCT and ANC surveillance groups (e.g., PMTCT versus ANC surveillance estimates), statistical testing was not done as the estimates were considered dependent. In these instances, only the descriptive results, including 95% binomial confidence intervals, are presented.

Factors potentially influencing the validity of the PMTCT-based estimates were also considered in both data sets. In the ANC surveillance data, associations between PMTCT testing and HIV prevalence were explored at the clinic level using a Cochran-Armitage test for trend [260]. Clinics were categorized according to whether overall testing levels were (i) high (75% or greater offered testing; n=2); (ii) medium high (50%-74% offered testing; n=8); (ii) medium low (25%-49% offered testing; n=8); or (i) low (<25% offered testing; n=2). Previous studies in SSA have only noted the extent to which estimates differed when the proportion of women testing in the PMTCT programme was less than 70% [89, 91].

At the individual level, a Poisson regression model with a robust error variance was used to compare HIV infection levels among women not tested and tested as part of the PMTCT programme. The prevalence proportion ratio (PPR) and robust 95% confidence interval (CI) from the regression model was used to determine the strength and direction of associations between HIV prevalence and PMTCT-based HIV testing. A PPR value greater than one would indicate that HIV-infected women were more likely to get tested in the PMTCT programme than uninfected women. Conversely, a PPR less than one would signal an avoidance of PMTCT-based testing by HIV-infected women as compared to uninfected women. The Poisson method is recommended, as opposed to a standard logistic regression model, when the outcome of interest is not rare (e.g. greater than 10%) [261, 262].

Poisson regression modelling also was used to determine which socio-demographic, health access and behavioural risk factors might explain differential testing in the PMTCT program by HIV status. A similar strategy using logistic regression was first used by Glynn and colleagues to compare HIV prevalence in ANC clinics and the general population in three cities in Africa, Yaoundé, Cameroon, Kisumu, Kenya, and Ndola, Zambia, and to isolate those factors that could explain the differences that were identified [51]. This method was also used later to explore differences in HIV prevalence estimates in the Karonga district in Malawi [53].

In the multivariate model for the Manicaland comparisons, factors that shifted the crude PPR for the association between HIV status and testing in the PMTCT programme toward the null after adjustment were considered to 'explain' the bias in PMTCT-based testing by HIV-infected women. Factors explored in both data sources included age, parity, time at current residence, socio-economic designation of the location of the area (e.g., town, estate), residence relative to the clinic where women sought prenatal care (i.e., local to or visiting), marital status, education, previous health status, and history of STDs.

Due to differences between the ANC and individual survey questionnaires, not all of the factors were comparable between data sets. In the ANC surveillance round, the socio-economic category of the clinic where a woman sought ANC services was collected, whereas in the household survey, this designation refers to a woman residence where she was interviewed. Also in ANC surveillance, women were asked about whether they had ever been treated for an STD, while in the household survey, women were asked about ever having had STD symptoms. For analysis purposes, women in the household survey with either no or one previous birth were grouped together when considering associations with parity, because only those women with at least one previous pregnancy who attended an ANC were eligible to

be included in the analysis (i.e., as a result, very few women had no previous births). Finally, data on the number of children dead, employment status, risk perception, and the number of lifetime regular and non-regular sexual partners were asked about in the household survey questionnaire only. Elsewhere in SSA, these factors have been found to be associated with higher infection levels and increased uptake of PMTCT testing [91, 98, 192].

6.4 Results

6.4.1 ANC surveillance data

During the ANC surveillance round, a total of 1277 women sought routine prenatal care at the 36 participating clinics in the study area. All attendees consented to be interviewed and to provide a blood sample for anonymous HIV testing in the ANC surveillance round, regardless of whether or not they were offered an opportunity or elected to participate in PMTCT services. ANC surveillance questionnaires were incomplete for 34 women, leaving 1243 women in the analysis.

Using the anonymous test results from ANC sentinel surveillance and knowledge of participation in the PMTCT programme, overall HIV prevalence was observed to be lower among ANC surveillance participants (13.4%) than among PMTCT participants (16.2%) in the study area. This difference corresponded to an upwards bias of 20.9% in the PMTCT estimate as compared to the ANC surveillance estimate across all 36 clinics.

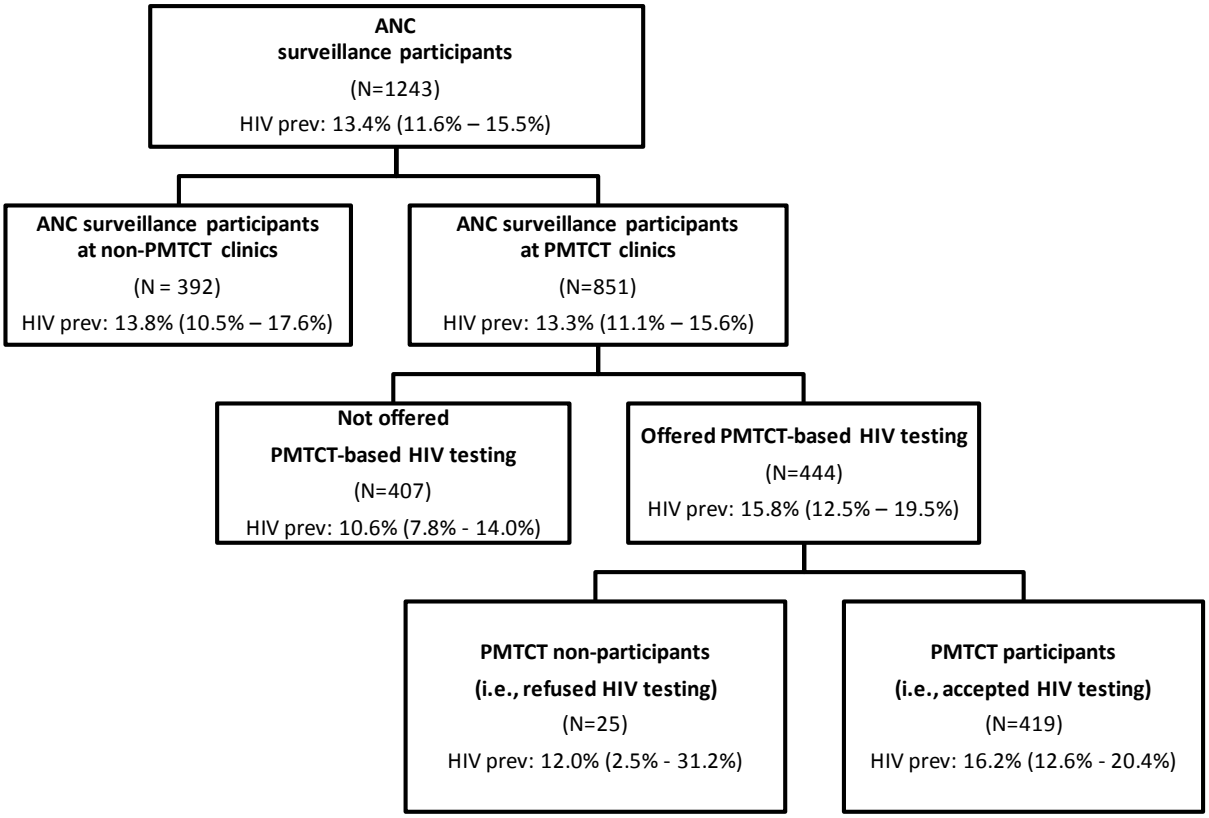


Figure 6.1 HIV prevalence estimates among women at non-PMTCT and PMTCT clinics at round 4 of the ANC surveillance in Manicaland, Zimbabwe, 2006-2008.

Stratification of the data by the 16 non-PMTCT and 20 PMTCT clinics showed that the geographic distribution of PMTCT services in the study area was not a likely source of bias since similar HIV prevalence among all ANC surveillance attendees was observed in both groups (13.3% versus 13.8%; p-value = 0.811). However, at those clinics where PMTCT services were offered, women who accepted testing in the PMTCT programme had markedly higher HIV prevalence than women who (i) were not offered testing as part of the PMTCT programme (10.6%) or (ii) who refused PMTCT-based HIV testing when offered (12.0%). Since the proportion of women accepting PMTCT-based HIV testing was so high (94.4%), the majority of bias in the PMTCT estimate would have come from the higher prevalence (15.8%) among the 52.2% of women who were offered the opportunity to test.

From clinic-specific comparisons of the testing data, it was clear that the level of bias in the PMTCT estimate at a clinic depended on the proportion of women offered and accepting testing there (See Figure 6.2). As this overall proportion declined, HIV prevalence among those women tested in the PMTCT programme increased significantly (test for trend p-value=0.021).

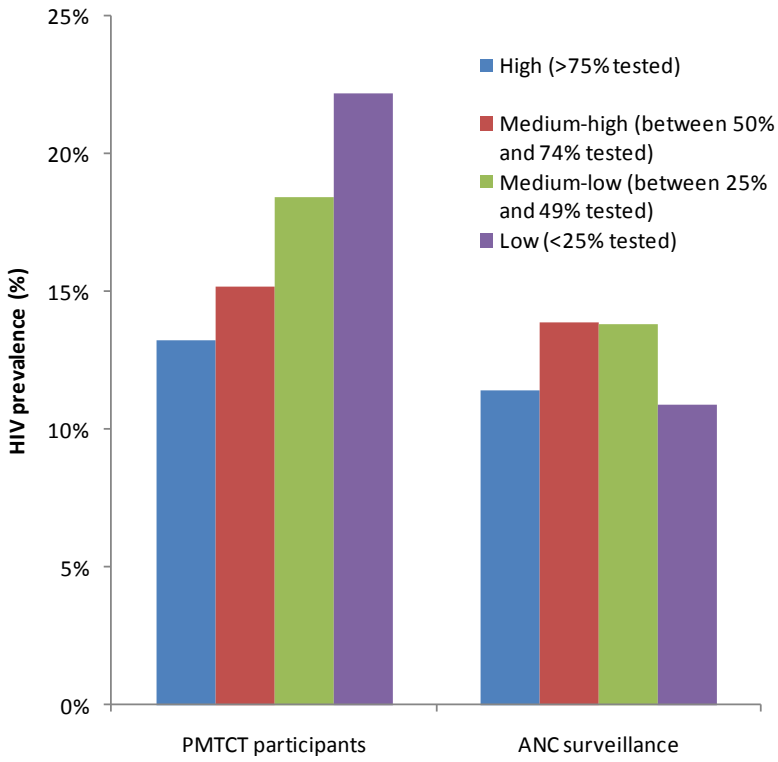


Figure 6.2 HIV prevalence estimates at 20 clinics where ANC surveillance and the provision of PMTCT services overlapped at round 4 in Manicaland, Zimbabwe, 2006-2008. The figure shows an increasing trend in HIV prevalence by level of testing (p-value=0.021) among those tested in the PMTCT programme versus all ANC surveillance attendees (p-value=0.873**)**.

Since HIV prevalence was comparable among all ANC surveillance participants when grouped according to the level of testing at the clinic (p-value=0.873), it is more likely that individual factors, rather the geographic location of clinics, explained the increasingly higher levels of HIV prevalence observed. This was especially true for the 10 clinics where the proportion of women testing in the PMTCT programme was less than 50% and the disparity in HIV prevalence between the two groups was

largest. The mean proportion of women tested in clinics offering PMTCT services during the study period was 49.2%.

Figure 6.3 illustrates in more detail clinic-specific differences between HIV prevalence estimates from PMTCT participants and ANC attendees according to the level at which women tested.

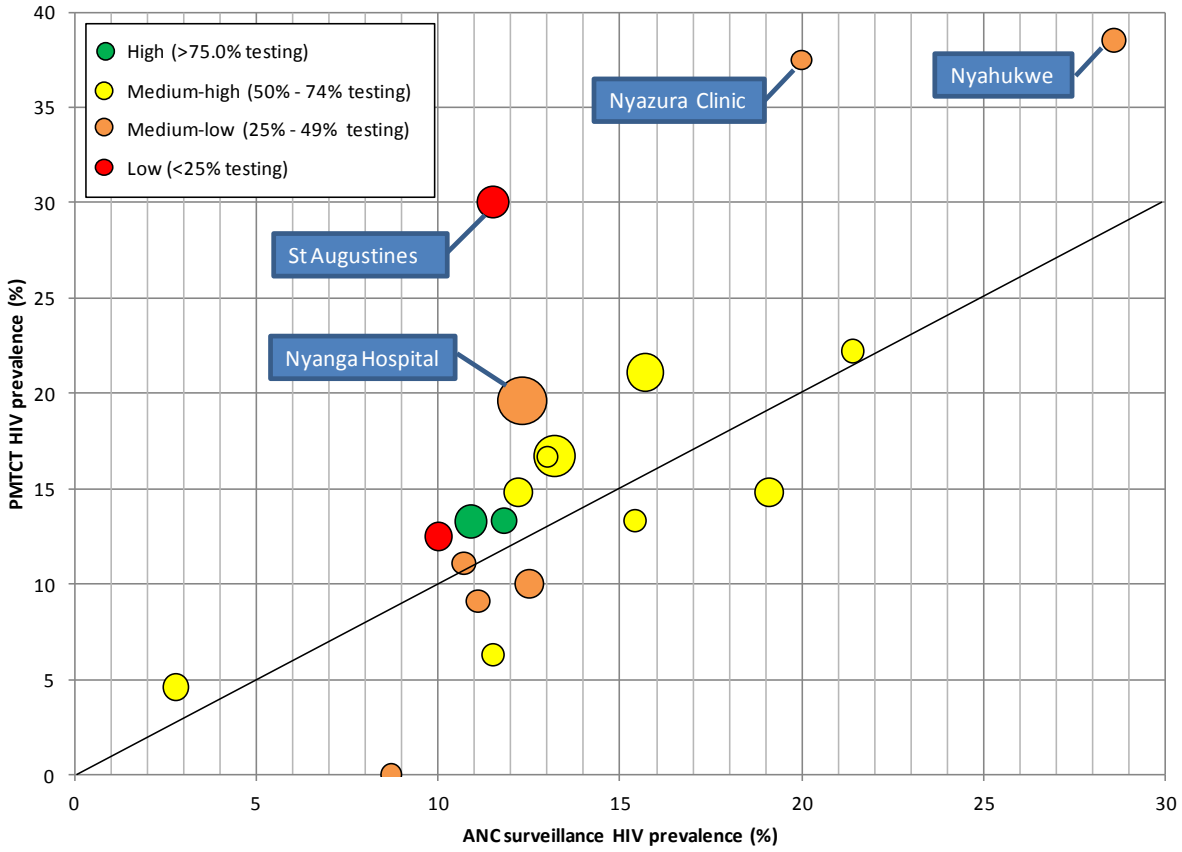


Figure 6.3 HIV prevalence among ANC surveillance and PMTCT participants in the 20 clinics in Manicaland, Zimbabwe, 2006-2008. Dot size represents the number of ANC surveillance participants. Dot colour represents the percent of women tested through the PMTCT programme during the surveillance period. Green dots indicate clinics that provided PMTCT-based testing to the most women (e.g., >75%). Those testing under a quarter of participants are marked with red dots. Dots closer to the bold parallel line indicate better agreement between ANC surveillance and PMTCT estimates.

In general, the tendency was for PMTCT-based estimates to be higher than those in the ANC clinic generally, with only 6 of the 20 clinics having PMTCT-based estimates that understated HIV prevalence among all ANC attendees. Half of these clinics were in facilities where between 25% and 49% of women were tested and the

other half were in clinics where between 50% and 74% of women were tested. In the four clinics where PMTCT-based estimates exceeded ANC surveillance-based estimates by the greatest margin (St Augustines, Nyanga Hospital, Nyazura Clinic and Nyahukwe Clinic), women tested had approximately four times the level of HIV-infection as women not tested (i.e., those not offered or refusing). Across all 20 PMTCT clinics, HIV prevalence was 50% higher among PMTCT participants as compared to non-PMTCT participants (PPR: 1.50; 95% CI: 1.06 – 2.13). This corresponded to an HIV prevalence of 16.0% among PMTCT participants and 10.6% among non-PMTCT participants.

Table 6.1 shows the individual socio-demographic, behavioural risk and health factors explored in the Poisson regression model for their association with HIV prevalence and PMTCT-based testing at the 20 clinics. Although many of the factors were associated with significantly higher HIV prevalence among ANC attendees generally, including increasing age above 20 years (with peak prevalence observed among those aged 25 to 29 years), having one or two previous live births, being unmarried, living in their current residence for more than two years, and reporting having had a serious illness or ever having sought treatment for an STD infection, only those having a recurring or serious illness were found to have significantly higher testing rates in the PMTCT programme. With regard to other significant factors differently distributed among those testing versus not, women with higher education compared to lower education were more likely to be tested through the PMTCT programme as were those in subsistence farming areas and roadside trading centres relative to those living in towns and estates. Notably, although marginally non-significant, visitors were less likely to test in the PMTCT programme as compared to local attendees and also less likely to test positive.

Factors	ANC surveillance (N=851) HIV prevalence (N)	% (n)	Crude PPR*	95% CI	Women tested (N=419) % (n)	Difference in distribution between women tested and not tested Crude PPR*	95% CI
Age group							
15-19 years	23.3 (198)	5.6 (11)	1.00	--	50.5 (100)	1.00	--
20-24 years	34.8 (305)	10.8 (33)	**1.94**	**(1.01 - 3.76)**	45.9 (140)	0.91	(0.76 - 1.09)
25-29 years	20.3 (173)	24.3 (42)	**4.37**	**(2.32 - 8.22)**	53.2 (92)	1.05	(0.87 - 1.28)
30 - 44 years	20.6 (175)	15.4 (27)	**2.78**	**(1.42 - 5.43)**	49.7 (87)	0.98	0.80 - 1.21)
Parity†							
0	40.4 (344)	8.1 (28)	1.00	--	46.5 (160)	1.00	--
1	28.3 (241)	15.8 (38)	**1.94**	**(1.22 - 3.07)**	51.9 (125)	1.12	(0.94 - 1.32)
2+	31.3 (266)	17.7 (47)	**2.17**	**(1.40 - 3.37)**	50.4 (134)	1.08	(0.91 - 1.27)
Marital status							
Married/Cohabitating	95.0 (808)	12.8 (103)	1.00	--	48.9 (395)	1.00	--
Not married	5.0 (43)	23.3 (10)	**1.82**	**(1.04 - 3.23)**	55.8 (24)	1.14	(0.87 - 1.50)
Education							
None/primary	22.6 (192)	13.5 (26)	1.00	--	39.6 (76)	1.00	--
Secondary/higher	77.4 (659)	13.2 (87)	0.98	(0.65 - 1.47)	52.1 (343)	**1.31**	**(1.09 - 1.59)**
Clinic location							
Town	24.4 (208)	13.5 (28)	1.00	--	38.0 (79)	1.00	--
Estate	15.0 (128)	12.4 (49)	0.92	(0.60 - 1.42)	31.3 (40)	0.82	(0.60 - 1.12)
Substistence farming area	40.8 (347)	11.7 (53)	0.87	(0.57 - 1.34)	58.8 (204)	**1.55**	**(1.27 - 1.88)**
Roadside trading centre	19.7 (168)	19.8 (37)	1.47	(0.94 - 2.30)	57.2 (96)	**1.50**	**(1.21 - 1.87)**
Time at current address							
<2 years	26.9 (229)	10.0 (23)	1.00	--	49.3 (113)	1.00	--
2+ years	73.1 (622)	14.5 (90)	**1.44**	**(0.94 - 2.22)**	49.2 (306)	1.00	(0.85 - 1.16)
Residence relative to clinic							
Local	70.6 (601)	14.5 (87)	1.00	--	51.4 (309)	1.00	--
Visitor	29.4 (250)	10.4 (26)	0.72	(0.48 - 1.09)	44.0 (110)	0.86	(0.73 - 1.00)
Health status							
Healthy	90.5 (770)	11.6 (89)	1.00	--	48.2 (371)	1.00	--
Recurring or serious illness	9.5 (81)	29.6 (24)	**2.56**	**(1.73 - 3.78)**	59.3 (48)	**1.23**	**(1.01 - 1.49)**
Ever been treated for an STD							
No	92.2 (785)	12.1 (95)	1.00	--	49.2 (386)	1.00	--
Yes	7.8 (66)	27.3 (18)	**2.25**	**(1.46 - 3.49)**	50.0 (33)	1.01	(0.79 - 1.31)

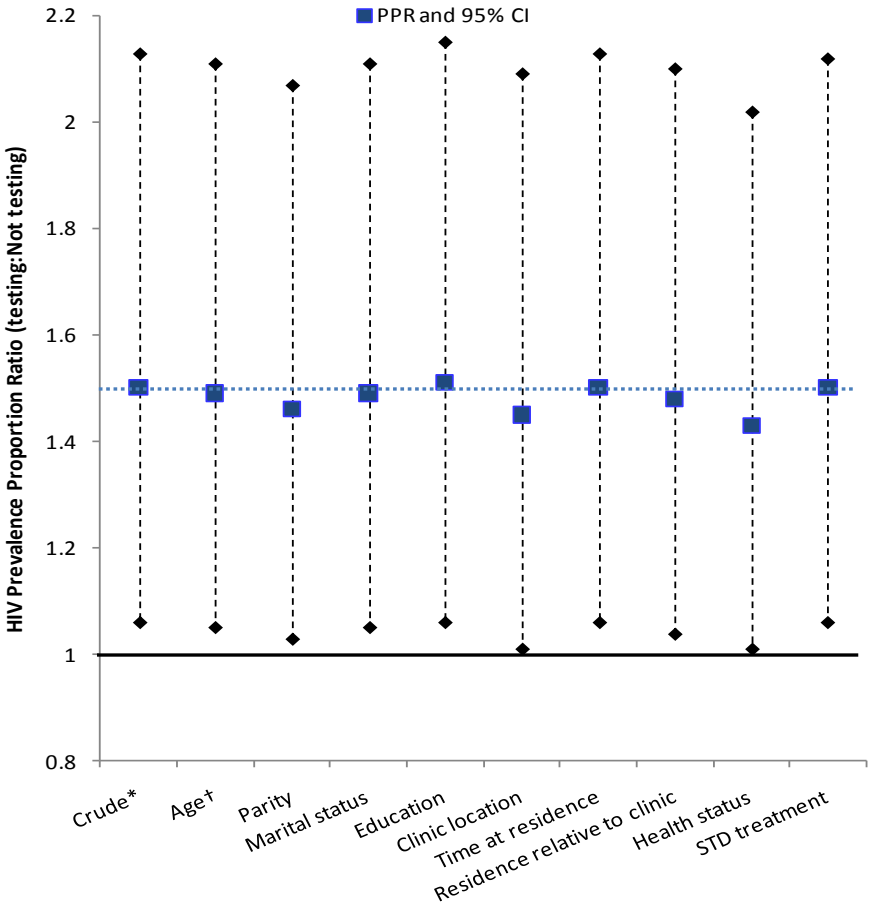
* Prevalence proportion ratios (PPRs) and 95% confidence intervals in bold indicate a significant difference for that factor.

† Higher HIV prevalence as parity increased was due to confounding by age. Adjusting age-specific HIV prevalence for parity resulted in a non-significant difference in risk for all parity groups.

Table 6.1 Factors associated with HIV prevalence among ANC surveillance participants and differentially distributed between women testing and not testing as part of the PMTCT programme in 20 ANC clinics in Manicaland, Zimbabwe, 2006-2008.

Results from the Poisson regression considering the relationship between HIV prevalence and PMTCT-based testing by the many factors showed bias in the PMTCT estimate to be due, in part, to differential uptake of testing depending on age, parity, marital status, geographic location of the clinic, residence (local versus visitors), and, as previously identified in the factor-specific analyses, the health status of those testing (see Figure 6.4). When adjusting for these factors individually,

the PPR shifted toward 1 (i.e., no difference in estimates between PMTCT and non-PMTCT participants). For some of the factors, including marital status, the proportion of the difference explained was relatively small.



* Blue boxes and upper and lower diamonds show the HIV prevalence proportion ratio (PPR) and 95% confidence interval (CI) of being tested as part of the PMTCT programme versus not when adjusted for a factor (e.g., age, parity, marital status, etc.). A PPR greater than 1 indicates that HIV prevalence among those tested is greater than that among those not tested. The dotted blue line represents the crude difference in HIV prevalence between PMTCT and non-PMTCT participants. The solid black line (at PPR=1) indicates no difference in HIV prevalence between PMTCT and non-PMTCT participants.
†Adjusted PPRs and 95% CIs reflect the extent to which the upwards bias in the estimate of HIV prevalence among those tested can be explained by confounding by this factor (e.g., age).

Figure 6.4 Comparison of HIV prevalence among PMTCT and non-PMTCT participants at 20 clinics where ANC surveillance and PMTCT services overlapped in Manicaland, Zimbabwe, 2006-2008.

Not surprisingly, having reported a recurring or serious illness accounted for the single largest proportion of the bias, reducing the crude PPR of 1.50 to an adjusted value of 1.43 (95% CI: 1.01-2.02). Education, time at residence and history of a self-reported STD treatment did not explain why HIV positive women were tested more

frequently, as adjusting for these factors either shifted the PPR away from 1 or the PPR remained unchanged from the crude value.

HIV prevalence estimates among women not testing and testing by the confounding factors are shown in Table 6.2. Although HIV prevalence estimates did not differ statistically between these two groups, the largest disparities were observed among those reporting a recurring or serious illness and among visitors.

Confounders	Non-testing participants HIV prevalence (N=432) %	PMTCT participants HIV prevalence (N=419) %	PPR (95% CI)
Age group*			
15-19 years	4.1 (4)	7.0 (7)	1.72 (0.52 - 5.7)
20-24 years	8.5 (14)	13.6 (19)	1.56 (0.81 - 3.02)
25-29 years	22.2 (18)	26.1 (24)	1.17 (0.68 - 1.99)
30 - 44 years	11.4 (10)	19.5 (17)	1.68 (0.82 - 3.43)
Parity†			
0	8.2 (15)	8.1 (13)	1.09 (0.54 - 2.23)
1	11.2 (13)	20.0 (25)	1.75 (0.94 - 3.26)
2+	14.6 (18)	21.6 (29)	1.60 (0.94 - 2.72)
Marital status†			
Married/Cohabitating	10.4 (43)	15.2 (60)	1.45 (1.00 - 2.09)
Not married	15.8 (3)	29.2 (7)	1.78 (0.56 - 5.60)
Clinic location			
Town	10.1 (13)	19.0 (15)	1.89 (0.95 - 3.75)
Estate	6.8 (6)	12.5 (5)	1.83 (0.59 - 5.68)
Substistence farming area	10.5 (15)	12.8 (26)	1.21 (0.67 - 2.21)
Roadside trading centre	16.7 (12)	21.9 (21)	1.31 (0.69 - 2.49)
Residence relative to clinic			
Local	12.3 (36)	16.5 (51)	1.34 (0.90 - 1.99)
Visitor	7.1 (10)	14.6 (16)	2.04 (0.96 - 4.32)
Health status			
Healthy	10.0 (40)	13.2 (49)	1.32 (0.89 - 1.95)
Recurring or serious illness	18.2 (6)	37.5 (18)	2.06 (0.91 - 4.66)
Adjusting for all confounders	--	--	1.32 (0.92 - 1.88)

* PPR adjusted for marital status

† PPR adjusted for age

Table 6.2 Comparison of HIV prevalence among non-tested and PMTCT participants at 20 ANC clinics where PMTCT services were available in round 4 ANC surveillance in Manicaland, Zimbabwe, 2006-2008.

Adjusting for these, and all other confounders, reduced the PPR from 1.50 to 1.32 (95% CI: 0.92 – 1.88). This also eliminated any significant difference in estimates among non-tested and PMTCT participants. Nonetheless, a large portion of the

overall bias in HIV prevalence among those women participating in the PMTCT programme still remained unexplained.

6.4.2 Household survey

Participation in the household survey at round 4 was high, with only 6.9% of eligible households not interviewed. In the household survey, 3.2% (216/6748) of eligible women were excluded due to refusals or because of incomplete pregnancy histories or socio-demographic information. Of the remaining women, 18.9% (1228/6532) provided information about a previous pregnancy between 2006 and 2008; 12.5% (846/6540) of women provided information about their last pregnancy, which occurred prior to 2006 and were excluded. Of the women with pregnancies between 2006 and 2008, 87.5% (1075/1228) reported attending an ANC at their last pregnancy.

Based on the results of the anonymous HIV testing conducted during round 4 of the individual household survey, the estimate of HIV prevalence among women accepting testing as part of the PMTCT programme from 2006 to 2008 was found to be lower than the estimate of HIV prevalence among all women reporting ANC attendance (13.5% versus 17.4%) from 2006 to 2008 (see Figure 6.5).

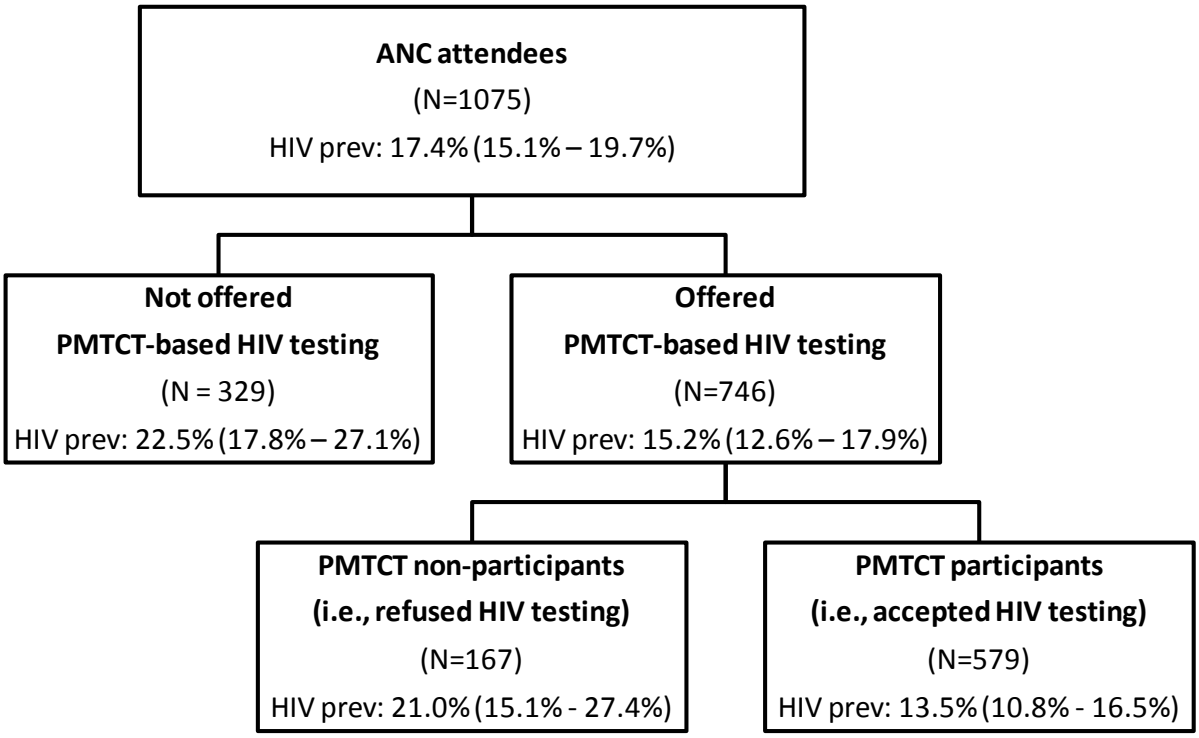


Figure 6.5 HIV prevalence estimates for women in the household survey at round 4 who reported ANC attendance at their last pregnancy in Manicaland, Zimbabwe, 2006-2008.

This difference would have resulted in an overall bias downwards in the PMTCT estimate by 22.4%. Unlike the ANC surveillance results where bias resulted primarily from not offering HIV-infected women an opportunity to test, in the population survey data, refusal to test in addition to not offering testing could both contribute to the bias. Overall, the proportion of women reporting having been offered PMTCT-based testing was 69.4%, and, of those, the proportion who reported accepting was 77.6%. Compared with HIV-uninfected women, HIV-infected women were 40% less likely to participate in PMTCT-based HIV testing (RR: 0.61; 95% CI: 0.47 – 0.80). This corresponded to a 13.5% (95% CI: 10.8% – 16.5%) HIV prevalence among PMTCT participants and a 22.0% (95% CI: 18.4% – 25.9%) prevalence among non-PMTCT participants.

With regard to whether socio-demographic, health and risk behaviour factors could explain why HIV-infected women reported less frequent participation in the PMTCT programme, higher HIV prevalence was associated significantly with age (25 to 44 years), greater parity (2 or more previous live births), and a history of one or more children having died. Women who were not married, who lived in a town, or who were employed were also at higher risk of HIV infection. Self-reported poorer health status and more risky sexual behaviours (as defined by having previously had an STD, a self-assessed past risk of HIV infection, and more regular and non-regular lifetime partners) were also associated with higher HIV prevalence among previously pregnant women generally.

In terms of the distribution of these factors between PMTCT and non-PMTCT participants, PMTCT participants were significantly more likely than non-PMTCT participants to have fewer children, a history of no children having died, to be better educated, to live outside of an estate, to have attended an ANC clinic other than their local clinic, and to have reported a self-assessed past risk of HIV infection. The only common significant factors explaining lower HIV prevalence among PMTCT participants as compared to non-participants was parity and the number of previous children who had died. Women with two or more births were more likely to be infected than those with no or one previous birth, but these women were also less likely to be offered testing. Similarly, women with more than one child who died were more likely to be infected but less likely to report having participated in the PMTCT programme.

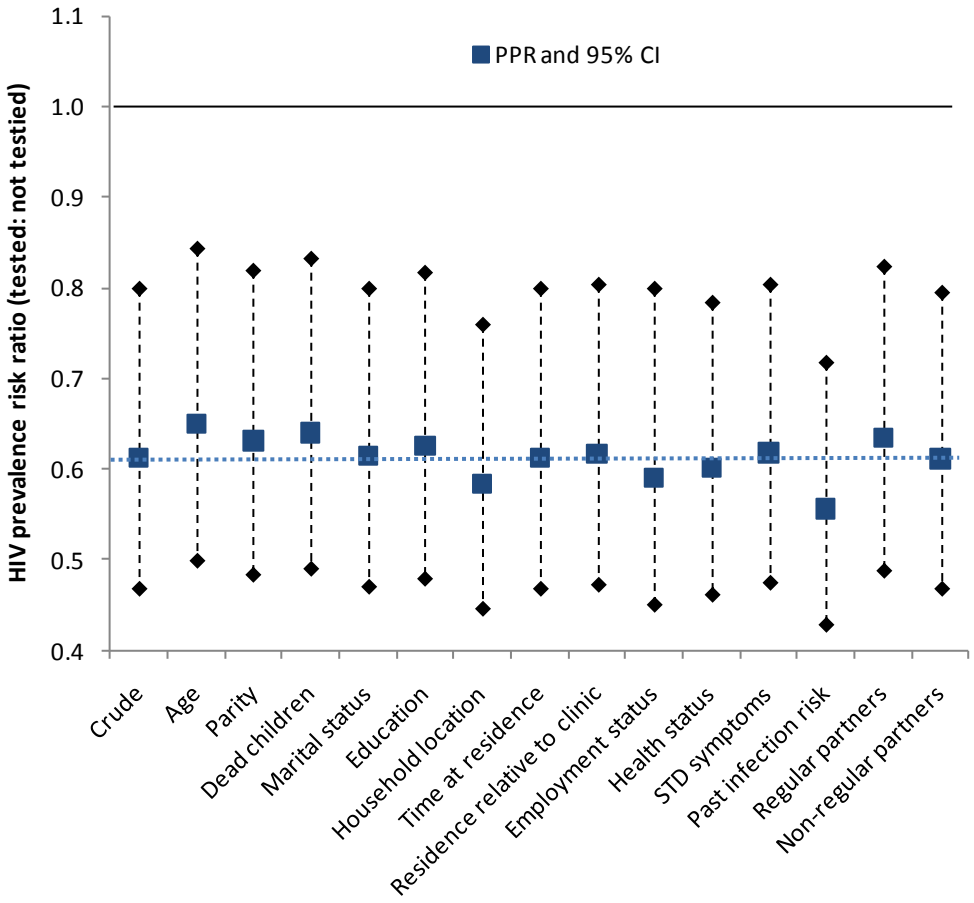
	Pregnant women attending an ANC* (N=1075) HIV prevalence				PMTCT participants (N=579)	Difference in distribution between PMTCT and non-PMTCT participants	
Factors	**(N)**	**% (n)**	**Crude RR**	**95% CI**	**% (n)**	**Crude PPR***	**95% CI**
Age group							
15-19 years	11.7 (126)	7.1 (9)	1.00	- - - - -	57.9 (73)	1.00	- - - - -
20-24 years	35.9 (385)	11.7 (45)	1.64	(0.823 - 3.25)	57.9 (223)	1.00	(0.84 - 1.19)
25-29 years	26.1 (280)	24.6 (69)	**3.45**[†]	**(1.78 - 6.69)**	48.2 (135)	0.83	(0.69 - 1.01)
30-44 years	26.4 (284)	22.5 (64)	**3.15**	**(1.62 - 6.14)**	52.1 (148)	0.90	(0.74 - 1.08)
Parity							
0/1	37.3 (401)	12.0 (48)	1.00	- - - - -	57.9 (232)	1.00	- - - - -
2+	62.7 (674)	20.6 (55)	**1.72**	**(1.27 - 2.33)**	51.5 (347)	**0.89**	**(0.80 - 0.99)**
Dead children							
0	88.5 (951)	15.3 (145)	1.00	- - - - -	55.1 (524)	1.00	- - - - -
1+	11.5 (124)	33.9 (42)	**2.22**	**(1.67 - 2.96)**	44.4 (55)	**0.80**	**(0.66 - 0.99)**
Marital status							
Married/Cohabitating	86.1 (926)	15.8 (146)	1.00	- - - - -	54.0 (500)	1.00	- - - - -
Not married	13.9 (149)	27.5 (41)	**1.74**	**(1.29 - 2.36)**	54.0 (79)	0.98	(0.83 - 1.16)
Education							
None/primary	23.2 (249)	20.9 (52)	1.00	- - - - -	41.4 (103)	1.00	- - - - -
Secondary/higher	826 (76.8)	15.2 (135)	0.78	(0.587 - 1.04)	57.6 (476)	**1.39**	**(1.19 - 1.63)**
Household location							
Town	14.2 (153)	30.1 (46)	1.00	- - - - -	61.4 (94)	1.00	- - - - -
Estate	18.2 (196)	**15.8 (31)**	**0.52**	**(0.35 - 79)**	28.1 (55)	**0.46**	**(0.35 - 0.59)**
Substistence farming	41.6 (447)	**15.6 (74)**	**0.55**	**(0.40 - 0.76)**	56.4 (252)	0.92	(0.79 - 1.07)
Roadside trading	26.0 (279)	**12.9 (36)**	**0.43**	**(0.29 - 0.63)**	63.8 (178)	1.04	(0.89 - 1.21)
Time at current address							
<2 years	16.1 (173)	17.3 (30)	1.00	- - - - -	56.01 (97)	1.00	- - - - -
2+ years	83.9 (902)	17.4 (157)	1.00	(0.703 - 1.41)	53.4 (482)	0.95	(0.82 - 1.10)
Residence relative to clinic							
Local	85.5 (919)	17.9 (164)	1.00	- - - - -	52.1 (479)	1.00	- - - - -
Visitor	14.5 (156)	14.7 (23)	0.82	(0.553 - 1.24)	64.1 (100)	**1.23**	**(1.08 - 1.40)**
Employment status							
Unemployed	81.6 (877)	16.0 (140)	1.00	- - - - -	51.7 (453)	1.00	- - - - -
Employed	18.4 (198)	23.7 (47)	**1.49**	**(1.11 - 1.99)**	63.6 (126)	**1.23**	**(1.09 - 1.39)**
Health status							
Healthy	86.0 (923)	15.9 (147)	1.00	- - - - -	53.1 (490)	1.00	- - - - -
Recurring or serious illness	14.0 (150)	26.7 (40)	**1.67**	**(1.23 - 2.27)**	58.7 (88)	1.11	(0.95 - 1.28)
Ever had STD symptoms (self-report)							
No	96.5 (1037)	16.4 (170)	1.00	- - - - -	54.0 (560)	1.00	- - - - -
Yes	3.5 (38)	44.7 (17)	**2.73**	**(1.86 - 3.99)**	50.0 (19)	0.93	(0.67 - 1.28)
Self-assessed past risk of HIV infection							
No	92.8 (986)	14.4 (142)	1.00	- - - - -	53.4 (526)	1.00	- - - - -
Yes	7.2 (76)	54.0 (41)	**3.74**	**(2.89 - 4.85)**	67.1 (51)	**1.25**	**(1.06 - 1.49)**
Regular lifetime partners							
0/1	87.4 (940)	14.7 (138)	1.00	- - - - -	54.7 (65)	1.00	- - - - -
2+	12.6 (135)	36.3 (135)	**2.47**	**(1.88 - 3.24)**	48.2 (65)	0.88	(0.73 - 1.06)
Non-regular lifetime partners							
0	75.7 (814)	15.9 (129)	1.00	- - - - -	53.6 (436)	1.00	- - - - -
1+	24.3 (261)	22.2 (58)	**1.40**	**(1.06 - 1.85)**	54.8 (143)	1.02	(0.90 - 1.16)

* HIV prevalence and other factors were measured at the time of the survey round rather than when the woman was pregnant. Only women pregnant from 2006 to 2008 were included in the analysis.

[†] Prevalence proportion ratios (PPRs) and 95% confidence intervals in bold indicate a significant difference for that factor.

Table 6.3 Factors associated with HIV prevalence among non-testing and women testing as part of the PMTCT programme and factors differentially distributed between these two groups among household survey participants at round 4 in Manicaland, Zimbabwe, 2006-2008.

Exploration of factors that might explain the bias in the estimates among those testing using Poisson regression modelling showed that most factors, other than employment status, health status and past risk of infection, were marginally influential (See Figure 6.6). Adjusting for these factors shifted the PPR toward 1.



* Blue boxes and upper and lower diamonds show the HIV prevalence proportion ratio (PPR) and 95% confidence interval (CI) of being tested as part of the PMTCT programme versus not when adjusted for a factor (e.g., age, parity, marital status, etc.). A PPR less than 1 indicates that HIV prevalence among PMTCT participants is lower than that among those not tested. The dotted blue line represents the crude difference in HIV prevalence between PMTCT and non-PMTCT participants. The solid black line (at PPR=1) indicates no difference in HIV prevalence between PMTCT and non-PMTCT participants.
†Adjusted PPRs and 95% CIs reflect the extent to which the downwards bias in the estimate of HIV prevalence among those tested can be explained by confounding by this factor (e.g., age).

Figure 6.6 Comparison of HIV prevalence in non-testing women and women testing as part of the PMTCT programme in Manicaland, Zimbabwe, 2006 to 2008.

The location of the household, employment status, and past risk of infection shifted the PPR away from one. Accounting for differences in the distribution of testers and non-testers by age, parity, the number of dead children, and the number of regular lifetime partners individually had the largest effect. Nevertheless, no single factor, or combination of factors, could completely explain the bias. As Table 6.4 shows, women reporting testing had consistently lower HIV prevalence when stratified by sub-groups within the factor. Also, for many factors, these differences were significant.

Confounders	HIV prevalence (N=496) % (n)	HIV prevalence (N=579) % (n)	PPR (95% CI)
Age group*			
15-19 years	13.2 (7)	2.7 (2)	0.258 (0.52 - 1.27)
20-24 years	13.6 (22)	10.3 (23)	0.757 (0.434 - 1.32)
25-29 years	29.0 (42)	20.0 (27)	0.734 (0.487 - 1.11)
30-44 years	27.9 (38)	17.6 (26)	**0.618 (0.400 - 0.956)**
Parity†			
0/1	14.8 (25)	9.9 (23)	0.706 (0.420 - 1.19)
2+	25.7 (84)	15.9 (55)	0.630 (0.463 - 857)
Dead children†			
0	19.7 (84)	11.6 (61)	**0.626 (0.464 - 0.846)**
1+	36.2 (25)	30.9 (17)	0.838 (0.501 - 1.40)
Marital status†			
Married/Cohabitating	20.2 (86)	12.0 (60)	**0.631 (0.467 - 0.853)**
Not married	32.9 (23)	22.8 (18)	0.825 (0.500 - 1.36)
Residence relative to clinic			
Local	22.5 (99)	13.6 (65)	**0.603 (0.454 - 0.802)**
Visitor	17.9 (10)	13.0 (13)	**0.728 (0.341 - 1.56)**
Ever had STD symptoms (self-report)			
No	20.8 (99)	12.7 (71)	**0.611 (0.462 - 0.808)**
Yes	52.6 (10)	36.8 (7)	0.700 (0.335 - 1.46)
Regular lifetime partners			
0/1	17.1 (73)	12.7 (65)	0.738 (0.542 - 1.00)
2+	51.4 (36)	20.0 (13)	**0.389 (0.227 - 0.667)**
Non-regular lifetime partners			
0	21.4 (81)	11.0 (48)	**0.514 (0.370 - 0.714)**
1+	23.7 (28)	21.0 (30)	0.884 (0.561 - 1.39)
Adjusting for age, dead children and regular lifetime partners			**0.692 (0.533 - 0.897)**

* Prevalence proportion ratio (PPR) adjusted for marital status

† PPR adjusted for age

Table 6.4 Comparison of HIV prevalence among non-testers and women testing in the round 4 household survey in Manicaland, Zimbabwe, 2006-2008.

Adjusting the crude PPR for the three most influential confounders (i.e., age, having previously children, and the number of regular lifetime partners) resulted in the least-biased adjusted PPR of 0.692 (95% CI: 0.533 – 0.897). Inclusion of the other remaining confounding factors did not explain any additional difference.

6.5 Discussion

Findings from this first single cross-sectional analysis of data from Manicaland, Zimbabwe suggest that PMTCT programme data would have provided an unsuitable estimate of HIV prevalence among ANC attendees in the study area, especially if adjustments for non-participation bias could not be made. In the ANC surveillance data, unadjusted HIV testing data from the PMTCT programme would have overstated HIV prevalence among ANC attendees by 20.9%. In the household survey, the crude estimate of HIV prevalence among PMTCT participants would have led to a 22.0% underestimate in the overall HIV prevalence among all pregnant women attending ANC clinics from 2006 to 2008.

Differences in the levels of PMTCT-based testing by HIV-infected and uninfected women were observed in both data sources, and these differences contributed to the biases described above. In the ANC surveillance data, the overall proportion of women who reported being offered testing in the PMTCT programme was just over half (52.2%). As the proportion of women tested declined at PMTCT-based clinics, the overall HIV prevalence of these women rose. Clinics where fewer than half of women were tested showed the largest difference in estimates between those tested and not tested. Across the 20 clinics offering PMTCT services during the study period, HIV prevalence was 50% higher among PMTCT participants

compared to those who did not participate in the PMTCT programme, despite the fact that when offered, almost all women accepted to participate.

In the ANC surveillance data, factors explaining why HIV-infected women were more likely to participate in the PMTCT programme than uninfected women were difficult to isolate. Although adjusting for the age of the woman, her parity, marital status, the location of the clinic where the woman was tested, her residence relative to the clinic and whether she had a recurring or serious illness partially explained the bias in estimates at the 20 clinics where ANC surveillance and PMTCT services overlapped, HIV prevalence among PMTCT participants were still biased by about 30% as compared to non-participants. While this level of bias is more extreme than what would have been observed in comparisons of PMTCT and ANC surveillance estimates generally, ANC surveillance data would have been required to further adjust these data to discount the remaining, unexplained bias.

The strongest reason for selective testing among HIV-infected women as identified through the Poisson regression analysis was having a recurring or serious illness. Although women were not asked how they defined a recurring or serious illness, this information appeared to be relevant in assessing a woman's risk of having acquired HIV infection and therefore influential in the decision about whether or not to be tested. Similar motivations for testing have been reported in urban Uganda where women who reported that they believed themselves exposed to HIV infection or who knew their partner to be infected were more likely to accept testing when offered and to test positive [91]. Discussions about illness, risk and a partner's status may alert healthcare providers to the importance of selectively testing women at higher risk, especially when overall access to or uptake of testing in the clinic generally is low.

The other large differential in HIV prevalence observed between PMTCT and non-PMTCT participants was with regard to a woman's residence relative to the clinic where she sought ANC care. In an earlier ANC surveillance round in this population, HIV prevalence estimates were hypothesized to be biased downwards by the attendance of visitors from more rural areas where HIV prevalence was lower biases [55]. Results from this analysis of more recent data suggest, however, that while some women from rural areas with low HIV prevalence continue to attend ANC clinics outside their local catchment areas, other visitors with a greater risk of HIV infection may be selectively attending clinics which are known to provide HIV-related prenatal care services. Women might opt to visit these clinics rather than their local clinic if the local clinic does not provide HIV care, they perceive the HIV services at another clinic to be superior, or they fear the stigma of accessing HIV testing and care services within their community. Regardless of the reason, it will be important to distinguish between these two different profiles of visitors when explaining and accounting for bias in PMTCT-based surveillance estimates at clinics in the study area.

Given that the ANC surveillance study was conducted during a time when the MOHCW policy for providing PMTCT services was an 'opt-out' HIV testing strategy, the tendency toward preferentially testing HIV-infected women in the PMTCT programme during ANC visits is somewhat surprising since all women should have been offered an opportunity to test who attend an ANC clinic. At ANC clinics, PMTCT services are typically described to all ANC attendees during a group pre-test counselling session. Estimates of HIV prevalence among women tested versus not at those clinics where participation was especially low, however, suggests that standard PMTCT policies and procedures were not being followed or that the 'opt-out' testing policy had not yet been fully adopted. Because the exact date of a

woman's visit was not recorded, it is difficult to ascertain information about testing strategies or approaches on a particular day; however, the disruption in services due to the political and economic turmoil in Zimbabwe at the time could explain the intermittent availability of PMTCT services in locations, even where they were described as available during the round 4 study period.

One other surprising aspect of the results from the ANC surveillance study is that nearly all of the bias would have resulted from women being offered testing as opposed to refusing or accepting differently by HIV status once offered. In previous studies elsewhere in SSA, bias has primarily resulted from women refusing testing when offered [91] [96]. Several factors might explain why few ANC attendees refused in this study, however, and some of these may be important when considering the generalizability of the findings. In terms of limitations, acceptance rates may have been pushed upwards (and resulted in greater participation bias) by the presence of the Manicaland Project study nurses, who were involved with service provision and data collection. For example, faced with the knowledge that testing opportunities were limited in some of clinics due to insufficient test kits or availability of trained personnel on a particular day, study staff may have encouraged women at higher risk of infection to return PMTCT services on another day or to be provided an HIV test even if test kits were scarce. Alternatively, participation bias may have been reduced compared to other periods or outside the study area if study staff presented additional information about the importance of HIV testing to ANC attendees that resulted in their accepting a service they might otherwise have refused.

Despite these potential limitations, the high acceptance levels observed in this study may not be unique to the study area, thus, the results may be generalizable beyond the study area. Elsewhere in Zimbabwe, very high levels of testing uptake among women who were offered testing were demonstrated in Harare, where

acceptance levels at a clinic rose from 65% in the six months before opt-in testing in 2005 to 99.9% in the six months after opt-out testing in 2006 [83]. In the Manicaland study, factors such as stigma around testing may have been of less of a concern since the majority of ANC attendees at PMTCT clinics were interviewed for pregnancies which occurred in 2007 and 2008, well after integrated PMTCT services were introduced into the area. Also, women may respond to the strong incentives for testing with the availability of HIV prophylaxis and antiretroviral therapy, thus may find few reasons to refuse to test when offered.

With regard to the household survey results, which contrasted with those from the ANC surveillance, conclusions about the usefulness of PMTCT data for surveillance purposes are more difficult to make as several limitations in the data affect interpretation of the results. First, and most importantly, in the household survey, women were asked to report on activities that occurred at their ANC visit for a pregnancy that could have occurred up to three years prior. Consequently, recall bias of women in the household survey data with regard to access to and acceptance of PMTCT services, including testing, is likely to be higher than in the ANC surveillance data, where the interview occurred on the same day as the provision of the ANC care being asked about. Also with regard to recall bias, women may have remembered receiving a battery of pre-natal tests, including syphilis, which requires a blood draw, and therefore may have believed themselves to have been tested for HIV also, even if that test was not offered. Finally, reports of testing may also have been influenced upwards by a social desirability bias, since many women may have heard about the importance of HIV testing subsequent to their pregnancy and preferred to answer interviewer's questions with what they now know to be the standard practice for HIV testing during pregnancy in the study area. As evidence of the likely influence of these sources of bias on the household survey

findings, the proportion of women reporting they were offered testing by their health care provider and accepted testing was substantially higher than in the ANC surveillance round, despite the fact that the majority of women in survey would have been pregnant earlier than women in ANC surveillance

A second reason why the household survey findings are more difficult to interpret and also are less credible compared to those in the ANC surveillance, is that the HIV status of the women in the household survey was determined up to three years after their most recent pregnancy; thus, some women may have been HIV-negative at the time of their pregnancy but sero-converted in the interim. The extent to which individual socio-demographic and behavioural factors are further confounded by this type of misclassification bias would be difficult to quantify, although preliminary comparisons of incidence between round 3 and round 4 has remained stable and low (personal communication from Simon Gregson, April 13, 2011). Nonetheless, without access to HIV test results from the PMTCT programme and knowledge of their behaviour at the time of the pregnancy, it is not possible to quantify the magnitude of this bias on estimates.

A third and final limitation in relying on the household survey data to assess the usefulness of PMTCT surveillance data is that the clinic where a woman sought prenatal care is unknown, thus making it difficult to determine whether particular clinics or geographic areas where a woman sought service might be responsible for or contribute to differential uptake of HIV testing by women. As was evident in the ANC surveillance data, knowing which clinic women attended was important with regard to explaining why participation bias may have been occurring.

Despite these caveats, there are still two interesting findings from the population household survey that merit further consideration. First, owing to the timing of the survey between 2006 and 2008, as mentioned previously, the majority

of women participating in the individual household interview would have reported on pregnancies that occurred earlier on during the survey period during a time when PMTCT services were being rolled out and the availability of nevirapine or ART treatment still might have been limited in the study area. As a result, HIV infected women may have refused to participate in PMTCT services more frequently because there were fewer incentives to learn their HIV status. In part, this could explain why HIV prevalence estimates among non-PMTCT participants were higher than those among PMTCT participants in the household survey and the reverse was observed in the ANC surveillance, where most women participating in ANC and PMTCT surveillance did so at a later time, on average, in 2007 and 2008.

Second, the higher HIV infection levels among those who refused PMTCT-based HIV testing could have reflected the early stigma toward testing among women who perceived themselves to be exposed or infected. Stigma has been identified as a reason for high refusal rates in many other studies in SSA and in Zimbabwe specifically [189, 193, 199, 263-266]. Perhaps as evidence of this shift in attitudes toward testing over time in the household survey data, 36.2% (21/58) of all HIV-positive women who were offered testing by their health care provider reported refusing testing in 2006. In 2007, this proportion fell to 27.9% (12/43). By 2008, only 15.4% (2/13) HIV-positive women had refused testing.

These latter data encouragingly suggest that over time, HIV prevalence estimates from PMTCT data might become more representative of prevalence among all ANC attendees as the proportion of clients refusing testing declines. Worryingly, however, the data also demonstrate the potential for participation bias to shift over time. Unfortunately, another limitation of the household survey is that women who reported refusing HIV testing for PMTCT purposes were not asked

about their motivation for refusing testing, thus it is difficult to ascertain exactly why HIV-infected women were not tested.

Given the limitations in the household survey, it is likely that the ANC surveillance data provide the most accurate insight into the potential usefulness of PMTCT data for surveillance purposes in the study area. Even still, reasons why certain women as opposed to others participated in the PMTCT programme were difficult to ascertain. In previous studies in SSA using similar methods to those used here, testing positive and accepting testing was weakly associated with such basic socio-demographic factors as having (i) lived at a current address for two years or less, (ii) cohabitated with but not married their current partner, (iii) a partner with a non-agricultural occupation [92], less education [91] and older age [192]. Behavioural risk factors that have been associated with increased HIV infection and testing included (i) reporting the self-perception of greater risk of HIV infection; (ii) having an HIV-infected partner; and (iii) believing themselves exposed to HIV [91]. Other factors associated with uptake of testing and testing positive included a history of miscarriage [192]. Two differences with these studies as compared to the Manicaland study, however, were that the former were conducted at a time when 'opt-in' client-initiated testing was in place and each took place in a single clinic only.

One possible way to understand the role of testing motivation better is to consider the subset of women who reported visiting a clinic that was not their own. In the ANC surveillance data, only 5% of women visiting clinics reported doing so because PMTCT services were offered there, while no women reported visiting a clinic because PMTCT services were not offered. These women were also significantly less likely to be offered testing. In the household survey, the opposite was true. There, visitors were much more likely to report being offered testing, although they were not more likely to accept testing when offered. These differences

in HIV prevalence and the level at which visitors were offered testing suggests that more detailed data about whether a women chooses to attend an ANC clinic outside her local residence and why should be collected as a routine variable in ANC and PMTCT-based surveillance activities.

While it is possible that other factors not measured in the study (such as knowing a partner's or a child's HIV status to be positive) were used by health care staff to determine whether or not a woman should be offered testing, it seems unlikely that these decisions would explain any large or substantial bias in the PMTCT estimates. Even when HIV prevalence in the area is high, only a small proportion of women would likely be subject to these other factors. As a result of this, and the limited insight into why particular women either were offered testing or accepted testing when offered, it seems difficult to apply a statistical adjustment factor that would account for the participation bias observed in the estimates across the clinics. This method was used successfully in a previous study in Uganda, although the adjustment was made for data from a single clinic only where biases in participation by HIV status and socio-demographic characteristics were smaller and more easily quantified [93]. Additional studies incorporating future rounds of data from the Manicaland Project would be required to assess the consistency of the magnitude of the bias over time in the two data sets also.

As previously mentioned, the structure of the ANC visit in most clinics in Manicaland includes offering HIV testing during a group pre-test counselling session which is provided to all women at the start of the day. If standard PMTCT policies and procedures are appropriately carried out at the clinic, it is possible that the bias from participation due to preferential offering of testing might dissipate with time. Other policies and practices specific to the provision of PMTCT services may be at odds with ANC surveillance though. Notably, in Uganda, where HIV testing only

occurs on the second visit, estimates of HIV prevalence from PMTCT data could be biased if those women who attend only one ANC visit differ with regard to their HIV status as compared to women who attend two or more visits [98]. In Uganda, one of the clinic-based studies compared basic socio-demographic characteristics of women offered versus not offered testing and found them to not differ substantially, although direct comparisons of HIV prevalence estimates was not possible [98]. In another location in Uganda, this possible source of bias was not able to be assessed due to lack of information [91]. Most studies conducted to date have not specifically reported the subset of the population that is not offered testing in PMTCT programmes.

In summary, the low levels of participation in PMTCT programme in the Manicaland, Zimbabwe study area and period generally, and the difficulties associated with identifying specific socio-demographic characteristics that adequately explained these differences in the ANC surveillance data in particular, make it difficult to recommend PMTCT data for HIV surveillance purposes. Nevertheless, it is possible that just as the proportion of women testing and the number of sites offering PMTCT services increased from round 3 to round 4, similar increases will be observed in future rounds to a point where most women are offered testing at ANC clinics and acceptance is nearly universal. When this is true, the utility of PMTCT data will be a welcome addition to or a replacement for ANC surveillance as means for monitoring HIV prevalence trends in this population.

Chapter 7: Conclusions

7.1 Aims and organization of the chapter

The aim of this chapter is to summarize the findings from this work and to discuss their broader implications for using HIV surveillance data to monitor the HIV epidemic in SSA. In the first section, the main conclusions of each chapter are summarized. Next, answers to the key research questions first referenced in this thesis are suggested. Those key questions were: (i) have trends in HIV prevalence among pregnant women mirrored those in the population historically in SSA?; and (ii) can ANC surveillance data be used to reliably monitor future population HIV prevalence trends? With regard to the use of PMTCT data, which is a relatively newer area of investigation, questions explored were: (i) do estimates of HIV prevalence among women participating in PMTCT programmes accurately reflect HIV prevalence among ANC attendees?; and (ii) what factors related to the geographic scale-up of services or selective participation (either being offered or accepting testing) by HIV status might bias these estimates? Finally, remaining gaps and suggested research priorities based on these gaps are outlined as future work along with a few concluding remarks.

7.2 Summary of main findings

Chapter 1 began with an overview of the HIV epidemic globally and in SSA, along with the methods typically used to collect HIV-related surveillance and programme data. This review highlighted the unique aspects of HIV infection, including the long asymptomatic period and the stigma associated with testing positive, which have made it difficult to measure infection levels and trends in the population accurately.

Given these challenges, the benefits of using anonymous, clinic-based ANC surveillance data and PMTCT data were explored in more detail, even though these

data also potentially suffer from selective biases that must be considered. These biases include (i) the purposeful selection of participating clinics; (ii) the self-selection of women who access ANC services and (iii) only testing women who became pregnant.

Due to biases from the purposeful selection of clinics, it was noted that ANC surveillance data are no longer used to estimate levels of HIV infection in the population. Nonetheless, ANC surveillance data are still thought to be a valid measure of population prevalence trends, since the latter two sources of selection bias are assumed to be largely static. A comprehensive discussion on the role of population surveys in SSA is provided to better understand the strengths and limitations of these data also. To the extent that refusals or absenteeism is differentially associated with HIV status or high risk population groups are missed, population survey data can also provide a distorted picture of true prevalence. For this reason, many countries in SSA have implemented a range of population and facility-based biomarker and behavioural surveys that permit triangulation of data to interpret how the epidemic is evolving over time. In the last section of Chapter 1, examples are provided of how ANC surveillance data have been used in SSA to monitor the epidemic and to measure the impact of intervention. A review of the methods for estimating population prevalence trends from ANC surveillance data using the UNAIDS EPP-Spectrum software package are also described in more detail, as ANC surveillance data are the cornerstone for producing projections for most countries in SSA.

Chapter 2 provided some insights through a literature review into why biases in ANC surveillance data might change in magnitude and direction with time. In the first section, the large body of literature describing how biases in ANC surveillance data have led to overestimates or underestimates of population and female HIV

prevalence in SSA were discussed. In summary, selection for more urban clinics, where prevalence is highest, often results in an overestimate of HIV prevalence among men and women. This bias is often balanced by lower estimates of HIV prevalence among pregnant women due to HIV-related sub-fertility. At the same time, high-risk sexual behaviour in ANC clinics often introduces an overestimation of HIV prevalence in the younger female population, especially when the age of sexual debut is late. Overall levels of contraception use and access to ANC and PMTCT services can also temper or exaggerate these differences.

Given that ANC data are well-known to be biased at the local level, the primary focus of Chapter 2 was to explore under what conditions these biases in ANC surveillance data might change with time. The three empirical studies and four mathematical models that informed much of the work in Chapters 3 through 5 were reviewed. These explorations primarily considered the potential for changes in the magnitude and direction of bias in ANC estimates to be influenced by the natural dynamics of the epidemic and the scale-up of effective HIV prevention and treatment interventions.

A final section following on from these discussions that summarize the work that has been done to adjust for biases in ANC data is provided. The methods proposed, which range from simple standardization for differences in age and other socio-demographic characteristics between the two populations to more complicated adjustments taking into account relative fertility differences between HIV infected and uninfected women, are reviewed. Studies validating or exploring these methods are also presented, with some limitations particularly with regard to the collection of additional surveillance data noted. The problems with adjusting ANC estimates by age are also described as this can lead to even greater differentials due to increasing the weight of lower prevalence in the older ANC population. Notably,

however, none of the proposed adjustments of studies validating or applying these adjustments considered their application over time with the exception of Garnett, who shows that age-standardization is one way to prevent changes in the magnitude of bias in ANC estimates over time. Given that UNAIDS recommends using ANC surveillance data to monitor population prevalence trends, there may be merit in reconsidering the usefulness of age-standardized estimates.

In addition to the review of literature on bias in ANC estimates and ANC trends, a secondary focus of Chapter 2 was to explore how PMTCT data have been used to monitor the HIV epidemic in SSA. In particular, Chapter 2 highlighted the possibility for selective participation bias in PMTCT programme data to either overstate or understate HIV prevalence among ANC attendees. This chapter also considered the extent to which changes in the scale-up of PMTCT services might result in differential levels of bias over time.

Country experiences varied with regard to their perception of the usefulness of PMTCT data for monitoring population HIV prevalence. In SSA, no country has begun using PMTCT data for surveillance purposes as of yet. Most importantly, as few of the countries evaluated PMTCT systems with “opt-out” testing programmes, the generalizability of findings from these earlier studies are limited. Selective participation biases in an “opt-out” setting (which is the recommended approach for providing PMTCT services currently) were examined in Manicaland, Zimbabwe and results described in Chapter 6.

Chapter 3 was the first of four chapters presenting new analytical work on bias in ANC HIV prevalence trends. In Chapter 3, estimates of HIV prevalence, stratified by gender and rural and urban areas, in seven countries in SSA, were compared using data from repeated ANC surveillance and DHS and DHS-like surveys conducted from 2001 through 2009. Results show that ANC surveillance

data performed reasonably well at capturing changes over time in HIV prevalence levels in many countries, especially in southern/eastern Africa, and especially when used to monitor trends among adult and young women living in urban areas. ANC surveillance performed especially poorly, however, when monitoring trends among young men and in some countries, including Kenya. Given the low prevalence among young men generally in SSA, it is not surprising that ANC surveillance data, which reflect the behaviour of the riskiest young women, do not perform well for this age group.

By adapting commonly used statistical methods, an approach to directly compare trends in ANC surveillance and population survey data was proposed in this chapter. Using this method, significant differences between trends from the two datasets were found for three countries: Kenya, South Africa and Tanzania. These differences were found to occur primarily among men (or nationally where data from men were included) or in rural areas. However, no consistent relationship with regard to the ways in which ANC data overstated or understated population HIV prevalence trends was evident. The chapter concluded by highlighting the possible reasons why ANC surveillance data might not have reflected accurately the underlying changes in population HIV prevalence in these settings, and in particular, the potential strengths and weaknesses of ANC surveillance and population surveys, each of which can introduce their own types of biases in estimates over time.

In Chapter 4, a stochastic cohort mathematical model was used to simulate HIV-prevalence trends among pregnant women and women in the population of reproductive ages. Using this model, it was possible to describe potential changes in the magnitude and direction of bias in ANC surveillance trends in settings similar to those in Botswana, Côte d'Ivoire and rural Zimbabwe since the start of the epidemic but before the introduction of ART (from 1985 to 2002) and in the ART era (from

2003 to 2030). In the ART era, a variety of scenarios were explored with regard to scale-up and interactions with fertility, including with what speed and coverage ART was made available in a country and to what degree in magnitude and direction ART use led to changes in fertility levels among HIV-infected women.

One of the most important findings from these simulations in the pre-ART era was that relying on ANC data to monitor true population prevalence trends for women of reproductive aged 15 to 49 years may have been problematic historically. From the start of the epidemic through the mid-1990s, ANC prevalence would have initially been representative of underlying population prevalence. As the epidemic progressed, though, ANC surveillance estimates over time would have likely understated the rise in population HIV prevalence in all three settings. When population prevalence began to decline in Côte d'Ivoire and rural Zimbabwe during this time period, ANC surveillance data would have overstated the decline. This was due to an increase in the average age of HIV-infected women beyond their most fertile years, especially as incidence declined. Fortunately, trends in ANC prevalence among younger women aged 15 to 24 years would have been a better indicator of true population prevalence trends among young women. Even for this younger age group, however, the model suggests that some modest over-estimation of declines in true population prevalence could have occurred between the mid-1990s and the early 2000s.

From the ART-era simulations, three noteworthy findings emerged. First, ANC trends continued to overstate declines in population prevalence among women aged 15 to 24 years for the first few years after treatment was introduced. Eventually, though, these biases either stabilized or reversed depending on the association between ART use and fertility and the speed and coverage with which ART was introduced. The second finding, which can be surmised from the first, is that the

magnitude and direction of bias in the ANC surveillance trends in the ART era differed across the settings and also over time, although the potential magnitude of bias was greater when fertility was reduced. Taking this into account, it would be difficult to develop a systematic approach to adjusting for changes in bias based on these findings without a clear indicator of fertility patterns among women on ART over time. Third, and finally, as was true in the pre-ART era, HIV prevalence trends from ANC surveillance data were generally more robust for younger ages (i.e., aged 15 to 24 years) compared to older ages (i.e. aged 25 to 49 years) regardless of the strength and direction of the association between ART and fertility or the level of scale-up of treatment services. As a result, this chapter concludes by suggesting that ANC prevalence should be considered a reasonably good indicator of underlying population prevalence trends for young women especially. Suggestions for future work with this model are also provided. For example, the model could be easily adapted to explore the validity of ANC surveillance data for monitoring trends in HIV incidence among youth and to consider the impact of associations between HIV and pregnancy or contraception use.

Chapter 5 also explores the representativeness of ANC surveillance data in comparison to population trends, this time using empirical data from a population cohort survey among young females aged 15 to 24 years and males aged 17 to 24 years resident in Manicaland, Zimbabwe from 1998 to 2003. Similar methods for comparing trends were used to those in Chapters' 3 and 4. To account for potential biases due to changes in the population survey inclusion criteria related to migration and changes in the demographic structure in general, which were especially evident at round 2, HIV prevalence estimates in the population survey were standardized by age, marital status and migration history. Results showed that after adjusting for demographic differences alone in the population (e.g., not migration), reductions of

around 47% in the general population survey (among women alone and men and women combined) and 46% in the ANC surveillance were observed. These levels were well above the 25% reduction target for 2005 set by UNGASS. A similar level of decline was observed using national population survey and ANC data by Gouws and colleagues in Zimbabwe. Taken as a whole, these findings suggest that the HIV epidemic in Zimbabwe among young people has declined substantially.

One interesting finding from this work was that the comparison of trends across survey rounds suggested that most of the declines in HIV prevalence in the population occurred early on in the epidemic from 1998 to 2003, while the declines in prevalence among young pregnant women were steadier over this period. This finding corresponds to the experience in Lusaka, Zambia, where ANC surveillance data also appeared to understate declines in population prevalence. Adjusting for demographic changes and changing patterns of migration in the population survey tempered some of the larger reductions originally observed in the population data early on, although reductions among women were still around 40%. Reductions among men were considerably smaller and less consistent with those in the ANC surveillance data set between rounds independent of whether the data were standardized or not.

One of the factors determined to contribute to the difference in estimates over time was in-migration. Exclusion of persons who had moved to the study area either two years in advance of the first study round or had newly moved into the area between subsequent survey rounds were resulted in a decline in HIV prevalence of around 30% from round 1 to round 2 among residents, which was very similar to the 26% decline observed among ANC attendees. In particular, it could be that ANC surveillance data do not adequately reflect HIV prevalence of people coming from outside of the study area, especially when they are very young, single and at higher

risk of HIV infection. This was the case in particular for young women moving into the study area between round 1 and round 2. Other possible biases in the ANC surveillance data, including changes in the demographic composition of the pregnant women and women from outside the study catchment area did not appear to introduce any particular bias.

Taking into account biases in the population survey, particularly at round 2, it was determined that ANC surveillance estimates were generally a good reflection of the underlying trends in population prevalence in the study area. Still, there were substantial changes in round 1 to round 2 behaviours among the population (including delays in sexual debut and increased condom use) that could also explain some of the differential bias in the ANC estimates where it was observed. Previous research by Zaba and colleagues (using a mathematical model) suggest that the patterns observed from round 1 to round 2 in Manicaland are consistent with these results. Additional analyses describing the sexual behaviour of women moving into the study area in comparison to usual residents may add additional insight into the extent to which migration is associated with riskier sexual behaviour and HIV transmission in SSA.

One final issue that the more detailed comparisons by sex illustrated, which was noted above, is that ANC surveillance trends, overall and by key socio-demographic factors, are more reflective of changes in population prevalence among women as compared to men. This finding was similar to the observations made in Chapter 3 when using national population survey data. In Manicaland, among men, reductions in HIV prevalence were generally smaller as compared to ANC trends, even when excluding in-migrants and adjusting for differences in age and marital status. This finding is considered in the following section.

In the last analysis chapter of this work, Chapter 6, HIV prevalence estimates from round 4 of the Manicaland Project ANC surveillance and household survey data were compared to estimates from women who were offered and who accepted PMTCT-based HIV testing. Round 4 occurred between 2006 and 2008 at a time when an 'opt-out' testing approach had been adopted by the MOHCW. Factors associated with testing and HIV status were determined for ANC surveillance participants and among previously pregnant women who reported attending ANCs during their last pregnancy.

Results from the comparison of ANC and PTMTCT estimates strongly suggested that data from the PMTCT programme would have been unsuitable for monitoring prevalence among ANC attendees during this period in Manicaland, Zimbabwe. In ANC surveillance, PMTCT data would have overstated HIV prevalence among ANC attendees around 20%. This differential appeared to result from the selective testing of women who were more likely to be HIV positive at clinics where the proportion of women offered testing was below 50%, although this was observed to vary by clinic.

To assess why this bias might have occurred, Poisson regression with a robust error variance was used to identify factors associated with testing and with HIV infection. Results from this analysis show confounding due to a variety of factors. In particular, the health status and visitors in the ANC surveillance data was most strongly identified with why HIV-infected women were more likely to participate in the PMTCT programme. Other factors including age, residence and parity also explained this difference but to a more limited extent. The role of residence with regard to the clinic where a woman attended was revealed to have an interesting effect on the PMTCT estimate, suggesting that the profile of visitors with regard to their HIV status may be changing over time due to the scale-up of PMTCT services.

This is in contrast to a previous study in this population where rural participants attending more urban clinics were thought to be uniformly at lower risk of HIV infection. Notably, not all of the bias in the PMTCT data could be explained, suggesting that other factors not measured in the study may be leading to differential participation in the PMTCT programme among HIV-infected women.

In the household data, a similar analysis was also undertaken to identify factors that might explain a downward bias of approximately 20% in the PMTCT estimate. Many factors were shown to marginally influence or explain the bias in estimates when adjusted for, although substantial bias remained unexplained. Due to the limitations of the household survey data, including recall bias and the potential for mis-classification, it is difficult to interpret these data as representative of the usefulness of PMTCT data for surveillance purposes in the area. Instead, ANC surveillance data may provide a more accurate indicator of the current strengths and limitations of using PMTCT data for surveillance purposes in Manicaland, Zimbabwe. This point is also considered in the following section.

7.3 Implications and recommendations for using data from pregnant women for HIV surveillance purposes

In the following sub-sections, an attempt is made to draw out some of the key answers to the four proposed research questions summarized in Section 7.1. Also, the wider implications of relying on HIV surveillance methods for monitoring the epidemic in SSA are considered in more detail.

7.3.1 Validity of historical ANC surveillance trends (1985 to 2010)

Within this body of work, Chapters' 3 through 5 have generated some insights into the question of the historical validity of ANC-based surveillance trends from 1985

through 2010. In part, these analyses confirm some of the assumptions that were originally made with regard to the usefulness of ANC surveillance data for monitoring HIV prevalence trends. For example, as analyses from Chapters 3, 4 and 5 illustrate, the UNAIDS recommendation to use ANC surveillance data to monitor population prevalence trends among young people aged 15-24 years was generally validated [64]. One important caveat that arose from this work, however, is that ANC surveillance data were not likely to have been particularly representative of prevalence among young men. Based on the results presented here, UNAIDS should consider revising the UNGASS core indicator in future years to specify that ANC surveillance data should be used to monitor reductions in prevalence among young women only. To monitor population prevalence trends among young men, more frequent household-based population surveys may be required.

The broader assumption about the representativeness of ANC surveillance data with regard to women of all ages, as originally hypothesised by Garnett, was determined to be slightly less robust in these analyses [115]. In the micro-simulation model used here, for example, there was a tendency for ANC surveillance trends to have historically overstated HIV population prevalence declines, both in the pre-ART era for Côte d'Ivoire and Zimbabwe (and in the early part of the ART era, regardless of the association between ART and fertility). In large part, this was due to the increasing age of HIV-infected women in the population, which led more HIV-infected women to be excluded from ANC surveillance.

One limitation of this model is that it does not reflect the additional sources of bias that routinely influence ANC data over time. For these reasons, the evidence from Chapter 3, which suggests that ANC surveillance data have provided a reasonably good measure of underlying female population prevalence trends in all countries except Kenya, is encouraging. Stratification of trends for women by age,

and possibly by rural and urban areas, should also be considered standard when presenting these data. The lack of representativeness of rural ANC estimates relative to female population prevalence that was observed in the empirical study has been previously reported, thus it is not surprising that these data also observed to perform poorly over time with respect to trends. Countries should consider this fact in particular when presenting trend data from EPP.

Similar to the caution raised with regard to using ANC surveillance data to monitor population prevalence trends among young men, the same caution should apply to using these data to monitor trends among adult men. Based on the results from the empirical study in Chapter 3, ANC surveillance data did not appear to reflect underlying trends in prevalence among adult men, and stratification by rural and urban areas did not appear to be particularly useful either, aside from in Zambia. As a lack of representatives in ANC surveillance data to monitor trends among men can influence the overall representativeness of trends nationally, countries should also be cautious when interpreting national prevalence curves obtained from EPP, particularly where only one national population survey has been done. For those countries without repeat surveys, it may be necessary to present these data with a caution that ANC surveillance data may not reflect changes in prevalence among men.

One finding that was previously noted in Chapter 3 to be particularly concerning was that it was difficult to discern any pattern in terms of the way in which ANC surveillance data were biased. In the mathematical model, the direction of the bias was clearer, however. For example, during the first few years of scale-up of ART, it does not appear as important to know the direction and magnitude of bias associated with changing fertility patterns, as regardless of this association, ANC surveillance were found to overstate population prevalence declines. This finding

should be taken into account when ANC surveillance data are used to estimate and project population HIV prevalence in EPP-Spectrum regardless of the other biases that can potentially influence ANC estimates over time. Already, EPP-Spectrum takes into account the impact of ART on the population when measuring incidence, but does not consider the impact that changes in the age patterns of HIV-infected pregnant women will have on artificially drawing down HIV prevalence estimates in the population [106]. Additional population survey data will be useful in determining the extent to which the modelled biases observed are similar to those observed in the countries themselves.

7.3.2 Prospects for using ANC surveillance data in the future (2011 and beyond)

Results from Chapter 4 represent the first attempt to determine if ANC surveillance data from countries in SSA can be used to monitor future HIV prevalence in the population, especially given the roll-out of ART and its potential association with fertility patterns among female users. In general, the model shows that the prospects for using ANC surveillance data in the future will be highly dependent on the speed with which the scale-up of treatment services occurs and the direction of the association between fertility and ART use. If ART use has a negative impact on fertility among users, fewer HIV-infected women will be included in the ANC sample, thereby making the ANC data less representative over time. If ART use results in greater fertility among users, then more HIV-infected women will return to the ANC sample. However, the changing age structure of the infected population, as well as the ageing out of HIV-infected women from the age groups typically included in population surveys (e.g., aged 15 to 49 years), will need to be

considered on a country-by-country basis. This is especially true when using EPP-Spectrum to produce short-term projections of HIV prevalence trends in the population. A functionality that could be added to a future version of EPP-Spectrum software to address the concern regarding the association between ART use and fertility is the ability to define age-specific fertility rates for women on ART that can vary with time.

At this time, however, (and as noted in Chapter 4), the primary limitation for predicting future changes in bias is that very little is known about how fertility patterns of HIV-infected women might vary with time. Also not known is the time period over which these variations might be detectable at the population-level or how other factors, such as changes in risk behaviour might influence the magnitude and direction of bias in ANC surveillance estimates. As a result, it is difficult to recommend a standard approach to adjusting for bias in ANC surveillance data that would work for all countries. Instead, countries will have to evaluate the impact of ART use on fertility rates over time, among other shifts, and take this into account when interpreting trends in prevalence at the population level.

The above recommendation to monitor associations between ART use and fertility patterns obviously will have a broader public health benefit, as countries will be able to determine whether family planning needs of HIV-infected individuals are being met. Still, these types of evaluations require technical and financial resources, on top of those already dedicated to conducting ANC surveillance on a bi-annual basis. Given this context, it is possible that some countries in SSA might consider whether it is more cost-effective to increase the frequency of nationally-representative population surveys, rather than to continue using ANC surveillance data to monitor population prevalence trends. Although nationally-representative population surveys will be on an order of magnitude more costly than ANC

surveillance, the data they provide are likely to be more widely used. As previously mentioned, repeated DHS data can be used to monitor changes in HIV incidence and transmission among men. Since DHS data also provide insight into reproductive and other health issues, however, other public health programmes would benefit from an increase in their frequency.

For countries that are not able to increase the frequency of population surveys, however, there is some reason to be hopeful that ANC surveillance data will continue to be useful for monitoring population HIV prevalence trends in the future, even if the associations between ART use and fertility remain unclear. As was true in the pre-ART era, HIV prevalence trends from ANC surveillance were generally more representative of population survey data for younger ages (i.e., aged 15 to 24 years), regardless of the strength and direction of the association between ART and fertility or the level of scale-up of treatment services. This should provide some level of assurance going forward to countries that rely on ANC surveillance data to monitor incidence among youth, aged 15 to 24 years -- so long as other biases due to changes in the age of sexual debut and behaviours remain largely stable.

7.3.3 The accuracy of PMTCT programme estimates in reflecting prevalence among ANC attendees

The study in Manicaland, Zimbabwe of PMTCT and ANC surveillance data, which is presented in Chapter 6, is one of the first outside Botswana (where uptake of testing is very high) to assess the accuracy of HIV prevalence estimates from PMTCT data in an opt-out testing setting. It is also one of the few studies to explicitly analyse the impact of offering HIV testing versus not offering HIV testing to women on the representativeness of PMTCT programme estimates. In previous studies, the

influence of not offering testing on bias has been assessed either superficially, through the comparison of socio-demographic characteristics in women offered versus not offered testing [98], or not at all [91].

The fact that HIV prevalence was found to differ by participation levels at individual clinics is not new. However, that this occurred as a result of not offering women testing is important. Future studies should consider the extent to which women are being differentially offered HIV testing. Even in Thailand, the evaluation of the usefulness of PMTCT data for surveillance purposes focused on acceptance rates and comparisons among women offered testing as opposed to all women, rather than women who had not been offered testing during their prenatal visit [267, 268].

7.3.4 Factors associated with being offered and accepting testing in PMTCT programmes

One of the most important findings from the Manicaland study is that adjusting for non-participation bias, as was recommended by Fabiani and colleagues in one clinic in rural Uganda [93] may be difficult in conditions that more closely mimic those under which ANC surveillance is typically carried out (e.g., at multiple clinics with different levels of and possible reasons for participation bias). In Manicaland, participation bias appeared to differ by individual clinics, and, it is unlikely that they would be similar for all participating clinics even if motivations for testing could be accurately captured. It would seem that the best – and most obvious – solution to addressing participation bias in PMTCT-derived estimates is to ensure that as many women as possible are encouraged to participate. Not coincidentally, this solution is consistent with the broader WHO and UNAIDS strategy to provide ‘opt-out’ testing to all women seeking ANC services.

A second concern is that as HIV testing opportunities increase in the future, HIV infected women may increasingly opt-out of testing or self-refer to clinics that provide comprehensive HIV treatment and care. In these cases, data collection and reporting forms will need to include all women and indicate their status, regardless of whether they are tested, so as to ensure that overall estimates of HIV prevalence among attendees is accurate and do not reflect biases due to the expansion of testing and treatment programmes.

7.4 Remaining research gaps and future directions

Despite the desirability of using ANC and PMTCT data for HIV surveillance purposes in SSA, there are still many uncertainties about the reliability of these data for monitoring population-level HIV prevalence trends. Most importantly, methods for quantifying, and describing factors leading to bias in ANC surveillance data are needed. In this thesis, an easy-to-use Excel spreadsheet was developed to compare trends in prevalence over time. When sample sizes are small, however, as they could be in ANC surveillance data, the confidence intervals around the relative proportional change estimates can become large and it is possible that they do not accurately reflect the public health importance of differences in trends. As a result, other statistical methods such as fixed-effects logistical models might be preferable. However, the limitation in these methods, including logistical regression, is that the outcome of the statistical model does not explicitly measure whether the difference in the proportional change is significant. Since UNAIDS recommends that countries measure the proportional change in HIV prevalence estimates over time, particularly when evaluating the UNGASS indicator for incidence among youth, the methods proposed here seem most suited to the task.

With regard to this latter point, additional consensus is needed regarding the statistical methods for determining the similarity in levels and trends, both between ANC surveillance and population survey data and between PMTCT and ANC surveillance data. Owing to small sample sizes at the clinic level, comparisons of site-specific estimates using overlapping 95% confidence intervals may be meaningless. Instead countries may need to conduct these statistical evaluations comparing trends at the national level, and stratified by rural and urban and age-specific categories only, and to determine an acceptable level of relative differences at the clinic-level that will be used to decide the comparability of estimates. This standardized approach to analysing bias in ANC surveillance data will improve the dialogue between the public health community and stakeholders about the overall confidence in using these data for monitoring the HIV epidemic over time.

In the case of ANC surveillance data, the scale-up of ART services and its potential interaction with the fertility of women on ART needs to be carefully documented. With regard to PMTCT programmes, bias in estimates due to low or changing levels of uptake over time need to be explored. Further mathematical modelling of biases may be one approach to dealing with the challenge of collecting data to describe these influences, as it can often be difficult to obtain nationally-representative repeated samples that permit such detailed analyses.

Of particular concern with regard to the representativeness of PMTCT data and bias over time is the extent to which the introduction of PMTCT services preferentially draws HIV-positive women to clinics. This factor needs to be better documented in SSA. The gradual roll-out of these services may temporarily or permanently shift catchment areas to the extent that estimates among pregnant women, whether derived from ANC surveillance or through PMTCT service data, no longer reflect trends in the population. Additional information on the providence of a

woman and the primary reasons for seeking services outside of their local clinic should be collected in PMTCT registries and in ANC surveillance to aid in these analyses.

7.5 Concluding remarks

During the past thirty years, one fact that remains unchanged is that the HIV virus has evolved and adapted to the world in which it exists. The purpose of this thesis has been to consider to what extent the methods used to monitor HIV prevalence in the population have also evolved and adapted over time, and what additional efforts will need to be considered in the future.

Over the next thirty years, the expansion of ART and PMTCT programmes, along with on-going efforts to change people's sexual behaviour, will have a sweeping, and perhaps even unpredictable, effect on the epidemic. As this thesis suggests, it cannot be assumed, however, that these changes will be similarly adopted by all population groups equally, and more specifically, by women who are of reproductive age and at risk of acquiring HIV through unprotected sex.

For this reason, the public health community will need to continually and carefully consider the role of data collected from testing HIV pregnant women and the extent to which these data reflect the true evolution of the epidemic. Anything less than a best effort to accurately monitor the epidemic with the limited resources available will undermine and diminish the even greater contributions that public health practitioners are making on a daily basis in SSA to mitigate the spread of this epidemic.

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Appendix A: Supplemental Tables 2.1-2.5

Supplemental Table 2.1 Bias in ANC estimates relative to population surveys

Author	Location	Population	Methods	Outcomes	Study limitations
Montana, et al. [46]	Multi-country study (Ethiopia, Kenya, Malawi, Tanzania, and Uganda)	DHS and ANC surveillance participants; Sample sizes varied by study and country.	Comparison of HIV prevalence estimates from ANC surveillance and DHS surveys nationally and within 15 kilometres of participating ANC surveillance site.	• ANC>DHS national HIV prevalence in all but Uganda, where ANC<DHS. • ANC=DHS in catchment areas. • ANC<DHS for older women (25+ years) ANC>DHS for young women (15-24 years). • DHS data can be used to calibrate ANC data but bias must be taken into account.	• Geographic comparisons assume that clinic catchment area can be captured by the 15km radius. • DHS data may be biased by differential non-response.
Gouws, et al. [45]	Multi-country study among those with generalized HIV epidemics (n=26, or which 24 are in SSA) in the 2000s	DHS and ANC surveillance participants; Sample sizes varied by study and country.	HIV prevalence estimates from national population-based surveys and ANC clinics. Correction factors proposed based on differences.	• ANC>DHS national HIV prevalence in most countries by about 20% (95% CI: 10% to 30%). Eastern/Western Africa differences (about 10%) < Western/Central African (up to 40%.) differences. Rural differences> urban differences. • Reduce ANC estimates by 20% for countries with no population survey.	• DHS data may be biased by non-response. • ANC surveillance data may be biased due to clinic selection; biases may change over time. • ART may affect HIV infection and fertility patterns, resulting in a change in the correction factor required over time.

Supplemental Table 2.1 Bias in ANC estimates relative to population surveys

Author	Location	Population	Methods	Outcomes	Study limitations
Gonese, et al. [108]	Zimbabwe, 2006 ANC and 2005-2006 DHS	7202 ANC participants; 6947 women in DHS, of which 2943 were in 30km of ANC clinic and 777 had a previous birth and attended an ANC.	Comparison of HIV prevalence estimates from ANC surveillance and DHS survey nationally, within 30 kilometres of ANC clinic, and with those who attended an ANC clinic at last birth.	• ANC of 17.9% (95% CI: 17.0%-18.8%)=DHS HIV prevalence nationally of 18.1% (16.9%-18.8%) • ANC<DHS HIV prevalence among women and women living within 30km of ANC clinic. • ANC surveillance data provide a reasonable estimate of national prevalence.	• Geographic comparisons assume that clinic catchment area can be captured by the 30km radius. • DHS data may be biased by differential non-response.
Kayibanda, et al. [109]	Rwanda ANC surveillance and DHS data from 2005	5641 women aged 15-49 years and 13745 women in 30 ANC clinics.	Comparison of ANC surveillance and female population survey estimates of HIV prevalence by rural and urban area. Comparisons made using log-binomial regression and direct standardization.	• ANC prevalence of 4.1% (3.8%-4.5%)>DHS nationally of 3.6%; (95% CI: 3.1%-4.1%), due to selection of more urban clinics. • ANC>DHS female estimates Data standardized by age, marital status and urban rural areas of residence reduced differences.	• Specific fertility-related differentials and biases were not explored. • Women in urban ANC clinics may have come from rural areas, thus estimates in urban areas may be biased by non-local attendees.

Supplemental Table 2.1 Bias in ANC estimates relative to population surveys

Author	Location	Population	Methods	Outcomes	Study limitations
Musinguzi, et al. [110]	Uganda population survey and ANC surveillance data in 2005	9688 ANC attendees and 16,936 population survey participants.	Comparison of ANC surveillance and population prevalence trends and within catchment areas (30km).	• ANC prevalence of 6.0% (95% CI: 5.5%-6.5%) = population survey estimate of prevalence 5.9%. • ANC prevalence>prevalence females in surrounding catchment areas among those aged 15-19 years, were similar for all other ages. • ANC prevalence<prevalence among women overall (6.0% vs. 7.4%) and urban women (7.6% vs. 12.7%) but was similar to rural women (5.3% vs. 4.9%).	• ANC sites clearly underestimate HIV prevalence in urban areas suggesting that urban clinics are misclassified. • Women resident to the area in ANC surveillance could not be determined, thus ANC estimates may be lower in urban areas due to rural participants. • Not able to assess trends, but authors noted the potential for these dynamics to shift over time.
Dzekedzeke, et al. [70]	Zambia 2001-2002 ANC surveillance and DHS data from 2001-2002	1484 in urban areas and 2322 in rural areas in DHS data (men and women combined); 7405 women in urban areas and 4584 women in rural areas.	Comparison of ANC surveillance and population survey estimates of HIV prevalence by rural and urban area.	• ANC (adjusted national 16.9%; 95% CI: 16.6-17.2)=DHS national HIV prevalence of 15.6% (95% CI: 14.4-16.9). • Non-response bias in DHS did not influence survey estimates. • ANC data can be used to provide a reasonable estimate of population HIV prevalence in Zambia.	• Non-response bias could affect validity of comparison; however, authors found no evidence for the levels needed to introduce a significant bias.

Supplemental Table 2.1 Bias in ANC estimates relative to population surveys

Author	Location	Population	Methods	Outcomes	Study limitations
Boisier, et al. [43]	Niger 2002	6055 participants in DHS; no sample size provided for ANC.	Comparison of ANC surveillance and population survey estimates of HIV prevalence .	• ANC of 2.8% >DHS national HIV prevalence of 0.87 (95% CI: 0.5-1.3%).	• Non-response bias could affect validity of comparison.
Grassly, et al. [40]	11 communities with estimates ranging from 1995 through 2003	ANC attendees and adult men and women in surrounding communities; Sample sizes varied by study and country.	Mathematical model to compare estimates of adult prevalence in community studies compared with prevalence estimates in ANCs in the same community around the same time.	• ANC sample slightly underestimates community prevalence among adult males and females but difference is not significant.	• Comparisons were at community not national level where other biases can be introduced. • Variance around the ANC estimate was high, suggesting that experience across communities may differ. • Comparisons were made from survey periods up to 1 year apart.

Supplemental Table 2.1 Bias in ANC estimates relative to population surveys

Author	Location	Population	Methods	Outcomes	Study limitations
Fylkenes, [48] (Note: data included in Grassley study)	Chelston, urban Lusaka and Kapiri Mposhi, 1994-1996	4195 population survey participants aged 15 and above, ANC attendees aged 15-39 years.	Comparison of unadjusted estimates of HIV prevalence in the population survey and ANC surveillance in urban and rural areas.	• ANC<population prevalence • ANC urban estimate of 24.4% (95% CI: 20.9-28.0)<overall HIV prevalence of 26.0% (95% CI: 23.4%-28.6%) but difference was not significant. • ANC rural estimate of 12.5% (95% CI: 9.3%-15.6%)<16.4% (95% CI: 12.1%-20.6%). • ANC prevalence for 15-19 year olds>prevalence in the population. • Women with higher levels of education, which was associated with lower HIV prevalence, were under-represented in the ANC sample.	• Differences in tests (saliva based in population survey, serum based in ANC) and no validation possible. • Non-consent among males was high relative to women in the population survey (71.3% versus 92%) mostly due to men being away from the home. • Rural survey occurred more than one year later than the ANC surveillance.

Supplemental Table 2.2 Bias in ANC estimates relative to female population prevalence

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Rice, et al. [269]	Rural sub-district of Hlabisa; six government clinics within the district, 2005	1111 ANC and 14476 general female population, of which 1444 were estimated to have been pregnant and attended a local ANC.	Comparison of estimates, standardized by age and location (e.g., clinic for ANC-based estimates and residence for population–based estimates).	• ANC prevalence of 37.7%>female population prevalence of 25.2%. • ANC prevalence of 37.7%>prevalence of 23.7% among pregnant women local to the catchment area. • Population survey data may be biased downward by unrepresentative testing by HIV status, residence and age. • ANC estimates are biased upwards due to selection bias in terms of age, sexual debut and contraceptive use.	• Contraceptive use was high and fertility in this rural population was low, thus results may not be generalizable to other countries in SSA.

Supplemental Table 2.2 Bias in ANC estimates relative to female population prevalence

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Gregson, et al. [113]	Less developed countries with high fertility rates	Simulated population of women of childbearing age and pregnant women assuming different fertility rates for HIV infected and uninfected women.	Mathematical modelling of age-specific fertility patterns in HIV infected and uninfected women and the impact on HIV prevalence estimates from pregnant women and all women of reproductive age.	• ANC>female prevalence for those <20 years. • ANC<female prevalence for those 20+ years. • Lower prevalence in older women will outweigh bias in younger women, thus ANC<female population prevalence. • Age standardization reduces ANC estimates further as it gives more weight to older ages, so unstandardized estimates are preferable. • Bias in ANC estimates increases as prevalence increases up to 50% in the female population. • ANC>female prevalence if condom use is widespread in less developed countries. • If female prevalence falls, due to successful condom promotion ANC could fail to capture the full extent of this decline.	• Very limited data on methods for constructing the model • Condom use levels are unlikely to reach those explored in the general population. • Model results do not consider influence of other contraceptive methods beside condoms or changes in sexual behaviour.

Supplemental Table 2.2 Bias in ANC estimates relative to female population prevalence

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Zaba, et al. [47]; Lewis, et al. [114] ;	Review of 19 community-based studies in sub-Saharan Africa, of which 6 were originally reviewed by Zaba and colleagues	Pregnant women and the general female population.	Fertility rate ratio for HIV-positive vs. HIV-negative women is calculated. The relative odds of being infected for pregnant women compared with the general female population provides a measure of difference between ANC and female population prevalence estimates.	• HIV-infected women have between 25 and 40% lower fertility than HIV-uninfected women, except for those at the youngest ages where selection for early sexual activity results in higher fertility for the HIV infected (from Zaba). • ANC estimates of HIV prevalence <female population prevalence in high fertility low contracepting areas.	• Assumes that fertility in HIV negative women is unaffected by HIV in the population. • Does not provide a direct measure of sub-fertility or infertility due to STIs other than HIV.
Crampin, et al. [53]	Karonga District ANC surveillance in 4 clinics and community-based survey, 1999-2000	342 women in the community and 3013 ANC attendees aged 15-49 years.	Logistic regression to identify demographic and fertility-related factors associated with differences in HIV prevalence among ANC attendees and females in the community.	• Unadjusted ANC prevalence of 9.2% in 1999-2001<age-location adjusted female prevalence of 13.9%. • Differences in distribution of ANC and general female population by age, area, marriage and migration (over the last 5 years) and associations with HIV infection explained differentials. Fertility differences found, but adjustments for parity and birth interval did not explain differences.	• Estimates of community prevalence may be biased by non-response. • Patterns of HIV infection across clinics and within the district varied greatly, thus aggregate findings may not be representative of any one smaller geographic area.

Supplemental Table 2.2 Bias in ANC estimates relative to female population prevalence

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Gregson, et al. [55]	Manicaland, Zimbabwe, 1998-2000	1215 ANC attendees in the surveillance round; 5138 females in the surrounding population, of which 576 were recently pregnant .	Comparison of ANC surveillance and population estimates using a risk ratio.	• Prevalence in recently pregnant women of 25.7% = all women 25.5% due to contraceptive use and delays in sexual activity. • ANC prevalence of 21.2%<prevalence in all women of 25.5% due to more rural attendees where prevalence is lower. • More educated ANC attendees have higher risk of HIV than female population, where HIV risk is highest among less educated young women.	• Catchment areas for comparison are difficult to validate. Information on residence was not able to be collected, thus it was not possible to verify rural estimates.
Glynn, et al. [51]	ANC and general population surveys in Yaoundé, Cameroon, Kisumu, Kenya, and Ndola, Zambia in 1997-1998	Sample sizes varied by study and setting.	Comparison of ANC and general population HIV prevalence estimates to identify factors associated with differences in HIV prevalence in the two groups (i.e., community and ANC) using logistic regression.	• ANC<female population in Cameroon and Ndola. • Factors explaining differences varied by site - Cameroon: age, marital status, contraception, no previous children; Kisumu: no previous children only; Ndola: age, marital status, contraception, marriage, no previous children. • Variation in factors explaining differences in prevalence makes it difficult to propose standard adjustment methods.	• Community survey data may be biased by differential non-response. • The prevalence of STIs other than syphilis (which was explored but not found to be important) could explain differences in HIV prevalence between the two groups.

Supplemental Table 2.2 Bias in ANC estimates relative to female population prevalence

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Glynn, et al. [112]	ANC surveillance in Yaoundé, Cameroon, Kisumu, Kenya, and Ndola, Zambia in 1998	Women attending ANC clinics in the three cities.	Cox regression to explore influence of HIV on time to first birth and birth interval in order to determine sub-fertility in HIV infected women.	• Birth interval for HIV positive women>HIV negative women, between 16% and 26% lower risk of pregnancy. • Interval between sexual debut and first birth in HIV infected women>interval in uninfected women (except in Ndola after adjusting for age and other socio-demographic factors. • ANC< female prevalence due to HIV-related sub-fertility. Timing of ANC visits may influence differences if HIV-infected women miscarry earlier or later in the pregnancy.	• Measures of STIs other than syphilis could not be taken into account as a source of non-HIV-related sub-fertility.
Fontanet, et al. [111]	Addis Ababa, Ethiopia, 1994 and 1996	1145 pregnant women at ANC clinics and 671 women in the catchment area.	Comparison of ANC surveillance estimates with those in the female population.	• ANC prevalence of 17.8%>5.2% prevalence among women in the surrounding area.	• Comparisons were made two years apart as the epidemic in Ethiopia was growing.
Changalucha, et al. [52]	12 rural communities in the Mwanza Region	2265 ANC attendees and 5676 women aged 15-44 years, 1991-1992	Comparison of unadjusted ANC and female population HIV prevalence.	• ANC prevalence of 3.6%<female prevalence in the population of 4.7% • ANC prevalence<female population prevalence in all age groups except those aged 15-19 years.	• Not able to analyse to what extent women from outside clinic catchment areas were attending ANCs.

Supplemental Table 2.3 Bias in ANC trends relative to female population trends

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Garnett, et al. [115]	Indicative of a generalized HIV epidemic in SSA	Pregnant women and women of all reproductive ages.	Sex, age, and sexual activity specific mathematical model of HIV transmission used to explore bias in ANC trends due to 1) low fertility from STIs other than HIV; 2) HIV-related sub-fertility unrelated to the stage of infection, and 3) HIV-related sub-fertility related to the stage of infection. Fertility rates vary by age, sexual activity, and HIV status. Trends are compared from time 0 to 30 years.	• ↑ANC trends >↑POP trends as the average age of HIV infected women increases until peak fertility as the epidemic evolves. • ↑ANC trends <↑POP trends as sub-fertility due to HIV increases as the epidemic evolves. • ↑ANC <↑POP due to morbidity from other STIs, but this quickly resolves. • ANC trends are a reasonably good measure of prevalence trends among females. • Bias in age-specific fertility levels over time is static after five years.	• Study assumes HIV prevalence levels remain high. • Does not quantify the level of bias in trends that suggest that ANC data reasonable measure of the underlying population HIV prevalence trend among female.

Supplemental Table 2.3 Bias in ANC trends relative to female population trends

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Zaba, et al. [117]	Indicative of a generalized HIV epidemic in SSA	Young pregnant women and young women aged 15 to 24 years.	Mathematical cohort model used to explore bias in ANC trends due to 1) reduced transmission due to changes in sexual activity; 2) delays in sexual debut; and 3) reductions due to 1 and 2. Trends are compared from time 0 to 25 years.	• Declines in transmission (from 5% to 2% incidence over 3 years) alone due to risk reduction behaviour (e.g., condom increase) resulted in stable bias throughout the 25 years (due to limited sub-fertility and mortality in young people). • Delays in sexual debut (rise in median age at first sex from 15 to 20 years over 3 years) alone or in addition to declines in transmission led ANC data to lag behind, then to underestimate declines, then to overestimate declines.	• Scenarios for increasing age of sexual debut by five years in the span of 3 years likely overstate the actual changes that would be observed in most countries.

Supplemental Table 2.3 Bias in ANC trends relative to female population trends

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Hallett, et al. [27] – describing modelling results only of bias in ANC estimates	Countries with generalised epidemics	Pregnant women and women of all reproductive ages.	Deterministic sex, age, and sexual activity specific mathematical model of HIV transmission.	• Initial exclusion of HIV infected women due to sub-fertility will lead ANC declines to overstate those in the population. Bias will stabilize rapidly once average time since infection stabilizes. • ANC prevalence increases and decreases will be most extreme since high risk women are most at risk of HIV and pregnancy and these women will be most likely to suffer from HIV-related sub-fertility (and therefore excluded). If not replaced in the population, ANC prevalence will fall more rapidly.	• Model assumes that fertility rates are constant over time.
Gregson, et al. [113]	Less developed and more developed countries	Pregnant women and all women.	Application of Bongaarts' proximate determinants model to explore fertility levels in HIV infected and uninfected women and HIV prevalence in both groups based on a range of differences in fertility levels.	• ANC data will understate decline in population prevalence in the case of successful condom promotion campaigns because only women at high risk of HIV (i.e., non-condom users) will become pregnant.	• Model assumes only condom use and no other contraceptives. • Risk associated with condom use is assumed to be low in the population.

Supplemental Table 2.3 Bias in ANC trends relative to female population trends

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Michelo, et al. [116]	Lusaka, Zambia. Population survey: 1995, 1999, and 2003; ANC surveillance: 1994, 1998 and 2002.	Pregnant women and all women.	Comparison of prevalence in ANC and population using linear regression.	• ANC prevalence declined from 20.0% (25.0%-19.9%) in the youngest women (aged 15-24 years). Prevalence declined in the general population by 49% (15-24 years) and by 44% in women only (15-24 years). • Declines in prevalence in the ANC understated declined in population prevalence trends due to changes in fertility and education patterns.	• Statistical tests do not allow for direct comparison of trends.

Supplemental Table 2.3 Bias in ANC trends relative to female population trends

Author	Location/Year	Population	Methods	Outcomes	Study limitations
Kwesibago, et al. [50]	Kagera, Tanzania, Buboka district. Population study 1987, 1993 and 1996; ANC surveillance in 1990, 1993 and 1996	Pregnant women and all women.	Comparison of age-adjusted prevalence in ANC and population using linear regression.	• ANC prevalence declined from 22.4% (20.6%-25.2%) in 1990 to 16.1% (95% CI: 15.9-18.8% in 1993 and 13.7% (95% CI: 11.8-14.3%) in 1996. Population prevalence declined from 29.1% (95% CI: 24.4%-34.6%) in 1987 to 18.7% (95% CI: 24.4%-34.6%) in 1993 to 14.9% (95% CCI: 12.0%-17.1%) in 1996. • Trends in prevalence were similar and ANC data can be used to monitor population HIV prevalence trends. • ANC uptake was above 90% for the country and well above in the district.	• Study occurred at a time when declines in prevalence were likely due to mortality and natural dynamics of the epidemic rather than behaviour change, thus comparability may be different if declines were due to behaviour change. • Refusal rates in population survey differed over time from 86% in 1987, 66% in 1993 and 74% in 1996. • Statistical tests do not allow for direct comparison of trends.
Gouws [21]	Zimbabwe (2001/2002 and 2006), Zambia (2001/2002 and 2007), South Africa (2002 to 2005)	Pregnant women and all women aged 15 to 24 years.	Comparison of HIV prevalence in repeated national surveys and among ANC attendees aged 15 to 24 years.	• Prevalence declines were consistent between the two data sets for Zimbabwe and Zambia. • In South Africa, HIV prevalence among young pregnant women was stable but observed to increase in the female population.	• Time periods for comparisons were different. • Statistical tests do not allow for direct comparison of trends.

Supplemental Table 2.4 Proposed methods and applications of methods for adjusting bias in ANC estimates due to HIV-related sub-fertility

Author	Location/Year	Population	Methods/Application	Outcome	Limitations
Lessner [178]	New York, United States, 1988	HIV positive women identified through Newborn HIV Seroprevalence Study.	Proposed method: Adjustment of number of women infected through age standardization to obtain estimate of total number of HIV infected women.	• Estimates number of infected=23,430 women aged 15-44 years; no estimate of original number of infections reported provide.	• Assumes HIV infected and uninfected women have the same fertility rates, thus will underestimate the total number of HIV infected women due to HIV-related sub-fertility. • No validation of estimates.
Nicoll, et al. [179]	England and Wales, 1994	Women with known HIV infections reported through an existing study (n=507).	Proposed method: ANC estimates are adjusted for differences between live birth rates and termination rates in women known to be HIV infected and those in the general population (called the relative inclusion ratio or RIR).	• Live birth rates among HIV infected and uninfected women in London were similar. Outside London, an RIR of 0.80 (CI: 0.71-0.89) indicates prevalence among pregnant women would underestimate prevalence in the female population.	• Requires knowing live birth rates and termination rates in HIV infected women. • RIR will be diluted if prevalence in the female population is high.

Supplemental Table 2.4 Proposed methods and applications of methods for adjusting bias in ANC estimates due to HIV-related sub-fertility

Author	Location/Year	Population	Methods/Application	Outcome	Limitations
Zaba, et al. [42]	Multi-country study (Tanzania, Uganda, Zimbabwe)	ANC attendees in Kisesa, Tanzania and Masaka, Uganda (n=5373), and in Manicaland, Zimbabwe (n=5129), Khutson, South Africa.	Proposed method: Estimates of ANC-based prevalence are adjusted for relative risks for infertility and sub-fertility in low (<20%) and high contraception (20%) areas and estimates are then adjusted to the overall distribution of these groups in the population using DHS data.	• Uganda and Tanzania: HIV prevalence in pregnant women: 7.7% adjusted to 10.3%. Similar to community-based female estimates. • Low contraception adjustment factors: 80% of prevalence in primigravida childless women; 150% of multigravida mother. • High contraception: 60% factor in primigravida childless women; 110% in multigravida mother.	• Requires the collection of birth interval data which is not routinely done, assuming that adjustments for sub-fertility as more important than infertility. • Does not take into account differences in ANC uptake by HIV infected and uninfected women. • Assumes the effect of HIV on fertility patterns has stabilized. • No quantification of acceptable differences in adjusted ANC surveillance and population survey estimates among females is provided.
Fabiani, et al. [57]	Gulu district ANC clinic in Northern Uganda, 1993-1997	8555 ANC attendees aged 15 to 39 years.	Proposed method: Age-specific ANC prevalence estimates adjusted for differences in fertility risk between HIV infected and uninfected women, and then the overall prevalence estimate is standardized to the general female population age structure.	• ANC estimates were 26.0% in 1993 and 16.1% in 1997. • Estimated prevalence in the population using the adjustment method was 25.4% in 1993-1994 to 17.8% in 1996-1997, indicating a slightly greater decline in prevalence among ANC surveillance participants.	• No data were available to validate female population estimates. • Assumes relative risks of fertility are constant over time and not changing (due to increases in age of sexual debut, condom use, etc.) in the calculation of female population prevalence trends. • May overstate population prevalence when applied to ANC surveillance data because some pregnant will abort before giving birth.

Supplemental Table 2.4 Proposed methods and applications of methods for adjusting bias in ANC estimates due to HIV-related sub-fertility

Author	Location/Year	Population	Methods/Application	Outcome	Limitations
Changalucha, et al. [52]	Rural Mwanza Tanzania, 1991-1992	2265 ANC attendees and 5675 women aged 15-44 years.	Application: Zaba's parity-based method.	• HIV prevalence among ANC attendees unadjusted was 3.6% compared with 4.7% in population (p-value-0.025). Adjusted prevalence of ANC data to account for fertility differences was 4.6% (p-value=0.95).	• Validation was done early on in the epidemic and the authors' question whether the method might work as the epidemic evolved.
Gregson, et al. [55]	Manicaland, Zimbabwe, 1998-2000	1215 local ANC attendees and 5138 women in population-based survey.	Application: Estimates of ANC prevalence were adjusted and compared to prevalence among women in the general population using a method proposed by Zaba, et al.	• HIV prevalence among women reporting local ANC attendance of 27.0% adjusted to 22.6% with adjustment for birth interval and 23.5% without adjustment for birth interval, which were lower than population survey estimates (25.5%). • Application to ANC surveillance data reduced HIV prevalence to 20.8% to 19.2%.	• Birth interval information in ANC surveillance was missing in 6% of the population. • No quantification of acceptable differences in adjusted ANC surveillance and population survey estimates among females is provided. Prevalence was still only two thirds as high as prevalence in the surrounding female population. • Non-response and refusals in both the population survey and the ANC surveillance data may have introduced other biases in estimates.

Supplemental Table 2.4 Proposed methods and applications of methods for adjusting bias in ANC estimates due to HIV-related sub-fertility

Author	Location/Year	Population	Methods/Application	Outcome	Limitations
Fabiani, et al. [180]	Multi-country study (Uganda, Tanzania, Zambia), data from mid-1990s	ANC and general female population; sample sizes varied.	Application/validation: HIV prevalence estimates among ANC attendees were adjusted using methods by Fabiani and Zaba.	• Estimates of prevalence using the Fabiani method were more accurate than estimates from the Zaba method in Lusaka, Zambia in 1994 and 1998. • Estimates using Zaba's methods were better in rural Mwanza and Ndola. • The Zaba method could not be applied to 4 sites due to lack of information on HIV prevalence by parity among ANC attendees.	• Adjustment method by Fabiani requires data on differences in fertility risks either from the population of interest or in other geographic areas (assuming similar relative risks can be applied). • Adjustment method by Zaba requires more detailed data on parity and birth intervals from ANC surveillance attendees and more complicated analyses to obtain estimates that take into account sub-fertility and infertility. • Validation was limited to settings where HIV prevalence was relatively high and contraceptive use was low.
Crampin, et al. [53]	Karonga District, Malawi, 1998-2001	ANC and general female population aged 15 to 49 years.	Application: Zaba method.	• ANC prevalence was estimated to be 9.2% (95% CI: 9.1%-10.3%), adjusted prevalence was 15.0% compared with 13.9% estimated from the community.	• Community estimates may be biased by non-response and missing mobile populations at higher risk of HIV.

Supplemental Table 2.4 Proposed methods and applications of methods for adjusting bias in ANC estimates due to HIV-related sub-fertility

Author	Location/Year	Population	Methods/Application	Outcome	Limitations
Rice, et al. [269]	Rural sub-district of Hlabisa; six government clinics within the district, 2005	1111 ANC and 14476 general female population, of which 1444 were estimated to have been pregnant and attended a local ANC.	Application: Comparison of crude and age-location standardized estimates of ANC surveillance data with population prevalence data. Crude ratios of HIV prevalence among pregnant women and the population are calculated and then compared to Zaba's proposed standard.	• ANC estimates were standardized by age and location. Adjustment factors were calculated to be 50% in primigravida to childless women and 70% in multi-gravida women.	• Population survey estimates were skewed by non-participation bias, which could in turn affect the accuracy of the adjustment factor as well as other standardized comparisons.

Supplemental Table 2.5 Associations between accepting HIV testing and HIV serostatus in PMTCT programmes

Author	Location/ Year	Population/ sample size	Methods	Research questions/outcomes	Study limitations
Fabiani, et al. [98]	Lacor Hospital, Gulu District, Northern Uganda (2001-2003)	*ANC surveillance*:* 3,580 *PMTCT:* 14,040; 13% not offered testing; 48% accepted; 39% refused.	Comparison of age-standardized HIV prevalence estimates in ANC and 'Opt-in' PMTCT attendees; Log binomial regression to identify factors associated with testing and testing positive.	• Is acceptance of HIV testing associated with HIV status? Yes, but weakly. • Are PMTCT and ANC estimates similar? Yes, when age-standardized or age-specific. • Should PMTCT data be used for surveillance purposes? Yes, in north Uganda.	• No method for comparing estimates. • Results are specific to one rural clinic; generalizability beyond unknown. • Evaluation of opt-in PMTCT services with low-uptake may introduce different biases than current recommended opt-out testing strategies. • No recommendation on what level of bias is acceptable.
Mpairwe, et al. [91]	Entebbe General Hospital, Wakiso district, Uganda (May 2002 – April 2003)	*ANC surveillance:* 833 *PMTCT:* 4,867; *25*% not offered testing; 54% accepted testing; 20% refused testing.	Comparison of HIV prevalence estimates in ANC and 'Opt-in PMTCT attendees using chi^2-test; Logistic regression to identify factors associated with testing and testing positive.	• Is accepting HIV testing associated with HIV status? Yes. • Are PMTCT and ANC estimates similar? Yes, when uptake is >70% or annual. • Should PMTCT data be used for surveillance purposes? Not useful when services are new or uptake is low (<70%).	• Results are specific to one urban clinic; generalizability unknown. • Strategies for implementing PMTCT programmes have changed. • HIV prevalence estimates are compared for those accepting vs. refusing testing, not vs. all attendees; Results will be more extreme.

Supplemental Table 2.5 Associations between accepting HIV testing and HIV serostatus in PMTCT programmes

Pignatelli, et al. [192]	St. Camille Medical Centre, Ouagadougou, Burkina Faso (May 2002-April 2004)	*ANC surveillance:* no sample size stated *PMTCT:* 6,639; 18% accepted; 82% refused.	Logistic regression to identify factors associated with 'opt-in' testing and testing positive.	• Is acceptance of HIV testing associated with HIV status? Yes, but women who test represent a select and motivated population. • Are PMTCT and ANC estimates similar? No.	• PMTCT and ANC estimates were from different times, thus not comparable. • No recommendation is made on what level of bias is acceptable.

Supplemental Table 2.6 Studies directly comparing PMTCT programme and ANC surveillance estimates

Author	Location/ Year	Population/ sample size	Methods	Research questions/outcomes	Study limitations
Seguy, et al. [89]	6 sites where ANC surveillance and PMTCT activities overlapped in Kenya (2003)	*ANC surveillance:* 1,852 *PMTCT:* 2,239; Overall uptake: 56%.	Comparison of estimates was not done as opt-in PMTCT and ANC surveillance groups were not independent.	• Are PMTCT and ANC estimates similar? Overall, yes, and even when uptake is <60%. ANC surveillance estimates were lower in 5 of 6 sites, however. • PMTCT data should not be used due to clinic-level disparities in estimates and data quality problems.	• Opt-out testing still resulted in low uptake, which could lead to greater levels of bias. • Recommendation made to collect five years of PMTCT data before evaluating usefulness of estimates. • No recommendation made on what level or temporal change in bias is acceptable.
Macauley, et al. [97]	Unknown number of PMTCT and surveillance sites in Cameroon's 10 provinces (2003)	*ANC surveillance:* 6,745 *PMTCT:* 69% (42,731 attendees).	Descriptive statistics presented.	• Are PMTCT and ANC estimates similar? Overall, yes, and in 9 of 10 provinces. • PMTCT data can be used to estimates HIV prevalence in place of ANC surveillance data.	• No additional data available on number of clinics participating, uptake levels, and magnitude of difference or similarity of estimates by province (personal communication with co-author). • No information on how estimates were compared/determined similar.

Supplemental Table 2.6 Studies directly comparing PMTCT programme and ANC surveillance estimates

Author	Location/ Year	Population/ sample size	Methods	Research questions/outcomes	Study limitations
Finkbeiner, et al. [94]	7 sites where ANC surveillance and PMTCT activities overlapped in Uganda (2003)	*ANC surveillance:* 11,946 *PMTCT:* No information on uptake 18,191 accepted.	No information on type of PMTCT provided, descriptive statistics presented.	• Are PMTCT and ANC estimates similar? Overall, yes, but estimates in 2 of 7 clinics showed significant disparities. • PMTCT data would be difficult to use because of clinic-level differences and data quality problems	• No recommendation made on what level of bias would be acceptable. • No information available on testing acceptance levels.
Gonese, et al. [95]	19 sites where ANC surveillance and PMTCT activities overlapped in Zimbabwe (2004);	*ANC surveillance:* sample size not stated. *PMTCT:* median clinic uptake 42%.	Opt-in testing, comparisons made without access to age of PMTCT acceptors. Descriptive presentation of PMTCT and ANC surveillance estimates.	• Are PMTCT and ANC estimates similar? Yes, but large clinic-level disparities in estimates. • PMTCT data cannot be used because of low uptake, clinic-level disparities, and aggregate data.	• PMTCT data were restricted to aggregate reports at the national level, thus did not include age and would not be useful in monitoring trends by age groups. • No recommendation made on what level of bias would be acceptable.

Supplemental Table 2.6 Studies directly comparing PMTCT programme and ANC surveillance estimates

Author	Location/ Year	Population/ sample size	Methods	Research questions/outcomes	Study limitations
Seipone, et al. [96]	48 of 270 sites (all with dual ANC surveillance and PMTCT activities) in Botswana	*ANC surveillance:* 2005: 2472; 2006: 2714; 2007: 2542 *PMTCT:* 2005: 2803; 2006: 2950; 2007: 2943; Uptake: 95%.	Opt-out testing; chi^2 test for differences in PMTCT and ANC surveillance estimates.	• Are PMTCT and ANC estimates similar? Yes, overall and by rural, urban distribution. Similar among 5 year age groups, particularly at youngest ages. • Can be used based on similarity in estimates. Improvements in data quality needed.	• No recommendation made on what level of bias would be acceptable when using PMTCT data for surveillance purposes.
Fabiani, et al. [93]	Lacor Hospital, Gulu District, Northern Uganda (2004-2005)	*ANC surveillance:* 1,059 in 2004; 1,166 in 2005 *Opt-in PMTCT for 2004:* 1,701; 49.9% (849/1,701); 275 not offered; 849 accepted; 577 refused. *Opt-in PMTCT:* 2005: Uptake: 54% (1,255/1,892); 388 not offered; 1,255 accepted; 249 refused.	Opt-in testing, Age-specific logistic regression models used to estimate risk coefficients of being infected for 10 predictor variables among PMTCT acceptors.	• Are PMTCT and ANC estimates similar? Age adjusted estimates not similar; Non-participation bias must be adjusted for. • Adjusted data useful in northern Uganda.	• No recommendation made on what level of bias would be acceptable when using PMTCT data. • Adjustment method for PMTCT estimate to account for refusers has not been validated beyond a single clinic.

Appendix B: Model parameters for Chapter 4

Female birth cohorts

Year	Botswana female population	Côte d'Ivoire female population	Zimbabwe female population
1955-1960	11155	80995	81830
1960-1965	12610	98940	96530
1965-1970	14550	121735	112210
1970-1975	16490	149380	132790
1975-1980	19400	183330	156800
1980-1985	22310	213885	177870
1985-1990	22795	239590	187180
1990-1995	22795	266750	193060
1995-2000	23280	294395	189630
2000-2005	22310	328345	184730
2005-2010	22795	347745	184730
2010-2015	23280	363750	191100
2015-2020	23280	372965	200900
2020-2025	22795	379270	198450
2025-2030	22310	385090	189140
2030-2035	21825	389455	184240

Female birth cohort size for Botswana, Côte d'Ivoire and Zimbabwe taken from UN POP Division [224].

HIV negative age-specific fertility rates (per 1000 women)

Age-group	Botswana	Côte d'Ivoire	Manicaland, Zimbabwe (1985-1988)	Manicaland, Zimbabwe (1998-2005)
15-19	125	151	114	98
20-24	212	245	289	220
25-29	202	240	276	171
30-34	191	227	251	140
35-39	148	172	184	80
40-44	83	82	93	29
45-49	38	26	40	6

Age specific fertility rates in Botswana from the 1989 Botswana Family Health Survey II [236], from the 1995 DHS in Côte d'Ivoire [237], and from the Manicaland DHS (1985-1988) [238] and the Manicaland Cohort Data (1998-2005), which was published previously [232].

Fertility ratio for HIV infected versus non infected women:

Time since infection	Fertility ratio (HIV+/HIV-)
≤4 years	0.66
>4years	0.40

Ratio of fertility for HIV-infected women relative to uninfected women by years since infection estimated from rural Uganda cohort data [158]

Age-specific HIV incidence for women of reproductive age

Age-group	Botswana	Côte d'Ivoire	Manicaland, Zimbabwe
15-19 years	1.10	0.49	1.34
20-24 years	1.35	0.80	1.43
25-29 years	1.62	1.39	1.87
30-34 years	1.36	0.99	0.65
35-39 years	0.81	0.46	0.73
40-44 years	0.53	1.11	0.46
45-49 years	0.25	1.76	0.54

Age-specific incidence rates for Botswana are based on national Zimbabwe population survey data [233, 234]. Côte d'Ivoire data were provided by Hallett based on previously methods published [75]. For rural Zimbabwe, direct measurement was made using previously published data from the Manicaland cohort [235].

Annual HIV Incidence (per 100 persons per year)

Year	Botswana (female)	Côte d'Ivoire (female)	Rural Zimbabwe (men and women)
1980	0.03	0.02	0.03
1981	0.04	0.03	0.05
1982	0.06	0.04	0.09
1983	0.10	0.06	0.15
1984	0.15	0.09	0.24
1985	0.24	0.14	0.40
1986	0.37	0.20	0.64
1987	0.57	0.29	1.03
1988	0.86	0.41	1.61
1999	1.29	0.56	2.40
1990	1.95	1.19	3.39
1991	2.76	1.50	4.39
1992	3.72	1.70	5.13
1993	4.71	1.69	5.37
1994	5.52	1.51	5.00
1995	5.96	1.26	4.28
1996	5.95	1.02	3.49
1997	5.58	0.84	2.82
1998	5.03	0.70	2.33
1999	4.44	0.60	1.99
2000	3.91	0.52	1.77
2001	3.51	0.45	1.62
2002	3.19	0.40	1.52
2003	2.86	0.30	1.45
2004	2.54	0.25	1.39
2005	2.32	0.25	1.33
2006	2.18	0.22	1.28
2007	2.06	0.19	1.23
2008	1.92	0.13	1.19
2009	1.82	0.13	1.13

Temporal trend in incidence is estimated using Spectrum and provided by UNAIDS for illustrative purposes only [Personal communication: Mary Mahy, January 2010]

Survival rates for HIV-negative individuals

Adult females: 5+weibull(shape: 7, scale: 61.8)

Survival rates for HIV-negative individuals taken from a previous publication by Hallett [75].

Survival with HIV at time of infection (no ART)

Age at infection	Weibull	Shape (kappa)
15-19	16	2
20-24	15.4	2
25-29	14.1	2
30-34	12.1	2
35-39	11.0	2
40-44	10.1	2
45-49	7.9	2

Survival times for HIV infected adults, stratified by age at infection, were taken to be Weibull distributed and based on estimates from African observational cohort studies [270].

Rate of disease progression

Disease progression	Average time in years
AIDS to death	**1**
CD4=200 to AIDS	**2**
Time to death on	**10**

CD4 counts for women reached 200 cells/mm3, approximately 3 years (exponentially distributed) before AIDS [271]. Time to death on treatment was taken from cohort estimates in SSA [25, 143].

Appendix C: Published manuscripts

Marsh et al. Journal of the International AIDS Society 2011, 14:27
http://www.jiasociety.org/content/14/1/27

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH Open Access

Monitoring trends in HIV prevalence among young people, aged 15 to 24 years, in Manicaland, Zimbabwe

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Abstract

Background: In June 2001, the United Nations General Assembly Special Session (UNGASS) set a target of reducing HIV prevalence among young women and men, aged 15 to 24 years, by 25% in the worst-affected countries by 2005, and by 25% globally by 2010. We assessed progress toward this target in Manicaland, Zimbabwe, using repeated household-based population serosurvey data. We also validated the representativeness of surveillance data from young pregnant women, aged 15 to 24 years, attending antenatal care (ANC) clinics, which UNAIDS recommends for monitoring population HIV prevalence trends in this age group. Changes in socio-demographic characteristics and reported sexual behaviour are investigated.

Methods: Progress towards the UNGASS target was measured by calculating the proportional change in HIV prevalence among youth and young ANC attendees over three survey periods (round 1: 1998-2000; round 2: 2001-2003; and round 3: 2003-2005). The Z-score test was used to compare differences in trends between the two data sources. Characteristics of participants and trends in sexual risk behaviour were analyzed using Student's and two-tailed Z-score tests.

Results: HIV prevalence among youth in the general population declined by 50.7% (from 12.2% to 6.0%) from round 1 to 3. Intermediary trends showed a large decline from round 1 to 2 of 60.9% (from 12.2% to 4.8%), offset by an increase from round 2 to 3 of 26.0% (from 4.8% to 6.0%). Among young ANC attendees, the proportional decline in prevalence of 43.5% (from 17.9% to 10.1%) was similar to that in the population (test for differences in trend: p value = 0.488) although ANC data significantly underestimated the population prevalence decline from round 1 to 2 (test for difference in trend: p value = 0.003) and underestimated the increase from round 2 to 3 (test for difference in trend: p value = 0.012). Reductions in risk behaviour between rounds 1 and 2 may have been responsible for general population prevalence declines.

Conclusions: In Manicaland, Zimbabwe, the 2005 UNGASS target to reduce HIV prevalence by 25% was achieved. However, most prevention gains occurred before 2003. ANC surveillance trends overall were an adequate indicator of trends in the population, although lags were observed. Behaviour data and socio-demographic characteristics of participants are needed to interpret ANC trends.

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Background

In June 2001, the United Nations General Assembly Special Session (UNGASS) set a target of reducing HIV prevalence among youth, aged 15 to 24 years, by 25% in the worst-affected countries by 2005, and by 25% globally by 2010 [1]. Recently infected youth experience low HIV-related mortality [2,3]. Accordingly, changes in prevalence over time among young people should signal underlying changes in incidence. Changes in incidence are useful when gauging the effectiveness of prevention and treatment efforts [4,5].

In countries worst affected by HIV, monitoring HIV prevalence trends in the general population is a challenge. Repeated national population surveys, which can be used to construct trends in prevalence or to derive changes in estimates of age-specific incidence over time, are often too costly and complex to conduct frequently [6]. Laboratory assays to detect recent infections have so far proven unreliable in sub-Saharan Africa [7,8]. As a result, the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommends using data from surveillance among pregnant women, also aged 15 to 24 years, attending antenatal care (ANC) clinics, to monitor progress toward the UNGASS target [9]. ANC surveillance data, which are available on an annual or biannual basis in most sub-Saharan Africa countries, have been found to be reasonably representative of general population prevalence, although they typically overestimate the number of infections in young people due to the selection of young women at higher risk of pregnancy and HIV infection [10-14].

Implicit in the UNAIDS recommendation is an assumption that ANC prevalence trends will mirror those among male and female youth in the general population. However, changes in sexual behaviour could cause ANC estimates to misrepresent general population trends. For example, prevention interventions promoting delays in initiating sex and/or consistent condom use could lead to general population HIV prevalence declines from reduced risk behaviour, even as prevalence at ANC clinics remains steady since, by definition, attendees are having unprotected sex. Conversely, if interventions, such as consistent condom use following HIV testing, successfully target infected individuals, a sudden drop in the ANC estimate of HIV prevalence could be observed (due to a fall in pregnancy rates in HIV-positive women) that would not be representative of the general population.

Beyond these sources of bias, ANC surveillance data are also subject to other biases that could change with time, including: clinics being sampled for convenience and that may change with time; ANC attendance varying with regard to availability and uptake; and HIV-infected women having different levels of contraceptive use and lower fertility rates [10,14-19]. To address these potential biases in ANC data, UNAIDS recommends excluding new clinics from analyses of trends, using population survey data to validate ANC estimates wherever possible, and analyzing sexual behaviour data and characteristics of the testing populations to provide context to observed changes in prevalence [6,9].

In this paper, we make use of an open-cohort, population-based household survey in Manicaland, Zimbabwe, conducted at three time intervals from 1998 to 2005 to assess directly whether the UNGASS indicator for prevalence reductions of 25% by 2005 was met among youth aged 15 to 24 years. As a secondary analysis, we also determine to what extent HIV prevalence trends in the general population mirrored those among ANC attendees, as many countries, including Zimbabwe as a whole, will not have access to repeated population survey data spanning the period covered by the UNGASS target. To validate the ANC surveillance data, we compare the proportional changes in HIV prevalence over the three rounds among pregnant women attending ANC clinics with those from the three parallel rounds of the general population survey in the same geographic areas.

Finally, we explore changes in participation, HIV prevalence by socio-demographic characteristics, such as educational status, and trends in sexual behaviour that could explain differences in the patterns of HIV estimates observed between the two datasets over time. Previous assessments in this population have shown substantial declines in population and ANC-derived HIV prevalence estimates for men and women aged 15 to 49 years in this mature epidemic, primarily linked to behaviour change [20,21].

Methods

Study population and data collection procedures

Data for the open-cohort, household-based population survey were collected in 12 communities in Manicaland Province, representing four geographic strata (two small rural towns, two roadside trading centres, four tea, coffee and forestry estates, and four subsistence farming areas). For the ANC surveillance, clinics offering services to pregnant women in the population survey catchment areas were selected.

Prior to each population survey round, all households and their residents were enumerated by local census. At round 1 and round 2, all men aged 17 to 54 years and women aged 15 to 44 years resident in the study households were considered eligible, except that only one member of each cohabitating or marital union was selected (at random) as eligible and, in round 2, new in-migrants were only included in communities 5 to 12. At round 3, eligibility was expanded to ages 15 to 54 years for both sexes, regardless of marital status.

In summary, the population cohort was open in nature, eligibility criteria changed over time, and individual participation could span rounds. In the parallel ANC surveillance, all women seeking ANC at participating clinics (29 in all three rounds and seven in one or two rounds only) during the population survey period (usually six to eight weeks per community) were considered eligible. Study enrolment was conditional on participants' written consent at each round, although ANC data were anonymous. The Medical Research Council of Zimbabwe and St Mary's Local Research Ethics Committee, London, provided ethical approval. Round 1 was completed from July 1998 to February 2000; round 2 began in July 2001; and round 3 began in July 2003. Further details on study methods have been published previously [20].

HIV diagnostics

The Biomedical Research and Training Institute laboratory in Harare, Zimbabwe, performed all HIV testing. At round 1, a highly sensitive and specific (both 99.6%) dipstick-dot ICL-HIV1 & 2 Dipstick EIA was used to detect HIV antibodies [20]. Combaids-HIV-1 & 2 Dipstick was used in subsequent rounds. Apart from the principal investigators, research staff were blinded to participants' HIV status.

Data analysis

Inclusion criteria

When identifying youth in the general population for inclusion in the analyses, we used two approaches. In the first, we transformed the open cohort into three cross-sectional population samples, which included all individuals aged 15 to 24 years participating in a single round only, plus one observation selected at random from those participating in multiple rounds (referred to as the "sample dataset"). This approach eliminated repeated test results for the same individual, thereby meeting the requirement of data independence for statistical testing. The total number of observations in the sample dataset was 3505 in round 1, 2151 in round 2 and 6374 in round 3.

A drawback to the sampling approach is that it could introduce a selection bias if HIV serostatus is differentially associated with the number of rounds in which an individual participates. Therefore, in a second approach, we included all men and women aged 15 to 24 years at each round, regardless of their participation in any other round (referred to as the "complete dataset"). The total number of observations in the complete dataset was 4226 in round 1, 3269 in round 2 and 7070 in round 3. While this approach captured true population point prevalence, it violated the assumption of data independence since approximately one-third of the total records belonged to individuals participating in two or more rounds. The impact of these different approaches on the study findings are considered further in the discussion.

In the ANC survey, all data from women aged 15 to 24 years seen at the 22 ANC clinics participating in all three surveillance rounds were included (i.e., data from seven clinics participating in one or two rounds were not used as recommended by UNAIDS and the World Health Organization to construct trends) [6]. The data were considered independent because very few women (5.8% in round 2 and 3.8% in round 3) reported participating in a previous surveillance round. The total numbers of participants were 671 in round 1, 624 in round 2 and 592 in round 3.

Statistical analyses

To describe HIV prevalence trends by data source, we calculated round-specific HIV prevalence with 95% binomial confidence intervals (CIs). CIs for round 1 and round 3 ANC estimates were adjusted for over-dispersion, as observed variance around the clinic-level estimates in these rounds was higher than expected under binomial assumptions [22]. To determine the relative proportional change in prevalence across rounds (round 1 to round 3) and between rounds (round 1 to round 2; round 2 to round 3), the difference between the earlier and the later round estimates was divided by the earlier estimate.

Confidence intervals for proportional changes using ANC data also were adjusted for over-dispersion. General population survey trends were assumed to be the "gold standard" or best representation of true underlying population prevalence in the study area; hence, the representativeness of ANC data was considered relative to that of the general population survey. Due to the rolling nature of the survey start date, the UNGASS indicator baseline measurement against which proportional prevalence change by 2005 was measured was assumed to be round 1, which spanned the period from 1998 to 2000.

When comparing proportional differences in HIV prevalence across (round 1 to round 3) and between rounds (round 1 to round 2; round 2 to round 3), we used the Z-score test-statistic. To approximate variance in these proportional differences, which was too complex to obtain analytically, we used the delta method based on the Taylor series expansion of the variance [22] The null hypothesis for trend similarity was rejected where $|Z| > 1.96$ (i.e., p value < 0.05). We adopted these approaches rather than an odds ratio to permit comparison of proportional change in HIV prevalence.

To explore whether changes in HIV prevalence within specific socio-demographic groups (such as age, marital status, education or geographic location) might be contributing to differences in intermediary trends between the sample and ANC surveillance datasets separate to or

associated with changes in sexual behaviour, we similarly used a Z-score test. As an example, differences in the proportional change in prevalence trends between the two data sources (i.e., sample general population survey compared with ANC surveillance) were compared for those aged 15 to 19 years versus those aged 20 to 24 years, with the null hypothesis of no difference similarly rejected where $|Z| > 1.96$ (i.e., p value <0.05).

Changes in behaviour between rounds in the sample dataset, including the proportion of non-sexually active youth, new partnership formation in the past year, consistent condom use among unmarried persons and partner's age for individuals reporting sex in the past two weeks were compared using a two-tailed Z-score and Student's t-tests. Behavioural data were collected using informal confidential voting interviews, which have been associated with less reported "social desirability bias" than conventional face-to-face interviewing methods in the study population [23].

The first three behavioural indicators from the survey data most closely approximate UNAIDS recommendations for monitoring behaviour change among youth as part of the 2001 UNGASS targets [9]. The fourth indicator, partner age, has been shown previously to be an important factor in HIV transmission in this population [24]. Other key factors, such as changes in sexually transmitted infections (STIs), were not investigated: biomarkers for STIs were not included in the survey, self-reported STI symptoms can be unreliable, and prevalence of STIs are thought to be low in this population [25].

Results

Study participants

Figure 1 shows the results of household- and individual-level consent in the population survey and ANC surveillance datasets by round.

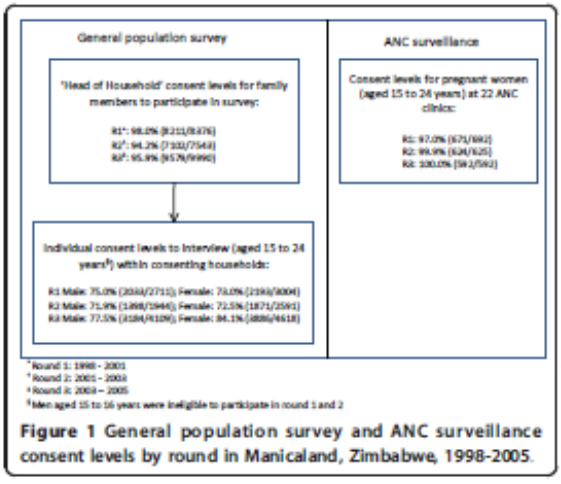


Figure 1 General population survey and ANC surveillance consent levels by round in Manicaland, Zimbabwe, 1998-2005.

Enrolment in the population survey was high, with more than 94% of households agreeing to participate in each round. Among youth in the participating households, consent levels were similar for males and females, except that fewer males (77.5%) than females (84.1%) participated in round 3 (p value <0.001). In the ANC surveillance, participation was nearly universal (97.0%-100%). The population survey distribution reflected the number of study sites, with 36.3% of participants living in subsistence farming areas, 28.9% in estates, 19.8% in roadside trading centres, and 15.9% in towns aggregated across all rounds. In the ANC survey, 31.8% of participants attended clinics in subsistence farming areas, 34.4% in estates, 14.8% in roadside trading centres, and 19.0% in towns.

Across rounds, the mean age of individuals in the population survey sample dataset was younger (19.2 years) than that in the ANC survey (20.2 years) (p <0.001). Similar mean ages were recorded in round 2 and round 3; in the latter, the eligibility criteria were expanded to include men aged 15 to 16 years. Reflecting their younger ages and the inclusion of men, fewer individuals in the population survey were married (13.2% versus 75.6% in ANC surveillance, p <0.001), but more had secondary or higher education (81.7% versus 63.7% in ANC surveillance, p <0.001).

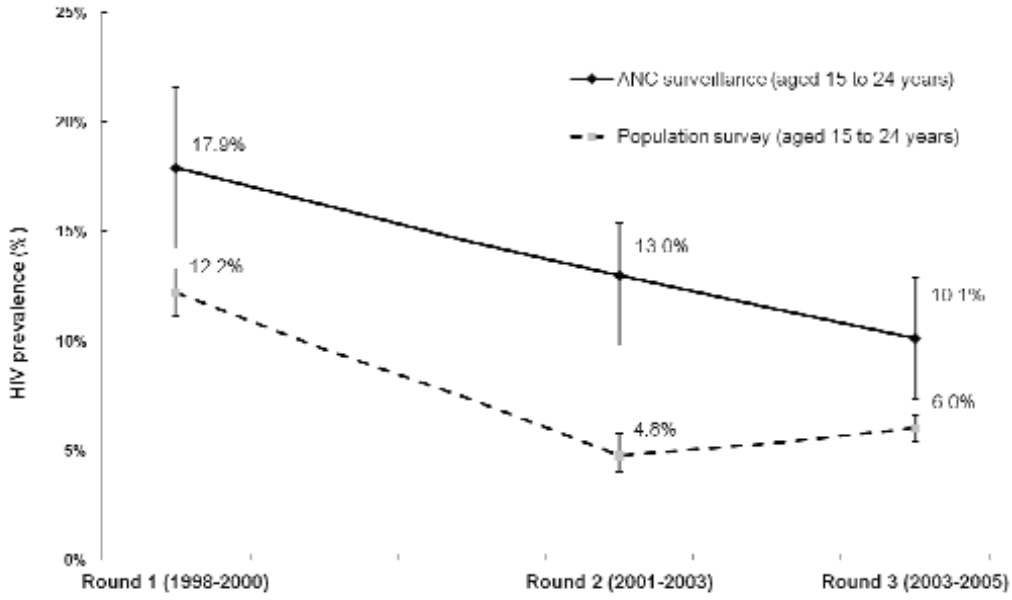
The sex ratio (males/females) fluctuated over time in the population survey sample dataset from 0.95 in round 1 to 0.76 in round 2 and 0.83 in round 3. ANC attendance among women in the population survey sample who were currently pregnant or had completed a pregnancy in the six months before the survey date was 80.6% in round 1, 81.3% in round 2 and 85.0% in round 3. Of those seeking antenatal care, approximately 80% at each round attended their local clinic. Overall, 13.0% of sexually active women in round 1, 9.2% in round 2 and 18.9% in round 3 reported a recent or current pregnancy. Similar distributions were observed in the complete population dataset.

Population-based and ANC HIV prevalence among youth

Figures 2 and 3 summarize HIV prevalence levels and trends among youth in the general population survey from 1998 to 2005 in the sample and complete datasets respectively. Levels and trends from the ANC surveillance for the same time periods are also shown.

In general, population prevalence was lower than ANC prevalence at each round, reflecting the increased risk of HIV infection in young women as compared with young men in this population, and the selection for high-risk sexual activity that exposes women to both pregnancy and HIV infection.

With regard to the UNGASS indicator, proportional HIV prevalence (as summarized in the table



Proportional change	Sample population survey %	(95% CI)	ANC surveillance %	(95% CI)	Trend comparison (Ho: ANC=Pop)
Round 1 to round 3	-50.7%	(-57.2, -44.3)	-43.5%	(-62.9, -24.2)	0.488
Round 1 to round 2	-60.9%	(-69.1, -52.7)	-27.4%	(-48.3, -6.5)	0.003
Round 2 to round 3	26.0%	(-0.8, 52.7)	-22.2%	(-48.8, 4.4)	0.012

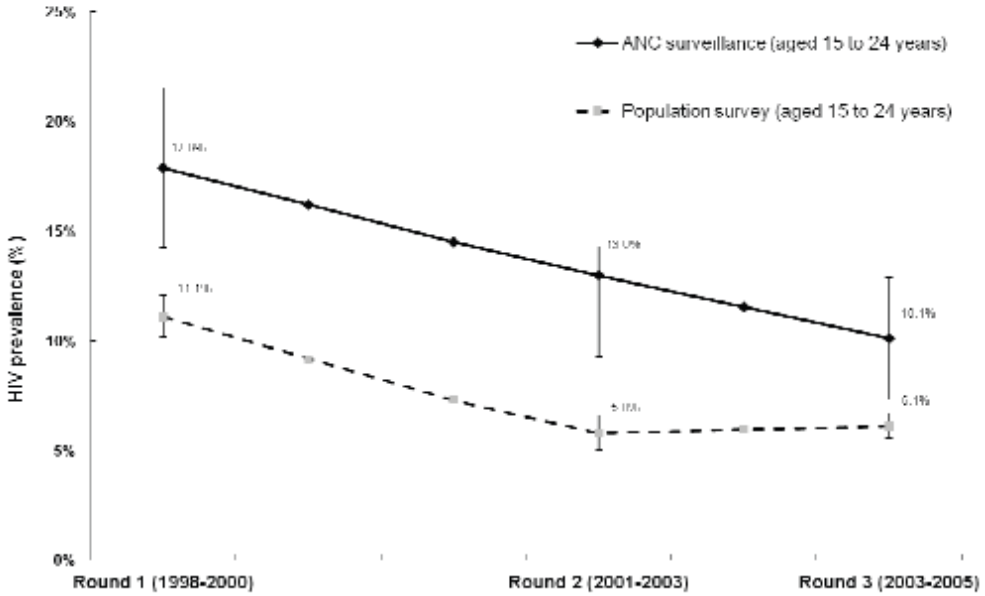
Figure 2 HIV prevalence among young men and women aged 15-24 years in the sample population survey dataset and from ANC surveillance from 1998 to 2005, Manicaland, Zimbabwe.

accompanying Figure 2a) declined by 50.7% (95% CI: -57.2%, -44.3%) in the sample general population dataset, from 12.2% in round 1 to 6.0% in round 3. This was similar to the reduction of 43.5% (95% CI: -62.9%, -24.2%) in the ANC surveillance, from 17.9% in round 1 to 10.1% in round 3 (test for difference in trend, p value = 0.488) (see Figure 2a). Reductions from both data sources exceeded the UNGASS target of 25% by 2005. Despite the overall similarities, there were differences in intermediary HIV prevalence trends. From round 1 to round 2, the proportional reduction in the ANC data of 27.4% (from 17.9% to 13.0%) was half that in the general population of 60.9% (from 12.2% to 4.8%) (test for difference in trend, p value = 0.003). From round 2 to round 3, HIV prevalence declined further in the ANC data, by 22.2% (from 13.0% to 10.1%), but rose in the general population, by 26% (from 4.8% to 6.0%) (p value = 0.012).

Similar round 1 to round 3 declines of 45.0% (95% CIs: -51.8%, -38.1%) were also observed in the complete population data set as compared with the 43.5% reduction (95% CI: -62.9%, -24.2%) in the ANC surveillance data (test for difference in trend, p value = 0.890) (see the table accompanying Figure 2b). Unlike the sample data set, however, intermediary differences were not statistically significant (round 1 to round 2, p = 0.078; round 2 to round 3, p = 0.090). Nevertheless, HIV prevalence rose minimally by 5.3% from round 2 to round 3 in the population data at a time when the ANC estimates declined by a further 22.2%, providing some evidence, albeit non-significant, for differences in ANC and general population prevalence trends for the complete data set, as well.

Socio-demographic predictors of trend differences

Using the Z-score test statistic to compare proportional changes in intermediary HIV prevalence trends (e.g., round 1 to round 2 and round 2 to round 3) from the ANC surveillance and sample population dataset by socio-demographic strata (e.g., 15-19 year olds versus 20-24 year olds), we observed the patterns of change to



Proportional change	Complete population survey (%)	(95% CI)	ANC surveillance (%)	(95% CI)	Trend comparison (Ho: ANC=Pop)
Round 1 to round 3	-45.0%	(-51.8, -38.1)	-43.5%	(-62.9, -24.2)	0.890
Round 1 to round 2	-47.7%	(-56.2, -39.3)	-27.4%	(-48.3, -6.5)	0.078
Round 2 to round 3	5.3%	(-12.1, 22.8)	-22.2%	(-48.8, 4.4)	0.090

Figure 3 HIV prevalence among young men and women aged 15-24 years in the complete population survey dataset and from ANC surveillance from 1998 to 2005, Manicaland, Zimbabwe.

be broadly similar (p values for differences in the proportional changes in intermediary prevalence trends between socio-demographic groups >0.10, except for education status where p value = 0.092) (see Table 1). This finding suggests that the significant round-to-round changes in the non-stratified trends did not occur within one particular socio-demographic group, but rather across the population as a whole.

Behavioural risk factors

Table 2 shows trends in selected behavioural indicators reported in the general population sample dataset that could explain observed intermediary differences.

For both sexes and age groups, the proportion of those not yet initiating sex increased significantly from round 1 to round 2. From round 2 to round 3, a smaller but still significant increase was observed among younger men (69.5% to 76.3%; p value 0.002), although this likely reflected the inclusion of men aged 15 to 16 years old in the survey at round 3. For women, a large reduction of those not yet initiating sex was seen among older women (19.2% to 11.8%; p value <0.001). For those who had sex within the past year, the number of men reporting no new partners increased from round 1 to round 2 (27.9% to 42.1%; p value <0.001), but declined from round 2 to round 3 (42.1 to 32.6%; p value = 0.001).

Women experienced a steady increase in the proportion reporting no new partners (from 69.2% in round 1 to 76.4% in round 3); however, round-to-round increases were not significant. Estimates of mean partner age of persons having sex in the past two weeks and consistent condom use among unmarried men generally tended toward less risky behaviour; however, only the reduction in mean partner age among women from 28.8 years in round 1 to 27.4 years in round 2 was statistically significant (p value = 0.010).

Discussion

Our results show that the UNGASS target of a reduction of 25% in HIV prevalence by 2005 among young men and women aged 15 to 24 years was achieved in

Table 1 HIV prevalence estimates by socio-demographic characteristics among youth (aged 15-24 years) in the sample general population survey and ANC surveillance in Manicaland, Zimbabwe, 1998-2005*

	Sample general population survey (Aged 15-24 years)			ANC surveillance (Aged 15-24 years)		
HIV prevalence estimates by socio-demographic characteristics	Round 1 (1998-2000) HIV % (n/N)	Round 2 (2001-2003) HIV % (n/N)	Round 3 (2003-2005) HIV % (n/N)	Round 1 (1998-2000) HIV % (n/N)	Round 2 (2001-2003) HIV % (n/N)	Round 3 (2003-2005) HIV % (n/N)
Age						
15-19 years	4.5 (72/1600)	1.9 (25/1328)	2.6 (96/3738)	12.6 (33/261)	7.8 (19/245)	4.6 (11/242)
20-24 years	18.6 (354/1905)	9.6 (79/823)	10.9 (288/2636)	21.2 (87/410)	16.4 (62/379)	14.0 (49/350)
Gender						
Male†	6.2 (106/1712)	2.3 (21/929)	2.7 (77/2886)			
Female	17.9 (320/1793)	6.8 (83/1222)	8.8 (307/3488)	17.9 (120/671)	13.0 (81/624)	10.1 (60/592)
Education						
None/primary	18.9 (155/819)	11.3 (37/329)	10.8 (113/1043)	18.3 (49/268)	11.3 (24/213)	10.8 (22/204)
Secondary/higher	10.1 (271/2686)	3.6 (66/1819)	5.0 (263/5287)	17.7 (71/402)	13.9 (57/411)	9.8 (38/388)
Residence‡						
Town	18.5 (109/588)	10.1 (31/308)	9.7 (99/1016)	19.7 (23/117)	12.3 (14/114)	9.4 (12/128)
Commercial estate	12.2 (140/1152)	5.3 (33/618)	7.0 (111/1595)	19.0 (41/216)	14.6 (32/220)	11.3 (24/213)
Subsistence farm	8.8 (103/1174)	3.5 (28/806)	4.4 (105/2386)	18.4 (40/217)	11.8 (26/220)	11.7 (19/163)
Roadside trading	12.5 (74/591)	2.9 (12/419)	5.0 (69/1377)	13.2 (16/121)	12.9 (9/70)	5.7 (5/88)

* P value results of Z-score tests for differences in the proportional change in prevalence trends between the two data sources (i.e., sample general population survey compared to ANC surveillance) by socio-demographic groupings (e.g., those aged 15-19 years versus those aged 20-24 years) for round 1 to round 2 and round 2 to round 3 were highly non-significant (p value >0.10), except for HIV prevalence trends by educational status where p = 0.092. As there was no evidence for any differences in trends by socio-demographic groupings, these results are not presented.

†Men aged 15-16 years were ineligible to participate in rounds 1 and 2.

‡ In ANC surveillance, "Residence" indicates the location of the ANC clinic where the woman sought prenatal services and not necessarily where she resides.

Manicaland, Zimbabwe, with reductions by 2005 nearly twice the targeted value. For both the sample and complete population-based datasets, the lower bounds of the 95% confidence intervals for round 1 to round 3 proportional reductions comfortably exceeded 25%. Despite this achievement, from the analysis of intermediary trends, it is evident that these declines have not been consistent over time. Reductions were greatest prior to 2003, most likely reflecting the rapid expansion and impact of HIV prevention campaigns in the early 2000s throughout the country [26,27]. As was the case in Uganda, another sub-Saharan Africa country with high prevalence early on in the epidemic, a visible increase in HIV-related mortality in the late 1990s among the participating communities also may have accelerated early behaviour change among youth [26].

Subsequent to 2003, however, the increase in prevalence could indicate that prevention efforts may have been less effective in reaching high-risk youth. This rise was accompanied by significant increases in the number of women aged 20 to 24 years initiating sex and an increase in the number of sexually active men with one new partner in the past year, and it took place despite the inclusion of young men aged 15 to 16 years in round 3 who are typically at lower risk of HIV infection compared with their female counterparts and men aged 17 years and older.

While our results suggest that behaviour change has been the driving force behind the observed trends, it is also possible that these changes could reflect shifts in the direction and magnitude of bias in the data. We assume that population survey estimates are representative of underlying population prevalence in the study area and that any biases in these estimates are stable with time. With regard to this assumption, however, two possible concerns could be raised.

First, participation levels and eligibility criteria changed across rounds of the general population survey, and these changes could have distorted our representation of true underlying population prevalence in the study area. Acceptance levels, however, are consistent with those achieved in other HIV population surveys [28], which have been shown to produce minimally biased HIV prevalence estimates [29]. Land reform and migration, coinciding with round 2, could have also caused variation in the composition of (particularly male) participants across rounds and skewed HIV prevalence estimates in this round in particular. However, individuals migrating to more urban areas during this period did not have higher levels of HIV prevalence [30].

In addition, the inclusion of men aged 15 to 16 years caused a significant increase in the percent of men aged 15 to 19 years not yet initiating sex; nevertheless, exclusion of these men from the analysis did not change the

Table 2 Selected behavioural indicators among youth (aged 15-24 years) in the sample general population survey in Manicaland, Zimbabwe, 1998-2005

	Round 1 (1998-2000)		Round 2 (2001-2003)		Round 3 (2003-2005)		Round 1 to round 2 p values	Round 2 to round 3 p values
Individuals not yet initiating sex (%, n/N)								
Male								
15-19 years of age*	49.4	(348/704)	69.5	(348/501)	76.3	(1475/1931)	**<0.001**	**0.002**
20-24 years of age	13.5	(136/1008)	18.2	(78/428)	22.2	(240/1079)	**0.021**	0.085
Female								
15-19 years of age	66.0	(591/896)	79.4	(657/827)	76.4	(1475/1931)	**<0.001**	0.079
20-24 years of age	9.5	(85/897)	19.2	(76/395)	11.8	(183/1557)	**<0.001**	**<0.001**
Number of new partners among those having sex in the last year (%, n/N)								
Male								
0	27.9	(276/989)	42.1	(150/356)	32.6	(309/947)	**<0.001**	**0.001**
1	39.4	(395/989)	37.4	(133/356)	47.2	(447/947)	0.507	**0.002**
2+	32.2	(318/989)	20.5	(73/356)	20.2	(191/947)	**<0.001**	0.905
Female								
0	69.2	(639/923)	74.0	(304/411)	76.4	(1224/1602)	0.075	0.310
1	27.2	(251/923)	23.8	(98/411)	21.7	(348/1602)	0.192	0.360
2+	3.6	(33/923)	2.2	(9/411)	1.9	(30/1602)	0.379	0.696
Partner's mean age and 95% CIs (in years) for those reporting sexual intercourse in the past two weeks								
Male	18.9	(18.5-19.2)	19.0	(18.5-19.4)	19.4	(19.1-19.8)	0.773	0.158
Female	28.8	(28.1-29.4)	27.4	(26.7-28.1)	27.6	(27.3-28.0)	**0.010**	0.552
Consistent condom use with the last partner in the previous two weeks among unmarried individuals								
Male	60.9	(145/238)	63.0	(46/73)	65.1	(123/189)	0.748	0.754
Female	36.8	(28/76)	45.2	(14/31)	45.5	(30/66)	0.424	0.978

*Men aged 15-16 years were ineligible to participate in rounds 1 and 2

overall conclusions. Given these findings, we are reasonably confident that HIV prevalence trends among youth reflected those of the underlying population study area. However, additional survey data from two upcoming rounds (round 4: 2006-2008; and round 5: 2009-2011) will provide for a stronger indication of overall trends, as well as the opportunity to directly measure changes in incidence.

Second, the two methods we used for constructing the general population data sets when analyzing trends also could have distorted our estimates. For example, the sampling approach using the three independent data sets led to a slight overstatement of population HIV prevalence in round 1 (risk ratio, RR, of sample prevalence divided by complete prevalence = 1.10), a more pronounced understatement of population prevalence at round 2 (RR = 0.83) and minimal bias in round 3 (RR = 0.98) since participation in multiple rounds was correlated with HIV status. Accounting for this bias, our sample estimates would have exaggerated the proportional decline from round 1 to round 2 by 27% and overstated the increase from round 2 to round 3 by 15%. In the second approach, repeated testing on the same individuals across rounds would have overstated the precision associated with the trends. Additional research is needed to improve the statistical analysis of trends measured in cohort surveys since none of the approaches explored were without limitation.

As most countries will not have access to repeated population survey data, the results of our secondary analysis, showing that ANC-based surveillance data broadly reflected the overall change in HIV prevalence among young men and women in the general population between 1998 and 2005, are encouraging. Despite this, the ANC estimates did fail to capture short-term or intermediary changes occurring in the general population, especially in the sample data set. The ANC data indicated a consistent steady decline in HIV prevalence from round 1 to round 2 to round 3, while a rapid fall was observed in the general population between round 1 and round 2, followed by a slight increase through round 3.

The intermediary divergence in trends is important to explore in this population because policymakers, who have typically relied on ANC surveillance data to measure the impact of interventions in Zimbabwe,

could have underestimated the effectiveness of early HIV prevention programmes that were scaled up in the late 1990s [31], but then overestimated their subsequent impact at a time when resources could have been used elsewhere or in more effective ways. Notably, the slow, steady decline in ANC prevalence observed here resembles that seen in national ANC surveillance data from 2000 to 2006 among those aged 15 to 24 years [32], suggesting that national-level estimates of trends in HIV incidence among youth could have been similarly distorted and incorrect conclusions drawn about the effectiveness of prevention interventions. A similar study from Lusaka, Zambia, also comparing trends in the general population and among ANC attendees found that HIV prevalence among youth between 1995 and 2003 declined more rapidly than among ANC attendees due to increases in educational attainment leading to postponement in ages at first sex and first pregnancy [33].

As was the case in Lusaka, the most reasonable explanation for these divergences is the previously described changes in sexual behaviour in the general population that would not have been reflected among ANC attendees. Primarily, the postponement of sexual debut and, to a lesser extent, reductions in the number of new partners and the age of partners, and increases in consistent condom use among youth generally from round 1 to round 2 could have rapidly reduced HIV transmission in this population while having a more limited impact on the declining fraction who continued to become pregnant by practicing unprotected sex.

Mathematical modelling by Zaba and colleagues supports this hypothesis, showing how young pregnant women become increasingly less representative of the general population with regard to their sexual behaviour as the age of sexual debut increases and risk of HIV transmission declines [12]. The more gradual reductions in HIV prevalence seen in the ANC data, which contrast with Zaba and colleagues' results, may reflect the benefits to young pregnant women of the reduced circulation of HIV in the adult population that occurred from round 1 to round 2 [20].

Other factors that could have contributed to the contrasting temporal patterns of change in HIV prevalence seen in the general population and ANC data include changes in the profile of women accessing ANC services. However, we observed only minor increases in ANC uptake from 80.6% (round 1) to 81.3% (round 3) and the proportion attending their local ANC remained steady at around 80%. Very few pregnant women refused to participate in the ANC surveys. Scale up of HIV testing and prophylaxis services for pregnant women could result in a selective increase in uptake of ANC services by HIV-positive women; however, in Mwanza, Tanzania, while the quality and type of ANC services influenced where women sought prenatal care, these preferences were not differentially associated with a woman's HIV status [34].

Furthermore, our study occurred during a period when HIV testing and prophylaxis services for pregnant women in Zimbabwe were limited; thus, a selective increase in uptake of ANC services by HIV-positive women is unlikely. Examination of access to ANC services and the characteristics of women seeking these services over time are nonetheless recommended as these may shift with time, particularly if HIV prevention and treatment programmes become more closely integrated with family planning efforts [35]. Finally, as antiretroviral therapy and, by extension, the number of years a person lives with HIV increases, prevalence trends may become a less accurate indicator of underlying incidence, especially if more recently infected individuals are placed on treatment. Methods for adjusting prevalence trends to reflect changes in survivorship bias over time will be needed.

Conclusions

In conclusion, this analysis of data from Manicaland, Zimbabwe, shows several important findings. First, for a population that has been greatly affected by HIV, substantial and successful efforts toward preventing new infections among youth aged 15 to 24 years were made in the late 1990s and early 2000s. The effects of prevention efforts in the general population appear to have stalled somewhat after 2003, although declines among young women attending ANC clinics were still evident and the UNGASS target for 2005 was reached.

Second, trends in reported sexual behaviour, rather than biases in the population survey data, seem the most likely explanation for these declines. As a result, trends in prevalence likely reflect trends in underlying population prevalence and incidence.

Finally, although, in general, the evidence for the usefulness of ANC surveillance data to monitor HIV prevalence trends among youth in this eastern Zimbabwe population is encouraging, intermediary trends were found to differ. Behavioural data collected in the population survey were critical to interpreting these differences, however, so caution should be exercised when interpreting ANC trends without broader indicators of population-level behaviour risk. In addition, we highlight the possible role that increased access to integrated prenatal HIV prevention and treatment interventions could play in changing the profile of women seeking ANC services over time, thereby possibly exacerbating differences in prospective trends. Examination of access to ANC services and the characteristics of women seeking

these services over time merits more careful consideration in future studies.

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Authors' contributions

KAM, with significant input from CAN, CAD, JMGC and SG, originally conceived of and designed the analysis and drafted the article. CAN, EM, PM and SG contributed to the collection and assembly of the data. All authors actively participated in the analysis and interpretation of the data and critical revision of the draft article. All authors approved the final submission of the article and its contents.

Competing interests

The authors declare that they have no competing interests.

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Issue Theme: New Strategies and Methods for HIV/AIDS Surveillance in Low and Middle Income Countries - 2009

How can PMTCT Program Data be Used for the Purposes of HIV Surveillance?

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Abstract

Background: In countries with severe HIV epidemics, including most in sub-Saharan Africa (SSA), monitoring of trends in HIV prevalence is primarily accomplished through annual or bi-annual ANC-based HIV surveillance using unlinked anonymous testing (UAT) methods. In recent years, the availability of effective measures for the prevention of mother-to-child transmission (PMTCT) has led to increased coverage of HIV testing among pregnant women at antenatal care (ANC) clinics. As a result, the use of routinely-available HIV testing data from rapidly expanding PMTCT programmes has been proposed for monitoring population-level HIV prevalence trends, possibly either as a complement to or a replacement for UAT-based ANC HIV surveillance.

Methods: We identified and reviewed 9 studies from 7 countries in SSA and proceedings from consultative meetings assessing the usefulness of PMTCT data for surveillance purposes to adapt PMTCT programme activities to meet surveillance needs.

Results: Evidence to date for the use of PMTCT data for surveillance purposes from the literature and presented in consultative meetings was mixed, although all of the studies except in Botswana occurred at a time when PMTCT services were characterized by low uptake and limited human and financial resources to appropriately monitor programme activities. In two studies in Uganda and one in Burkina Faso, associations between characteristics of women accepting testing and their serostatus varied, leading in some cases to biases in PMTCT-based estimates of HIV prevalence. Direct comparisons of PMTCT and UAT-based ANC prevalence from Botswana, Cameroon and rural Uganda demonstrated that PMTCT data could be used for surveillance purposes, whereas at multiple clinics in Kenya, Uganda, and Zimbabwe, problems with the quality of PMTCT data and differences in clinic-level estimates made it difficult to use. We take into account the recent improvements in the quality and availability of PMTCT data when making recommendations for how countries might better begin to use these data for monitoring HIV prevalence trends.

Conclusion: Using PMTCT-based data is desirable and feasible for surveillance purposes, however, additional efforts will be required to ensure that HIV testing uptake is such that it does not bias prevalence estimates and that operational challenges to their collection, availability and interpretation are overcome.

BACKGROUND

In resource-limited countries with severe HIV epidemics such as those in sub-Saharan Africa (SSA), trends in HIV prevalence are typically monitored through annual or bi-annual HIV surveillance among pregnant women routinely seeking antenatal care (ANC) [1]. The primary strategy used to collect ANC surveillance data is unlinked anonymous testing (UAT), in which leftover blood is tested for HIV antibodies and women are not typically asked for their consent to participate. Because HIV prevalence estimates from UAT ANC surveillance (hereafter referred to as ANC surveillance) conducted on an annual or biannual basis are generally considered representative of prevalence in the surrounding community [2], data from participating clinics are used to produce country-specific and global HIV/AIDS epidemic trends [3] and to monitor an UNGASS target to reduce by 50% globally by 2010 the number of newly infected youth aged 15-24 years [4].

In recent years, availability of effective measures for the prevention of mother-to-child transmission (PMTCT) has led to substantial increases in access to and uptake of HIV testing and counselling among pregnant women attending ANC clinics [5]. In terms of access, by 2008, more than 75% of ANC clinics in 25 of 46 SSA countries offered HIV testing and counselling [5]. In terms of uptake, WHO-published guidance encouraging provider-initiated testing and counselling (PITC) or "opt-out" -- rather than client-initiated testing and counselling or "opt-in" -- has substantially increased HIV testing at ANC, in many clinics and some countries exceeding 90% uptake [6-10]. Given these advances, the extent to which HIV testing data from PMTCT services could complement, or even replace, ANC HIV surveillance in the future is being debated.

Using PMTCT data for surveillance purposes offers certain advantages over ANC surveillance in that more ANC clinics can participate, ethical concerns of testing women without consent are avoided, and data on the number of women testing and their HIV status are routinely available as part of programme monitoring activities. However, possible disadvantages have also been raised. Of greatest concern has been that women refusing or, conversely, preferentially seeking out HIV testing could bias PMTCT-based estimates [11, 12]. The impact of this bias on prevalence estimates could also vary in magnitude and direction with time as uptake levels or approaches to delivering HIV testing and counselling services change [13]. Finally, whether PMTCT data are sufficiently standardized across clinics, detailed enough for surveillance purposes, and accessible in their current form has also been debatable [14-18].

In this paper, we examine previous literature on this topic to understand advantages and disadvantages to using PMTCT data for surveillance purposes. To identify relevant published studies, we conducted a comprehensive online literature review in April 2009 using Google Scholar and PubMed. Key words included: Antenatal Care, HIV prevalence, HIV testing determinants, HIV risk factors, pregnant women, prevention of mother-to-child transmission, sentinel surveillance, seroprevalence, and voluntary counselling and testing. To identify unpublished studies, we reviewed proceedings from international meetings on these subjects and we contacted HIV surveillance and PMTCT experts. The 9 studies included in the final review representing 7 countries (See Table 1) assessed either: 1) the extent to which accepting HIV testing is associated with HIV serostatus (which can be used in turn to measure the impact of non-participation bias on PMTCT-based estimates) [11, 12, 19]; or 2) whether PMTCT-based data from clinics were as accurate and of sufficient quality as ANC surveillance data to monitor HIV prevalence [11, 13-16, 18, 20]. Based on the these studies and consultative reports [17, 21], we collaboratively developed recommendations on measures to adapt PMTCT programme activities to meet

Table 1a: Review of 9 published and unpublished literature from 7 sub-Saharan African countries on the use of PMTCT data for HIV surveillance purposes

	Location/Year/Citation	Study description (population size, PMTCT type, uptake)	Primary analysis question and primary results	Conclusion
1	Lacor Hospital, Gulu District, Northern Uganda (2001-2003) [11]	*ANC surveillance**: 3,580 *'Opt-in' PMTCT*: Overall uptake: 48% (6,785/14,040). 1,841 not offered testing; 6,785 accepted; 5,411 refused.	• Is acceptance of HIV testing associated with HIV status? Yes, but weakly. • Are PMTCT and ANC estimates similar? Yes, when age-standardized and in age-specific estimates.	PMTCT data are useful in north Uganda for surveillance purposes.
2	Entebbe General Hospital, Wakiso district, Uganda (May 2002 – April 2003) [12]	*ANC surveillance*: 833 *'Opt-in' PMTCT*: Overall uptake: 54% (2,635/4,867). 1,239 not offered testing; 2,635 accepted; 993 refused.	• Is acceptance of HIV testing associated with HIV status? Yes • Are PMTCT and ANC estimates similar? Yes using annual data or when uptake is >70%	Not useful when services are recently introduced or uptake is low (<70%)
3	St. Camille Medical Centre, Ouagadougou, Burkina Faso (May 2002-April 2004) [19]	*ANC surveillance*: sample size not stated *'Opt-in' PMTCT (VCT offered without cost)*: Overall uptake: 18.3% (1,216/6,639). 1,216 accepted; 5,423 refused	• Is acceptance of HIV testing associated with HIV status? Yes • Are PMTCT and ANC estimates similar? No (but PMTCT and ANC estimates were from different time periods)	Women who accept testing represent a select and motivated population
4	8 sites where ANC surveillance and PMTCT activities overlapped in Kenya (2003) [16]	*ANC surveillance*: 1,852 *PITC** PMTCT*: Overall uptake: 56%, (1,258/2,239); median clinic uptake: 51%; Range: 48%-69%)	• Are PMTCT and ANC estimates similar? Overall, yes, and even when uptake is <60%. ANC surveillance estimates were lower in 5 of 8 sites, however	Should not be used due to clinic-level disparities in estimates and data quality problems
5	Unknown number of PMTCT and surveillance sites in Cameroon's 10 provinces (2003) [20]	*ANC surveillance*: 6,745 *'Opt-in' PMTCT (consent obtained to enroll in testing)*: 69% (42,731 responded)	• Are PMTCT and ANC estimates similar? Overall, yes, and in 9 of 10 provinces	Can be used

* Refers to Unlinked Anonymous Testing ANC-based HIV surveillance
** PITC – Provider-initiated testing and counselling

Table 1a continued in Table 1b

Table 1b (continuation of Table 1a): Review of 9 published and unpublished literature from 7 sub-Saharan African countries on the use of PMTCT data for HIV surveillance purposes

	Location/Year/Citation	Study description (population size, PMTCT type, uptake)	Primary analysis question and primary results	Conclusion
6	7 sites where ANC surveillance and PMTCT activities overlapped in Uganda (2003) [14]	*ANC surveillance*: 11,946 *PMTCT*: No information on uptake 18,191 accepted;	• Are PMTCT and ANC estimates similar? Overall, yes, but estimates in 2 of 7 clinics showed significant disparities.	Difficult to use because of clinic-level differences as well as data quality problems
7	19 sites where ANC surveillance and PMTCT activities overlapped in Zimbabwe (2004); National-level PTMCT data used [15]	*ANC surveillance*: sample size not stated *Opt-in PMTCT*: Overall calculated mean uptake: 39.6% (4,983/12,587); median clinic-specific uptake: 42.1%; Range: 2.3%-89.4%)	• Are PMTCT and ANC estimates similar? Yes, but significant clinic-level disparities in estimates	Cannot be used, because of low uptake, clinic-level disparities, and insufficiently-detailed data
8	48 of 270 sites (all with dual ANC surveillance and PMTCT activities) in Botswana [18]	*ANC surveillance*: 2005: 2472; 2006: 2714; 2007: 2542 *PITC PMTCT*: Overall uptake: 95%. 2005: 2803; 2006: 2950; 2007: 2943;	• Are PMTCT and ANC estimates similar? Yes, overall and by rural, urban distribution. Similar among 5 year age groups, particularly at youngest ages	Can be used due to similarity in estimates. Data quality improvements in completeness are needed
9	Lacor Hospital, Gulu District, Northern Uganda (2004-2005) [13]	*ANC surveillance*: 1,059 in 2004; 1,166 in 2005 *Opt-in PMTCT for 2004*: Overall uptake: 49.9% (849/1,701); 275 not offered; 849 accepted; 577 refused. *Opt-in PMTCT for 2005*: Overall uptake: 54.2% (1,255/1,892); 388 not offered; 1,255 accepted; 249 refused.	• Are PMTCT and ANC estimates similar? Crude comparison of estimates of estimates	Data adjusted for non-participation bias may be useful

* Refers to Unlinked Anonymous Testing ANC-based HIV surveillance
** PITC – Provider-initiated testing and counselling

surveillance needs. We conclude by suggesting areas for further research.

STUDIES OF THE ASSOCIATION BETWEEN ACCEPTING HIV TESTING AND HIV SEROSTATUS

Bias in HIV prevalence estimates from PMTCT data can occur if women preferentially are offered or accept HIV testing according to their suspected (or known) serostatus. In situations where stigma prevents women with a suspected HIV positive status from getting tested or attending a particular clinic, PMTCT estimates might underestimate true community HIV prevalence. Alternatively, if women most at risk of infection seek testing, PMTCT-based estimates could overstate community HIV prevalence. The extent to which these biases change with time could impede interpretation of trends arising from PMTCT data.

While many studies have considered determinants of testing among pregnant women with the goal of increasing uptake, only three have directly linked these determinants to HIV serostatus in order to assess bias [11, 12, 19]. In a first study at a rural North Uganda hospital from 2001 to 2003, 48% of women (6,785/14,040) accepted 'opt-in' HIV testing when initially offered at their second prenatal visit. Thirty nine percent (5,414/14,040) did not[11]. Furthermore, 13% (1,841/14,040) of women failed to return for a second visit and therefore were not offered testing. Compared to those who did not agree to test, accepting and testing positive was weakly associated with having lived at a current address for two years or less, cohabitating but not being married, and having a partner with a non-agricultural occupation. Given the weakness of the associations, however, PMTCT-based and ANC surveillance estimates were judged similar (10.9% and 11.1% respectively). Also, because those women offered and not offered testing had similar demographic characteristics, the authors hypothesised that this type of non-participation bias would have had minimal impact on PMTCT-based estimates.

In a second study, also in Uganda, Mpairwe et al., [12] followed 4,867 women from May 2002 to April 2003 at an urban Entebbe ANC clinic providing 'opt-in' PMTCT services. Similar to the rural Northern Uganda site, 25% (1,239/4,867) of the women were not offered testing, resulting in an overall uptake of 54% (2,635/4,867). The 20% who refused (993/4,867) were tested anonymously. Results showed most importantly that women who perceived themselves to be at risk for HIV were more likely to accept testing and to test positive. Also, women with no education or only primary education, those who had an HIV infected partner and those who believed themselves exposed to HIV also accepted testing and tested positive more often than others without these characteristics. Despite these associations, no differences in prevalence levels were observed between individuals accepting (14%) or refusing (12%) testing (p-value=0.26) during the study. Differences in estimates were observed, however, in the month following introduction of PMTCT services (20% among accepters vs. 11% among non-acceptors; p-value=0.05) and in months with testing uptake below 70%, (17% in accepters vs. 8% among non-acceptors; p-value<0.001). The authors suggest that women who accept testing when services are initially introduced or when testing uptake is low represent a higher risk group which could bias PMTCT estimates upwards.

In the third study in Burkina Faso, Pignatelli et al., primarily considered a woman's obstetrical history, age, risk and associations between HIV serostatus and testing uptake in an urban ANC clinic providing 'opt-in' PMTCT services from 2002 to 2004 [19]. During the study period, uptake was extremely low at 18.1% (1,216/6,639) and of those accepting and testing positive, 45% (97/215) already knew their status to be positive from previous testing. Excluding those known HIV-positive women, factors associated with testing uptake and a positive HIV status included older age and a history of miscarriage. Unlike Mpairwe's findings, however, perceived risk was not associated with testing and an HIV-positive result. Still, the authors suggested that a higher HIV prevalence based on the 2002-2004 PMTCT data (10.6%) compared to ANC surveillance (4%) at the clinic in 2002 could have

resulted from a more motivated group at higher risk for HIV infection seeking PMTCT services [19]. Since these estimates arose from different time periods, natural changes in the dynamics of the epidemic could also explain this disparity.

STUDIES DIRECTLY COMPARING PMTCT PROGRAM AND ANC SURVEILLANCE ACTIVITIES

Direct comparison of PMTCT and ANC surveillance data to evaluate their suitability for monitoring HIV population prevalence trends first occurred in Thailand in the late 1990s as PMTCT services, including HIV testing, were rapidly expanded [22]. By 2001, 96.7% of women accepted testing through PMTCT programmes [22]. Given this near complete uptake, ANC surveillance and PMTCT estimates differed by just 0.1% in 2001 and 2002 [23]. Since 2003, Thailand has relied on PMTCT data alone to monitor HIV prevalence trends [23]. Using the Thailand experience as a model, five SSA countries have conducted studies to assess the usefulness of PMTCT data for surveillance purposes. Of these, Kenya [16], Cameroon [20], Uganda [14] and Zimbabwe [15] conducted evaluations at all clinics where PMTCT services overlapped with ANC surveillance activities.

In Botswana, PMTCT-based HIV testing data from two of the most frequently attended clinics per health district were compared to ANC surveillance estimates from those same clinics. Finally, the remaining two studies [11, 13] by Fabiani, et al., occurred at a single hospital in rural Uganda (where the determinants of uptake associated with HIV serostatus had previously been explored) [11]. As part of these latter studies, the authors also considered whether the overall magnitude and direction of bias in PMTCT estimates had changed with time and whether bias could be reduced by adjusting for women refusing to test.

In Kenya, Seguy et al., used 2003 ANC surveillance and PMTCT program data from six clinics to compare HIV prevalence estimates [16]. PITC uptake was 56% (1,258/2,239). Overall median prevalence estimates were similar (ANC: 12.8% (range: 8.1%-26.3%) vs. PMTCT: 14.4% (range: 7.0%-27.2%)) as were estimates from those clinics with low (<60%) versus high testing uptake (≥60%). Despite these similarities, the authors found evidence for large relative differences in estimates by clinic (-30% to +38%) and problems with accessing PMTCT registers, interpreting nurses' handwriting, a lack of standardization in the format and number of variables collected across clinic and substantial missing data. Based on these findings, the authors did not recommend using PMTCT data for surveillance purposes.

Also in 2003, Macauley et al., in Cameroon compared ANC surveillance and PMTCT-based HIV prevalence estimates from clinics with a reported 69% uptake level [20]. No additional details from the study authors could be obtained on whether 'opt-in' or PITC was offered or the number of participating clinics. Findings from the study, however, showed overall estimates for the participating clinics to be similar (PMTCT: 7.8% (95% CI=7.5-7.9) versus ANC surveillance: 7.3% (95% CI=6.7-7.9%)) and in nine of 10 provinces. Given these results, the authors concluded that PMTCT data could be used to monitor the HIV epidemic in Cameroon.

In Uganda, Finkbeiner et al., compared 2003 ANC surveillance and PMTCT-based prevalence estimates in the seven clinics where these activities overlapped [14]. Data on uptake levels and whether 'opt-in' or PITC testing was unavailable. While HIV prevalence estimates were determined to be similar (8.3% in ANC versus 9.8% in PMTCT), substantial differences in estimates at two clinics were observed. In these clinics, the authors found that confusion regarding PMTCT and ANC surveillance protocols led some women to be sampled twice while others were excluded inappropriately. Stock-outs in syphilis and HIV test kits also contributed to non-consecutive sampling during ANC surveillance. Substantial inconsistencies in documentation procedures across clinics and incorrect application of testing algorithms applied to discordant test results were also found. Based on these findings, PMTCT data were deemed difficult to use for surveillance purposes. As well, the authors cautioned that jointly conducting

PMTCT and ANC surveillance in the same clinics could jeopardize both sets of estimates.

Similar to the Cameroonian, Kenyan and Ugandan experience, the Ministry of Health and Child Welfare (MOHCW) in Zimbabwe evaluated the comparability of HIV prevalence estimates from all 19 clinics with overlapping ANC surveillance and opt-in PMTCT data in 2004 [15].Unlike these previous evaluations, however, nationally-reported rather than clinic-level PMTCT data were used. Median uptake of 'opt-in' testing at the 19 clinics was found to be 42.1% (range: 2.3%-89.4%) and reportedly low due to insufficient test kits and trained staff. Although overall HIV prevalence was similar (21.3% in ANC data versus 21.8% in PMTCT data) in the study, substantial differences in clinic-specific estimates were observed. As national data were used, no age or socio-demographic data were available to further interpret trends. Based on these results, the Zimbabwean MOHCW concluded that national-level PMTCT data were an unacceptable replacement to ANC surveillance activities.

Seipone et al., in Botswana carried out an evaluation using data from two of the most highly attended ANC clinics in each of their 24 health districts during the 2005, 2006 and 2007 surveillance periods [18]. Uptake of PITC in Botswana exceeded 95% during the study period. In general, estimates by year overall (see Figure 1a) were similar, although the overall comparison masked some differences in estimates by age groups for urban (see Figure 1b) and rural clinics (see Figure 1c). In the case of the urban clinics, ANC surveillance estimates were typically greater than PMTCT estimates, especially among those aged 40-49 years. In the rural clinics, estimates were generally similar, although PMTCT estimates were typically greater than ANC surveillance estimates among 40-49 year olds. In addition to these empirical results, the authors noted that socio-demographic data collected during ANC surveillance were more complete than PMTCT data, although availability was considered sufficient. Subsequent to this study, a working group has been created to transition from using ANC surveillance data to PMTCT program data for surveillance purposes in Botswana.

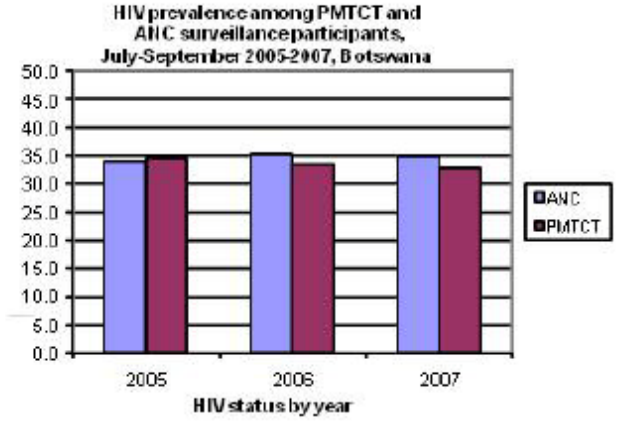
Finally, at a clinic in rural North Uganda, Fabiani et al., compared ANC surveillance and PMTCT data collected from 2001-2003 [11] and 2004-2005 [13]. During the 2001-2003 period, the authors found that despite relatively low but slowly increasing levels of client-initiated HIV testing each year (45.8% in 2001 to 48.2% in 2003), age-adjusted HIV prevalence from the two data sources were similar overall (11.1% in ANC surveillance and 10.9% in PMTCT) and for each year [11]. In the follow-up study, however, PMTCT data underestimated ANC surveillance prevalence in 2004 (9.0% vs. 10.5%) yet overestimated it in 2005 (11.8% vs. 10.9%) despite only marginal increases in uptake (49.9% in 2004 and 52.2% in 2005) [13]. To adjust for non-participation bias in 2004 and 2005, the authors used socio-demographic profiles of accepters and their HIV status to create risk coefficients, which, when applied to the non-testing population, produced similar PMTCT and ANC surveillance estimates respectively (10.1% vs. 10.5% in 2004 and 11.2% vs. 10.9 in 2005). While this method proved successful among younger women, it was less accurate when applied to older women where risk coefficients were less predictive. Moreover, the authors noted that these risk coefficients may vary from clinic to clinic, thus further studies were recommended before transitioning to using either unadjusted or risk-adjusted PMTCT estimates for surveillance purposes.

EVIDENCE SUPPORTING THE USE OF PMTCT DATA FOR SURVEILLANCE PURPOSES

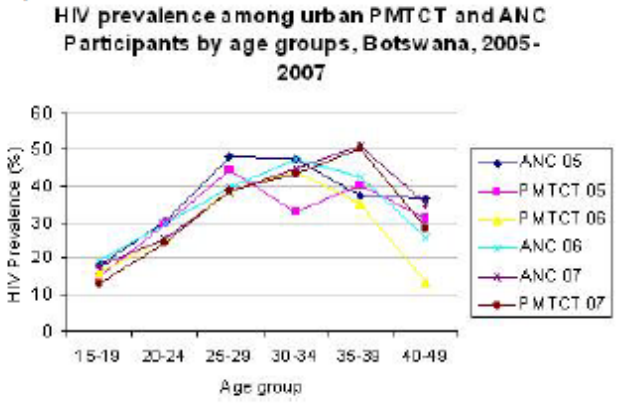
Evidence from the nine studies in seven SSA countries is mixed regarding the usefulness of PMTCT data for surveillance purposes. While most studies found overall crude or adjusted ANC surveillance and PMTCT estimates to be similar, non-participation bias, either at the clinic-level or when services had just commenced or participation was low, affected the accuracy of these estimates.

Figure 1: Comparison of HIV prevalence data from PMTCT and ANC surveillance in Botswana.

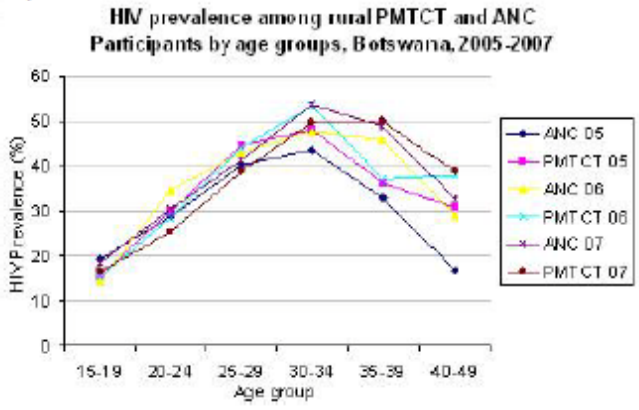
1a)



1b)



1c)



Unfortunately, factors predicting HIV testing uptake and association with serostatus that could help account for non-participation bias appeared to vary by age and across studies [11, 12, 19] and in the northern Uganda rural study, with time [13].

Adjustment for this bias without knowledge of the socio-demographic characteristics of the non-testing population would not be possible. Application of this approach across multiple clinics or nationally is also untested.

Specific to the quality and availability of PMTCT data, operational challenges were reported in four of the six studies directly comparing PMTCT and ANC surveillance data (Kenya [16], Uganda [14], Zimbabwe [15], and Botswana [18]. Commonly reported problems included missing and illegible data. In Zimbabwe, age data to stratify results for an UNGASS indicator was not available. In the case of Botswana, the authors concluded that problems encountered there, primarily missing data, could be addressed with additional resources and staff training when PMTCT data would be collected for surveillance purposes. The other three countries, however, reported problems of a sufficient scale such that they did not recommend PMTCT data be used for surveillance purposes.

While the above conclusions could generate more concern than confidence in using PMTCT data for surveillance purposes, the primary limitation is that all by the Kenya and Botswana studies were conducted when HIV testing in PMTCT services made use of 'opt-in' rather than

PITC. As well, while Botswana's system is considered a model for integrating PMTCT services into ANC care, other countries initially struggled in the early 2000s to dedicate sufficient financial and human resources to rapidly scale-up services. However, since this time, many of the previously-reported challenges have been addressed. For example, non-participation bias in most of SSA has declined dramatically since implementation of PITC, group pre-test counselling sessions, and rapid HIV testing with same-day results [24]. PMTCT programmes have also incorporated the use of lay counsellors to provide sufficient staffing so that testing is offered to all first-time attendees [25]. Finally, ensuring the consistent availability of rapid HIV test kits and program monitoring tools such as standardized logbooks, in conjunction with increased emphasis and training on data quality, has been prioritized. Given this new context, some countries may now find it reasonable to consider PITC data useful for surveillance purposes.

RECOMMENDED MEASURES FOR USING PMTCT DATA FOR SURVEILLANCE PURPOSES

Based on the evidence and discussions to date, we have identified four key recommendations to adapt PMTCT programme activities to meet surveillance needs. These recommendations assume that countries have confidence in the accuracy of PMTCT-based estimates for monitoring population-level HIV prevalence trends. This assumption is discussed further in the final section.

First, we recommend that countries work with PMTCT programme staff to modify clinic-level data collection tools to create a single logbook for all first-time ANC attendees that contains socio-demographic data (including age, marital status, parity and gravidity), whether testing was offered and accepted, the test result for those accepting, and an indication of their HIV status for those previously testing positive. For those refusing to test with an unknown HIV status, socio-demographic data could be useful in creating risk-profiles to adjust estimates for non-participation biases [13]. For those testing or with a previously known HIV-positive status, socio-demographic data will be required to permit basic stratified data analyses to aid in interpreting trends in addition to being necessary to construct risk-profiles.

Second, we recommend that countries work with PMTCT programme staff to identify strategies for accessing and abstracting PMTCT data for surveillance purposes. As evidenced in Zimbabwe, national data may be insufficiently detailed to use for surveillance purposes [15], while in Kenya [16], Botswana [18] and Uganda [14], clinic-level data may be illegible or missing. One possible strategy to address data needs is that countries modify national PMTCT programme paper-based or electronic reporting systems to include line-listed data. Otherwise, they may need to develop special forms or methods for hands-on abstraction of clinic-level data. In either case, the ethics of accessing name-based records containing HIV information for purposes other than patient monitoring may need to be addressed in surveillance protocols.

Third, we recommend that countries ensure that the PMTCT clinics participating in surveillance activities use standardized HIV testing algorithm, as well as internal and external quality assurance and control programmes to assure consistency. In Uganda, Finkbeiner, et al., noted that confusion regarding the PMTCT testing algorithm and insufficient test kits led to a failure to resolve and accurately report discordant results [14]. Additional resources may be required to strengthen existing PMTCT systems.

Fourth, we recommend that consensus be reached internationally and within countries regarding how PMTCT data should be used for surveillance purposes. To date, ANC-based surveillance data have been used to construct national trends in prevalence and among youth aged 15-24 years. These trends in most SSA countries date back to the early 1990s. With the volume of PMTCT data routinely arising from many clinics however, it has been suggested that data from all or a broader selection of clinics be used to more accurately capture population

prevalence trends. We see this suggestion to be difficult to implement in the short-term, however, because a) the transition to collecting sufficiently detailed and high-quality PMTCT data from a greater number of clinics will likely be a non-trivial undertaking for most countries; and b) measures for validating estimates from an expanded number of clinics could be resource intensive. To date, no country has yet validated PMTCT data against broader population prevalence estimates, which would be required if clinics beyond those participating in ANC surveillance activities are included. For these reasons, we suggest that countries initially focus on using PMTCT data from clinics where ANC surveillance has previously occurred and only over a period of time in which a sample size of 250-300 women per clinic can be achieved [1]. While the inclusion of additional clinics beyond those currently participating in ANC surveillance could constitute a longer-term objective, the importance of being able to ensure the highest quality and ongoing consistency of HIV prevalence trends among pregnant women cannot be underscored.

FUTURE RESEARCH PRIORITIES AND CONCLUSIONS

Despite the potential for using PMTCT data for surveillance purposes, there are still some uncertainties about the reliability of these estimates. Most importantly, although uptake of HIV testing through PMTCT continues to increase, non-participation bias remains a concern for many countries, especially in Western and Northern Africa [5]. Evidence from the studies summarized here demonstrates, albeit inconsistently, that lower levels of HIV testing can bias PMTCT-based estimates. Taking this into account, countries must ensure high HIV testing uptake levels independent of HIV status are achieved before relying on PMTCT data for surveillance purposes. How high these levels must be, the extent to which changes in these levels could introduce unpredictable levels of bias over time, and the most appropriate methods for adjusting for bias clearly warrants further research.

We also highlight the need to identify within the international community consensus on how accurate PMTCT-based estimates of HIV prevalence need to be for use for surveillance purposes. For example, some studies have relied on non-statistical measures to judge whether PMTCT estimates are sufficiently comparable to ANC estimates while others have used chi-squared tests to directly compare estimates. In some countries, evidence of disparities in clinic-level comparisons has been sufficient to decide that PMTCT data were not useful, even though overall estimates were similar. Specific to clinic-level comparisons, we also note that owing to small sample sizes, validating PMTCT and ANC surveillance estimates using overlapping 95% CIs may be meaningless since upper and lower bounds will be large. Until a common set of criteria regarding the level of accuracy required can be generated and appropriate methods for assessing this accuracy agreed upon, countries may struggle to make use fully of PMTCT data.

Even as these future research priorities are debated internationally and within countries, there is clear and mounting evidence for the future use of PMTCT data for surveillance purposes. Recognizing this, surveillance staff, in addition to taking steps to adopt the recommendations described above, should be working with PMTCT staff to advocate for the expansion of PMTCT programs at all ANC clinics, for efforts to increase testing uptake, and for strengthening of PMTCT reporting systems that will generate complete, high-quality data. These efforts will represent not only an opportunity for improving the use of PMTCT data for surveillance purposes but also an opportunity to promote PMTCT programs and the services that are offered to those women most in need.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

All authors contributed to this work, including reading and approving the final manuscript. JMGC and OB planned the 2008 Bangkok session on the topic of using PMTCT data for surveillance purposes in which the invited speakers, SB, KS, SW and FB presented work included here. KAM conducted the initial literature review and, with OB and JMGC, developed proposed recommendations and future directions for research. KAM with substantial input from OB, JMGC, AY and CEW drafted the paper.

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