UNDERSTANDING HETEROGENEITY IN HIV TRANSMISSION DYNAMICS AMONG KEY POPULATIONS AT HIGHEST RISK OF ACQUISITION

By

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ABSTRACT

The HIV epidemic in Pakistan is most concentrated among key populations (KPs): people who inject drugs (PWIDs) and sex workers (SWs), with the epidemic largely driven by PWIDs. A significant proportion of SWs have overlapping risks due to their interaction with PWIDs through sexual and/or drug injecting networks, thus augmenting their own risk of HIV acquisition. As a result, there is a growing concern that the epidemic in Pakistan will increase substantially among SWs due to their interaction with PWIDs, and perhaps with increasing sexual transmission to the general population through their sexual clients. However, little is known about regional disparities in the trends and patterns of HIV transmission dynamics among KPs in Pakistan.

The overall goal of this research was to investigate the dynamic interplay among KPs in Pakistan in order to improve our understanding of heterogeneity in the emergence, persistence, and spread of HIV infection. Combined with epidemiological analyses, mathematical modeling methods were utilized to explore the complex social and sexual interactions among KPs to elucidate pathways leading to heterogeneity in HIV transmission dynamics. In addition to data from mapping, four rounds of cross-sectional biological and behavioral surveillances data of KPs collected from 20 cities in Pakistan between 2005-2011 were used for analyses.

This research revealed that the HIV epidemic in Pakistan is immensely heterogeneous, comprised of multiple sub-epidemics among KPs, and with substantial variation in geographical trends. Social and sexual networking between SWs and PWIDs may play a key role in the emergence, persistence and spread of HIV among SWs. Findings suggested that there was up to a 3-fold difference in drug injecting probability among SW groups, dependent on where and/or how the SW solicited sexual clients. Nearly one-in-five infections among SWs in Pakistan are estimated to be attributed to sexual transmission from PWIDs; however, results vary substantially by region. The incidence rate among SWs is projected to continue to rise through 2020, while it reached peak among PWIDs in 2011.

This research provided key information that can be used for: national and regional level target setting and resource mobilization, geographical prioritization of HIV response, local level programme planning, target setting and monitoring, and advocacy.

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DEDICATION

I dedicate this thesis work to my parents: my father, Yizengaw Melesse, and my mother, Feten Workineh, who both made great sacrifices to ensure that I had the best possible opportunity to pursue my academic interests. It is unfortunate that my father passed away untimely during early years of my academic career.

To the loving memory of my father:
Although you are no longer physically present in my life, I still feel your impact every day.
You left fingerprints of grace, strength and perseverance in my life.
Your Memories Live on Forever in My Heart.

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LIST OF ABBREVIATIONS AND ACRONYMS

AIDS:	Acquired immune deficiency syndrome
ANC:	Antenatal care
AOR:	Adjusted odds ratio
ART:	Antiretroviral treatment
CI:	Confidence interval / credible interval
CIDA-PAK:	Canadian International Development Agency – Pakistan
EPP:	The UNAIDS Estimation and Projection Package model
FSWs:	Female sex workers
HASP:	Canada-Pakistan HIV/AIDS Surveillance Project
HIV:	Human immunodeficiency virus
HSWs:	Hijra/transgender sex workers
H/MSWs:	Hijra/transgender and male sex workers combined
IBBS:	Integrated biological and behavioral surveillance
KPK:	Khyber Pakhtunkhwa – one of the administrative provinces in Pakistan
KPs:	Key populations
MSWs:	Male sex workers
OR:	Odds ratio
PWIDs:	People who inject drugs
SD:	Standard deviation
STIs:	Sexually transmitted infections
SWs:	sex workers
UN:	United Nations
UNAIDS:	Joint United Nations Programme on HIV/AIDS
WHO:	World Health Organization

1 INTRODUCTION

1.1 GLOBAL HIV/AIDS EPIDEMICS

The human immune-deficiency virus (HIV), and its associated syndrome of opportunistic infections also known as the acquired immunodeficiency syndrome (AIDS), continues to be one of the leading causes of death globally, claiming nearly 76.1 million infections and 35.0 million AIDS-related deaths since its emergence in the 1980s[1,2]. Data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) suggests that there has been a significant decline in AIDS-related deaths globally in the past decade, with reductions estimated at 48% since the peak in 2005; the number of deaths due to AIDS-related illness reduced from 1.9 million in 2005 to 1.5 million in 2010, then to 1 million in 2016[1]. The number of new HIV infections among adults has fallen by an estimated 11%, from 1.9 million in 2010 to 1.7 million in 2016[1]. At the end of 2016, nearly 36.7 million people were living with HIV[1].

Despite remarkable progress in reducing new infections globally, there remains many public health challenges in the development, implementation and evaluation of HIV prevention programs. Some of these challenges include lack of capacity (health infrastructure and human resources), lack of integrated approaches with other programs and services such as tuberculosis control, inadequate implementation of intervention programs, stigma and social discrimination, equitable access to HIV antiretroviral treatment and care, and lack of sustained political will to support research and services.

Evidence shows that key populations (KPs) bear a disproportionate burden of the HIV epidemic globally[1,2]. KPs is a term that refers to groups of people who engage in behaviours that increased the risk for transmission or acquisition of HIV or are otherwise vulnerable to HIV infection in certain situations or contexts. These KPs include people who inject drugs, people who sell sex, men who have sex with men and transgender people. These KPs not only have an increased risk of HIV acquisition due to their vulnerability; they are also affected by legal and social factors that limit access to programs and services, such as HIV testing and treatment[1,2]. With gaps persisting along with public health challenges, it has been suggested that ending HIV epidemic is only possible if KPs at highest risk of infection have access to comprehensive prevention services. Therefore, public health programs are often recommended to be tailored so the right services reach the KPs that are most vulnerable and affected, ensuring that individuals have access to approaches that work.

In countries with concentrated epidemics, such as in Pakistan, there is heterogeneity in the distribution and contribution of different KPs to the HIV epidemic. A concentrated epidemic is defined as an epidemic established among specific sub-populations, also known as KPs, who engage in high risk activities such as frequent unprotected sex and/or drug injection[3,4]. A concentrated epidemic requires the presence of adequate population size and structured networks of KPs for the epidemic to persist, and ongoing transmission is often dependent on bridging infections among KPs[5]. Therefore, in concentrated epidemics, an area that needs more research relates to the intersection of different KPs and how that influences HIV transmission dynamics and control strategies.

1.2 HIV EPIDEMICS IN PAKISTAN

Pakistan has a concentrated HIV epidemic involving complex and diverse populations and overlapping of high risk networks of KPs[6–11]. Overlapping of high risk networks among KPs has been considered as a key factor in emerging HIV epidemic dynamics, as it allows an infection already established in one KP to be bridged to another KP. The context of overlapping of high risk networks here refers to overlap between high risk behaviours within individuals, resulting from a high risk mixing between two different KPs, for example, between people who inject drugs (PWIDs) and sex workers (SWs) through sex and/or drug injection. As such, controlling an epidemic with substantial overlap of sexual risk behaviour and injection drug use among KPs in Pakistan will require a better understanding of the contribution of each risk population group and the role of overlapping risk on HIV transmission dynamics.

Pakistan lies within a large opiate-producing region of South and Southeast Asia (Figure 1.1), and it has a long history of drug use[12]. For instance, 83% of the global supply of heroin is produced in Afghanistan[12–14], and over 75% of this is trafficked through Iran and Pakistan[13]. This makes the region more vulnerable for transmission of HIV through drug injection. Studies have suggested that the HIV epidemic in Pakistan is part of a sub-regional pattern that includes Iran and Afghanistan, particularly in terms of drug injection as the dominant risk behaviour for HIV transmission[13,14]. That said, despite interconnected drug trade routes in the sub-region, there is yet no conclusive evidence to suggest the origin and distinct pattern of HIV transmission among these three countries[15]. The HIV prevalence among PWIDs in the region was estimated at 28.8% in 2014, and Pakistan bears the highest burden of the epidemic in the region[12].

Figure 1.1 Map of Pakistan and neighbouring countries

The two main modes of HIV transmission in the adult population of Pakistan are through needle/syringes sharing and unsafe sex, and as a result, the KPs in which the epidemic is most concentrated are PWIDs and SWs[16,17], with the epidemic predominantly driven by PWIDs[6–11]. SWs in Pakistan include female, male and *hijra*/transgender SWs (hereafter denoted by FSWs, MSWs and HSWs respectively). FSWs, MSWs and HSWs are defined as persons who receive money or goods in exchange for sexual services, either regularly or casually. *Hijras,* a unique form of gender role expression in South Asia, is a term used for individuals who are transgender, trans-sexual, or bi-sexual, and recognized as a third gender although they are most often biologically male[18,19]. These KPs in Pakistan are disproportionately affected by HIV, and they often face legal and social obstacles related to behaviours that increase their vulnerability to HIV transmission[17]. Because of the legal and social implications of their lifestyles, KPs are often forced to inject drugs or engage in sex work in unsafe environments, limiting their access to programs and services, and further subjecting them to harassment and violence[19–22].

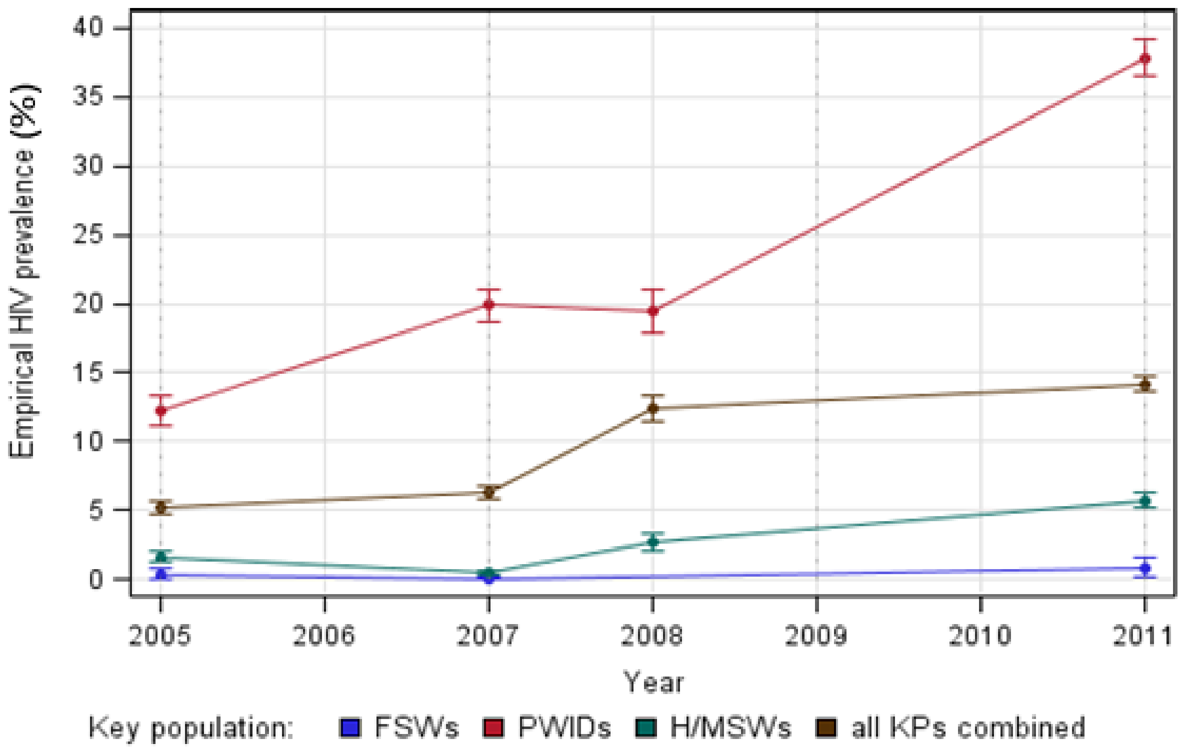
The HIV epidemic in Pakistan has established a firm foothold among PWIDs[6–11], and is perhaps expanding among SWs and to the general population through sexual partners and clients[23–27]. It is important to note that such an epidemic pattern is consistent with the HIV epidemics in many South and Southeast Asian countries, whereby the epidemic begins with PWIDs and subsequently spreads to SWs, and, finally, to the general population through clients[17,28,29].

Epidemiological studies have shown that social and sexual networking between KPs in Pakistan, particularly between PWIDs and SWs, is linked to an upsurge of the epidemic among SWs over the past decade[23–25]. Furthermore, the expansion of HIV among KPs is also related to structural and sociocultural aspects of the KPs, such as cultural stigma, poor knowledge about how to prevent HIV, low literacy and inadequate access to prevention programs and services[30,31].

1.2.1 THE STATE OF HIV EPIDEMICS IN PAKISTAN

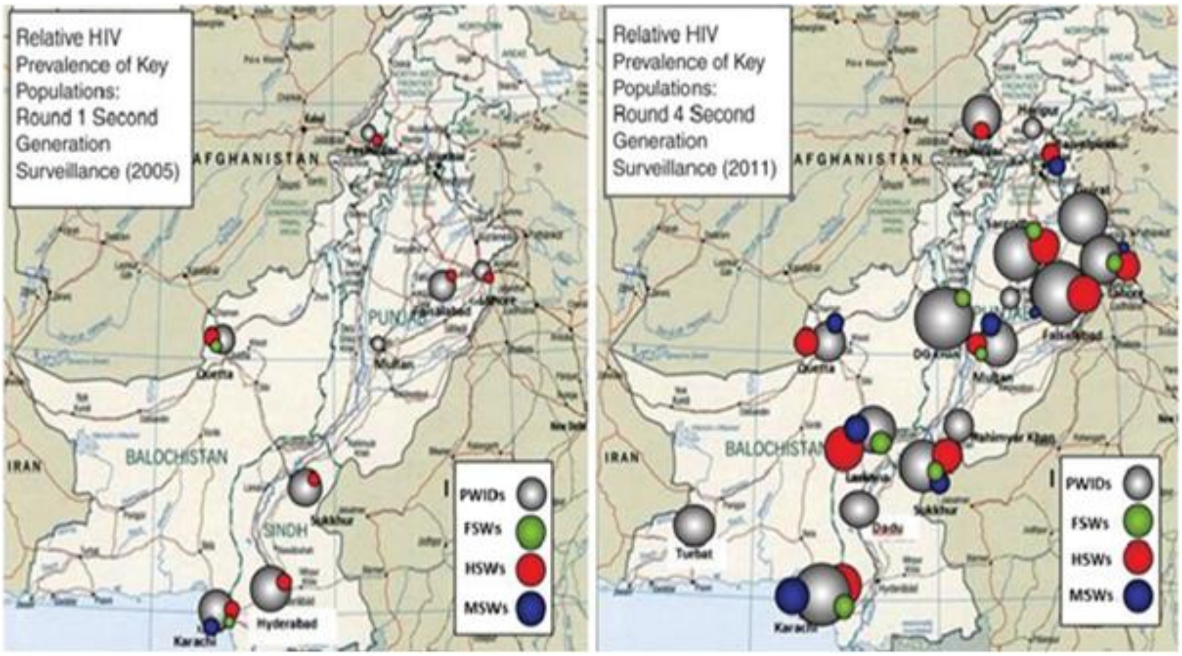
Although the overall HIV epidemic burden in Pakistan remains low, with an estimated prevalence of less than 0.1% among the adult population in 2015[32], the epidemic disproportionately affects KPs. Empirical evidence suggests that the HIV epidemic among PWIDs in Pakistan is well-established, with nearly two-in-five (37.8%) PWIDs living with HIV in 2011 – almost quadruple the prevalence of 10.8% in 2005[7,10,33]. Compared to HIV prevalence among PWIDs, the prevalence among other KPs in Pakistan has remained relatively low. In 2011, the overall prevalence among HSWs and MSWs in Pakistan was reported at 7.2% and 3.1% respectively, while it remained below 1.0% among FSWs[7]. Figure 1.2 presents the overall prevalence of HIV among KPs, combining four rounds of surveillance data collected from 20 major cities between 2005-2011, and Figure 1.3 shows the relative prevalence among KPs in various cities in Pakistan using only the 2005 and 2011 data for comparison[7–10,20]. In addition to data presented in Figure 1.2 and Figure 1.3 below, further details can be found in previous reports[7,10,33].

Figure 1.2 Overall empirical HIV prevalence among KPs in Pakistan, 2005-2011



FSWs = Female sex workers; PWIDs = People who inject drugs;
H/MSWs = Hijra/trangender/male sex workers; KPs = Key populations.
Dots/bars represent empirical HIV prevalence/(95% confidence interval), weighted.

Figure 1.3 Relative HIV prevalence among KPs in various cities in Pakistan, 2005 and 2011[34]



Note that the figure above is reported in a previous study[34], and here it is presented to highlight the relative level of HIV prevalence among KPs in major cities in Pakistan using the two rounds of surveillance data collected in 2005 and 2011.

In a context of concentrated epidemics, it is critical to gain a better understanding of the dynamic interplay among the different KPs and how those interactions influence the emergence, spread and persistence of HIV epidemics among KPs and the general population. For instance, in Pakistan, multiple reports have indicated that a significant proportion of bridging populations – those who engage in risk behaviours that create potential HIV transmission routes between different KPs – engaged in multiple high-risk activities[19,24,35,36].

A study conducted in 2004 reported that nearly one-fifth (20.0%) of FSWs had male clients who also injected drugs, and only 22.0% reported condom use at last sex with a paying sexual client[21]. Another study in 2008 reported that 7.3% of surveyed FSWs in the city of Larkana had sex with a man who also injected drugs in a 6 months period[22]. Data from a 2011 survey also indicated that the proportion of SWs who injected drugs ranged from 0% in Peshawar to 7% in Quetta (more detailed data on bridge populations can be found elsewhere[7,8]). These data suggest that the rising prevalence among SWs may partly be due to their elevated risk exposure through both injection and sexual contacts with PWIDs, among whom the epidemic is already well-established.

Heterogeneity in mixing patterns among KPs has been shown to sustain HIV epidemics and complicate the delivery of HIV intervention strategies[37–39]. An important factor influencing heterogeneity in the HIV epidemic in Pakistan relates to the overlapping of high risk networks. One of the factors that has been cited for the rapid spread of HIV in South and Southeast Asia is the overlap between high-risk behaviours within individuals (i.e., individuals with more than one risk behaviours)[40,41]. Another major concern arises from heterogeneity in the mixing patterns of SWs with PWID networks (through sex and/or drug injection) that play major roles in the variation of observed epidemiological patterns of HIV transmission[16,38,42–44]. However, much remains unknown about heterogeneity in the magnitude and trajectory of the HIV epidemics among KPs, and the factors that drive epidemic heterogeneity in Pakistan. Also, the dynamic interplay between KPs, particularly the overlapping patterns of risk behaviours and the heterogeneity in network structure in HIV transmission between KPs, is not fully understood.

Assessing patterns and trends in new infections is key to better understanding HIV epidemics and is best done through monitoring changes in incidence over time. However, monitoring global changes in incidence is no longer sufficient, and more disaggregated and fine-grained assessments have been suggested for improved estimation of HIV epidemic trajectories and better understanding the heterogeneity of epidemics[45]. While incidence data generate the most useful insights about potential factors contributing to HIV epidemics, it is prevalence data that is often available and used in Pakistan to inform policy and guide the design of intervention programs. Furthermore, prevalence data are currently only available in certain cities and years in Pakistan[7,20,46–50], these empirical prevalence estimates are not globally available across all of Pakistan, and are often limited to estimates only among certain KPs such as PWIDs[49].

Using multiple rounds of mapping and surveillance data collected among KPs in major cities of Pakistan between 2005-2011, this research investigates the complex social and sexual networking within and between KPs to elucidate pathways leading to heterogeneity in the emergence, persistence, spread of HIV transmission dynamics within and between geographies in Pakistan.

1.3 OBJECTIVES OF THE RESEARCH

The overall goal of this research is to understand the heterogeneity of HIV transmission dynamics among KPs in Pakistan. This research has three main objectives:

1. To explore variations in the degree to which SWs are vulnerable to increased risk due to their interaction with PWIDs.
2. To investigate heterogeneity in the patterns and trends of HIV transmission dynamics among KPs within and between regions in Pakistan.
3. To assess the role of sexual networking with PWIDs in HIV transmission among SWs.

In order to achieve stated objectives, up to four rounds of mapping and integrated biological and behavioural surveillance (IBBS) data collected from a total of 20 cities in Pakistan between

2005-2011 were utilized to explore underlying factors contributing to heterogeneity in the emergence, spread and persistence of HIV transmission among KPs. Combined with epidemiological tools, dynamical and context-specific deterministic mathematical models were utilized to examine potential epidemiological drivers that may lead to variations in the emergence, persistence, and spread of HIV epidemics within and between regions in Pakistan. In addition to basic transmission routes of HIV between persons, biological, behavioural and socio-demographic factors that may lead to disparities in HIV transmission were identified and used as input parameters as appropriate to fit models. Our estimates are based on models parameterized by the state-of-art empirical data obtained from representative samples of each KP in each city.

1.4 FRAMEWORK FOR ANALYZING RESEARCH PROBLEMS

Epidemiological analyses and complex dynamical modeling were employed to better understand the heterogeneity in the transmission dynamics of HIV among KPs within and between geographies in Pakistan. Two modeling exercises were performed: statistical modeling for a study in Chapter 2 and mathematical modeling for studies in Chapters 3, 4 and 5. In addition to details provided below and in the methods section of each study, further details can be found in APPENDIX B, APPENDIX C and APPENDIX D.

1.4.1 MATERIALS AND METHODS

1.4.1.1 DATA SOURCES

This research utilized four rounds of comprehensive IBBS and mapping datasets collected from KPs in Pakistan. These datasets, housed at the National AIDS Control Programme in Pakistan, and available for analysis through a collaborative agreement with the Centre for Global Public

Health at the University of Manitoba, are wide-ranging, and comprehensively examine the risk behaviours, network configuration and environments in which each KP is embedded.

Since 2004/05, mapping and IBBS data have been collected among KPs to monitor HIV prevalence and associated risk factors[7–10]. A total of four rounds of data were collected among KPs in 20 cities in Pakistan between 2005-2011. Rounds of data were collected in less than two years apart in each, and these datasets include HIV-specific epidemiological, behavioural and biological variables, which were used to contextualize the epidemiological analyses and mathematical modeling framework.

1.4.1.2 STUDY POPULATIONS

The study populations of this research are mainly PWIDs, HSWs, MSWs and FSWs. MSWs and HSWs are men and transgender women aged 13 and 15 or older, respectively, and FSWs are women aged 15 or older who sell sex in exchange for money or gifts. Many MSWs in Pakistan start sex work at a younger age than FSWs or HSWs[7–10], and therefore the age limit for inclusion of MSWs sample was lower. While most *hijras* are transgender women (i.e., individuals born biologically male, but present as women in public, particularly through wearing conventionally feminine attire), smaller proportions are intersex individuals or have undergone sex reassignment (or gender confirmatory) surgery[18,51,52]. PWIDs were defined as persons aged 18 or older who had injected drugs in the past six months.

The different age cut-offs in the inclusion criteria are based on anecdotal evidence from key informants and the age distribution of each KP observed in subsequent IBBS surveys. Inclusion and exclusion criteria during all IBBS rounds were ascertained through a broad national consultative process in which all stakeholders along with National and Provincial AIDS Control Programs participated. These KPs were described in previous IBBS reports[7–11]. In addition to details provided on the inclusion and exclusion criteria used in each study, further details on each KP can be found in APPENDIX A. The characteristics of each KP studied in this research have also been discussed previously[7–10,19,20,34,35].

1.4.1.3 DATA COLLECTION

The methodology of data collection has two parts: mapping exercises for size estimation of KPs and conducting IBBS surveys. Each round of IBBS began with an in-depth geographic and networking mapping exercise to estimate the size, distribution and operational typology of PWIDs and SWs in targeted cities, except the third round (2008) where the second-round mapping (2006/07) was used as a basis to recruit study samples. Mapping exercises involved systematically identifying key informants, contact tracing, and triangulating of results done through a process of validating identified hotspots and estimated number of KPs in each hotspot. Hotspots are places where high-risk places take place.

Overall size estimations were made for each KP in each city, obtained by combining estimates obtained from all validated spots. Cities were selected based on anecdotal evidence from key informants about high risk activity, the presence of multiple KPs, as well as the geographical accessibility of the area. Following mapping, a representative sample of each KP was drawn from estimated population sizes of each KP in each city. IBBS cities were identified before the start of each round of surveillance through a broad national consultative process in which all stakeholders along with National/Provincial AIDS Control Programs participated.

Various techniques in different rounds of IBBS were utilized to draw representative samples of each KP in selected cities. For instance, in IBBS-2011, HSWs were recruited through information obtained from network mapping of *gurus* (teachers, "retired" HSWs, or who were *hijras* with past experience in sex work) to gather information on their operational typologies, and that is either as "*dera*-based" or home-based *hijras*[53]. Of note, *dera* refers to a house, operated and supervised by *gurus,* where student *hijras* live. Street-based FSWs were recruited using time-location cluster sampling, PWIDs and MSWs were recruited using multistage cluster sampling, and brothel-based FSWs were selected through systematic random sampling (i.e., systematic sampling from a list of FSWs using a random start). Home-based FSWs (those who live with their families and are involved in covert sex work activities and those who live and operate in small houses rented by network operators[7–10]) were recruited through similar sampling techniques used for HSWs. Respondent driven sampling was used to recruit samples from most hidden MSWs, while HSWs and PWIDs were recruited through cluster sampling and time-location cluster sampling techniques respectively. A "take all" approach was also used in cities where the estimated number of KPs was smaller than the required sample size.

Behavioural data were then collected from sample population using structured questionnaire covering socio-demographic information and risk behaviour indicators identified from literature on HIV. Biological data were gathered using capillary Dried Blood Specified (DBS) methodology, chosen for its easy of collection, storage, shipping, and serological accurac[7–11]. Data was collected by trained interviewers using structured questionnaires. Data from FSWs were not collected in the third round (2008/09) because of low HIV prevalence observed in 2006/07. Because HSWs and MSWs are both biologically male and they have overlapping of networks, including client networks, IBBS data among these KPs were collected together except in the fourth round conducted in 2011. Stratified by survey round, city, and KP, the average sample size per strata ranged, approximately, between 350-400. In addition to the information provided in each study, further details can be found in APPENDIX A. The methods used for mapping, sampling and data collection of these KPs have also been described previously[7–11,34,53].

1.4.2 STATISTICAL ANALYSIS

In Chapter 2, results of statistical modeling analyses, which explored the extent to which sexual interactions between SWs and PWIDs was related to drug injection, are presented. Data from the 2011 IBBS data were used for analyses, and all relevant epidemiological, biological, behavioural and socio-demographic factors were identified and examined descriptively. Empirical HIV prevalence was estimated from the number of HIV-infected people divided by the total number of people surveyed.

Multivariable logistic regression analysis was conducted to identify factors that were related to drug injection. The Wald test was used as appropriate to select these factors at a significance level of $p<0.10$. These covariates were added to the multivariable model, and were chosen based on the literature and on epidemiological relevance. In all analyses, appropriate sampling weights were used based on the respective population size estimates for each KP in each city obtained from the mapping exercise. Survey weights based on the respective estimated population sizes of each KP in each city were utilized in order to account for the complex sampling design used. In survey weights (also called sampling or probability weights), an observation represents a certain number of people in a finite population and are often the reciprocals of the selection probabilities for the survey design. In addition to details provided in Chapter 2, further information can be found in APPENDIX B.

1.4.3 MATHEMATICAL MODELLING

Conceptual frameworks and mathematical models that reflect realistic dynamical scenarios can elucidate specific pathways that lead to heterogeneity in HIV risk, and ultimately inform intervention priorities. However, because of the complicated nature of population-level HIV outcomes which are dependent upon the cumulative impact of individual behaviours, methods used to quantify complex outcome measures (such as heterogeneity in the dynamical relationships of HIV transmission) are often restricted to conventional methodological tools and heavily rely on statistical approaches – which overlooks nonlinear HIV transmission pathways[54–56]. In order to address such limitations, complex mathematical dynamic modeling has been suggested as a conceptual and methodological step forward[54,55], although its broader use has often been hampered by the lack of appropriate empirical data to fit models[55]. Given the availability of four rounds of in-depth mapping and empirical data collected among KPs, it was feasible to utilize both the epidemiological and mathematical conceptualization of the dynamic interplay among KPs. As the utility of findings from a specific setting is limited, data collected from up to 20 different cities in Pakistan were used to expand the generalizability of this study's findings.

In Chapters 3 and 4, the UNAIDS Estimation and Projection Package model (EPP)[57–59] was adapted, validated and utilized for modeling. Because the EPP model lacked the flexibility to contextualize and carry out the study in Chapter 5, different mathematical models were constructed and utilized to accommodate the context of sexual interaction between SWs and PWIDs.

In order to explore the level of behavioural complexity required to realistically simulate the transmission of HIV amongst KPs in different city of Pakistan, different context-specific models were considered and each model was fit to the observed epidemiological IBBS data. Input parameters from observed data, detailing behavioural, biological, and sexual and injection networks within and between KPs were used to fit each model. In utilizing these complex compartmental models, potential variations of HIV transmission were considered by region, by biological and behavioural risk susceptibility and by mixing patterns between SWs and PWIDs to reflect heterogeneity in observed HIV epidemics by city.

A good level of understanding of sizes of networks of KPs (i.e., sexual and injection networks) is crucial to produce reliable, and local HIV estimations and projections. This helps to make evidence-informed decisions for resource allocation, geographical prioritisations, and local level programming, target setting and monitoring. Weighted estimates of KPs were used to account for the potential impact of size of each KP's network and potential bias in sampling techniques. Frequent partner turnover increases the risk of encountering infectious individuals, and is, in turn, associated with onward transmission of HIV. As such, this study took into account the duration of time that KPs engaged in high risk behaviours as appropriate to examine the turnover rate among KPs and assess how that affects estimated prevalence and incidence.

In HIV transmission, the type of risk behaviour to which susceptible individuals are exposed, and the degree to which KPs interact within and between themselves, strongly determines the potential of the epidemic to either persist or die out. This suggests that it is crucial to account for variations in HIV transmission risk due to the risk behaviour in which individuals are most engaged. Efforts were made to ensure that models were realistic and had an adequate level of complexity to illustrate the complex interaction within and between members of KPs. Taking all of these factors, as well as biological factors into account, model compartments were constructed to represent either all females or males, but with different levels of risk to acquire or transmit HIV due to the risk exposure (unsafe sex or injection drug use), or the socially constructed roles associated to each risk group (e.g. assuming no sexual mixing within and between female and *hijra*/male sex workers).

As complex models may not be solved analytically, a numerical approach may be the only way to understand the behaviour of complex models utilized in this study. Furthermore, complex models may also be structurally complex and fit to estimated values of input parameters which exhibit high degrees of uncertainty. Thus, we performed uncertainty and sensitivity analyses when appropriate to explore the behaviour of such complex models. Note that uncertainty analysis is helpful to assess the variability (prediction imprecision) in the outcome variable that may occur due to the uncertainty surrounding the estimated values of input parameter whereas sensitivity analysis helps to identify the input parameter which may contribute to the imprecision of the outcome variable[60–62]. Further details on each mathematical model utilized in this research can be found in APPENDIX C and APPENDIX D.

1.4.4 ETHICAL APPROVAL

This research received ethics approval from the University of Manitoba (APPENDIX E). Further details on ethical approvals of each round of IBBS data collection is also provided in each of the studies included in this research.

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2 HETEROGENEITY AMONG SEX WORKERS IN OVERLAPPING INTERACTIONS WITH PEOPLE WHO INJECT DRUGS: A CROSS-SECTIONAL STUDY FROM 8 MAJOR CITIES IN PAKISTAN

2.1 CHAPTER OVERVIEW

This study investigates heterogeneity in the level of overlapping HIV risk behaviours and the risk mediating environments along the pathway to overlapping HIV risk vulnerability among SWs. The HIV epidemic in Pakistan is most concentrated in KPs, with the epidemic predominantly driven by PWIDs. However, in addition to having sexual clients who are PWID, a significant proportion of SWs inject drugs, increasing their risk of HIV exposure. As a result, there is a growing concern that the virus may be expanding from PWIDs to SWs, and perhaps to the general population through non-KP sexual clients of SWs. This study is important for two reasons. First, it highlights heterogeneity in the mixing patterns among KPs which has been shown to sustain HIV epidemics. Second, it provides the justification to consider social contexts and the risk environments in designing priority focused interventions.

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2.2 ABSTRACT

Background: Concerns remain regarding the heterogeneity in overlapping HIV risk behaviors among sex workers (SWs) in Pakistan; specifically, the degree to which SWs interact with people who inject drugs (PWID) through sex and/or needle sharing.

Methods: Following an in-depth mapping performed in 2011 to determine the size and distribution of key populations at highest risk of HIV acquisition in Pakistan, a cross-sectional biological and behavioral survey was conducted among PWID, and female (FSWs), male (MSWs) and *hijra* /transgender (HSWs) sex workers and data from 8 major cities were used for analyses. Logistic regression was used to identify factors, including city of residence and mode of SW-client solicitation, contributing to the overlapping risks of drug injection and sexual interaction with PWID.

Results: The study comprised 8,483 SWs (34.5% FSWs, 32.4% HSWs, 33.1% MSWs). Among SWs who had sex with PWID, HSWs were 2.61 (95% CI, 1.19-5.74) and 1.99 (95% CI, 0.94-4.22) times more likely to inject drugs than MSWs and FSWs, respectively. There was up to a 3-fold difference in drug injecting probability, dependent on where and/or how the SW solicited clients. Compared with SWs in Larkana, the highest likelihood of drug injection use was among SWs in Multan (OR=4.52; 95% CI: 3.27-6.26), followed by those in Lahore, Quetta, and Faisalabad.

Conclusions: Heterogeneity exists in the overlapping patterns of HIV risk behaviors of SWs. The risk of drug injection among SWs also varies by city. Some means of sexual client solicitation may be along the pathway to overlapping HIV risk vulnerability due to increased

likelihood of drug injection among SWs. There is a need to closely monitor the mixing patterns between SWs and PWID and underlying structural factors, such as means of sexual client solicitation, that mediate HIV risk, and implement prevention programs customized to local sub-epidemics.

2.3 INTRODUCTION

The HIV epidemic in Pakistan is concentrated among key populations (KPs), including sex workers (SWs) and people who inject drugs (PWID).[1–5] Stigmatized populations in Pakistan, such as PWID and SWs, engage in drug injection and transactional sex underground, limiting their access to services and subjecting them to harassment and violence.[6–8] Understanding important aspects of HIV transmission dynamics is required to facilitate containment of the epidemic. This includes understanding risk behaviors of each KP, as well as mixing patterns among and between KPs.

The prevalence of opiate drug use has been estimated at 0.7% among the adult population in Pakistan.[9] Recent studies have demonstrated that HIV in Pakistan is concentrated largely among PWID, with an estimated prevalence of 11.0% in 2004, increasing steadily to 27.2% by 2011.[1] There is geographic variation in HIV prevalence among PWID in Pakistan. In 2011, this ranged from 19.2% in Sukkur to 30.7% in Lahore, 43.0% in Karachi and 52.5% in Faisalabad.[2,4,10,11] While HIV prevalence is concentrated mainly among PWID in Pakistan,[1,3,10,12–15] there is a concern that the virus is expanding to their sexual contacts, particularly SWs.[2–4,10,16] This in turn may lead to the spread from SWs, through their non-PWID clients, to the general population.

In addition to having sexual clients who are PWID, a significant proportion of SWs may inject drugs,[3,4] increasing their risk of HIV exposure.[17] Thus, the potential for a substantial increase in transmission within networks of SWs and their clients exists,[7,16,18,19] consistent with the pattern of HIV epidemics in other countries in Asia, whereby HIV transmission begins among PWID and subsequently spreads to SWs and their clients.[20–24]

Understanding heterogeneity in mixing patterns among KPs in concentrated HIV epidemics may help in the design of more effective intervention strategies.[1,3,4,11,17] For example, the degree to which SWs interact, either through sex or drug injection, with PWID, may play a major role in the variation of observed epidemiological patterns of HIV transmission.[1,3,4,7,23,24] Similarly, multiple risk behaviors within individuals is considered to be one of the factors fueling the rapid spread of HIV in South and South East Asia,[1,3,7,24] and a similar situation may exist in Pakistan. Using cross-sectional, integrated biological and behavioral surveillance (IBBS) data collected among KPs in 2011,[2] the objectives of this study were to examine heterogeneity in overlapping HIV risk behaviors among SWs, specifically the degree to which SWs interact with PWIDs through sex and/or needle sharing, and to identify factors associated with drug injection risk vulnerability among SWs in Pakistan.

2.4 METHODS

2.4.1 DATA SOURCES AND STUDY POPULATIONS

The IBBS data for this study was collected by the Canada-Pakistan HIV/AIDS Surveillance Project (HASP) from March 2011 to September 2011. The data collected among KPs were from 17 cities in Pakistan. The 8 cities with data available among all KPs were included in this analysis. These cities are Lahore, Faisalabad, Multan, Sargodha, Karachi, Sukkur, Larkana, and Quetta.

IBBS was conducted following an in-depth mapping of all KPs aimed to estimate the SW population size in each city.[3,25,26] The KPs mapped and surveyed in each city were male (MSW), female (FSW) and *hijra/*transgender *(*HSW) sex workers, and PWID. Inclusion criteria included selling sex in exchange for money or other benefits, and age 13 or older among MSWs, and 15 or older among FSWs and HSWs. Evidence from previous IBBS data suggests that many MSWs start sex work at a younger age than FSWs or HSWs, and therefore the age limit for inclusion in the 2011 MSWs sample was lowered to 13 years. PWIDs refer to persons aged 18 or older who had injected drugs for non-therapeutic purposes in the past six months. Further details of the IBBS methods, including the sampling design and how study participants of each KP in each city were recruited, have been described previously.[2–4,10,11,25] In this study, we describe SW risk behavior and mixing patterns, specifically their mixing with PWID.

2.4.2 STUDY MEASURES

Among SWs, the main outcomes of interest were overlapping risk behaviors that would link the SW and PWID populations; that is, having vaginal or anal sex with a PWID in the past 6 months, and/or drug injection (at least one of the four drugs: *avil, diazepam, tamgesic* or *heroin*) in the past 6 months. The heterogeneity in the overlapping of HIV risk behavior among KPs was assessed by examining the likelihood of injecting drugs among SWs, and comparing this likelihood of injecting drugs across SWs who differed in terms of their sexual interaction with PWID in the past 6 months.

In addition to sexual interactions with PWID, we explored several factors that may explain the heterogeneity in the risk of drug injection among SWs. Specifically, we examined socio-demographic indicators, including city of residence, as well as a potential structural or risk-mediating factor that describes how SWs usually find or communicate with clients. Possible network structures include “network operators” (also called pimps/gurus), roaming around the streets, referral from old clients, and using mobile phones. The potential impact of this structural factor along the pathway to drug injection vulnerability was examined.

2.4.3 STATISTICAL ANALYSIS

We described SWs in terms of how they interacted with PWID. HIV prevalence of each KP was estimated as the number of HIV-infected people divided by the total number of people surveyed in each of the respective KPs. Demographic, geographic, and risk-taking characteristics of study participants were examined descriptively. Mean and standard deviations (SD) of age during interview and the number of years (duration) that people remain in respective KPs as of the time of interview were calculated to further describe study participants.

Bivariate logistic regression analysis was used to identify factors for multivariable analyses that may be significantly related to drug injection. These factors included having had sex with PWID in the past 6 months, the structural indicator of how the SW connects with clients, and socio-demographic indicators including geographic residence. Further analysis was performed to assess the significant interaction effect of any two independent variables of interest. Unless otherwise stated, Wald tests were used to select factors that were associated with drug injection at a significance level of $p<0.10$. After variables were assessed independently, multivariable logistic regression analyses were performed to examine the impact of included variables on the likelihood of injecting drugs after adjusting for covariates. In the process of examining the impact of variables of interest, some variables were thought *a priori* to be important, so they were included in multivariable analyses even if not statistically significant in bivariate analyses. These included age, education level, marital status, income, duration in sex work and HIV status. In all analyses, survey weights based on the respective estimated population sizes of each KP in each city were utilized in order to account for the complex sampling design used. In survey weights (also called sampling or probability weights), an observation represents a certain number of people in a finite population, and are often the reciprocals of the selection probabilities for the survey design. Further details of weighting was identified as described previously.[27–29] All analyses were conducted using SAS (version 9.3; SAS Institute Inc., Cary, North Carolina).

2.4.4 ETHICAL APPROVALS AND STUDY PARTICIPANT CONSENTS

All participants were interviewed following informed consent and referred for voluntary counselling and HIV testing, post-interview. They were also provided with HIV prevention and service information. HIV test results were linked to the corresponding interview data by an encrypted unique identifier and unique study site; no personal information accompanied the data and only authorized personnel had access to the data files. The study received ethical approval from HOPE International and Public Health Agency of Canada.

2.5 RESULTS

A total of 8,483 SWs (34.5% FSWs, 32.4% HSWs and 33.1% MSWs) from 8 major cities from Punjab, Sindh and Balochistan provinces in Pakistan were included in the study. The mean age of SWs was 26.3 years (SD 6.5), and the mean number of years that they had been in sex work by the time of their interview was 6.2 (SD 5.7).

Table 2.1 displays the distribution of socio-demographic characteristics of SWs in terms of their exposure to drug injection. Table 2.2 characterizes SWs in terms of overlapping HIV risk behaviors (i.e., injected drugs and/or had sex with a PWID during the past 6 months), their age during interview, and the duration in practicing high risk behavior. The HIV risks studied were having sex with PWID, injecting drugs, or overlapping risks (both sexual interaction with PWID and drug injection). In total, 2.23% of SWs reported that they were engaged in overlapping risk behaviors (both injecting drugs and having sex with PWID) in the past 6 months. The percentage of SWs who both injected drugs and had sex with PWID in the past 6 months varied by KP. The highest proportion of overlapping risk behaviors were observed among HSWs (2.99%) followed by FSWs (2.25%) and MSWs (1.20%). Among all surveyed, 4.48% of SWs reported that they injected drugs while 11.65% of SWs reported that they had had sex with a PWID in the past 6 months. A total of 13.90% of SWs reported that they had sex with a PWID or injected drugs in the past 6 months. Among the group with at least one risk exposure, 16.05% were exposed to overlapping HIV risk; that is, they both injected drugs and had sex with PWID. The proportion with exposure to at least one risk behavior, either injecting drugs or having sex with a PWID, was highest among FSWs (14.32%) followed by HSWs (13.55%) and MSWs (12.24%), though the difference was not statistically significant (p=0.25).

Table 2.2 also presents the distribution of age and duration in practicing high-risk behavior among all SWs. Analyses among all PWID (whether or not had sex with SWs in the past 6 months) were also performed for comparison purposes, and results indicated that the overall mean age and duration in practicing drug injection among PWID were estimated at 31.0 years (SD 7.9) and 5.0 years (SD 4.8), respectively. Among PWID who exchanged sex for money, the mean duration in practicing drug injection was 4.1 (SD 3.9). The mean duration of sex work among the population of SWs who injected drugs (mean = 6.8, Table 2.2) was approximately 2.7 years longer than the mean duration of drug injection among PWID who exchanged sex for money (p<0.01, independent t-test).

We further explored trends of condom use among SWs. Overall, less than half (45.55%) of SWs used a condom in the last sexual intercourse with any paying client, and this varied from 53.47% among FSWs to 31.87% and 22.87% among HSWs and MSWs, respectively (p<0.001). In general, those who injected drugs were less likely to use a condom with paying clients (Table 2.2). Worryingly, those who had sex with a PWID in the past 6 months were also less likely to use a condom with paying clients (Table 2.2). We were unable to determine specifically whether a condom was used during sex with the PWID.

The overall HIV prevalence among SWs was 2.55% (95% CI: 2.08-3.00) (Table 2.3). This varied by SW population, with the highest prevalence among HSWs (8.14%), followed by 3.57% among MSWs and 0.97% among FSWs (p<0.01, Fisher's Exact test). The highest HIV prevalence among SWs with at least one interactive risk exposure with PWID was observed among SWs who only had sex with PWID, but did not inject drugs (2.84%). This was followed by the prevalence among SWs who only injected drugs but did not have sex with PWID (2.10%) and SWs engaged in overlapping risk (2.09%) (p<0 .05, Fisher's exact test for difference between the three groups).

There is also variation in HIV prevalence between KPs with respect to the type of risk behavior(s) that SWs engaged in with PWID (Table 2.3). Among HSWs with known risks, the highest HIV prevalence (11.23%) was observed among those who only had sex with PWID, but did not inject drugs, followed by a prevalence of 7.35% among those with overlapping risk and 5.88% among those who injected drugs, but did not have sex with PWID ($p<0.05$, Fisher's Exact test). Interestingly, although with wide confidence intervals, the highest prevalence among HSWs was found among those who did not know whether they had had sex with a PWID in the past 6 months. While the highest HIV prevalence among HSWs with known risks was among those who had had sex with a PWID but who did not inject drugs, a contrasting result was found among FSWs and MSWs. That is, among both FSWs and MSWs, those who injected drugs but had not had sex with a PWID in the past 6 months had higher HIV prevalence than those who had had sex with PWID but did not inject drugs ($p<0.05$, Fisher's Exact test). Those SWs exposed to at least one risk behavior involving PWID (injecting, or sex with PWID, or both) had a lower overall HIV prevalence (2.56%, not shown in Table 2.3) than those with no interaction with PWID (2.79%), though the difference was not statistically significant ($p=0.26$, Fisher's Exact test).

2.5.1 LOGISTIC REGRESSION ASSOCIATIONS WITH DRUG INJECTION

Risk factors associated with drug injection during the past 6 months, after adjusting for potential confounding variables, are presented in Table 2.4. Income is associated with injection, with those making > 15,000 rupees per month being 1.89 (95% CI: 1.06-3.35) times more likely to inject than those making < 10,000 rupees per month. Similarly, there is variation in the odds of injecting by city. For example, SWs from Multan and Lahore are 4.52 (95% CI: 3.27-6.26) and 2.20 (95% CI: 1.36-3.56) times more likely to inject than SWs from Larkana. Compared to SWs who recruited their sexual clients using mobile phone, SWs who solicited through a mediator (pimp/network operator), by roaming around in public places, and through old clients were 1.91 (95% CI: 1.13-3.22), 2.16 (95% CI: 1.28-3.66) and 2.94 (95% CI: 1.38-6.28) times more likely to be engaged in drug injection, respectively.

The type of SW (FSWs, HSWs, or MSWs), exposure to sexual interaction with PWID, and the interaction of these two factors were significantly associated with drug injection. The adjusted odds ratios comparing interaction groups are displayed in Table 2.4; to ease interpretation, Figure 2.1 displays the unadjusted odds of drug injection. Although having had sex with a PWID was significantly associated with having injected drugs across all SWs, the impact varied by SW group. The largest impact of sex with a PWID on having injected drugs was seen among HSWs. Among HSWs, those who had had sex with PWID in the past 6 months were 27.62 (95% CI: 14.41-53.29) times more likely to have injected drugs, compared to HSWs who had no sexual interaction with PWIDs. By contrast, among FSWs and MSWs, those who had had sex with a PWID in the past 6 months were 5.83 (95% CI: 3.54-9.59) and 14.26 (95% CI: 6.44-31.60) times more likely to have injected drugs, respectively, compared to their respective SW group who had no sex with PWID. Among the SWs groups who had sex with PWID in the past 6 months, HSWs were 2.61 (95% CI: 1.19-5.74) and 1.99 (95% CI: 0.94-4.22) times more likely to have injected drugs than MSWs and FSWs, respectively.

2.6 DISCUSSION

There is heterogeneity in the overlapping patterns of HIV risk behavior between SWs and PWID. Results of this study indicate that SWs who interacted with PWID sexually have higher odds of exposure to drug injection. Thus, SWs who had sex with PWID can be expected to be at a higher risk of HIV infection due to overlapping risk exposure (i.e., the risk of injection and having sex with PWID). This overlapping risk, however, varies among KPs. HSWs in our study were more likely to be engaged in overlapping risk behavior than other SW populations. Thus, given that the HIV epidemic is driven by PWID in Pakistan, HSW might be at a higher risk of HIV transmission compared to other SW groups. It is likely that social and structural factors such as legal, cultural and policy aspects are factors contributing to pushing HSWs to society's margins, and perhaps leading to social exclusion and economic vulnerability that exacerbate individual vulnerability to multiple risk exposures and compromise the ability to protect oneself from infection.

Consistent with previous work[10], we found that the pattern of interaction between SWs and PWID was heterogeneous by city and SW population. For instance, compared to Larkana where only about 1% of SWs reported having injected drugs, SWs from Multan followed by Lahore, Quetta, and Faisalabad might be at a higher risk of HIV transmission due to the higher odds of drug injection. Additionally, those SWs who do interact with PWID may have differing degrees of HIV exposure. In 2011, the overall HIV prevalence among PWID in 16 cities in Pakistan was estimated at 27.2%, but varied among cities, with the highest prevalence from Faisalabad (52.5%) followed by Karachi (42.2%), Sargodha (40.6%), Lahore (30.8%), Multan (24.9%), Sukkur (19.2%), Larkana (18.6%) and Quetta (7.1%).[2,3]

2.6.1 STRUCTURAL FACTORS ASSOCIATED WITH SEX WORKER RISK-TAKING BEHAVIOURS

An important factor associated with drug injection that was discovered in this study is the usual means through which SWs solicit or communicate with their sexual clients. It highlighted that some modes of client solicitation, though not direct risks for HIV, are along the pathway to HIV risk because of the potential association with drug injection use. SWs who operationalize through mediators (network operators, pimps), by roaming around in public places, and through referral by old clients, might be exposed to a greater risk of HIV transmission than those who operationalize by phone, due to their increased risk of drug injection. Thus, in designing intervention strategies, understanding this variation in structural factors that may drive the HIV risk is crucial. This evidence may help to design interventions that explicitly aim to target structural factors that lie along the pathways to HIV risk.

The risk of HIV acquisition varies widely, dependent on many individual factors, such as condom use,[30] circumcision,[31–34] antiretroviral treatment initiation by both the infected and uninfected partner,[35] and use of sterilized needle and syringe during needle-sharing. Thus, accounting for all these individual factors, alongside the heterogeneous networking structure (how SWs solicit or communicate with clients) and overlapping of risks between SWs and PWID, is crucial to halt the trajectory of HIV transmission in a concentrated epidemic.

2.6.2 SWS INTERACTIONS WITH PWIDS, AND HIV PREVALENCE

HIV prevalence among SWs, who injected drugs in the past 6 months, was much lower (1.99%) than has been shown in previous work among all PWID in this population (27.2%).[1] This is likely explained partly by the lower age of SWs in our study, on average, than PWID. The minimum age in years for study eligibility was 15 among FSWs and HSWs, 13 among MSWs, and 18 among PWID. SWs in our sample who injected drugs were thus younger, on average, than all PWID. More importantly, this may be explained by the duration in practicing drug injection. SWs who had injected drugs in the past 6 months had practiced sex work for approximately 2.7 years longer, on average, than the length of time that PWID who exchanged sex for money had injected drugs. We did not ask people who were recruited into the study because of sex work how long they had injected drugs, but among those SWs who did inject drugs, the duration of exposure to HIV through drug injection could be as short as in the past 6 months compared to the average duration of drug injection among the PWID. The difference in HIV prevalence may also be explained by the frequency of injection after SWs started practicing drug injection. We do not have information among the SW population on frequency of injection, but as their recruitment into the study was based on sex work and not based on injecting, they may be more casual or less frequent injectors than the population that was specifically recruited into the study based on their injecting behavior.

We found that estimated HIV prevalence was slightly lower among those with one (2.56%) or both (2.09%) of the overlapping risks of sex with a PWID and injecting drugs, than among those with neither of the two risks (2.79%). This seemed counter-intuitive, so it was investigated. We explored whether it was possible that those with both overlapping risks may have been younger, thus having fewer years of exposure to HIV on average, than those with none or one mode of interaction with PWID. We also explored whether those with both overlapping risks may have more consistently used condoms, thus their safer condom behavior may have offset their more risky interactions with PWID. We found very minimal differences in mean age between those SWs who injected drugs and/or had had sex with a PWID, and those SWs who had not interacted with PWID. Neither did we find a significant difference in condom use at last sex with a paying client. In fact, what differences we did find in condom use were in the opposite direction – those who interacted with PWID were also *less* likely to use condoms (Table 2.2). It is possible that the disparity in HIV prevalence could be due to condom use with non-paying clients or partners. Perhaps those with greater interaction with PWID practice safer condom behavior with their non-paying sexual partners, than those with less interaction with PWID. It is also possible that the disparity in HIV prevalence could be explained by changes in risk-taking behavior after becoming HIV infected. The HIV infected individuals may have had higher risks before they were HIV infected, and lowered their risk-taking after learning of their HIV status. The questions on our survey refer to drug injection and sex with a PWID *during the past 6 months*.

The main demographic distinction between HSWs, compared with FSWs and MSWs, is that HSWs were 4 to 5 years older than FSWs and MSWs, on average. In addition, HSWs had been practicing sex work approximately 5 to 6 years longer than FSWs and MSWs, on average. This difference in time of potential HIV exposure could explain why HIV prevalence patterns among HSW differed from those among FSWs and MSWs.

2.6.3 LIMITATIONS

We acknowledge the limitations in this study and results must be interpreted cautiously. First, these results relied on self-reported data on behaviours among SWs who responded that they knew they had sexual interaction with PWIDs and/or injected drugs is the past six months. These behavioural responses could potentially be influenced by factors such as presentation biases, social desirability, or a participant's ability to recall whether or not the person had sex with a PWIDs or injected drugs. A participant might have also been unwilling to report having used or injected drugs due to fear of social stigma and/or legal repercussions. While we were able to assess whether or not the SW had injected drugs, details of frequency and needle sharing were unavailable. Although data on condom use among SWs with any paying client was available, we were unable to assess specifically condom use with PWID. This study was also limited in ability to assess underlying factors that may drive SWs to inject drugs. For instance, some SWs may offer sexual services in exchange for drugs. These SWs may have begun by injecting and moved into SW to support their injecting habit. They may differ in risk-taking exposures with those SWs who may have begun to inject drugs as a means of coping with the unpleasant aspects of their occupation. Thus, we suggest further work to better understand why SWs inject drugs and how their SW is related to drug injection. We also acknowledge that the utility of age as a determinant of overlapping HIV risk is limited due to the different age cut-off criteria used to recruit among SW groups.

2.6.4 CONCLUSIONS

There is a need in Pakistan, as in other areas with concentrated HIV epidemics, to closely monitor high-risk behaviors that drive the mixing patterns among KPs and underlying structural factors along the pathway to HIV risk vulnerability. HIV prevention programs that combine behavioral and structural interventions, customized to local sub-epidemics based on key epidemiological trends, is recommended so as to have the greatest sustained impact on reducing potential spread of HIV among KPs and to the general population.

2.7 AUTHOR CONTRIBUTIONS

Performed the data analyses, drafted the manuscript and critically reviewed the manuscript: DYM; co-wrote the manuscript, led the data analysis and critically reviewed the manuscript: LAS; critically reviewed the manuscript and revised later drafts: SYS, TR, FE and JFB; involved in the design of the study: LHT, BKA, SF, TR, FE and JFB; all authors interpreted the results and made a substantial contribution to the final version of the article.

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2.9 CONFLICT OF INTERESTS

The funder had no role in study design, data collection and analyses, decision to publish, or preparation of this manuscript. All authors have no conflict of interest to declare.

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Table 2.1 Characteristics of sex workers

Characteristic		Injected drugs in the past 6 months		p-value*
		No	Yes	
Age during interview, mean (SD)		26.3 (6.5)	26.0 (5.9)	<.01
Currently married, %	Yes	49.90	49.39	.91
	No	50.10	50.61	
Education level, %	illiterate	48.40	58.63	<.02
	Primary or above	51.60	41.37	
Duration in sex work (years), %	≤ 4	47.96	46.37	.40
	5-10	36.44	34.53	
	≥ 11	15.60	19.10	
Income per month (in rupees), %	<10,000	23.25	14.17	<.05
	10,000-15,000	37.54	34.41	
	>15,000	39.21	51.42	
City, %	Faisalabad	8.16	8.12	<.001
	Karachi	41.91	22.82	
	Lahore	24.42	27.43	
	Multan	7.25	23.58	
	Quetta	5.46	7.81	
	Sargodha	5.20	5.30	
	Sukkur	4.68	3.90	
	Larkana	2.90	1.02	
Usual means of soliciting clients, %	Network operators	31.11	40.95	<.001
	Old clients	9.05	13.17	
	Roaming	31.07	32.86	
	Phone	28.77	13.02	
HIV status	Positive	2.56	1.99	.54
	Negative	97.44	98.02	
Used condom with paying client**, %	Yes	45.97	36.91	<.05
	No	54.03	63.08	
Key populations[1], %	FSWs	68.70	77.84	<.001
	HSWs	17.03	15.98	
	MSWs	14.27	6.19	
Sex with PWID in the past 6 months, %	Yes	9.86	49.62	<.001
	Do not know	14.05	6.61	
	No	76.09	43.77	

[1]Proportions are all weighted by estimated population size of key populations within city. For example, while FSWs form approximately 1/3 of our sample, they represent approximately 70% of all SWs; *p-values using Rao-Scott Chi-square test for categorical variables and simple logistic regression for continuous variable when appropriate; SD=standard deviation; **condom use at last; FSWs = female sex workers; HSWs = *hijra*/transgender sex workers; MSWs = male sex workers. Note that 3.97% (337/8483; unweighted) sex workers responded that they had injected drugs in the past 6 months.

Table 2.2 HIV risk behaviours among sex workers in relation to their interaction with PWIDs

Variable	Sex with PWIDs	Sex workers							
		FSWs		HSWs		MSWs		All SWs	
		Injected drugs		Injected drugs		Injected drugs		Injected drugs	
		Yes	No	Yes	No	Yes	No	Yes	No
KP overall, %	Yes	2.25	9.27	2.99	9.34	1.20	10.27	2.23	9.42
	No	2.39	69.69	1.17	83.52	0.72	74.29	1.95	72.68
	DK	0.41	15.99	0.05	2.93	0.05	13.48	0.30	13.42
	Overall*	5.05	94.95	4.21	95.79	1.97	98.03	4.48	95.52
Age during interview, mean (SD)	Yes	25.2 (5.4)	28.1 (6.1)	28.4 (6.5)	27.2 (6.6)	23.7 (5.5)	20.2 (5.8)	25.8 (6.0)	26.7 (6.6)
	No	25.7 (5.4)	27.1 (6.3)	29.4 (6.0)	27.4 (6.3)	24.1 (6.7)	21.8 (5.2)	26.0 (6.0)	26.4 (6.6)
	DK	27.1 (6.1)	26.2 (5.6)	23.4 (2.6)	25.3 (6.0)	22.4 (3.1)	21.1 (4.2)	26.9 (5.6)	25.5 (5.9)
	Overall	25.6 (5.4)	27.0 (6.2)	28.6 (6.3)	27.3 (6.3)	23.9 (5.9)	21.5 (5.1)	26.0 (5.9)	26.3 (6.5)
Duration as sex worker, mean (SD)	Yes	6.7 (4.8)	6.8 (5.0)	11.4 (6.6)	10.6 (5.7)	6.1 (4.8)	4.5 (5.1)	7.7 (6.0)	7.1 (5.6)
	No	4.8 (3.5)	4.9 (4.4)	13.5 (6.7)	11.6 (6.1)	7.4 (7.5)	5.9 (4.5)	5.8 (6.0)	6.4 (5.8)
	DK	6.3 (3.5)	4.8 (3.6)	5.8 (3.5)	9.6 (5.5)	5.9 (3.0)	4.5 (2.9)	6.2 (3.4)	4.9 (3.6)
	Overall	5.8 (4.4)	5.1 (4.4)	11.9 (6.6)	11.5 (6.1)	6.7 (5.5)	5.6 (4.3)	6.8 (5.9)	6.2 (5.6)
Used condom at last sex with a paying client**, %	Yes	35.38	48.76	13.25	18.73	18.47	16.44	29.07	38.81
	No	44.09	54.85	33.73	32.95	61.33	24.35	43.92	46.25
	DK	50.23	54.21	29.98	61.36	21.54	17.75	48.89	49.39
	Overall	40.70	54.15	19.12	32.44	34.20	22.64	36.85	45.96

All percentages are weighted by estimated population size of key population within city. KP=key population; PWID=people who inject drugs; FSWs = female sex workers; HSWs = *hijra/*transgender sex workers; MSWs = male sex workers; SWs= sex workers; SD=standard deviation; DK=Do not know. *Overall proportions in each key population add up to 100%. **These proportions refer to sex workers who used condom at last sex with a paying client among those who injected drugs and did not inject drugs in the past 6 months, and thus the overall percentages do not add up to 100% (for instance, 40.70% refers to proportion of FSWs who used condom at last sex with a paying client among those who injected drugs in the past 6 months and 54.15% refers to proportion of FSWs who used condom at least sex with a paying client among those who did not inject drugs in the past 6 months).

Table 2.3 HIV prevalence (95% CI) by pattern of overlapping HIV risk behaviour among SWs

Sex with PWID*	**Key populations and drug injection***							
	FSWs		HSWs		MSWs		All SWs	
	Injected drugs		Injected drugs		Injected drugs		Injected drugs	
	Yes	No	Yes	No	Yes	No	Yes	No
Yes	0.59 (0.00-1.15)	0.10 (0.00-0.25)	7.35 (0.00-12.66)	11.23 (4.31-15.86)	0.00 (---)	5.81 (0.72-9.31)	2.09 (0.00-3.63)	2.84 (1.49-3.95)
No	0.63 (0.00-1.42)	1.20 (0.44-1.92)	5.88 (0.00-8.58)	7.59 (5.84-9.25)	18.9 (0.00-37.31)	3.58 (2.23-4.86)	2.10 (0.00-3.34)	2.79 (2.21-3.33)
DK	0.00 (---)	0.58 (0.00-1.54)	15.00 (0.00-18.23)	15.62 (0.00-23.39)	0.00 (---)	1.30 (0.43-1.97)	0.47 (0.00-2.45)	1.24 (0.14-2.14)
Overall	0.97 (0.40-1.54)		8.14 (6.33-9.96)		3.57 (2.36-4.79)		2.55 (2.08-3.00)	

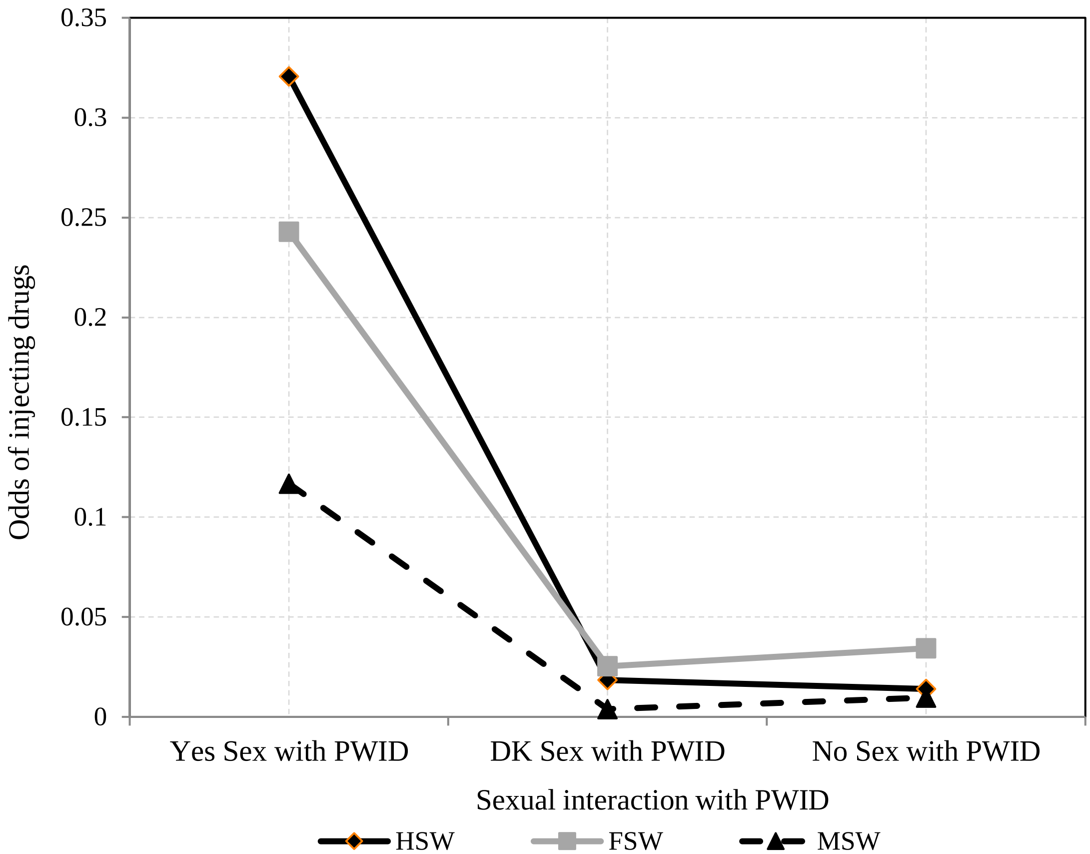
HIV prevalence is in percentage. All prevalence estimates are weighted by estimated population size of key populatio within city. *Drug injection and sex with PWID refers to interaction between SWs and PWID in the past 6 months.
CI = confidence interval; SWs = sex workers; PWID=people who inject drugs; FSWs = female sex workers; HSWs = h*ijra/*transgender sex workers; MSWs = male sex workers; SWs = sex workers; DK=Do not know.

Table 2.4 Crude and AOR (95% CI), reporting the risk of injecting drugs among SWs

Effect		Injected drugs, %	OR	(95% CI)	AOR	(95% CI)	p-value*
Age during interview, mean(SD)		26.0 (5.9)	0.99	(0.97-1.02)	0.97	(0.93-1.01)	.18
Currently married	No	4.52	1.02	(0.73-1.43)	1.09	(0.72-1.66)	.68
Education level	illiterate	5.37	1.51	(1.08-2.11)	1.18	(0.79-1.77)	.41
Duration in sex work (years)	≤ 4	4.34	Ref	---	Ref	---	---
	5-10	4.25	0.98	(0.67 -1.44)	0.98	(0.60-1.61)	.93
	≥ 11	5.43	1.27	(0.86 -1.88)	1.21	(0.64-2.27)	.56
Income per month (in rupees)	<10,000	2.77	Ref	---	Ref	---	---
	10,000-15,000	4.12	1.51	(0.88-2.58)	1.73	(0.95-3.16)	07
	>15,000	5.79	2.16	(1.35-3.44)	1.89	(1.06-3.35)	< .05
City	Faisalabad	4.46	2.83	(2.05-3.91)	1.70	(1.08-2.68)	< .05
	Karachi	2.49	1.55	(1.03-2.33)	0.89	(0.56-1.42)	.62
	Lahore	5.00	3.19	(2.04-5.00)	2.20	(1.36-3.56)	< .01
	Multan	13.22	9.25	(7.45-11.47)	4.52	(3.27-6.26)	< .001
	Quetta	6.27	4.05	(3.08-5.33)	1.78	(1.14-2.78)	< .05
	Sargodha	4.56	2.90	(2.05-4.09)	1.28	(0.77-2.13)	.34
	Sukkur	3.76	2.37	(1.81-3.10)	1.21	(0.73-2.01)	.46
	Larkana	1.62	Ref	---	Ref	---	---
Usual means of soliciting clients	Mediators/pimps	5.81	2.91	(1.83-4.61)	1.91	(1.13-3.22)	< .05
	Old clients	6.38	3.22	(1.61-6.44)	2.94	(1.38-6.28)	< .01
	Roaming	4.72	2.34	(1.47-3.72)	2.16	(1.28-3.66)	< .01
	Phone	2.08	Ref	---	Ref	---	---
HIV status	Positive	3.50	0.77	(0.35-1.69)	0.98	(0.37-2.56)	.96
	Negative	4.50	Ref	---	Ref	---	---
Condom use with paying client**	Yes	3.63	Ref	---	Ref	---	---
	No	5.19	1.45	(1.02-2.07)	1.32	(0.87-2.01)	.19
KP	FSWs	5.04	2.61	(1.74-3.93)			
	HSWs	4.21	2.16	(1.36-3.44)			
	MSWs	1.99	Ref	---			
Sex with PWID in the past 6 months	Yes	19.15	8.12	(6.17-12.61)			
	Do not know	2.16	0.82	(0.41-1.65)			
	No	2.62	Ref	---			
KP × sex with PWID (Only a selection of interaction combinations are shown)	HSWs (Yes) vs. MSWs (Yes)				2.61	(1.19-5.74)	<.05
	HSWs (Yes) vs. MSWs (No)				37.26	(17.83-77.87)	< .001
	HSWs (Yes) vs. FSWs (Yes)				1.99	(0.94-4.22)	.07
	HSWs (Yes) vs. FSWs (No)				11.63	(5.70-23.70)	< .001
	HSWs (Yes) vs. HSWs (No)				27.62	(14.41-53.29)	< .001
	HSWs (No) vs. MSWs (No)				1.35	(0.67-2.72)	.40
	HSWs (No) vs. FSWs (No)				0.42	(0.22-0.80)	< .01
	FSWs (Yes) vs. MSWs (Yes)				1.31	(0.55-3.12)	.54
	FSWs (No) vs. MSWs (No)				3.21	(1.53-6.73)	< .01
	FSWs (Yes) vs. FSWs (No)				5.83	(3.54-9.59)	< .01
	MSWs (Yes) vs. MSWs (No)				14.26	(6.44-31.60)	< .001

Analysis weighted by estimated population size of key population within city. *p-values reported for adjusted analyses only; OR = crude odds ratio; AOR =adjusted odds ratio; CI = Confidence Interval; SD=standard deviation; **condom use during last sex with a paying client; KP=key population; FSWs = female sex workers; HSWs = h*ijra*/transgender sex workers; MSWs = male sex workers; PWID=people who inject drugs.

Figure 2.1 Unadjusted odds of injecting drugs in the past 6 months, by type of sex worker



PWID = people who inject drugs; HSW = *hijra*/transgender sex workers;
FSW = female sex workers; MSW = male sex workers. DK = Do not know.

3 PATTERNS AND TRENDS IN PAKISTAN'S HETEROGENEOUS HIV EPIDEMICS

3.1 CHAPTER OVERVIEW

This manuscript examines geographical disparities in the sizes of bridge populations of PWIDs and SWs, and patterns and trends of HIV epidemics in Pakistan. The HIV epidemic in Pakistan is largely driven by PWIDs, and recently, HIV prevalence has been increasing among SWs. This study describes past and projected future patterns of HIV prevalence among KPs in four major cities in Pakistan. The study highlights that cities across Pakistan have variable degrees of bridging between KPs of PWIDs and SWs, representing potential HIV transmission routes. Model estimates suggest that HIV prevalence may reach 17-22% among H/MSWs in Karachi and 46-56% among PWIDs in Faisalabad by 2015. The HIV prevalence is likely to increase among FSWs, particularly in Karachi and Larkana. This study provides evidence that there is a need to closely monitor regional and sub-population epidemic patterns and implement prevention programs customized to local epidemics.

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3.2 ABSTRACT

Background: Considerable HIV transmission occurs among people who injection drug (PWIDs) in Pakistan and recently the HIV prevalence has been increasing among male (MSWs), *hijra* (transgender; HSWs), and female (FSWs) sex workers. We describe past and estimate future patterns of HIV emergence among these populations in several cities in Pakistan.

Methods: The density of these key populations per 1,000 adult males was calculated using 2011 mapping data from Karachi, Lahore, Faisalabad, Larkana, Peshawar, and Quetta and surveillance data were used to assess bridging between these key populations. We used the UNAIDS Estimation and Projection Package model to estimate and project HIV epidemics among these key populations in Karachi, Lahore, Faisalabad, and Larkana.

Results: The density and bridging of key populations varied across cities. Lahore had the largest FSW population (11.5/1,000 adult males) and the smallest PWID population (1.7/1,000 adult males). Quetta had the most sexual and drug injection bridging between sex workers and PWIDs (6.7%, 7.0%, and 3.8% of FSW, MSW, and HSW, respectively, reported injecting drugs). Model evidence suggests that by 2015 HIV prevalence is likely to reach 17-22% among MSWs/HSWs in Karachi, 44-49% among PWIDs in Lahore, and 46-66% among PWIDs in Karachi. Projection suggests the prevalence may reach as high as 65-75% among PWIDs in Faisalabad by 2025. HIV prevalence also is estimated to increase among FSWs, particularly in Karachi and Larkana.

Conclusions: There is a need to closely monitor regional and sub-population epidemic patterns and implement prevention programs customized to local epidemics.

3.3 INTRODUCTION

HIV transmission in the context of injection drug use has been well-documented in many regions of the world[1-7]. Pakistan lies within a large opiate-producing region and has a long history of drug use.[8] Recent evidence suggests that Pakistan has large networks of people who inject drugs (PWIDs).[9,10] Cross-sectional survey results have indicated high rates of needle sharing in some cities[11-13] and a highly variable HIV prevalence among PWIDs across the country [12,13], as high as 52% in Faisalabad in 2011.[13] Pakistan also has large populations of male (MSW), *hijra* (transgender; HSW), and female (FSW) sex workers[14], generally with low rates of consistent condom use.[13] *Hijras* form a distinct sociocultural group unique to South Asia. Considered the third gender, most *hijras* are born as physiological males and dress in feminine attire, and some undergo castration. Many perform sex work, and clients are male. Typically, Asian epidemics are ignited by HIV transmission among PWIDs and expand into other populations through sexual networks, influenced by the size and characteristics of local key populations at greater risk for HIV infection.[15-17]

Pakistan's HIV epidemic is concentrated among PWIDs (37% weighted prevalence in 2011)[13], with a recent increase in prevalence among sex workers. The overall weighted HIV prevalence in 2011 was found to be 5.1% among HSWs, 1.6% among MSWs, and 0.6% among FSWs.[13] This is consistent with the patterns of other HIV epidemics in Asia [18]; however, Pakistan's HIV epidemics exhibit substantial geographic heterogeneity.[13]

In this paper, we describe the emergence of HIV in several cities in Pakistan, with an examination of differences in the size and characteristics of key populations. Specifically, we present the density of key populations in six cities and assess the sexual and drug injection bridging between these key populations. Modelling results which describe and estimate future patterns of emergence of HIV among these key populations in four cities are presented. This will provide a deeper understanding of Pakistan's heterogeneous HIV epidemics, providing valuable information to inform the design, implementation, and scale up of effective HIV prevention interventions in Pakistan.

3.4 METHODS

3.4.1 STUDY SETTING AND DATA COLLECTION

The study setting, data collection, recruitment, and questionnaire development and interview technique have been described elsewhere.[19-21] Briefly, four rounds of mapping and integrated behavioural and biological surveillance (IBBS) took place among PWIDs and male, *hijra* (transgender), and female sex workers in several cities in Pakistan from November to December 2005 (Round 1), July 2006 to March 2007 (Round 2), March to June 2008 (Round 3), and March to September 2011 (Round 4).

The mapping exercise involved systematically identifying key informants, contact tracing, and triangulating of results through a process of validating identified hot spots and estimated number of KPs in each hotspot. Hotspots are places where high risk activities take place. Overall estimates of sizes of each KP in each city were obtained by combining estimates obtained from all validated spots. Cities were selected based on anecdotal evidence of high risk activity, the presence of multiple KPs, and geographical accessibility. The study was restricted to MSWs age 13 and older, HSWs and FSWs age 15 and older, and PWIDs age 18 and older.

FSWs were not included in Round 3 data collection as the prevalence was extremely low in Round 2, but were included again in Round 4. Unlike in the first three rounds, MSWs and HSWs were surveyed separately in Round 4. For consistency, we combined the MSWs and HSWs Round 4 data into one group for the modelling analysis (hereafter denoted by H/MSWs). MSWs and HSWs are similar in terms of their behaviour as both groups were born as biological males and have male clients; however, HSWs are transgender.

Capillary blood was collected for dried blood spot sampling and stored at room temperature. Samples were transported weekly to the reference laboratories for enzyme immunoassay screening (HIV Genetic Systems rLAV ELISA/EIA, Bio-Rad, United States) and positive tests were confirmed in duplicate with an alternative enzyme immunoassay (Vironostika HIV Uni-Form II EIA, Biomeriux, The Netherlands). Indeterminate results were resolved using Genetic Systems HIV-1 Western Blot (Bio-Rad, United States). All participants received an honorarium for their time and were referred for voluntary counselling and HIV testing and provided with HIV prevention and services information. This study was approved by the institutional ethical review boards of HOPE International in Pakistan and the Public Health Agency of Canada.

3.4.2 STATISTICAL ANALYSIS

Four rounds of data from Karachi, Lahore, Faisalabad, and Peshawar and three rounds from Larkana and Quetta were included in the analysis of key population sizes and bridging between populations. Over all four rounds, 7,118 PWIDs, 6,638 FSWs, and 10,760 H/MSWs were sampled from these six cities. Round 1 data collection did not take place in Larkana or among PWIDs in Karachi, and Quetta was not included in Round 3.

Using Round 4 mapping data, the population density of each key population and city was calculated per 1,000 adult males. Using Round 4 IBBS data, bridging of sexual and drug injection networks was assessed by calculating the proportion of sex workers who had sex with PWIDs, the proportion of PWIDs who paid for sex, and the proportion of sex workers who had injected drugs in the past six months. We determined HIV prevalence and confidence intervals in each round, city, and key population. HIV prevalence was calculated as the number of HIV-infected people divided by the total number of people surveyed in each of the respective years, cities, and key populations.

3.4.3 MATHEMATICAL MODELLING

Data from Karachi, Lahore, Faisalabad, and Larkana were included in the modelling analysis. As there were no data from Larkana in the first round, only three rounds of data were used for this city. Cities were selected based on the following criteria: size of KPs and characteristics of high risk activities, availability of empirical data from all KPs for comparison, size of observed bridge populations, and relatively higher HIV prevalence among all or some KPs compared to other cities. The total sample size from these four cities was 5,459 PWIDs, 4,331 FSWs, and 7,317 MSWs/HSWs. All mathematical modelling was conducted using the UNAIDS Estimation and Projection Package (EPP). This compartmental model in which people move from susceptible to HIV infected compartments, has been described previously.[22-24] The goal of the EPP model is to estimate and project HIV epidemics.

Within each key population group and city, we fit the model to empirically estimated HIV prevalence. To fit, we provided the following input parameters: empirically estimated HIV prevalence from two to four years of survey data depending on the key population and city, population size of the respective cities in 2011, birth rates and background (non HIV-related) mortality rates, the estimated population sizes of the key populations in 2011, the mean number of years (duration) that people remain in respective key populations, and the estimated population sizes of the clients of FSWs and H/MSWs. The population size of respective cities was obtained from the Pakistan Statistics Division[25] and was extended to 2011 using a population growth rate supplied by the United Nations (UN)[26]. The population sizes of key populations were estimated from mapping exercises conducted by our study group[19]. The population sizes of clients were estimated from a combination of the estimated population of FSWs or H/MSWs, and the response to the survey question asking the number of clients that each respondent had sex with in the past month was used to estimate the total population size of sexual clients in a year.

EPP varies four parameters in order to fit to the empirically estimated HIV prevalence; it fits to prevalence data points by minimizing the least squares difference between the fitted curve and the full set of data points[27,28]. These four parameters are the start year of the epidemic, the rate of growth of the epidemic – determined by the rate of spread of the epidemic or reproduction potential (also directly proportional to the basic reproduction number), the peak prevalence – obtained by the proportion of the population who are at risk of infection at the start of the epidemic, and the recruitment rate or the rate at which at risk people who die due to AIDS or otherwise leave are replaced by new at-risk people. Including the start year of the epidemic, these four parameters were estimated from the prevalence data from the survey. The goodness-of-fit procedure used by the mathematical model fits to the empirical point estimates of HIV prevalence. However, there is uncertainty in the underlying prevalence in each key population, which is why we estimate 95% confidence intervals, in addition to point estimates. Due, in part, to the uncertainty in the value of the true prevalence for the years in which we empirically estimated prevalence, mathematical model projections are also uncertain.

We therefore examined a range of plausible HIV epidemic trends as follows. We used the year-specific point estimates of empirical prevalence to fit the model, and for this we initially ran the EPP model with many (3,000) Latin Hypercube Sample (LHS) intervals as recommended by UNAIDS. However, we also fit to each scenario – each city and key population – 30 times, using sample intervals of 100. Using 100 intervals produced more variance in the estimated HIV epidemic and thus produced a range of possible HIV epidemics. With the exception of fitting to Faisalabad, we considered any model estimated epidemic to be plausible if it fit through at least two of the 95% confidence intervals of empirically estimated prevalence for the respective city and key population. Using this method, we only discarded two model runs as 'implausible' – both of the discarded runs were among PWIDs in Larkana. Faisalabad was an exception. As presented in our results, the first three empirical prevalence estimates among PWIDs in Faisalabad were near 15%, and the fourth estimate was > 50%. As no model estimated prevalence fit through more than one 95% confidence interval of empirically estimated prevalence among PWIDs in Faisalabad, we present the results of all model runs for this city, even those that did not meet the criteria used for fitting with the other three cities.

Using mathematical modelling to project many years into the future is always risky because of uncertainty. Using the EPP model, it is particularly risky because one cannot allow EPP to change its four varying input parameters over time. In practice, risk behaviour may change over time, which could be reflected by changing one or more of the EPP parameters if this were possible. For this reason, our main results provide HIV prevalence estimates up to 2015. Nonetheless, while relying on estimated projections more than three or four years into the future should be done with caution, we extended the model to project through 2025 in order to roughly estimate when we might expect to experience peak prevalence in the three key populations and four cities.

In an attempt to validate our model projections to the future, we compared model estimates of HIV prevalence with the 2016 empirical prevalence obtained from the most recent 2016 IBBS report. Of note, the 2016 IBBS was made available most recently after results in this paper were already published.

3.5 RESULTS

3.5.1 DENSITY OF KEY POPULATIONS

The density of each population group per 1,000 adult males varies considerably across cities (Figure 3.1). The H/MSW population density is smallest in Peshawar and largest in Larkana (1.8 and 12.4 per 1,000 adult males). The FSW population density is smallest in Peshawar and largest in Lahore (4.2 and 11.5 per 1,000 adult males). Lahore has the smallest PWID population density and Faisalabad the largest (1.7 and 8.1 per 1,000 adult males). Karachi is a very large city and has the largest population size of all groups, particularly FSWs (estimated 25,399 individuals) and PWIDs (estimated 16,544 individuals) (Figure 3.2).

3.5.2 BRIDGE BETWEEN KEY POPULATIONS

The bridge population comprises individuals who engage in behaviours that create potential HIV transmission routes between different key populations (Figure 3.2). The smallest proportion of MSW, HSW, and FSWs reported injecting drugs in Peshawar (0%, 0.3%, and 0%), and the largest proportion reported injecting drugs in Quetta (7.0%, 3.8%, and 6.7%). Larkana was distinctive as many (8.7%) HSWs reported injecting drugs, but few FSWs (0.3%) and no MSWs did. Many (12.1%) HSWs in Larkana also reported sex with PWIDs. Karachi also had relatively large sexual and drug injection bridging between HSWs and PWIDs. Quetta had the largest percent of PWIDs reporting paying for sex with H/MSWs (10.6%) and FSWs (54.6%) while in Karachi very few PWIDs reported paying for sex. In Quetta, a relatively large percent of MSWs, HSWs, and FSWs reported having sex with PWIDs (16.2%, 17.2%, and 30.3%), while very few in Peshawar reported having sex with PWIDs (0%, 0.9%, and 0.3%, respectively). Also, Faisalabad and Lahore had much sexual and drug injection bridging between FSWs and PWIDs and Faisalabad had much sexual bridging between HSWs and PWIDs. Generally, Peshawar had the smallest bridging of key populations and Quetta had the most bridging between sex workers and PWIDs, both sexual and drug injection.

3.5.3 EMPIRICALLY ESTIMATED PREVALENCE

Empirically estimated HIV prevalence trends from the four survey rounds varied by city and key population (Figure 3.3). In general, FSWs had the lowest prevalence among the three key populations, rising to just under 2% by 2011, while PWIDs had the highest prevalence, with estimates in some cities and years as high as 30-40% and reaching 42.2% in Karachi and 52.5%

in Faisalabad in 2011. HIV prevalence among H/MSWs was higher than among FSWs, but lower than among PWIDs. As with other key populations, the prevalence among H/MSWs increased over time in most cities, with a maximum prevalence of 14.0% in Larkana in 2008. An exception to the rising trend in prevalence among H/MSWs occurred in 2011 in Larkana, where the estimated prevalence fell from 14.0% (2008) to 9.8% (2011).

HIV prevalence also varied by city, with the lowest prevalence among all three key populations in Lahore and, other than PWIDs in 2011, Faisalabad. From 2005 to 2011, the trend in prevalence was only clear in Lahore, where prevalence increased across all three key populations. In Karachi, HIV prevalence may be expanding, after having declined during the mid-2000s. By contrast, among PWIDs and H/MSWs in Larkana, it appears that the epidemic may be declining after having peaked around 2008.

3.5.4 MODEL ESTIMATED PREVALENCE

In Karachi, Lahore, and Faisalabad, the range of model estimated prevalence produced similar epidemic pictures. In each of these three cities, the 30 plausible epidemic trajectories that were found by fitting to empirical data had no overlap between the prevalence trends of PWIDs, H/MSWs, and FSWs, respectively (Figure 3.3). Our model estimates give evidence that prevalence among PWIDs is likely to peak very high. By 2015, it may already rise to as high as 55-60% in both Karachi and Lahore, and 65-70% in Faisalabad. The 30 model estimates among PWIDs range from 46.2% to 55.9% in 2015 in Karachi, from 40.9% to 49.1% in 2015 in Lahore, from 58.8% to 62.5% in Faisalabad, and from 12.3%-26.1% in Larkana.

While empirically estimated HIV prevalence among PWIDs in 2007 and 2008 was lower in Faisalabad than in Karachi, the estimated prevalence in 2011 was higher in Faisalabad. However, none of the 30 model estimated epidemics in Faisalabad were able to completely replicate this (Figure 3.3). The model estimated prevalence among PWIDs in 2011 in Faisalabad ranged from 40.5% to 44.5%, which was significantly lower than the empirical estimate of 52.5% and more in line with the Karachi estimates in that year. With the caveat described previously that projections too far into the future should be interpreted cautiously, it appears that without intervention or behaviour change, prevalence among PWIDs will continue to rise beyond 2015 in Faisalabad, Karachi, and Lahore (Figure 3.3), while the outlook in Larkana is less clear and will be described separately later in this paper.

We also examined model estimated prevalence among FSWs and H/MSWs. In Karachi, the estimated prevalence by 2015 ranged from 17.0% to 22.1% among H/MSWs, and 2.9% to 5.6% among FSW. In Lahore, the model suggests that the 2015 prevalence to be in the range of 5.9% to 8.3% among H/MSWs, and 0.4% to 1.0% among FSWs. In Faisalabad, the 2015 estimates ranged from 4.4% to 6.3% among H/MSWs and were consistently 0% among FSWs.

Despite consistent estimates of HIV prevalence across all 30 model estimates in Karachi, Lahore, and Faisalabad through 2025, extending estimates this far into the future is uncertain. Even projecting through 2025, however, indicates that HIV prevalence in all cities but Larkana is unlikely to peak soon. The model evidence suggests that HIV prevalence among H/MSW may be nearing a peak in Karachi by 2025, but will still be expanding among MSWs/HSWs in the three cities of Karachi, Faisalabad, and Lahore, and among FSWs in Karachi and Lahore. Model estimated prevalence among FSWs in Faisalabad was 0% from 2005 to 2011, mirroring the empirically estimated prevalence among FSWs in this city.

In Larkana, the model estimates of prevalence among FSWs was consistent, with all 30 plausible model estimates suggesting that prevalence will continue to rise through 2015 and onto 2025. The range of model estimated prevalence among FSWs in Larkana in 2015 was 2.6% to 5.4%. When extended to 2025, there was more uncertainty, and the range widened to 11.9% - 20.3%.

Model estimated prevalence for PWIDs and H/MSWs in Larkana was considerably less consistent (Figure 3.3). This is due to the model fitting to empirical prevalence estimates which, in these two key populations, rose considerably from 2007 to 2008, and were lower in 2011. The EPP mathematical model was unable to simultaneously fit within the 95% confidence intervals of the three years of empirical prevalence data for these two key populations. Among PWIDs, approximately half of the 30 model estimates suggest that the HIV prevalence will continue to rise through 2015, while approximately half suggest a peak happened in the mid-2000s, followed by a decline. If the prevalence continues to rise, the expected prevalence among PWIDs in 2025 will range from 26.8% to 30.6%. However, if the prevalence is now declining, then the expected prevalence among PWIDs in 2025 will range from 6.2% to 19.8%. The maximum among these estimates occurred between 2008 and 2011, and ranged from 18.1% to 34.2%.

Similar to PWIDs, the model estimated prevalence trends for H/MSWs in Larkana show two distinct and divergent patterns. About half of the estimates suggest that the prevalence among H/MSWs may reach its highest point by 2020 and then approximately stabilize. The other half of the estimates suggest that the prevalence in this key population peaked in the early 2000s, and is currently declining. If the prevalence rises until 2020, then the expected prevalence among H/MSWs by 2020 ranges from 11.7% to 13.7%, and by 2025, the expected prevalence is very similar with a range from 12.5% to 14.4%. However, if prevalence is now declining, then the expected prevalence among this key population by 2025 ranges from 3.6% to 6.4%. The highest estimates occurred between 2003 and 2007, and ranged from 8.7% to 15.5%.

When compared to the most recent empirical prevalence data obtained from the 2016 IBBS, most model projections of prevalence to 2015/16 were reasonably consistent. Data from the 2016 IBBS indicated that the empirical HIV prevalence among PWIDs in 2016 was 48.7% (95%CI: 43.1%-54.3%) in Karachi and 16.2% (95% CI: 12.5%-20.8%) in Larkana[32]. Like wise, the empirical prevalence among H/MSWs and FSWs in Karachi was 22.1% (95% CI: 16.1-29.9%) and 2.6% (95%CI: 1.4-4.7%), respectively. The 2016 empirical prevalence among H/MSWs in Lahore and Faisalabad was 4.5% (95% CI: 2.7-7.4%) and 2.2% (95% CI: 1.1-4.5%), respectively[32]. In Larkana, the 2016 empirical prevalence among PWIDs, H/MSWs and FSWs was estimated at 4.1% (95% CI: 2.5-6.7%)[32], consistent with our model projections (range: 3.6-5.3%). We were unable to make comparison between projected and empirical prevalence among PWIDs and FSWs in Faisalabad and Lahore where no empirical data were collected in the 2016 IBBS.

3.6 DISCUSSION

The results, from modelling estimates and analyses of 'bridge' populations due to injecting and sexual networks, presented in this paper indicate the overall potential for an HIV epidemic expansion beyond the PWID population to other key populations in Pakistan. Specifically, considering the rising HIV prevalence among PWIDs, low condom usage, risky injecting practises[27,28] and large population densities of FSWs and MSWs/HSWs in certain cities, there is the risk of spill-over from the PWID populations into networks of sex workers and their clients. This inference is consistent with HIV transmission trends in other regions, particularly Eastern Europe, the Russian Federation and Central Asia, where transmission began among PWIDs and subsequently moved into sex worker populations and onward to the general population.[29,30] As a result, there is an urgent need to develop and scale up HIV prevention programs designed specifically for PWIDs, the intersection between PWIDs and sex workers in Pakistan, and within sex worker networks. Furthermore, given the variable degrees of bridging between key populations of PWIDs and sex workers, any intervention need to also be tailored to the population composition and behavioural dynamics in particular cities.

Karachi is a large city with the largest key population sizes, particularly PWIDs and FSWs, and had a high HIV prevalence among PWIDs in 2011 (42.2%) and a high projected prevalence in 2015 (ranging from 46.2% to 55.9%) among PWIDs, and identified trend was reasonably consistent with the empirical prevalence reported in the 2016 IBBS[32]. There was also much sexual and drug injection bridging between HSWs and PWIDs in Karachi and the 2015 projected prevalence among H/MSWs was high (ranging from 17.0% to 22.1%), a little higher estimate than the recently reported empirical prevalence in 2016[32]. This evidence may warrant implementing HIV prevention programs targeting all key populations and particularly targeting risky sexual and drug injection behaviours linking HSWs and PWIDs.

Lahore has a large population density of FSWs, with sex and drug injection linking FSW and PWID populations. The 2015 projected HIV prevalence is high among PWIDs in Lahore (ranging from 43.7% to 49.1%). HIV prevention programs in Lahore may therefore benefit from targeting risky sexual and drug injection behaviours between these two populations.

In Larkana, PWIDs and HSWs are linked through sex and drug injection which may warrant HIV prevention programs in this city targeting this link. Furthermore, as HIV prevalence among FSWs in the model estimates rises significantly higher in Larkana than in Lahore and Faisalabad, and to approximately the same level as in Karachi, more aggressive interventions may be required to contain the epidemic among FSWs, than among PWIDs or H/MSWs in this city. It is important to note that estimated data on the levels and trends of HIV prevalence among key population in Larkana is consistent with the empirical prevalence data reported in the 2016 IBBS[32].

Faisalabad has a high HIV prevalence among PWIDs (52.5% in 2011) and the prevalence may increase to range approximately from 57.0% to 62.5% by 2015, assuming that current trends continue. Sexual behaviours link PWIDs to HSWs and both sex and drug injection links PWIDs to FSWs in Faisalabad. As a result, it would be important to implement large-scale HIV prevention programs in Faisalabad, particularly targeting PWIDs, their sexual behaviours with HSWs and FSWs, and the drug injection behaviours of FSWs.

Quetta has the most significant bridging of all of the cities, with a large proportion of all sex workers reporting sex with PWIDs and drug injection. HIV prevention programs in Quetta should therefore target risky sexual and drug injection behaviours among all key populations.

Peshawar is a more conservative city, with relatively low key population sizes and low reported bridging. Key populations may be more difficult to reach by programs (and surveillance), and therefore programs designed for these populations may benefit from both venue- and network-based outreach.

Characterizing cities in terms of their key population composition and HIV transmission dynamics is useful for the design of HIV prevention programs. Prevention among key populations remains a key challenge for Pakistan's efforts to curtail the HIV epidemic. Without intervention or behaviour change, the HIV prevalence is expected to continue to rise among key populations in cities across Pakistan over the next 10 to 15 years. However, intensive efforts are required to bring about these changes. Modelling work to explore the potential impact of various interventions across the cities may help to inform policy makers about the most cost-effective options. Understanding the extent and pattern of interactions between the different key populations in the cities and the coverage of prevention programs targeting these groups is also vital to contain or reverse epidemic trends.

3.6.1 LIMITATIONS

The UNAIDS EPP model is designed to estimate and project HIV epidemics, but is not designed to evaluate potential interventions. As such, the model does not incorporate changes in behaviour over time or turnover of members of key populations. We therefore estimated the HIV epidemic under the assumption of unchanging behaviour. Model results were not able to replicate the high empirical prevalence estimates among PWIDs and H/MSWs in Larkana in 2008, or the high empirical prevalence estimates among PWIDs in Faisalabad in 2011. It is possible that these estimates were simply spuriously high. However, it is also possible that behaviour change accounts for the varying prevalence estimates. For example, if something occurred in Faisalabad between 2008 to 2011 which made it more difficult for PWIDs to obtain clean syringes, this change could result in a very rapid increase in HIV prevalence among this group. We were unable to test this possibility using the EPP mathematical model.

Because antiretroviral therapy (ART) use in Pakistan is extremely low[31], we did not consider the distribution of ART in the model. The IBBS did not include questions about antiretroviral therapy use initiation and distribution among HIV-infected individuals in each sub-population. The model estimated prevalence among FSWs in Faisalabad was 0% through 2025. This is likely an underestimate, but was based on the fact that no FSW participants from Faisalabad were infected. As there is evidence of population bridging in Faisalabad, the true prevalence is probably greater than 0%, but would require a larger sample size to detect. If the model were being fit to low but positive prevalence among FSWs, then the projections through 2025 would likely have showed an increasing trend.

Although our main results present findings of model-estimated HIV prevalence through 2015, we wanted to assess when we might see a peak in prevalence. For this reason, we also projected HIV prevalence to 2025. Projecting as far as 2025 comes with much uncertainty, primarily because changes in behaviours and public health policies impacting HIV incidence are likely to occur over time. Estimates through 2025 should therefore be interpreted cautiously and with the caveat that these estimates assume that behaviour, population growth, and migration remain unchanged.

3.7 AUTHOR CONTRIBUTIONS

DYM: performed the data analysis and mathematical modeling, and co-wrote the manuscript, critically reviewed the manuscript, revised later drafts. TR: involved with the design of the study and interpretation of results and critically reviewed the manuscript. LAS: co-wrote the manuscript, led the data analysis, critically reviewed the manuscript, and revised later drafts. MS, AA and AS: involved in the design of the study and critically reviewed the manuscript. GCJ: critically reviewed and revised the manuscript. LHT: co-wrote the manuscript, critically reviewed the manuscript, and revised later drafts. FE and JFB: involved with the design of the study and interpretation of results and critically reviewed the manuscript. JFB: led the development of the special supplement strategy.

3.8 ACKNOWLEDGMENTS

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3.9 COMPETING INTERESTS

The authors have no competing interests.

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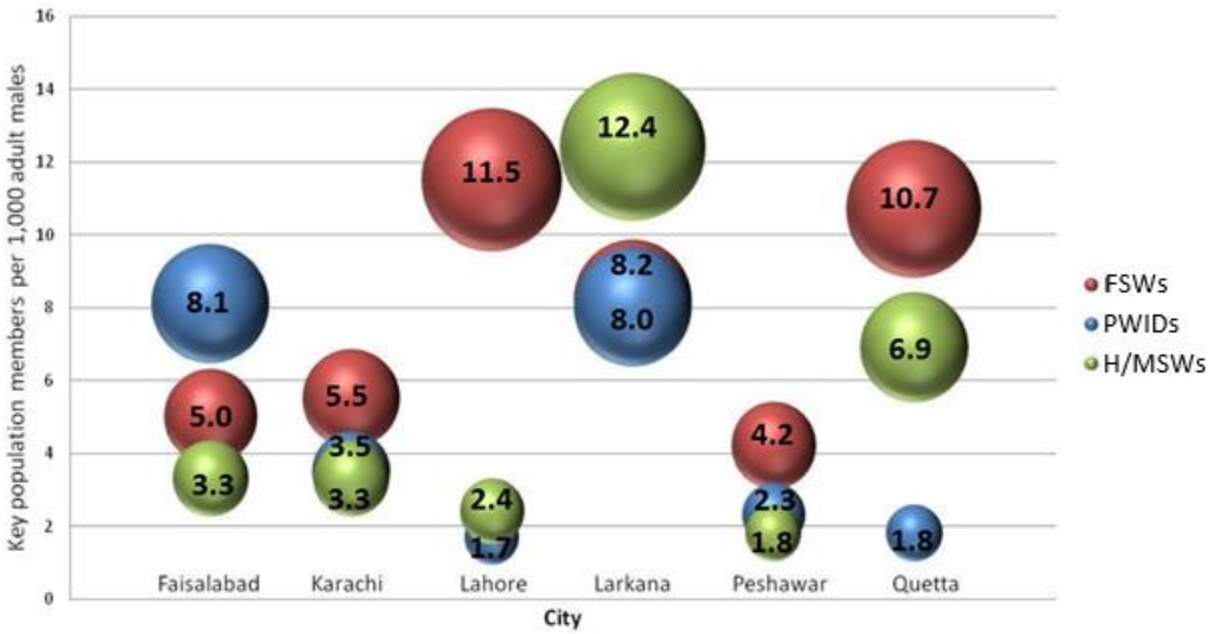
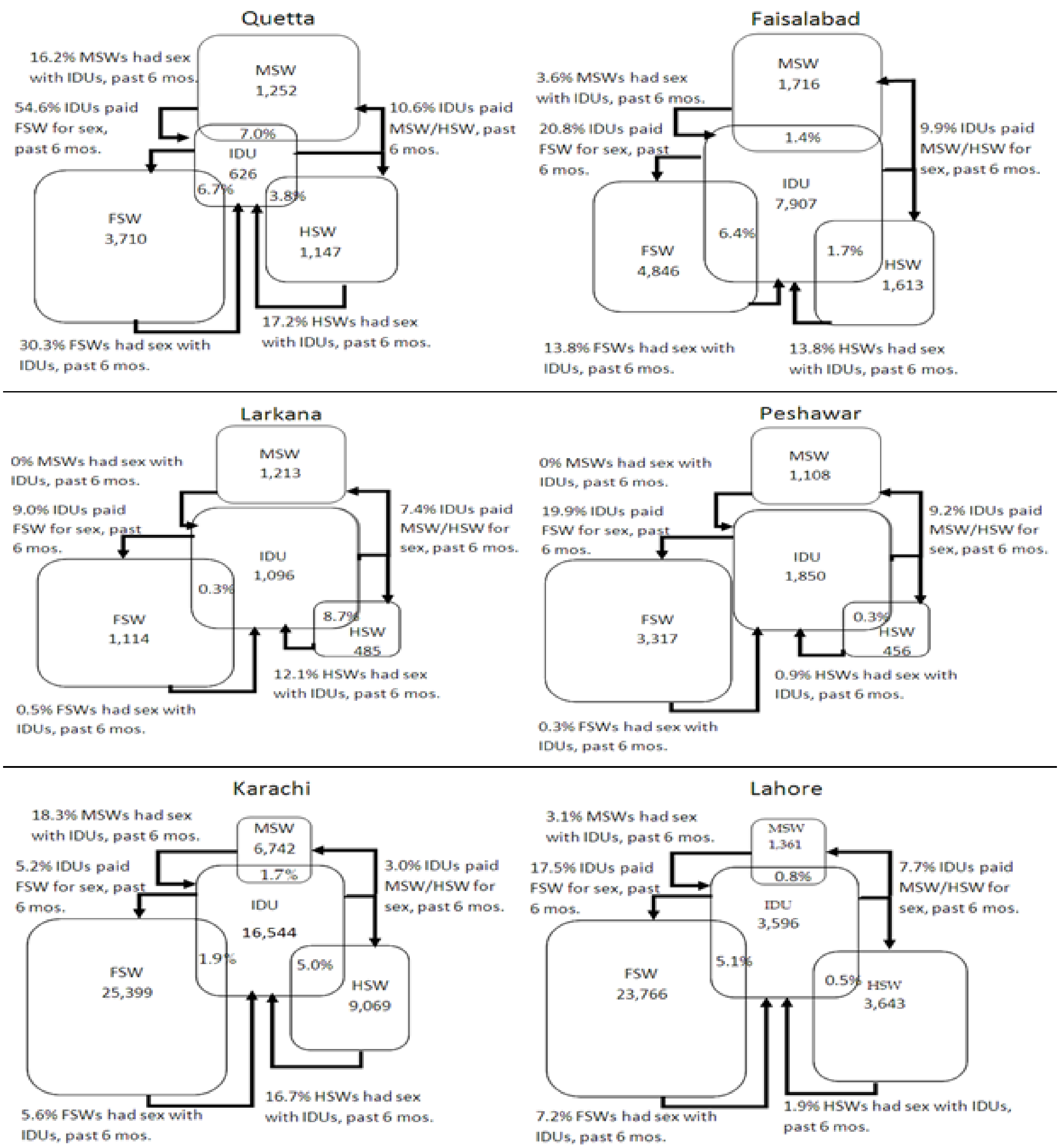
Figure 3.1 PWIDs, FSWs, and H/MSWs population per 1,000 adult males by city, 2011



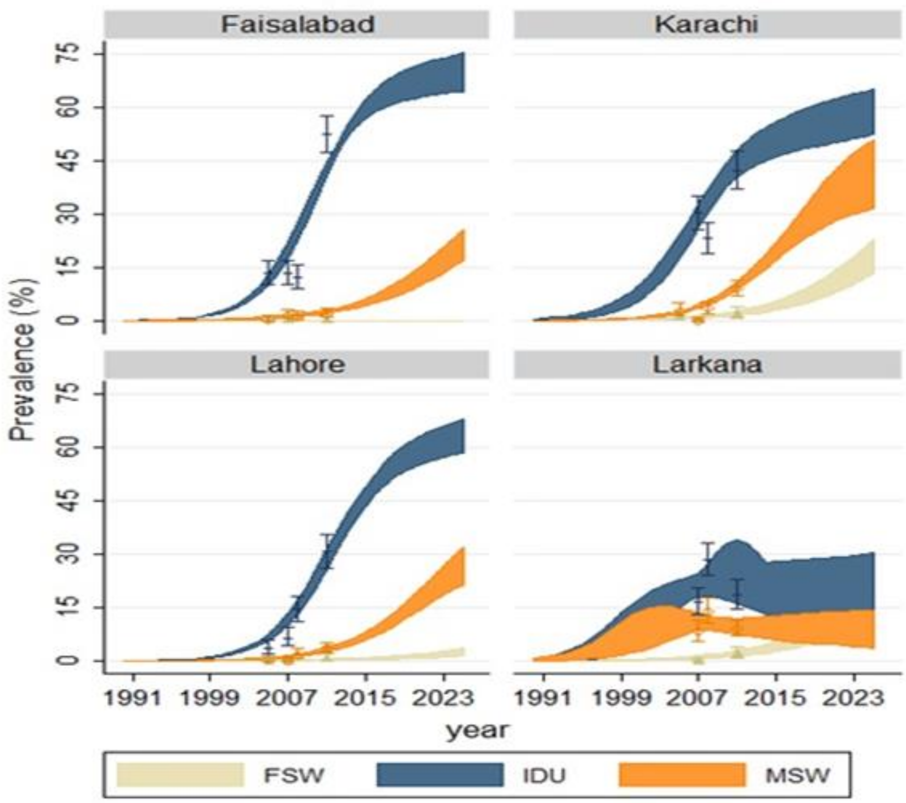
MSWs = male sex workers, HSW = hijra/transgender sex workers; FSWs = female sex workers; PWIDs = people who inject drugs (also appreviated as IDUs = injection drug users).

Figure 3.2 Bridging of injection drug use and sexual networks in 6 cities in Pakistan, 2011



MSWs = male sex workers, HSW = hijra/transgender sex workers; FSWs = female sex workers; IDU = injection drug user (also appreviated as PWIDs = people who injected drugs)

Figure 3.3 Estimated HIV prevalence among FSW, PWIDs, and H/MSW in 4 cities



FSWs = female sex worker; IDU (also appreciated as PWIDs) = people who inject drugs;
MSWs = male/hijra/transgender sex workers as combined.

Dots/bars = Empirical estimates / (95% confidence interval); Shading = Range of model estimates

4 HETEROGENEITY IN GEOGRAPHICAL TRENDS OF HIV EPIDEMICS AMONG KEY POPULATIONS IN PAKISTAN: A MATHEMATICAL MODELING STUDY OF SURVEY DATA

4.1 CHAPTER OVERVIEW

As a continuation of the previous study, this manuscript presents a comprehensive assessment of disparities in the geographical trends and patterns of HIV epidemics among KPs in Pakistan. Assessing the burden of HIV using incidence patterns is key to better understanding epidemics and informing policy. Furthermore, monitoring global changes in incidence is no longer sufficient, and thus, more disaggregated and fine-grained assessments of HIV incidence have been suggested moving forward for designing more effective intervention strategies. This study provides disaggregated assessments of the levels and trends of the HIV epidemics in Pakistan. It highlights that the epidemics in Pakistan are heterogeneous and are comprised of multiple sub-epidemics among KPs, with substantial variations in geographical trends. It provides evidence for potential epidemiological drivers of epidemics that may lead to variations in the emergence, persistence, and spread of HIV epidemics within and between cities, and thus it has practical implications for policy setting at national and regional levels in Pakistan.

Publication details:

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4.2 ABSTRACT

Background: Assessing patterns and trends in new infections is key to better understanding of HIV epidemics, and is best done through monitoring changes in incidence over time. In this study, we examined disparities in geographical trends of HIV epidemics among people who inject drugs (PWIDs), female sex workers (FSWs) and *hijra*/transgender/male sex workers (H/MSWs), in Pakistan.

Methods: The UNAIDS Estimation and Projection Package (EPP) mathematical model was used to explore geographical trends in HIV epidemics. Four rounds of mapping and surveillance data collected among key populations (KPs) across 20 cities in Pakistan between 2005-2011 was used for modeling. Empirical estimates of HIV prevalence of each KP in each city were used to fit the model to estimate prevalence and incidence over time.

Results: HIV incidence among PWIDs in Pakistan reached its peak in 2011, estimated at 45.3 per 1000 person-years. Incidence was projected to continue to rise from 18.9 in 2015 to 24.3 in 2020 among H/MSWs and from 3.2 in 2015 to 6.3 in 2020 among FSWs. The number of people living with HIV in Pakistan was estimated to steadily increase through at least 2020. HIV incidence peak among PWIDs ranged from 16.2 in 1997 in Quetta to 71.0 in 2010 in Faisalabad (per 1000 person-years). Incidence among H/MSWs may continue to rise through 2020 in all the cities, except in Larkana where it peaked in the early 2000s. In 2015, model estimated incidence among FSWs was 8.1 in Karachi, 6.6 in Larkana, 2.0 in Sukkur and 1.2 in Lahore (per 1000 person-years).

Conclusions: There exists significant geographical heterogeneity in patterns and trends of HIV sub-epidemics in Pakistan. Focused interventions and service delivery approaches, different by KP and city, are recommended.

4.3 INTRODUCTION

Pakistan is facing concentrated HIV epidemics among key populations (KPs), specifically people who inject drugs (PWIDs) and sex workers (SWs)[1–5]. KPs in Pakistan, particularly female, male and transgender sex worker populations (FSWs, MSWs and HSWs), engage in transactional sex underground, limiting their access to services and potentially subjecting them to harassment and violence[6–9]. The HIV epidemic is well established among PWIDs, and is perhaps expanding among SWs in Pakistan. It has been suggested that the expansion of HIV to SWs may be related to structural and sociocultural aspects of the KPs, such as cultural stigma, poor knowledge about how to prevent HIV, low literacy and inadequate access to services[10,11].

Empirical evidence obtained from integrated biological and behavioural surveillance (IBBS) data suggested that HIV prevalence among PWIDs increased from an estimated (unweighted) 11% in 2005 to 27% by 2011[12–15]. Evidence from these IBBS data also indicated that prevalence among HSWs, MSWs and FSWs in 2011 was estimated at 5.2%, 1.6% and 0.6%[12–15]. Studies have shown that SWs in Pakistan are at a higher risk of HIV exposure due to their interaction with PWIDs through sex and/or needle sharing[12–15]. Although vulnerability varies by KP and city, there is growing concern that the virus may be expanding to sexual contacts of PWIDs, particularly SWs, as well as to the general population through sexual networks of SWs and their clients[12,16–20].

Assessing incidence patterns helps to better understand HIV epidemic trends. Monitoring global changes in incidence is no longer sufficient, and more disaggregated and fine-grained assessments have been suggested for improved estimation of HIV epidemics[21]. Incidence as opposed to prevalence may generate insights about potential factors contributing to the epidemics. However, it is prevalence data that is often available and used in Pakistan to inform policy and guide the design of intervention programs. Although prevalence data are currently available in certain cities and years in Pakistan [12,17,20,22–25], these empirical prevalence estimates are not globally available across all of Pakistan, and are often limited to estimates only among certain higher risk groups[24]. Furthermore, there is limited data on the change in number of new HIV infections over time on a more disaggregate level.

Using mathematical modeling, we examined geographic disparities in the trends and emerging patterns of HIV sub-epidemics using model estimated prevalence and incidence among KPs in Pakistan. This study provides disaggregated assessments of the levels and trends of the HIV epidemics in Pakistan.

4.4 METHODS

4.4.1 STUDY SETTING

Between 2005 and 2011, the Canada-Pakistan HIV/AIDS Surveillance Project (HASP) collected four rounds of IBBS data across Pakistan[12–15,26]. The number of cities (up to 20) and KPs surveyed in each round varied. Details on cities included can be found in previous reports [12–15]. Maps of cities surveyed in 2005 and 2011, depicting relative prevalence among KPs, can be found elsewhere[27].

4.4.2 STUDY POPULATIONS

The KPs surveyed were PWIDs, HSWs, MSWs and FSWS. MSWs and HSWs refer to men aged 13 and 15 or older, respectively, and FSWs refers to women aged 15 or older who sell sex in exchange for money or gifts. Many MSWs start sex work at a younger age than FSWs or HSWs, and therefore the age limit for inclusion in MSWs sample was lower. Most h*ijras* are transgender individuals who are born males and often cross-dress in feminine attire, only a few having been born with intersex variations, and some having undergone surgical sex change[28–30]. They form a distinct sociocultural group unique to South Asia, and are considered to be a third gender[28–30]. PWIDs refers to persons aged 18 or older who had injected drugs in the past six months. Because HSWs and MSWs share similar biological susceptibility and have overlapping of networks, including client networks, IBBS data among these KPs were collected together except in the fourth round conducted in 2011. The difference age cut-offs in the inclusion criteria is based on anecdotal evidence and age distribution of each KP in subsequent IBBS. It is also important to note that inclusion and exclusion criteria were ascertained through a broad National consultative process in which all stakeholders along with National and Provincial AIDS Control Programs participated.

4.4.3 DATA COLLECTION

Each round of IBBS began with an in-depth network mapping exercise to estimate the size, distribution and operational typology of PWIDs and SWs in targeted cities[12–15], except the third round (in 2008) where the second round mapping (in 2006/7) was used as a basis to recruit study samples[13]. Details of the mapping can be found elsewhere[12–15,31]. Cities were selected based on anecdotal evidence of high risk activity, the presence of multiple KPs, and the geographical accessibility of the area. Following mapping, a representative sample of each KP was drawn in each city. These cities were identified before the start of each round of surveillance through a broad National consultative process in which all stakeholders along with National/Provincial AIDS Control Programs participated.

Various techniques were utilized to recruit representative KP samples. For instance, MSWs were recruited through respondent driven sampling, while HSWs were recruited through network sampling whereby *gurus*, “retired” HSWs, were selected randomly from a list compiled from the previous mapping results and asked to recruit eligible subjects. Street-based FSWs were recruited using time-location cluster sampling and PWIDs were recruited using multistage cluster sampling. Data was then collected from samples of each KP in each city by trained interviewers using structured questionnaires. Data from FSWs were not collected in the third round (2009) because of low HIV prevalence observed in 2006/7. Stratified by survey round, city, and KP, the sample size was greater than 350 in more than 86% of the strata (average sample size per strata ~400). Further details on the methods and techniques of mapping, sampling and data collection have been described previously[12–15,31].

4.4.4 STATISTICAL ANALYSIS AND MATHEMATICAL MODELLING

4.4.4.1 STATISTICAL ANALYSIS

Empirical HIV prevalence and 95% confidence intervals (CI) in each round, city and KP were computed. Sampling weights based on the respective estimated population sizes of each KP in each city were utilized as appropriate to take the stratified sampling design into account.

Using empirical HIV prevalence estimates from each survey round as inputs, mathematical modeling was performed to estimate and project the prevalence of HIV among each KP in each city and year (even those years not surveyed). Along with estimated HIV prevalence by KP, the model provided estimates of the total number of people living with HIV, the number of people who died from HIV, and the population size of the HIV uninfected people (i.e., susceptible population) over time. Using these model outputs, we then estimated HIV incidence. The combined data of MSWs and HSWs (abbreviated here as H/MSWs) were used for analysis because they are similar in terms of their behavior and risk to HIV acquisition.

Both groups were born as biological males and have male clients; however, HSWs are transgender.

4.4.4.2 MATHEMATICAL MODELLING

We used the UNAIDS Estimation and Projection Package model (EPP) to estimate and project HIV prevalence[32–34]. The EPP model, a deterministic compartmental model which estimates HIV prevalence over time by fitting to empirically estimated HIV prevalence at certain time points, has been described previously[33–35]. Further details on our modeling using EPP, including sources and method used to compute input parameters to fit the model, model scenarios, plausible estimates of prevalence, and sensitivity analysis has been described previously[24].

EPP allows separate model fitting for different subpopulations of different cities and may combine them for aggregate prevalence estimates. Model estimates of prevalence were assessed by uncertainty analysis. In uncertainty analyses, we ran the model multiple times, and fit to lower and upper bounds of the 95% CIs of empirically estimated HIV prevalence of each city. In addition to city-specific HIV prevalence, EPP generates an estimated national prevalence by combining each KP subpopulations' and cities' estimated prevalence. Given that the HIV epidemic in Pakistan is largely concentrated among KPs in urban and semi-urban areas, this study assumed that HIV prevalence in rural Pakistan, while not non-existent, is almost negligible[36,37].

In this study, we used data from all 20 cities surveyed to produce national (among KP) and all-KP estimates of HIV incidence and prevalence. In our disaggregated analyses, however, we focused on the 10 cities that were represented in at least two rounds of the IBBS in each

KP: Faisalabad, Hyderabad, Karachi, Lahore, Larkana, Multan, Peshawar, Quetta, Sargodha, and Sukkur.

In an attempt to validate model projections to the future, we compared model estimates of HIV prevalence with the 2016 empirical prevalence obtained from the most recent IBBS-2016 report. Comparison was performed for only cities with empirical prevalence data available in the 2016 IBBS report. Of note, the 2016 IBBS report was made available after modeling was completed and this paper was in process for publication.

4.5 RESULTS

Analysis was based on 43,522 individuals (27.8% FSWs, 33.1% PWIDs, and 39.1% H/MSWs) from 20 Pakistani cities. The mean age of PWIDs, FSWs and H/MSWs was 32.5 (SD=8.4), 27.3 (SD=6.6) and 24.5 (SD=6.4) years, respectively. The average number of years that they had been involved in high-risk activities (i.e., in sex work or drug injection) by the time of their interview was 5.1 (PWIDs), 5.4 (FSWs) and 8.3 (H/MSWs) years.

4.5.1 ESTIMATED PREVALENCE OF HIV

Model estimates suggest that HIV prevalence in the adult population will continue to rise in Pakistan, increasing from 0.05% (plausible range, 0.04%-0.06%) in 2015 to 0.07% (plausible range, 0.06-0.08%) by 2020. Prevalence among all KPs in Pakistan was projected to increase from 16.1% (plausible range, 15.2%-16.8%) in 2015 to 20.8% (plausible range, 19.6%-21.9%) in 2020, although our results suggest that the burden of the epidemics will vary considerably between KPs (Figure 4.1) and cities (Figure 4.2). More than half of PWIDs (54.7%, plausible range: 52.4%-56.9%) and nearly one-fifth of H/MSWs (19.6%, plausible range: 17.7%-22.4%) may be living with HIV by 2020. By the same year, HIV prevalence among FSWs may reach 3.5% (plausible range, 2.8%-4.3%).

Among FSWs, estimated prevalence in all cities is estimated to rise throughout the projection period (Figure 4.2 and Figure 4.3). Among H/MSWs, estimated prevalence rises throughout the projection period, except in Larkana, where it peaked around 2007, estimated at 10.9%. Estimated HIV prevalence among PWIDs in Quetta might have peaked in the early 2000s, followed by a relatively constant prevalence around 8.1%. In all other cities, prevalence among PWIDs is estimated to continue rising throughout the projection period.

4.5.2 ESTIMATED INCIDENCE OF HIV

In the adult populations of Pakistan, model-estimated HIV incidence rate peaked in 2015, at 0.06 per 1000 person-years (plausible range, 0.05-0.07). By contrast, HIV incidence among all KPs combined was projected to increase, rising from 15.8 (plausible range, 15.1-16.9) in 2015 to 16.7 (plausible range, 15.5-17.9) per 1000 person-years by 2020 (Figure 4.3). This increase is a result of rising incidence among H/MSWs and FSWs. In Pakistan, HIV incidence among PWIDs peaked in 2011, estimated at 45.3 new infections per 1000 person-years (range, 42.7-46.8), and is projected to fall to 30.8 (plausible range, 29.7-32.3) by 2020, before stabilizing. By contrast, estimated incidence among H/MSWs has increased from 9.1 new infections per 1000 person-years (plausible range, 8.6-10.0) in 2010 to 18.9 (plausible range, 16.7-22.0) in 2015 and projected to continue rising to 24.3 (plausible range, 20.7-28.3) by 2020. Although incidence among FSWs is lower than among other KPs, it is estimated to increase from 1.4 new infections per 1000 person-years (plausible range, 1.0-1.7) in 2010 to 6.2 (plausible range, 4.6-7.3) by 2020.

Similar to the variation in prevalence trends by city, our modeling suggests three distinctively different incidence patterns among all KPs by city (Figure 4.4). These geographical disparities in the patterns of the HIV epidemic are related to: the timing that the epidemic started, the timing that the epidemic is likely to have peaked, the number of new infections at a given time, and the change in the trajectory of HIV transmission overtime. The HIV incidence among all KPs combined is highest in Karachi and Faisalabad. Incidence peaked early in Hyderabad, Larkana, Sargodha, and Sukkur, but after a period of decline, it began to rise again. In Sukkur in particular, current HIV incidence among all KPs is estimated to be higher than it was at its early peak, and is estimated to continue rising beyond the year 2020. Incidence in Lahore, Multan, Peshawar, and Quetta is lower and with less pronounced peaks and troughs than in the other cities.

At a further disaggregated level, each KP has geographically different HIV incidence patterns (Figure 4.5). HIV incidence among PWIDs in each city peaked on or before 2015, with peak incidence ranging from 16.2 (plausible range, 7.6-19.8) in 1997 in Quetta to 71.0 (plausible range, 69.1-72.1) in 2010 in Faisalabad (per 1000 person-years). Incidence among H/MSWs was projected to continue to increase through 2020 in all cities, except in Larkana. HIV epidemics began to emerge among FSWs in the past 15 years, and will likely continue rising in most cities. By 2020, incidence among FSWs is estimated at 16.4 (plausible range, 11.6-19.0) in Karachi, 14.9 (10.3-18.7) in Larkana, 4.0 (plausible range, 2.6-5.4) in Sukkur and 2.1 (plausible range, 1.6-2.5) in Lahore (per 1000 person-years) (to better distinguish trends, incidence among FSWs is presented on a different scale in Supplementary Figure 4.6).

Figure 4.7 depicts model projection estimates of prevalence among KPs in each city plotted against the 2016 empirical prevalence obtained from the most recent IBBS-2016 data. The projected estimates of HIV prevalence in 2016 among PWIDs and FSWs in Pakistan ranged from 47.5% - 51.3% and 1.5-2.3%, respectively, and that compares to the 2016 empirical prevalence reported at 38.4% (95% CI: 37.9-38.9%) among PWIDs and 2.2% (95% CI: 2.1-2.3%) among FSWs.

Figure 4.8 presents model projected estimates of prevalence among KPs in Pakistan plotted against the overall empirical prevalence reported in the 2016 IBBS for comparison purpose.

4.6 DISCUSSION

Pakistan is experiencing an increase in HIV infections among KPs, particularly among H/MSWs and FSWs. The epidemic continues to vary considerably by KP and city, and the time lag in the emerging trends of the epidemics among KPs perhaps suggesting multiple interconnected sub-epidemics within the country. In addition to heterogenous HIV incidence and prevalence trends, there is also variation in the mean duration that each KP were engaged in high-risk activity. The youngest KP (H/MSWs, mean age 24.5 years) have the longest duration of activity (mean 8.3 years).

PWIDs, followed by H/MSWs, remain most severely affected KPs, with nearly 1 in every 2 PWIDs and 1 in every 5 H/MSWs living with HIV by 2020 (Figure 4.1). Previously estimated rising HIV prevalence among FSWs in Karachi, Larkana and Lahore will likely be seen in most cities across Pakistan[24]. While HIV incidence among all KPs in Pakistan is estimated to increase through 2020, it will vary by KP. HIV incidence among SWs, for example, is estimated to emerge and remain increasing, while incidence among PWIDs possibly peaked in 2011. HIV incidence among H/MSWs may peak in the early 2020s. This highlights public concerns that HIV incidence might be spreading from PWIDs to the rest of the population through sexual networks [12–15,26].

4.6.1 HIV PREVALENCE AND INCIDENCE IN THE GENERAL POPULATION

HIV prevalence in the general adult population is estimated to rise from a range of 0.04%-0.06% in 2015 to 0.06%-0.08% by 2020. Although we only used empirically estimated prevalence from KPs as input for our modeling, our model estimates of HIV prevalence in the adult population of Pakistan in 2011 is similar to the empirical prevalence estimate obtained from a large national population-based Antenatal Care (ANC) study conducted in 2011[26]. Also, the 2015 model estimates of HIV prevalence in the general population are similar to those reported previously by UNAIDS[36,37].

HIV incidence in the general adult population of Pakistan peaked in 2015, estimated at 0.062 per 1000 person-years. This contrasts with worldwide HIV incidence which peaked around 1997 [21,38]. Our estimate of the number of new infections in 2015 (10,756; plausible range: 8,049-14,414) is between the slightly higher estimate reported by UNAIDS (approximately 11,500)[37] and the somewhat lower estimate provided by the Global Burden of Disease Study (8,550)[21]. The difference with the UNAIDS estimate may be partly due to unavailability in our data on HIV prevalence from sex worker clients and low-risk populations such as rural Pakistan, the age and estimated size of key population used, and the lack of data on antiretroviral therapy (ART) coverage.

4.6.2 SOCIAL AND SEXUAL NETWORKING AND HIV SUB-EPIDEMICS IN PAKISTAN

The emerging patterns of HIV epidemics among KPs in Pakistan is consistent with the patterns observed in other Asian countries[3,39,40], whereby HIV transmission begins among PWIDs and subsequently spreads to SWs and their clients. In most cities in Pakistan, rising

HIV incidence first occurred among PWIDs before or early in the 1990s, followed by H/MSWs later in the 1990s, and then FSWs early in the 2000s. Following global trends in HIV epidemic, whereby increased migration precedes the spread of HIV infection among PWIDs[41], the HIV epidemic in Pakistan might have been introduced by migrant workers returned from Gulf states[42,43], and then spread to KPs[44,45]. It has been highlighted that high prevalence of HIV among returned migrant workers from Gulf countries, with nearly 61%-86% of reported HIV cases in any given year during the 1996-1998 period[42], followed by reported outbreaks of HIV infections among PWIDs in subsequent years[44,45]. It is important to highlight that the high HIV cases in the 1990s might be related with the fact that these migrants were all tested, and perhaps repeatedly.

Though HIV incidence among PWIDs declined after 2011, HIV prevalence continued to rise in most cities. Among all KPs combined in Pakistan, both incidence and prevalence is estimated to continue increasing. This is due to the rapid upsurge of HIV transmission among H/MSWs followed by FSWs. What are the possible mechanisms that explain the emergence of SW epidemics following those of PWIDs in Pakistan? One explanation is the extent to which SW populations mix with PWIDs, which impacts HIV transmission risk vulnerability through overlapping social and sexual networks. The greater the overlap between SWs and PWIDs, the quicker HIV reaches the wider population. Evidence from IBBS data has suggested that there is a significant proportion of KPs with overlapping risk behaviour, also called “bridge” populations – individuals who in this case engage in multiple risk behaviours (i.e., through having sex and/or needle-sharing with a different KP)[12–15,24]. SWs who interact sexually with PWIDs increase their HIV risk in two ways – they are having sex with other higher risk populations, and they have higher odds of injecting drugs themselves. Our previous epidemiological study indicated that H/MSWs have higher odds of interacting with

PWIDs through sex and/or needle sharing than do FSWs[46]. This implies that H/MSWs are more vulnerable than FSWs to HIV transmission from PWIDs. Furthermore, because male-to-male HIV transmission is more efficient than both male-to-female and female-to-male transmission, H/MSWs are at higher risk of acquiring HIV from their male sexual partners who inject drugs. Therefore, in Pakistan, where the epidemic is predominantly driven by PWIDs, H/MSWs are more vulnerable than FSWs as a result of their interaction with PWIDs[46]. The H/MSWs are presumably at a higher risk of an emergent epidemic, followed by FSWs.

4.6.3 HIV EPIDEMIC IN KARACHI

Karachi is currently experiencing escalated HIV incidence among KPs. Although this is largely due to a rapid upsurge of new infections among both H/MSWs and FSWs, all three KPs might have substantial contributions to sustain steadily increasing incidence in Karachi through at least 2020. HIV incidence among H/MSWs in Karachi likely surpassed that of among PWIDs in 2015 and will remain higher through the early 2020s. Given the increasing trend of HIV incidence among FSWs in Karachi, the epidemic may become as explosive among FSWs as among the other two KPs in the future. This study is consistent with previous work suggesting that HIV incidence among PWIDs in Karachi may have risen rapidly in early 2000s, and perhaps the epidemic subsequently spilled over into H/MSWs followed by FSWs[17].

4.6.4 HIV EPIDEMIC IN FAISALABAD

Faisalabad is similar to Karachi in terms of high HIV prevalence and incidence, which may be largely due to increased incidence among PWIDs followed by H/MSWs (Figure 4.5). Patterns among KPs, however, differ. Unlike in Karachi, the rapidly increasing incidence among H/MSWs in Faisalabad is likely to peak around 2018. New infections among FSWs have negligible effect on the overall incidence among KPs in Faisalabad. As there is evidence of population bridging between PWIDs and FSWs in Faisalabad, the true prevalence is probably greater than 0%, but would require a larger sample size to detect. If the model were being fit to low but positive prevalence among FSWs, then the epidemic would likely to emerge and projections through 2025 would likely have showed an increasing trend.

4.6.5 HIV EPIDEMIC IN LARKANA, QUETTA, SUKKUR, HYDERABAD AND SARGODHA

Unlike other cities, where PWIDs have been the driving force in HIV incidence, SWs have had a major role in incidence in Larkana, Quetta and Sukkur since 2010. That said, the SW group driving the epidemic varies considerably between these cities. The upsurge of new infections in Larkana remains mostly among FSWs, while the epidemics in Quetta and Sukkur are largely driven by H/MSWs. HIV incidence among FSWs in Larkana, and H/MSWs in Quetta and Sukkur, might have surpassed that of PWIDs in the early 2010s.

The HIV epidemics among PWIDs in these cities (Larkana, Quetta, Sukkur, Sargodha and Hyderabad) peaked early and has remained relatively low and stable since 2005. This may imply that HIV infections among PWIDs are circulating among clusters of individuals, but the epidemic is likely expanding into the SW population through sexual networks. We may speculate that heterosexual networking in Larkana and homosexual networking in the other cities may have played a role in the spread of the epidemics among SWs.

4.6.6 HIV EPIDEMIC IN LAHORE, MULTAN AND PESHAWAR

HIV incidence in Lahore, Multan and Peshawar is largely driven by PWIDs, followed by H/MSWs. HIV incidence among all KPs in these cities may have started rising more recently than in other cities, and may have reached their peaks later, in the mid-2010s. Though it is very small due to being the city more conservative, there is evidence of population bridging between PWIDs and FSWs in Peshawar. As such, the true prevalence is probably greater than 0%, but would require a larger sample size to detect. If the model were being fit to low but positive prevalence among FSWs, then the epidemic would likely to emerge and projections through 2025 would likely have showed an increasing trend.

4.6.7 COMPARISON BETWEEN PROJECTED AND EMPIRICAL PREVALENCE IN 2016

When compared to the empirical prevalence reported in the 2016 IBBS[48], over 85% of KP-city estimates and overall estimates by KP in Pakistan corroborate with the 2016 empirical prevalence and trends described by model projections to 2016 are reasonably consistent. Except H/MSWs in Karachi, PWIDs in Peshawar and FSWs in Sukkur, model projections among all KPs demonstrated that the levels and trends of estimates prevalence are reasonably consistent with the 2016 empirical prevalence reported in the 2016 IBBS (Figure 4.7).

Estimated prevalence among H/MSWs in Karachi and PWIDs in Peshawar in 2016 were higher than empirical prevalence. In Sukkur, our model underestimated the prevalence in 2016 when compared to the empirical prevalence in the 2016 IBBS. The discrepancy in projected versus empirical prevalence in Karachi and Peshawar may perhaps be related to one or more of the following factors: the effect of interventions implemented in the past few years, high-AIDs related mortality, estimated sizes of KPs, and/or survey design biases. In regards to the discrepancy in Sukkur, we can speculate that a rapid upsurge of HIV infections among FSWs occurred in the past few years likely yielded higher empirical prevalence than estimated. Further analyses of the 2016 IBBS data is warranted to better speculate the potential sources of discrepancies between projected versus empirical prevalence in 2016.

We also compared the overall prevalence by KP and found that the levels and trends of estimated prevalence among FSWs and H/MSWs in Pakistan were very consistent with the empirical prevalence reported in the 2016 IBBS (

Figure 4.8). The projected prevalence among PWIDs, however, was a little higher than the overall weighted empirical prevalence among PWIDs in Pakistan. The lower empirical prevalence reported among PWIDs in 2016 may perhaps be explained by the exclusion of cities from the 2016 IBBS where we know from previous surveys that they have high HIV prevalence. Most of excluded cities in the 2016 IBBS among PWIDs are from Punjab Province and include Faisalabad, Multan, Lahore and Sargodha. Furthermore, given Karachi is one of the two cities with the highest prevalence among PWIDs, the discrepancy in the overall prevalence among PWIDs in Pakistan may also be attributed to lower than estimated prevalence observed in Karachi. The lower than estimated prevalence reported in the 2016 IBBS could also be due to the effects of prevention efforts made in the past 5 years or significantly high mortality among PWIDs due to AIDS.

It is worth noting that HIV incidence among PWIDs in Pakistan peaked and started declining around 2011, and has become a stable epidemic around 2015. As such, a decreasing trend in incidence rate among PWIDs after it peaked in 2011 may also perhaps relate to a lower empirical prevalence in the 2016 IBBS. Another important aspect to consider is that both the 2011 and 2016 IBBS indicated that the overall weighed empirical prevalence was almost similar (range 37-39%), perhaps implying that the epidemic among PWIDs in Pakistan peaked around 2011 and is consistent with the conclusion drawn based on estimated incidence.

4.6.8 LIMITATIONS

EPP is not a perfect model, and we share limitations that were discussed in previous studies[34,35,47]. In addition, the absence of data on ART distribution, data on HIV prevalence among clients of SWs and ex-PWIDs, and data on HIV prevalence among adults with unknown higher risk of HIV transmission, were limitations of this study. Although scenarios were considered to capture potential variations in the estimation and projection of HIV prevalence and incidence that may arise due to variation in duration of time that persons in each KP were engaged in high-risk behaviour, it was difficult to make accurate estimates of these durations. Finally, the range between the minimum and maximum prevalence and incidence consistently increased over time through 2025, which underlines the uncertainty in estimating this far into the future. Thus, it is our results are not definitive, but suggest a good description of the underlying aggregate and disaggregate HIV dynamics in Pakistan. National level estimations and projection based on the assumption of HIV prevalence in rural population and other populations (such as non-KP sexual clients of SWs) in Pakistan as negligible during surveys may not reflect the true nature of the epidemic in subsequent years, and thus results must be interpreted cautiously.

4.6.9 CONCLUSIONS

In addition to the fact that the HIV epidemic in Pakistan is predominantly driven by PWIDs, the epidemic among SWs in Pakistan has emerged and continues to rise, and is perhaps expanding to the general population through sexual networks. The HIV epidemic in Pakistan is comprised of multiple sub-epidemics among KPs, with considerable variations in geographical trends. Both sexual and injection networks in Pakistan may have uniquely contributed to the spread of the epidemic from PWIDs to SWs. The combination of high HIV prevalence among PWIDs along with emerging epidemics among SWs calls for an urgent response and implementation of targeted interventions and service delivery approaches in Pakistan. Attention should be paid to drug injection and sexual mixing patterns of sex workers with PWIDs, largely because sexual networks are a gateway through which HIV could spread to the general population. In order to explore what specific interventions may have the largest impact on mitigating the HIV sub-epidemics in Pakistan, research is warranted for a more in-depth understanding of underlying social and structural factors along the pathway to HIV risk vulnerabilities among SWs, as well as in the general population.

4.7 AUTHOR CONTRIBUTIONS

Performed the data analyses, modeling, interpretation of results, drafted the manuscript and critically reviewed the manuscript: DYM; modeling, interpretation of results, and critically reviewed the manuscript and revised later drafts: LAS; contributed in the design of the study, interpretation of results, critically reviewed the manuscript and revised later drafts; BE, TR, BKA, SF, and JFB; all authors interpreted the results and made a substantial contribution to the final version of the article.

4.8 ACKNOWLEDGMENTS

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4.9 COMPETING INTERESTS

All authors declared no conflict of interest.

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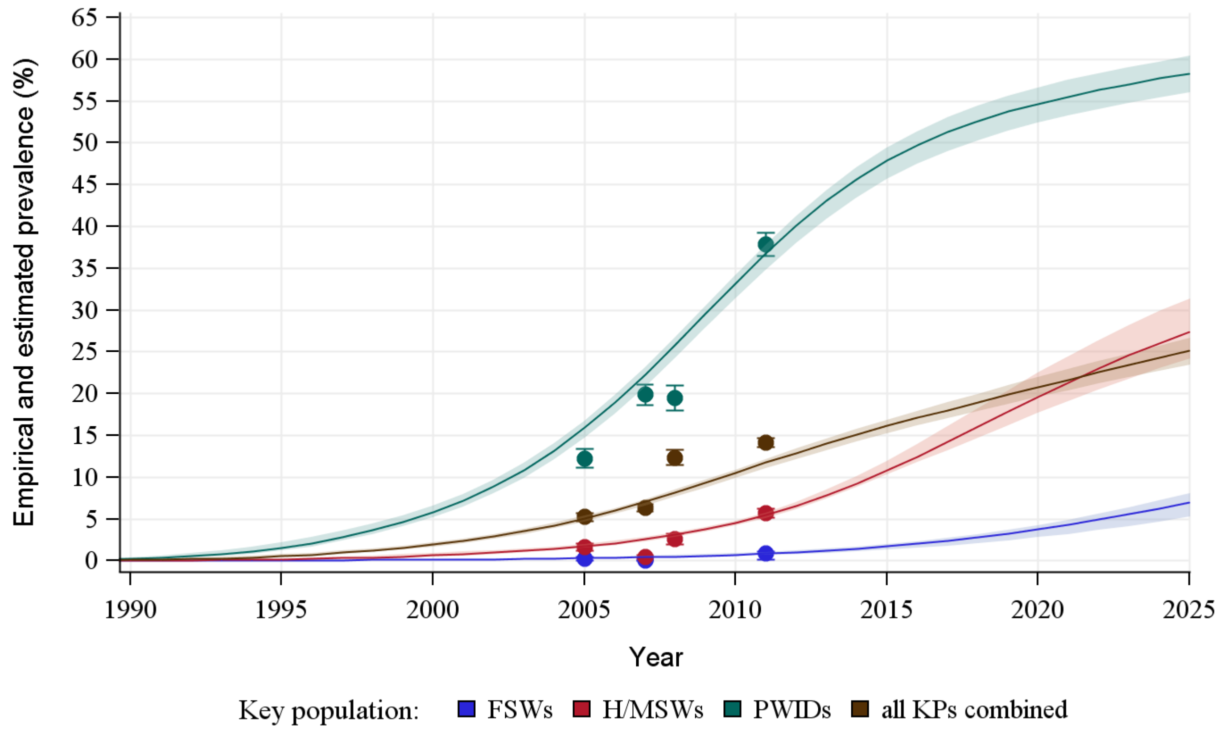
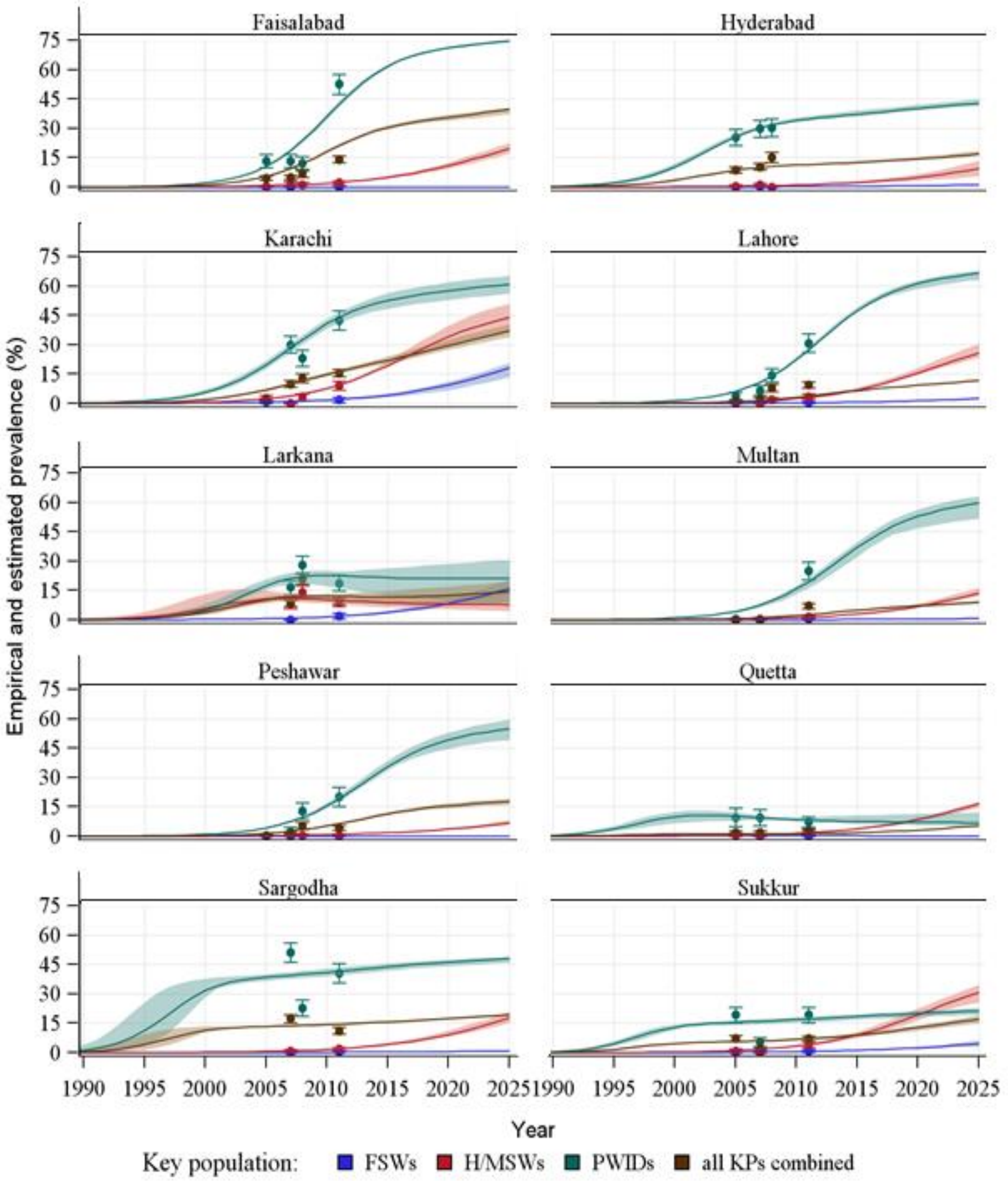
Figure 4.1 Empirical and model estimated prevalence of HIV among KPs in Pakistan



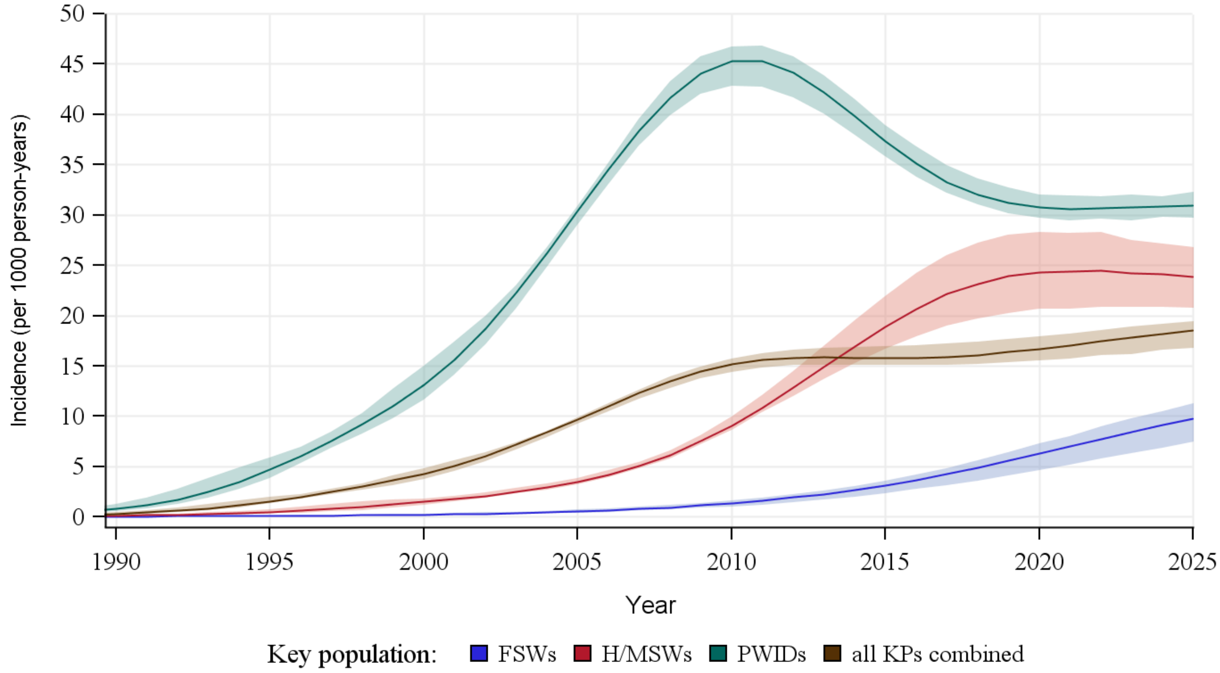
KPs = Key populations.
PWIDs = People who inject drugs; FSWs = Female sex workers; H/MSWs = Hijra/trangender/male sex workers.
Dots/bars indicates empirical estimates /(95% confidence interval) of prevalence.
Shaded region indicates the range of model estimated prevalence.

Figure 4.2 Empirical and model estimated prevalence of HIV among each KP by city



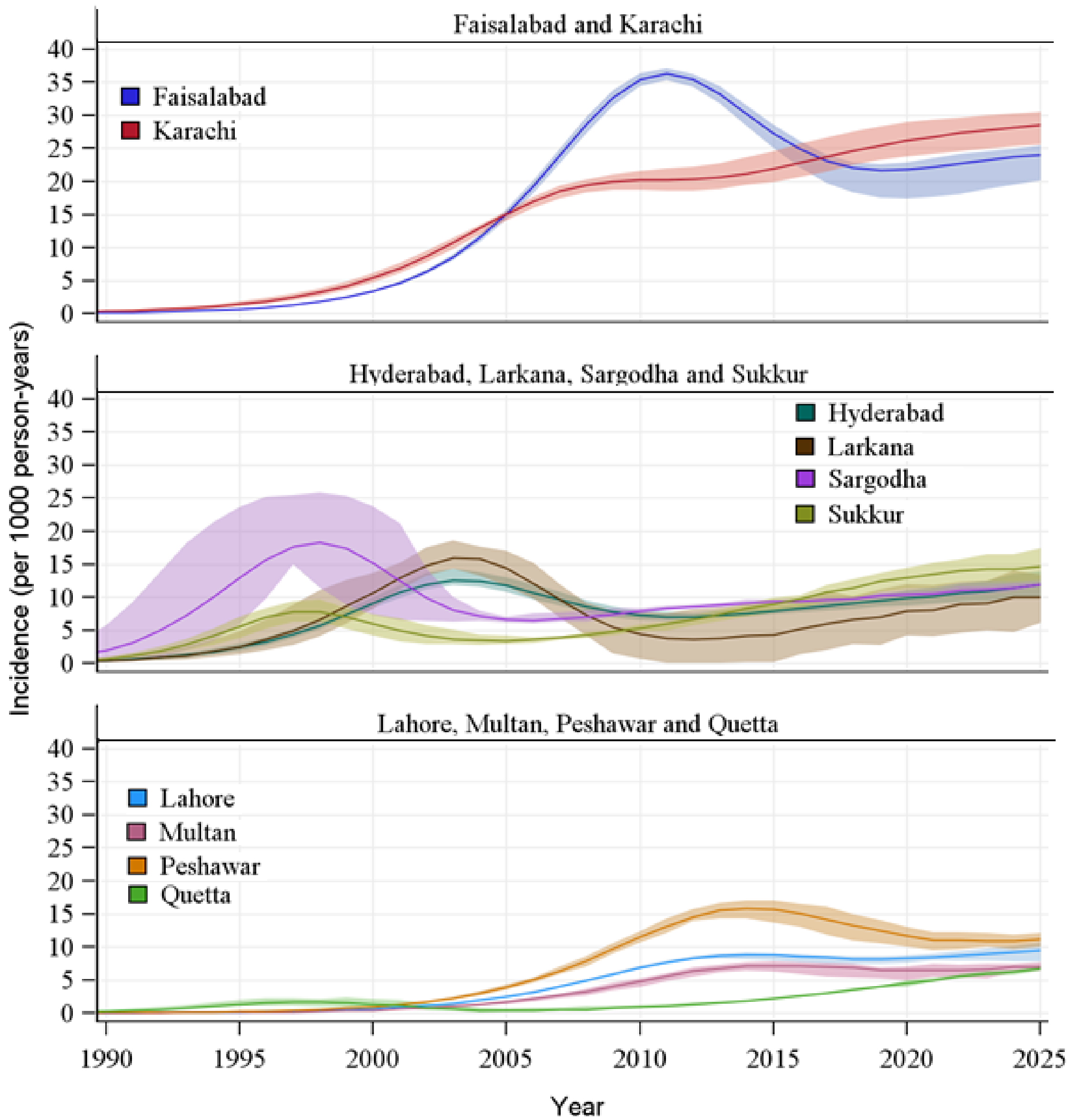
KPs = Key populations.
PWIDs = People who inject drugs, FSWs = Female sex workers; H/MSWs = Hijra/trangender/male sex workers.
Dots/bars indicates empirical estimates /(95% confidence interval) of prevalence.
Shaded region indicates the range of model estimated prevalence.

Figure 4.3 Estimated HIV incidence among key populations in Pakistan



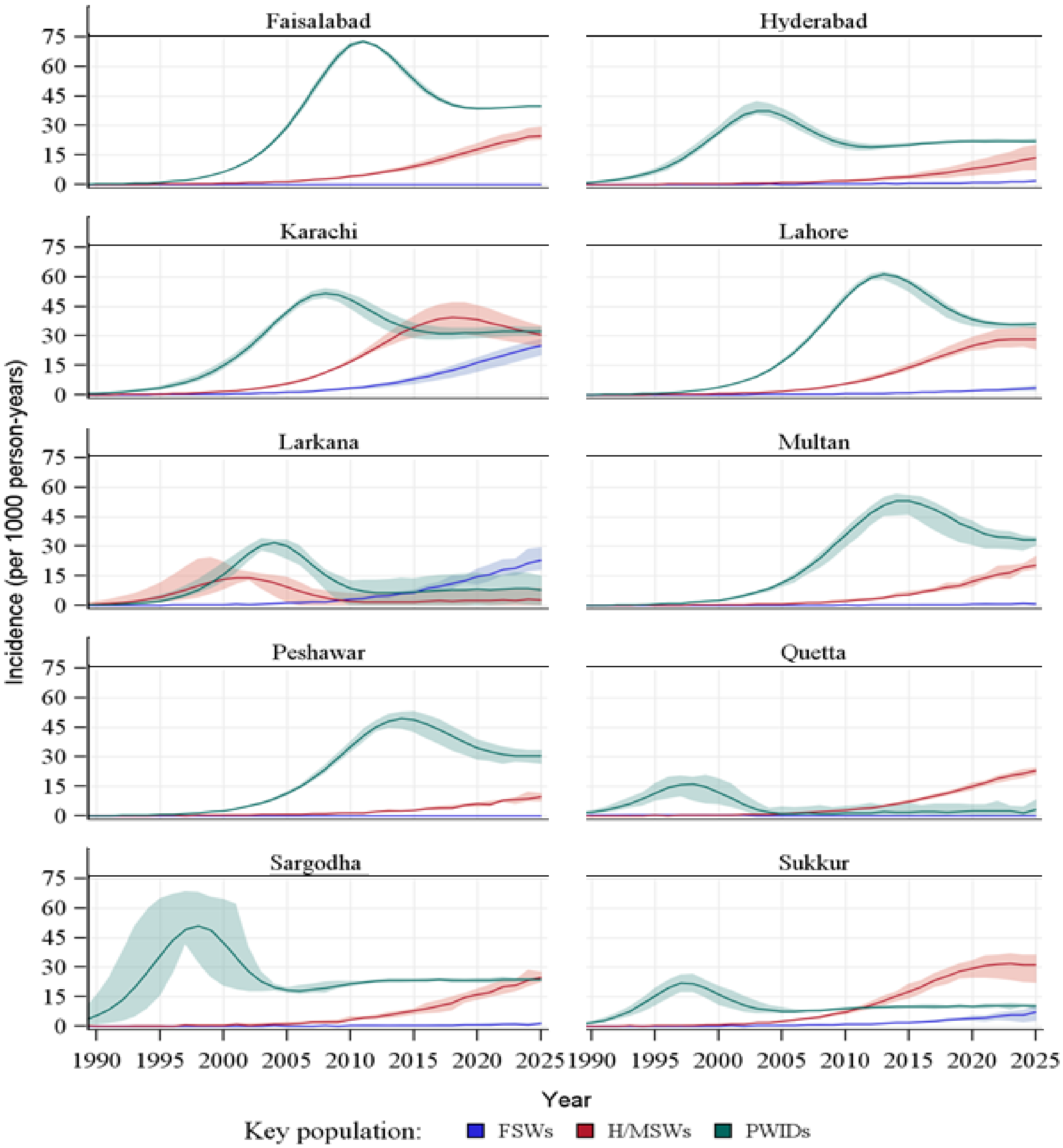
PWIDs = People who inject drugs; FSWs = Female sex workers; H/MSWs = Hijra/trangender/male sex workers.
KPs = Key populations.
Shaded region indicates the range of estimated incidence.

Figure 4.4 Estimated HIV incidence among all key populations combined in each city



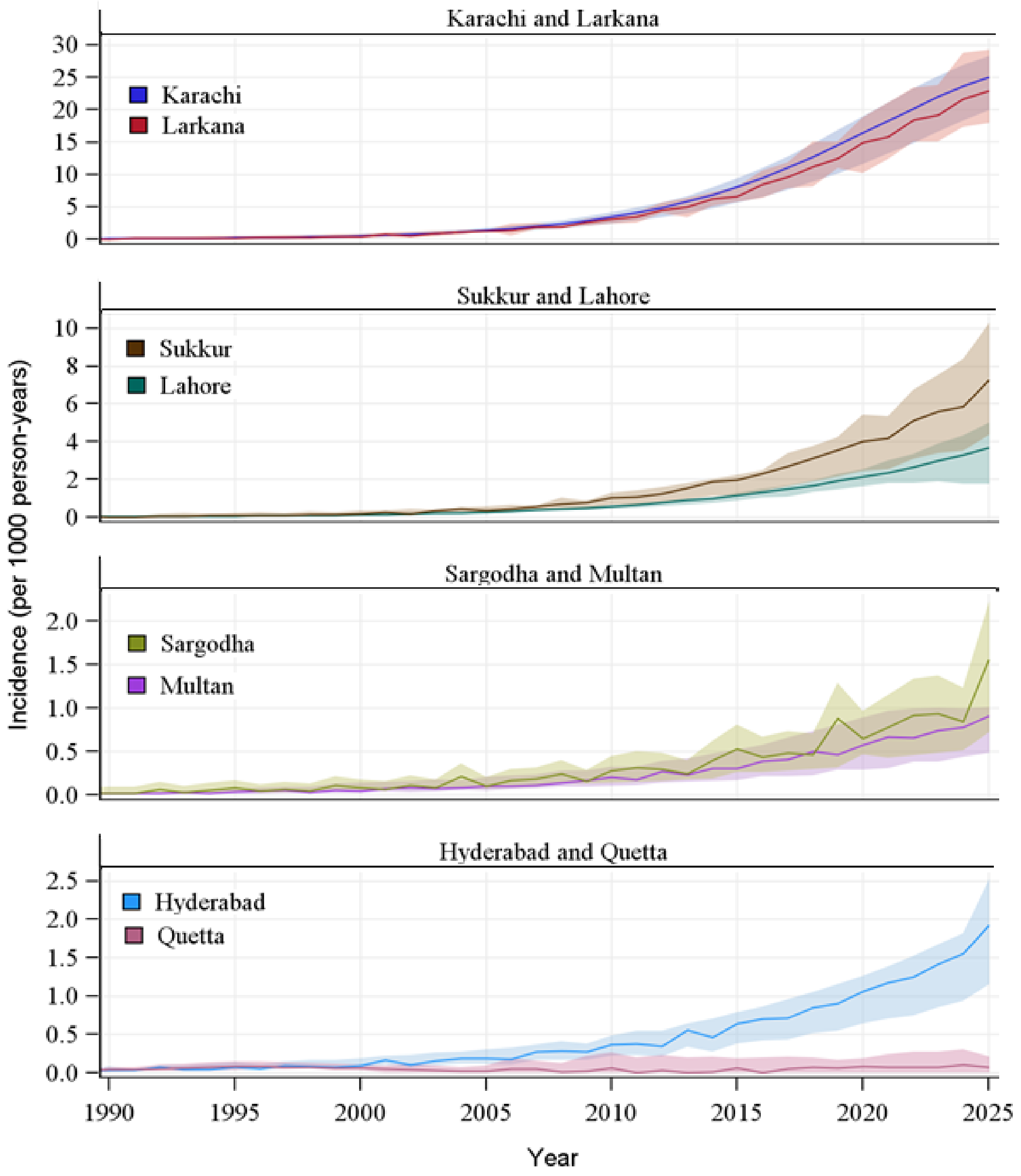
KPs = Key populations.
Shaded region indicates the range of estimated incidence among all KPs combined.

Figure 4.5 Estimated HIV incidence among key populations within each city



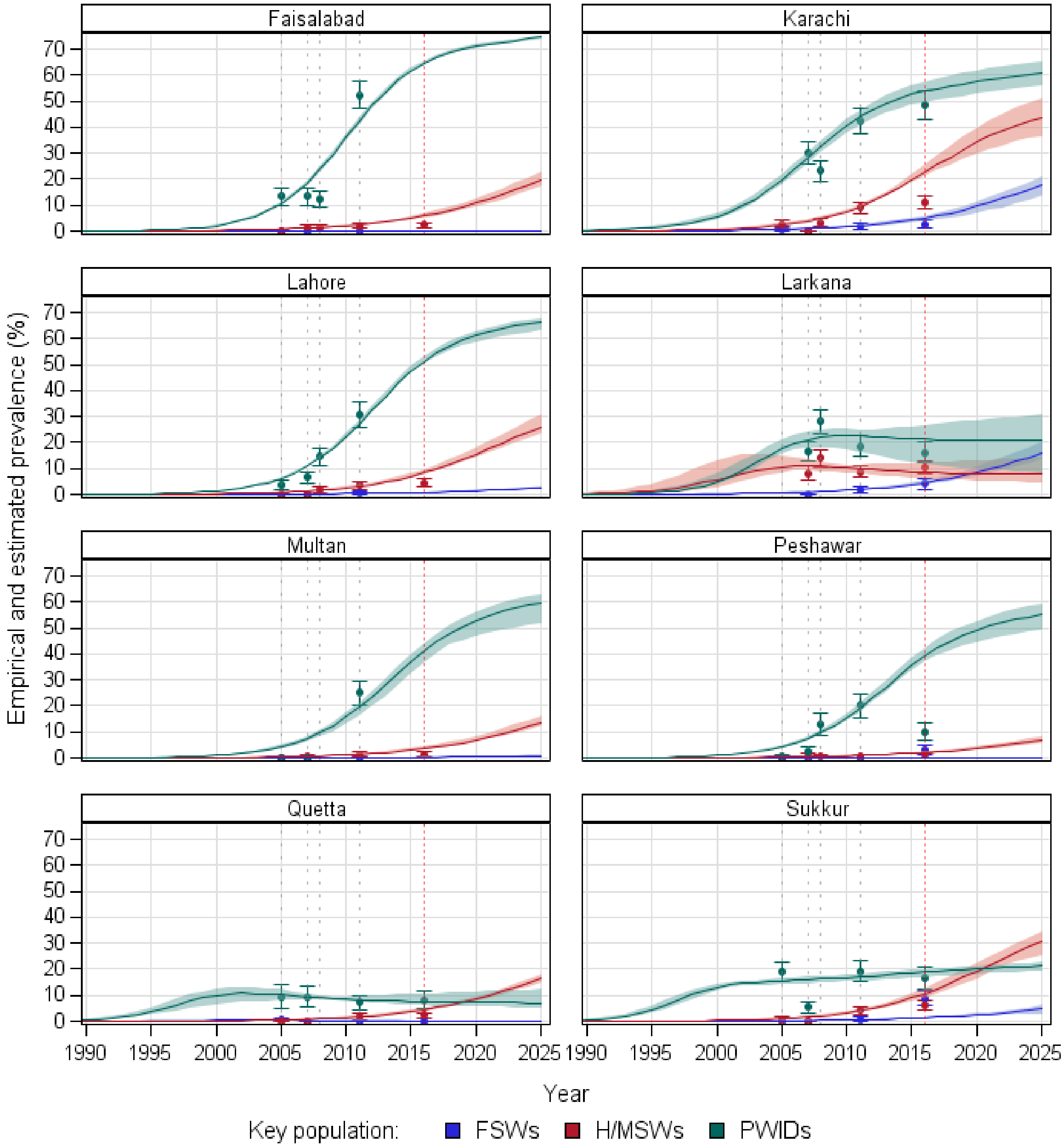
KPs = Key populations.
PWIDs = People who inject drugs; FSWs = Female sex workers; H/MSWs = Hijra/male sex workers.
Shaded region indicates the range of estimated incidence.

Figure 4.6 Supplementary Figure: Estimated incidence among FSWs by city



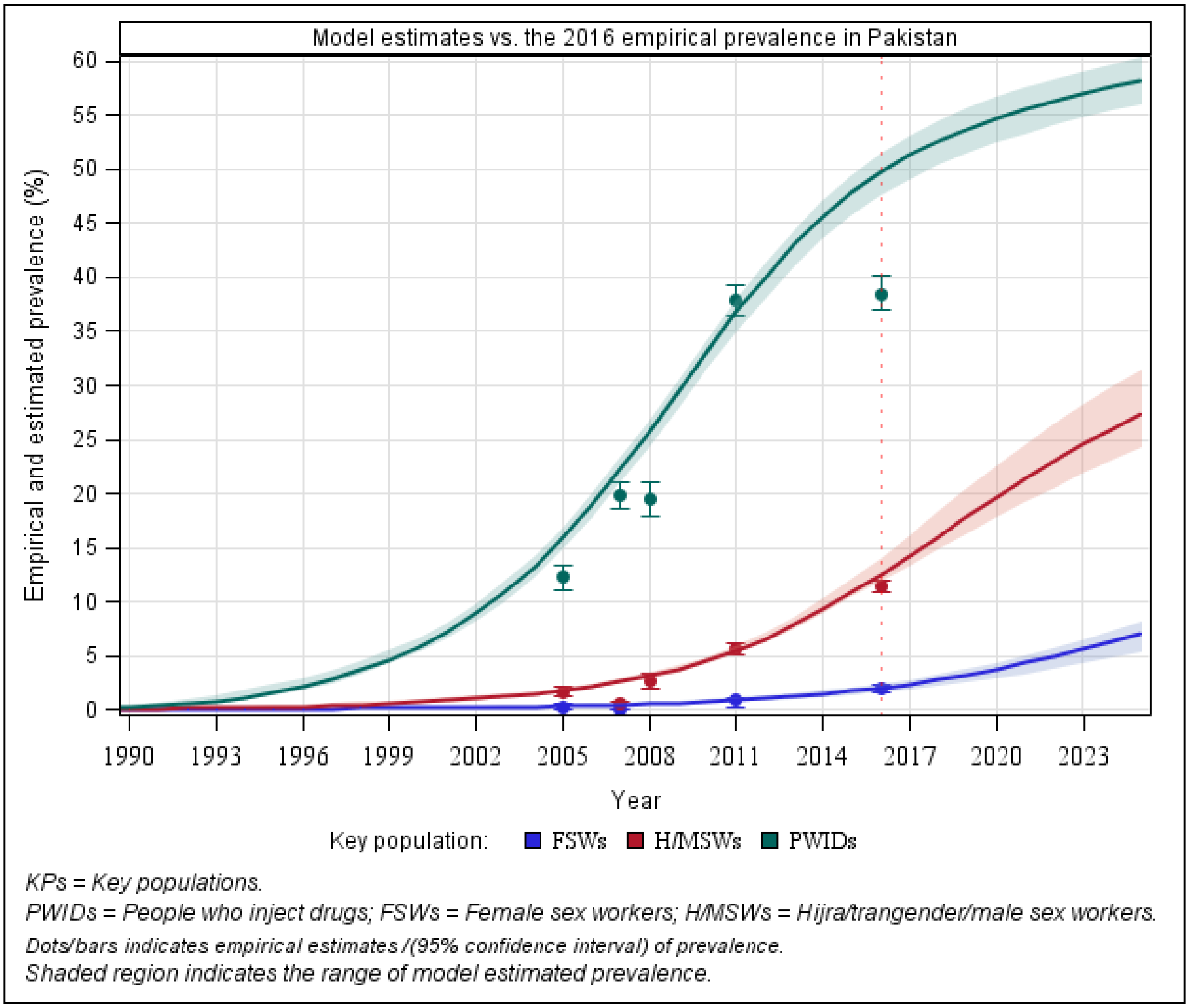
Shaded region indicates the range of estimated incidence among FSWs.
FSWs = Female sex workers.
**Note: 1. Faisalabad and Peshawar are not included as they have zero empirical prevalence.*
2. Different scales were used on the vertical (incidence) axis.

Figure 4.7 Supplementary Figure: Model estimated prevalence vs. the 2016 empirical prevalence by KP in each city



KPs = Key populations.
PWIDs = People who inject drugs, FSWs = Female sex workers; H/MSWs = Hijra/trangender/male sex workers.
Dots/bars indicates empirical estimates /(95% confidence interval) of prevalence.
Shaded region indicates the range of model estimated prevalence.
**Figure shows model validation - estimated prevalence fitted to the 2016 empirical survey data to validate model projections. Note that estimated prevalece was obatined by fitting to four rounds of previous;y collected data, 2005-2011.*
***In 2016, no data was collected among PWIDs in Faisalabad, Lahore and Multan.*

Figure 4.8 Supplementary Figure: Model estimates of HIV prevalence vs. the 2016 empirical prevalence among each KP in Pakistan



5 THE ROLE OF SEXUAL NETWORKING WITH PEOPLE WHO INJECT DRUGS IN HIV TRANSMISSION AMONG SEX WORKERS

5.1 CHAPTER OVERVIEW

Studies in Chapters 3 and 4 indicated that the HIV epidemic among SWs has emerged and continues to rise, suggesting Pakistan's epidemic is similar to the trends in the region, whereby it begins among PWIDs and subsequently spread to SWs and their sexual networks. This expansion of the HIV epidemic among SWs in Pakistan has become a growing challenge. The rising prevalence and incidence among SWs in Pakistan may partly be due to their elevated risk exposure through sexual contact with PWIDs, among whom the epidemic is already well-established. Building on insights gained from our previous studies, this manuscript investigates the role of sexual networking with PWIDs in HIV transmission among SWs. Findings from this study are important for two reasons. First, it provides evidence that sexual transmission from PWIDs to SWs contributes to the emergence, persistence and spread of HIV among SWs, and perhaps from SWs to the general population in Pakistan. Second, it supports the notion that mixing patterns among KPs should be assessed and quantified in future epidemic appraisals to better plan HIV prevention programs, particularly in the context of concentrated epidemics.

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5.2 ABSTRACT

Background: The expansion of HIV epidemic among sex workers (SWs) in Pakistan is a growing challenge. The rising prevalence and incidence in Pakistan may partly be due to their elevated risk exposure through sexual contact with people who inject drugs (PWIDs), among whom the epidemic is already well-established. In this study, we examined the role of sexual mixing with PWIDs in HIV transmission among SWs in Pakistan.

Methods: We developed a mathematical model of HIV transmission and fitted it to behavioral and biological surveillance (IBBS) data collected among key populations (KPs) from 17 major cities in Pakistan in 2011. We informed the model with information from KPs including whether or not they sexually interacted with one another in the six-months period prior to the survey, and HIV prevalence within each KP in 2011. Among SWs, we estimated the overall incidence and proportional transmission of HIV attributed to sex with PWIDs in a six-month period between 2011-2012.

Result: Of 16,644 KPs (70.5% SWs, 29.5% PWIDs) surveyed in 2011**,** a total of 2,158 KPs (13.1%) had engaged in sex with someone from a different transmission risk group (i.e, SWs with PWIDs, or conversely, PWIDs with SWs) within the previous 6 months. The overall weighted prevalence among PWIDs who had sex with SWs, and those of female sex workers (FSWs) and hijra/transgender/male sex workers (H/MSWs) who had sex with PWIDs was 34.9%, and 3.6% and 8.9%, respectively. By contrast, weighted prevalence among PWIDs, FSWs and H/MSWs who either did not have or did not know whether they had PWID-SW sex was 38.5%, 0.57% and 5.2%, respectively. It is estimated that nearly 18.2% (credible interval

[CI]: 9.0% - 33.0%) and 19.5% (CI: 16.4%-25.5%) of HIV incidence among FSWs and H/MSWs, respectively, is attributed to sex with PWIDs. More than half of FSWs with HIV (62.6%; range: 37.4%-81.1%) and nearly three-quarters of H/MSWs with HIV (74.2%: range: 63.6%-80.6%) are likely from the cities of Karachi, Sukkur and Larkana combined, all in the Province of Sindh. Among FSWs, it is estimated that the highest proportion of HIV attributed to sexual encounters with PWIDs is in the city of Sukkur (59.4%; CI: 54.4%-64.0%), while among H/MSWs, the highest estimated attribution of HIV transmission due to sexual encounters with PWIDs is in the city of Peshawar (35.5%; CI: 17.5%-57.0%).

Conclusions: Nearly one-in-five infections among SWs in Pakistan are estimated to be attributed to sexual transmission from PWIDs, though results vary substantially by region. Any epidemic appraisal to prioritize particular SWs needs to incorporate monitoring of sexual mixing patterns with PWIDs to better plan HIV prevention programs.

5.3 INTRODUCTION

In concentrated HIV epidemics, such as in Pakistan, key populations (KPs) bear a disproportionate burden of HIV infections. In the Pakistan context, these KPs include people who inject drugs (PWIDs) and sex workers (SWs), namely female, *hijra*/transgender and male sex workers (hereafter denoted by FSWs, HSWs and MSWs, respectively)[1–4]. The HIV epidemic in Pakistan has established a firm foothold among PWIDs[5–8]. Epidemiological evidence has suggested an upsurge of the epidemic among SWs in Pakistan, perhaps linked to their social and sexual networking with PWIDs[9–11]. It has become a growing concern that the epidemic may be expanding to marriage partners of SWs and the general population through non-PWIDs sexual partners of SWs and resulting in general epidemics. This epidemic pattern is consistent with the HIV epidemic in many South and Southeast Asian countries, whereby the epidemic begins with PWIDs and subsequently spreads to SWs, and, finally, to the general population through sexual clients[12–14].

Heterogeneity in mixing patterns among KPs plays a key role in sustaining HIV epidemics and complicating the delivery of HIV intervention strategies[13,15–17]. An important factor influencing heterogeneity in the HIV sub-epidemics within a country or region relates to the overlapping of high risk networks. One concern arises, in part, due to the overlap between high-risk behaviors within individuals, which is considered as one of the factors that has been cited for the rapid spread of HIV in South and East Asia[18–20]. Another major concern arises from heterogeneity in the mixing pattern with PWIDs networks that play major roles in the variation of observed epidemiological patterns of HIV transmission[13,18,19]. In this paper, overlapping of high risk networks refers to a high risk mixing between two different KPs, for example, between PWIDs and SWs through sex and/or drug injection. We define overlapping risk exposure as risk exposure from more than one – a SW who inject drugs has an overlapping risk exposure from more than one source, as does a SW who has sex with a PWID.

Previous epidemiological studies from Pakistan reported that there is considerable overlap of risk behaviour between PWIDs and SWs, and this could perhaps play a role in emerging epidemics as it creates the opportunity for an infection circulating in one KP group to be bridged to another KP group. For instance, in 2011, an estimated 16.1% of SWs were exposed to overlapping HIV risk (i.e., they injected drugs and/or had sex with PWID)[1,21]. Among the SWs with at least one overlapping risk exposure, 4.5% injected drugs, 11.7% had had sex with a PWID, and 13.9% had sex with a PWID or injected drugs in the past 6 months[21]. A total of 2.2% of SWs were engaged in both overlapping risk behaviors (i.e., both injecting drugs and having sex with PWID) in the past 6 months[21]. These risk exposures vary by type of SW. The proportion with exposure to at least one overlapping risk behavior (i.e., either injecting drugs or having sex with a PWID) was highest among FSWs (14.3%), followed by HSWs (13.5%) and MSWs (12.2%)[21]. HIV prevalence among SWs with both overlapping risk exposures (i.e., had sex with PWIDs and injected drugs) also varies by SW group, ranging from 0.6% among FSWs to 7.5% among HSWs[21].

Among HSWs who mixed with PWIDs, the highest HIV prevalence was reported among those who had sex with PWIDs, but did not inject drugs (11.2%), followed by a prevalence of 7.4% among those with both overlapping risks, and 5.9% among those who injected drugs, but did not have sex with PWIDs[21]. Consistent condom use with paying clients among these KPs with both overlapping risk exposures was also low, estimated at 13.3% among HSWs who both injected drugs and had sex with PWIDs[21].

Much remains unknown about the role of sexual networking between PWIDs and SWs in HIV transmission in a concentrated epidemic context. In addition to the type of overlapping risk behaviors that SWs may have through interaction with PWIDs, some SWs do not mix with PWIDs at all or do not know if they had sex with a PWID. Taking such extent and type of SW-PWIDs mixing into account, this study investigated the magnitude of HIV transmission to SWs due to their sexual networking with PWIDs.

5.4 METHODS

5.4.1 DATA SOURCE AND STUDY POPULATION

We used the 2011 integrated behavioural and biological surveillance (IBBS) data collected among PWIDs, FSWs, HSWs and MSWs in 17 cities in Pakistan. PWIDs refers to persons aged 18 or older who had injected drugs in the past six months. MSWs and HSWs refer to men aged 13 and 15 or older, respectively, and FSWs refers to women aged 15 or older who sell sex in exchange for money or gifts. Many MSWs start sex work at a younger age than FSWs or HSWs, and therefore the age limit for inclusion in MSWs sample was lower. Most h*ijras* are transgender individuals who are born males and often cross-dress in feminine attire, only a few having been born with intersex variations, and some undergo surgical sex change; they form a distinct sociocultural group unique to South Asia, and are considered to be a third gender[22–24].

Data was collected following an in-depth networking mapping exercise aimed to estimate the size, distribution and operational typology of KPs in targeted cities. The mapping exercise involved systematically identifying key informants, contact tracing, and triangulating of results through a process of validating identified hot spots and estimated number of KPs in each hotspot. Overall estimates of sizes of each KP in each city were obtained by combining estimates obtained from all validated spots. It is important to note that cities were selected based on anecdotal evidence of high risk activity, the presence of multiple KPs, and the geographical accessibility. Maps of cities surveyed in 2011, depicting relative prevalence among KPs, can also be found elsewhere[5]

Following mapping, a representative sample of each KP was drawn from estimated population sizes of each KP in each city. The sample size of each KP surveyed in each city ranges from 350-400. Various sampling techniques were utilized to recruit a representative of each KP in each city. MSWs were recruited through respondent driven sampling, while HSWs were recruited through network sampling whereby “retired” HSWs who provide support and clients, were selected randomly from a list compiled during mapping and asked to recruit eligible participants. Depending on the typology of FSWs, both time location cluster sampling and conventional cluster sampling were used to recruit street-based FSWs and brothel- and home-based FSWs, respectively. PWIDs were recruited using multistage cluster sampling. Data was then collected from samples of each KP in each city by trained interviewers using structured questionnaires. Because HSWs and MSWs are both biologically males, combined data among these KPs was used for analysis (hereafter denoted by H/MSWs). Further details on the characteristics of each KP, methods and techniques of mapping, sampling and data collection can be found elsewhere[1,25].

5.4.2 CHARACTERISTICS OF STUDY POPULATION

The 2011 IBBS data collected from all 17 cities were combined and used for provincial- and country-level analysis, while only cities with data available among all KPs were included for city-specific analysis. Data from SWs and PWIDs who had sex with one another were identified and used to estimate the incidence of HIV attributed to sexual transmission from PWIDs to SWs. Sexual interaction between PWIDs and FSWs refers to having vaginal sex, while sexual interaction between PWIDs and H/MSWs refers to anal sex. Female PWIDs in the survey were very small in number (<0.1%), and thus were excluded from analysis. Therefore, PWIDs in this study are all males.

In order to examine sexual transmission of HIV between PWIDs and SWs, two sexual interaction scenarios between SWs and PWIDs (i.e., FSWs with PWIDs and H/MSWs with PWIDs) were considered and analyzed independently. To describe overlapping risk interactions, we examined sexual risk behaviour that link SWs and PWIDs based on their response when asked whether or not a SW had sex with PWIDs and vice-versa in the past 6 months. Therefore, SW groups and PWIDs who responded that they had sex with one another were identified and used to estimate infections among SWs probably occurred due to sex with PWIDs. Data was further used to examine the proportional contribution of sexual transmission among SWs due to sex with PWIDs. Further details on the characteristics of these KPs and their interaction is also available in previous studies[1,19,26].

Our analysis relies heavily on information about the prevalence of infectious HIV-positive individuals by KP and the self-reported risk behaviour activity about their sexual interaction with PWIDs. Each KPs' HIV status was identified and utilized to stratify each KP by sero-status. In all analyses, sampling weights based on the respective estimated population sizes of each KP in each city were utilized. Weighting was identified as described previously[27–29].

5.4.3 MODEL ANALYSIS

We constructed a mathematical model to estimate the risk of infection among SWs due to their sexual interaction with PWIDs. For each SW who sexually interacted with a PWID, we considered two routes of HIV transmission: infection due to sexual interaction with a PWID or infection outside of sexual interaction with a PWID. For each KP, there were four hazard rates where each rate is the product of SW-specific transmission coefficient (male vs. female and insertive vs. receptive) and the probability that the sexual partner from among PWIDs was HIV sero-positive. The probability of transmission to a KP (FSW or H/MSW) is estimated as the current infectious HIV prevalence in the other respective KP that they likely had sex with (i.e., PWIDs). Because this probability varies depending on behavioral factors such as consistent condom use, other sexually transmitted infections, male-circumcision and average number of sexual clients, the coefficient of transmission (i.e., transmission rate) is defined as the product of behavioral factors and the probability of transmission per sexual partnership. Note that we did not take account the effect of ART effect or viral load among infectious KPs due to limited data.

The proportion of HIV transmissions that arose from sexual transmission was estimated from model fits. The total infection occurring from each route of transmission (i.e., through sex with PWIDs or outside sexual interaction with PWIDs) was calculated from the probabilities of each route of transmission for every SW group. Furthermore, transmission coefficients were used to estimate the proportional contribution of sexually transmitted HIV infections that likely occurred from PWIDs to SWs. Each KP group are assumed homogenous in terms of their transmission coefficients. As per the information captured in the IBBS data about sexual interaction between SWs and PWIDs, we assumed that the incidence of HIV infections among KPs who sexually interacted with each other was calculated as the rate at which new infections were likely to occur in a 6-months period between 2011-2012.

In the sexual relationship between PWIDs and SWs, we assumed FSWs and H/MSWs were performing receptive vaginal and receptive anal sex with PWIDs, respectively. This also means that PWIDs are all insertive, performing anal sex with PWIDs and vaginal sex with FSWs. We assumed no sexual interaction between FSWs and H/MSWs, and thus no transmission of HIV between FSWs and H/MSWs was considered. Given the HIV prevalence in the general population of Pakistan is low, we also assumed very little infections occurred due to any sexual interaction with non-client persons in the general population. It is worth noting that data from KPs of all cities were combined and utilized to estimate the overall HIV incidence and proportion of sexually transmitted HIV infections occurred among SWs due to sexual networking with PWIDs by province and in Pakistan.

Because of uncertainties surrounding behavioral factors and empirical prevalence, confidence intervals of transmission coefficients were also used to determine the range of credible intervals (CI) for estimating overall incidence of infections and proportional contributions of HIV transmission to SWs due sex with PWIDs. Furthermore, there is uncertainty surrounding the mean duration that PWIDs were involved in drug injection[15], and that in turn affects the estimated rate of partner turnover rate among PWIDs. This also highlights the sensitivity surrounding the assumption of a homogenous and constant population that the out flow of susceptible and infectious individual is immediately compensated by the inflow of a new susceptible. The assumption that PWIDs surveyed will remain in their respective KP for the six months period or are compensated by a constant in-and-out flow of KP may be biased because the rate of those interviewed PWIDs leaving (quitting) their respective KP is, in part, due to the difference in HIV prevalence and the risk vulnerability of those newly in-coming PWIDs to sexually interact with SWs is different. In a sensitivity analysis, we therefore examined this scenario using PWIDs whose duration of time in high risk activity falls in the 95% confidence interval of the average duration of time.

5.5 RESULTS

Of 16,644 KPs (unweighted; 70.5% SWs and 29.5% PWIDs) surveyed in 2011**,** a total of 2,158 KPs (13.1%; unweighted) had engaged in sex with someone from a different transmission risk group (i.e., SWs with PWIDs, or conversely, PWIDs with SWs) within the previous 6 months. Population sizes and HIV prevalence from each KP in each city is key for better estimate of new infections, and thus weighted data was used for modeling. Weighted data from a total of 1122 PWIDs and 1036 SWs (53.3% FSWs and 46.7% H/MSWs) in Pakistan who had sexual interaction with one another in six months period were identified and used to estimate the HIV infections attributed to sexual transmission from PWIDs to SWs.

The overall weighted prevalence among PWIDs who had sex with SWs, and those of FSWs and H/MSWs who had sex with PWIDs was 34.9%, and 3.6% and 8.9%, respectively. By contrast, weighted prevalence among PWIDs, FSWs and H/MSWs who either did not have or did not know whether they had PWID-SW sex was 38.5%, 0.57% and 5.2%, respectively.

Nearly half of PWIDs (48.5%) in Quetta had sex with FSWs, followed by PWIDs in Dadu (29.9%) and Sukkur (26.8%). Similarly, nearly a quarter of PWIDs (23.8%) in Sukkur also had sex with H/MSWs, followed by PWIDs in the city of Gujirat (18.3%). On the other hand, the highest proportion of FSWs who had sex with PWIDs were from Sukkur (39.7%), followed by those in Quetta (30.1%), while nearly one-in-five H/MSWs both in Karachi and Quetta were reported to have sex with PWIDs.

The weighted HIV prevalence among PWIDs who had sex with FSWs was highest in Karachi (43.8%) followed by Faisalabad (42.9%) and Multan (36.8%). PWIDs who had sex with H/MSWs in Karachi were all HIV positive, followed by Peshawar (45.5%) and Sargodha (43.8%). Table 5.1 presents population size and weighted HIV prevalence data among PWIDs and SWs who had sex with each other in six months period.

In 2011, the overall empirical HIV prevalence among FSWs and H/MSWs who sexually interacted with PWIDs in Pakistan was estimated at 2.1% and 7.8% respectively (Table 5.1). The overall HIV prevalence was highest in Sindh Province (3.6% among FSWs and 8.9% among H/MSWs) followed by those from Punjab Province (1.7% among FSWs and 5.7% among H/MSWs). Of all PWIDs who had sex with SWs, nearly half of PWIDs who had sex with FSWs and a little over one-third of PWIDs who had sex with H/MSWs were HIV positive (Table 5.1).

In Larkana, though there were fewer FSWs who reported that they had sex with PWIDs (n=6), half of them were HIV positive. A relatively high HIV prevalence among FSWs who had sex with PWIDs was also seen in Karachi (4.8%), followed by those from Lahore (3.7%) and Sukkur (1.3%). Note that the city of Larkana, Karachi and Sukkur are all from Sindh province. Among H/MSWs who had sex with PWIDs, HIV prevalence was also relatively highest in Karachi (9.2%) and Larkana (9.3%) – both from Sindh Province, followed by Faisalabad (6.5%) and Lahore (5.6%) – both from Punjab province. Though there were only few number of H/MSWs who had sex with PWIDs in Peshawar (n=7), nearly one-third of them were HIV positive.

Figure 5.1 presents estimated proportion of HIV transmission among FSWs and H/MSWS attributed to sexual transmission from PWIDs in the 6 months period of 2011/12, with estimated data presented by city, province, and the whole Pakistan. Model fits demonstrated that a significant proportion of HIV infections among SWs in Pakistan occurred through sexual transmission from PWIDs, estimated at 18.2% (CI: 9.0% - 33.0%) of FSWs infections and 19.5% (CI: 16.4% - 25.5%) of H/MSWs infections, and the remainder of infections occurring through anything else but sexual intercourse with PWIDs. Using data combined at a provincial level, the overall HIV transmission among FSWs attributed to sexual interaction with PWIDs was highest in Sindh Province, estimated at 20.6% (CI: 12.0%-32.6%), while HIV transmission due to sexual interaction with PWIDs among H/MSWs was highest in the province of KPK followed by Balochistan (Figure 5.1). However, these results vary substantially by city. The proportion of HIV transmission among FSWs attributed to sexual interaction with PWIDs was highest in the city of Sukkur, with an estimate of 59.4% (CI: 54.4%-64.0%), while the highest proportional transmission among H/MSWs was seen in the city of Peshawar (35.5%; CI: 17.5%-57.0%) followed by Faisalabad (28.4%; 14.4%-47.6%). Figure 5.2 presents estimated proportional contribution of sexual transmission from PWIDs to SWs or everything else by KP, city, province, and at a national level in Pakistan.

In an attempt to characterize provinces in terms of sexual mixing patterns leading to HIV transmission between SWs and PWIDs, we combined all new infections and compared provinces using proportional contributions of HIV infections attributed to sexual transmission from PWIDs to SWs in Pakistan. Data suggests that more than half of infected FSWs (62.6%; range: 37.4%-81.1%) and nearly three-quarter of infected H/MSWs (74.2%: range: 63.6%-80.6%) were likely from the Province of Sindh followed by Punjab. A little over one-third (34.8%: range: 16.6%-60.9%) of infected FSWs and more than one-firth (22.8%; 18.0%-30.0%) of infected H/MSWs attributed to sexual transmission from PWIDs to H/MSWs might be from Punjab Province. Figure 5.3 shows the overall incidence of HIV among FSWs and H/MSWs who had sex with PWIDs occurred in the 6 months period of 2011/12. In a sensitivity analysis, no significantly different findings in incidence of new infections among SWs were found when using only KPs whose duration of time to remain in their respective KPs in the six months period falls in the 95% confidence interval of mean duration of risk activity. Note that estimation was made for six months period, and thus it is probably that no difference was observed due to very few PWIDs being excluded. Furthermore, the HIV prevalence among PWIDs leaving early from risk activity is likely to be compensated by those who were leaving from high risk activity after a long period of time.

5.6 DISCUSSION

This study found a considerable overlap of sexual interaction between KPs leading to HIV transmission from PWIDs to SWs; this could potentially play a role in the emergence and spread of HIV epidemics among SWs in the past decade. This study demonstrated that nearly one-in-five HIV infections among SWs in Pakistan can be attributed to sexual transmission from PWIDs, with estimates in the range 9.0%-33.0% of FSWs and 14.6%-25.5% of H/MSWs infected through sex with PWIDs. This suggests that sexual networking with PWIDs in Pakistan plays significant roles in the emergence and spread of HIV to SWs. Most HIV infections among SWs attributed to sexual transmission form PWIDs likely to occur in the Province of Sindh followed by Punjab; however, results substantially vary by city and SW groups within each Province.

This study highlighted that critical differences in HIV transmission dynamics leading to regional heterogeneity in the epidemics of HIV among SWs in Pakistan relates to the level of overlapped risk behaviour, and the social and sexual mixing patterns with PWIDs. This is also consistent with previously reported evidence that suggested regional and temporal variations among KPs is linked to level of risk and structural vulnerabilities[21], size and distribution of KPs[5], time lag in emerging trends of the epidemic among SWs[21], and mediating risk factors such as violence and program exposure[6,9,10,30,31].

5.6.1 SEXUAL TRANSMISSION FROM PWIDS TO FSWS

The highest proportional transmission of HIV from PWIDs to FSWs through sex is likely to occur in Sukkur followed by Larkana. More than half of HIV infections among FSWs in Sukkur are attributed to sexual transmission from PWID, while more than a quarter of new infections among FSWs in Larkana are likely to occur through sex with PWIDs.

Empirical evidence from the 2016 IBBS data also supported this assertion that HIV prevalence among FSWs in Sukkur and Larkana has continued to rise in recent years, increased from a prevalence of 0.8% (95% CI: 0.3-2.3%) in 2011 to 8.8% (95% CI: 6.3-12.2%) in 2016 in Sukkur and from 1.9% (95% CI: 0.9-3.8%) in 2011 to 4.1% (95% CI: 2.5-6.7%) in 2016 in Larkana[1,38]. In our previous study, we highlighted that the empirical prevalence among FSWs in Sukkur is also higher than projected prevalence in 2016 and speculated that this may perhaps be related to a rapid upsurge of HIV infections in the past few years between 2011-2016. Findings from this study also corroborates with this speculation that social and sexual networking with PWIDs among FSWs in Sukkur is likely to play role in the spread of HIV infections in the past few years that perhaps yielded a higher empirical prevalence than estimated in 2016.

Karachi has the highest incidence rate among FSWs who had sex with PWIDs regardless of the route of transmission, but the proportional contribution attributed to sexual transmission from PWIDs is lower than those in Larkana and Sukkur. This perhaps suggests that the degree of sexual mixing between SWs and PWIDs may be lower than those cities in the Province of Sindh, and perhaps non-sexual mixing with PWIDs and/or interactions with non-PWIDs clients or spouses are playing significant role in HIV infections among FSWs. It is worth noting that we did not assess the proportional transmission of HIV through sex with PWIDs in other provinces due to very low HIV prevalence to perform modeling analyses. However, we estimated the overall incidence regardless of route of transmission, and results indicated that new infections among FSWs are likely to occur in most cities outside of Sindh Province such as in Lahore, Faisalabad, Peshawar and Sargodha. Note that the 2016 IBBS also demonstrated an increase in prevalence among FSWs in many of these cities, including those cities where they had negligible prevalence in previous surveys such as in Peshawar[1,38].

5.6.2 SEXUAL TRANSMISSION FROM PWIDS TO H/MSWS

The incidence rate of HIV infection regardless of transmission route was higher in the Province of KPK, perhaps due to the size and distribution of KPs in the Province and high number of infections observed in the city of Peshawar. Following Peshawar, the proportional contribution of HIV attributed to sexual transmission among H/MSWs is relatively higher in the city of Quetta from the Province of Balochistan, followed by Faisalabad from Punjab and Karachi from

Sindh Province. However, when all HIV infections attributed to sexual transmission from PWIDs to H/MSWs was combined, the proportion of infections among H/MSWs due to sex with PWIDs remains highest in the Province of Sindh. Though HSWs and MSWs were surveyed separately in the 2016 IBBS and is difficult to make comparison with results from this study, the 2016 empirical prevalence among each HSWs and MSWs was reported the highest in most of the cities in Sindh and Punjab Provinces[38].

Epidemiological evidence is well-established showing the epidemic in Pakistan has a firm foothold among PWIDs[5,32]. There are also observational studies highlighting concerns that the epidemic might be expanding to their sexual contacts, particularly SWs, and in turn lead to the general population through sexual clients[5,9,10,15,30,33]. However, these concerns were based on consistent patterns of HIV epidemics seen in other countries in Asia[19,31,34], whereby HIV transmission begins with PWIDs and subsequently spreads to SWs and their sexual clients[21], and increasing trends of HIV prevalence seen among SWs[5,30]. This study suggests that HIV transmission is in fact occurring among SWs through sex with PWIDs in Pakistan, and is likely to expand to the general population through non-KP sexual partners. This pattern, however, varies substantially by region, and is perhaps relate to the size and distribution of KPs, the degree of social and sexual mixing patterns between KPs and underlying structural factors along the pathway to HIV risk vulnerability.

The novel aspect of this study is that it quantifies the proportional contribution of sexual transmission from PWIDs to SWs in a context of concentrated epidemic, largely driven by PWIDs, including the scale and comparative analysis between cities.

5.6.3 LIMITATIONS

We emphasize that the results presented in this study should be interpreted cautiously for the following reasons. First, these results relied on self-reported behavioral data on HIV risk and behaviours among SWs who responded that they knew they had sex with a PWID is the past six months. It is important to note the limitation and uncertainty due to a significant proportion of SWs in the survey who responded that they did not know whether or not they had sex with PWIDs. Since a SW may not know whether or the client is a PWID, our results may be biased to underestimate the contribution of sexual transmission, and this may perhaps relate to the large variations observed in the contribution across cities. Details on the size and distribution of this SW population can be found in our previous study[33]. Second, specific information was not available to determine the number and nature of PWIDs as sexual clients to SWs (as casual vs. regular) per specified time, and thus overall number of sexual clients proportional to PWIDs who had sex with SWs were assumed for analysis. Third, evidence that show direct relationship between viral loads and the risk of HIV transmission is well established; lower viral load related with reduced risk of HIV transmission, and a high viral load significantly increases the risk of transmission[35–37]. However, this study did not take account its potential impact on the transmission of HIV due to lack of data among infectious KPs. Fourth, this study did not take the effect of ART into account due to lack of data on coverage among KPs. Fifth, this study is limited in assessing the potential contribution of other routes of transmission, including through drug injection within and between SWs and PWIDs, and impacts of social and structural factors along the pathway to risk behaviours and vulnerabilities to HIV infection.

5.6.4 CONCLUSIONS

Nearly one-in-five HIV infections among SWs are due to sexual transmission from PWIDs; however, results vary substantially by region and SW group. This study highlighted the potential role of sexual mixing with PWIDs on the emergence, spread and persistence of HIV among SWs. This is consistent with our previous findings on the emerging and increasing trends of sub-epidemics observed among SWs in Pakistan[21]. Our findings reinforce the need to develop and implement context-specific behavioural strategies customized to sexual mixing patterns between SWs and PWIDs in Pakistan. Further research is warranted to have complete understanding on the proportional contribution of other routes of transmission (such as injection), as well as social and structural factors along the pathway to HIV risk leading to heterogeneity in the emergence, spread and persistence of HIV transmission among SWs in Pakistan.

5.7 AUTHOR CONTRIBUTIONS

Performed the data analyses, modeling, drafted the manuscript and critically reviewed the manuscript: DYM; critically reviewed the manuscript and revised later drafts: LAS; involved in the design of the study, critically reviewed the manuscript and revised later drafts; BE, TR, BKA, SF, and JFB; all authors interpreted the results and made a substantial contribution to the final version of the article.

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5.9 COMPETING INTERESTS

All authors declared no conflict of interest.

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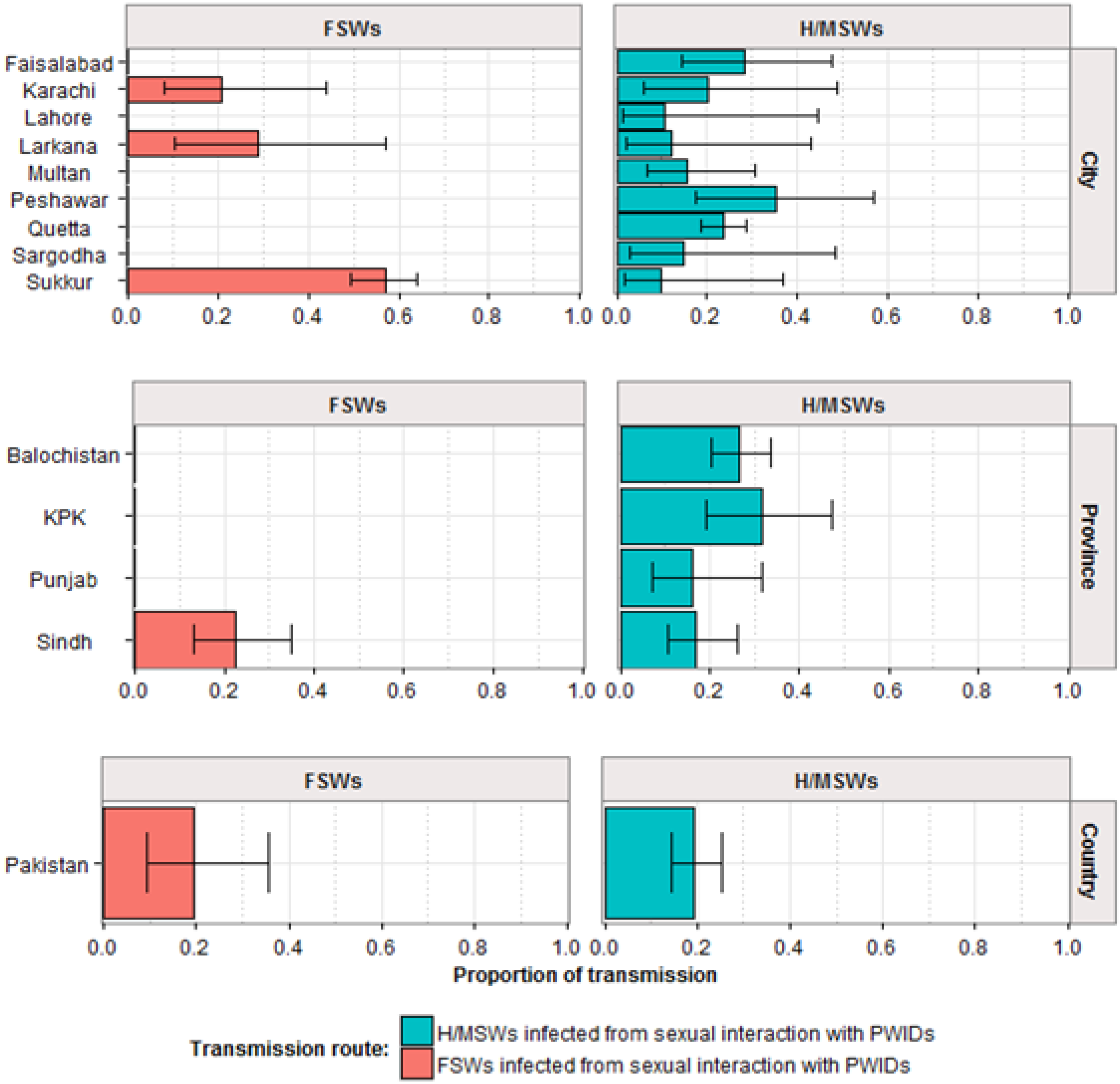
Table 5.1 Summary of data analyzed from the 2011 IBBS

City / province / Country		PWIDs vs. FSWs: had sex with one another				PWIDs vs. H/MSWs: had sex with one another			
		PWIDs		FSWs		PWIDs		H/MSWs	
		N	HIV (%)	N	HIV (%)	N	HIV (%)	N	HIV (%)
Selected cities	Quetta	298	4.6%	1118	1.0%	48	0.0%	391	2.7%
	Peshawar	192	29.6%	9	0.0%	78	45.5%	7	33.3%
	Multan	162	36.8%	1316	1.0%	50	23.8%	88	4.3%
	Faisalabad	1521	42.9%	670	0.0%	326	40.0%	289	6.5%
	Sargodha	142	37.5%	884	0.0%	71	43.8%	64	2.9%
	Lahore	571	25.9%	1711	3.7%	138	28.6%	46	5.6%
	Karachi	729	43.8%	1415	4.8%	91	100.0%	2699	9.2%
	Sukkur	531	23.5%	921	1.3%	244	15.6%	108	3.0%
	Larkana	87	20.7%	12	50.0%	12	25.0%	110	9.3%
Provinces	Balochistan	341	7.1%	1118	1.0%	55	4.1%	391	2.7%
	KPK	268	31.7%	66	0.0%	93	38.1%	10	22.1%
	Punjab	2781	58.3%	4674	1.7%	694	34.6%	536	5.3%
	Sindh	1488	47.1%	2347	3.6%	386	36.1%	2917	8.9%
Pakistan		4879	48.3%	8205	2.1%	1228	34.0%	3854	7.8%

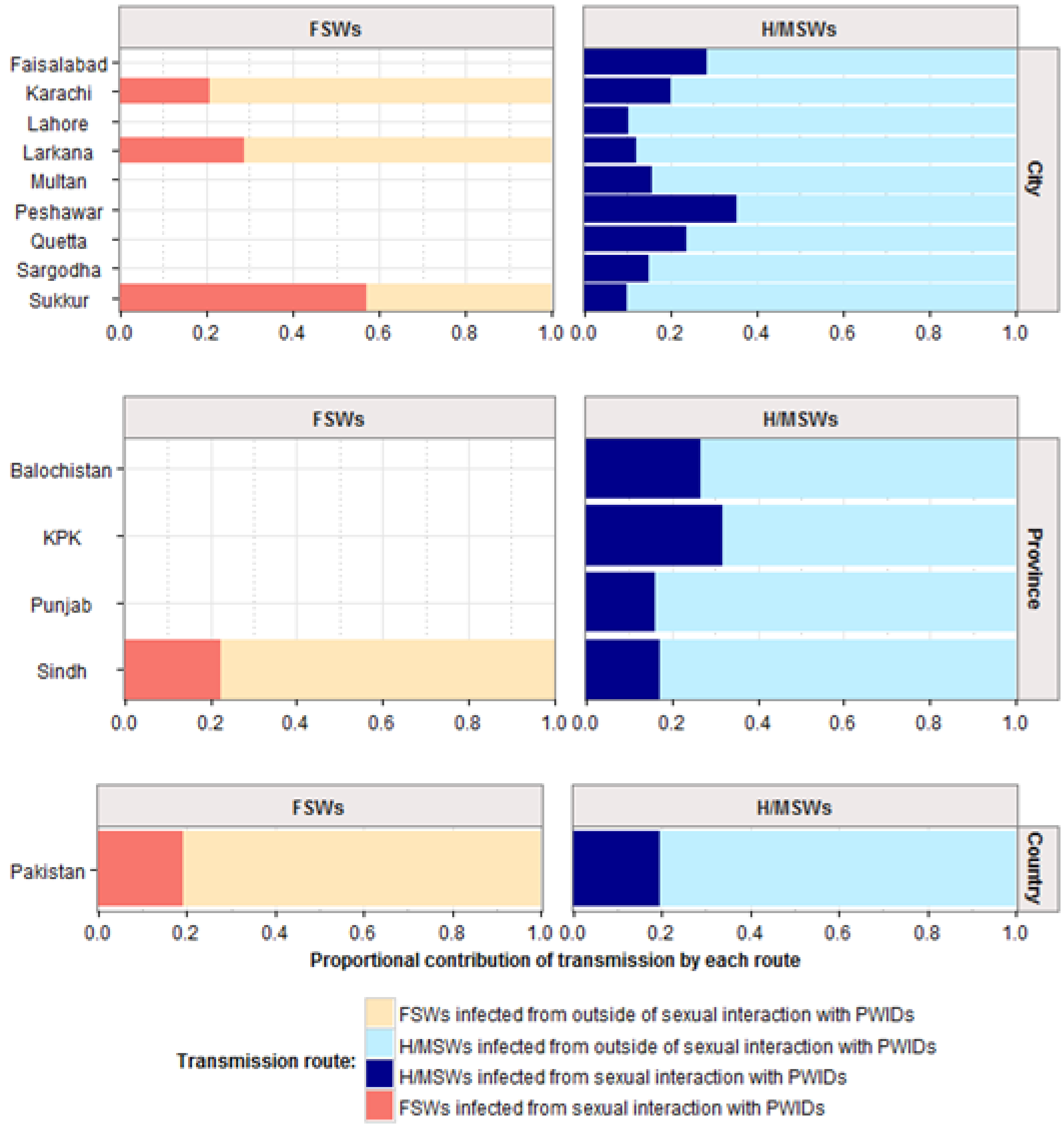
All data are weighted to estimated sizes of each KP in each city to ensure a better estimate of the likelihood of sexual transmission between KPs. HIV prevalence in each KP was obtained from total number of individuals tested positive divided by total size of KP as appropriate.
PWIDs = people who inject drugs. FSWs-=Female sex workers; H/MSWs=*Hijra*/male sex workers; KPK stands for province of Khyber Pakhtunkhwa in Pakistan.
Only cities with data from all KPs were included in the table.
Note that summary of provincial and country level data was obtained from all cities surveyed regardless of KPs surveyed, and thus data from cities in this table may not add up to summary of provincial data.

Figure 5.1 Estimated proportion of sexually transmitted HIV infections among SWs acquired through sexual interaction with PWIDs



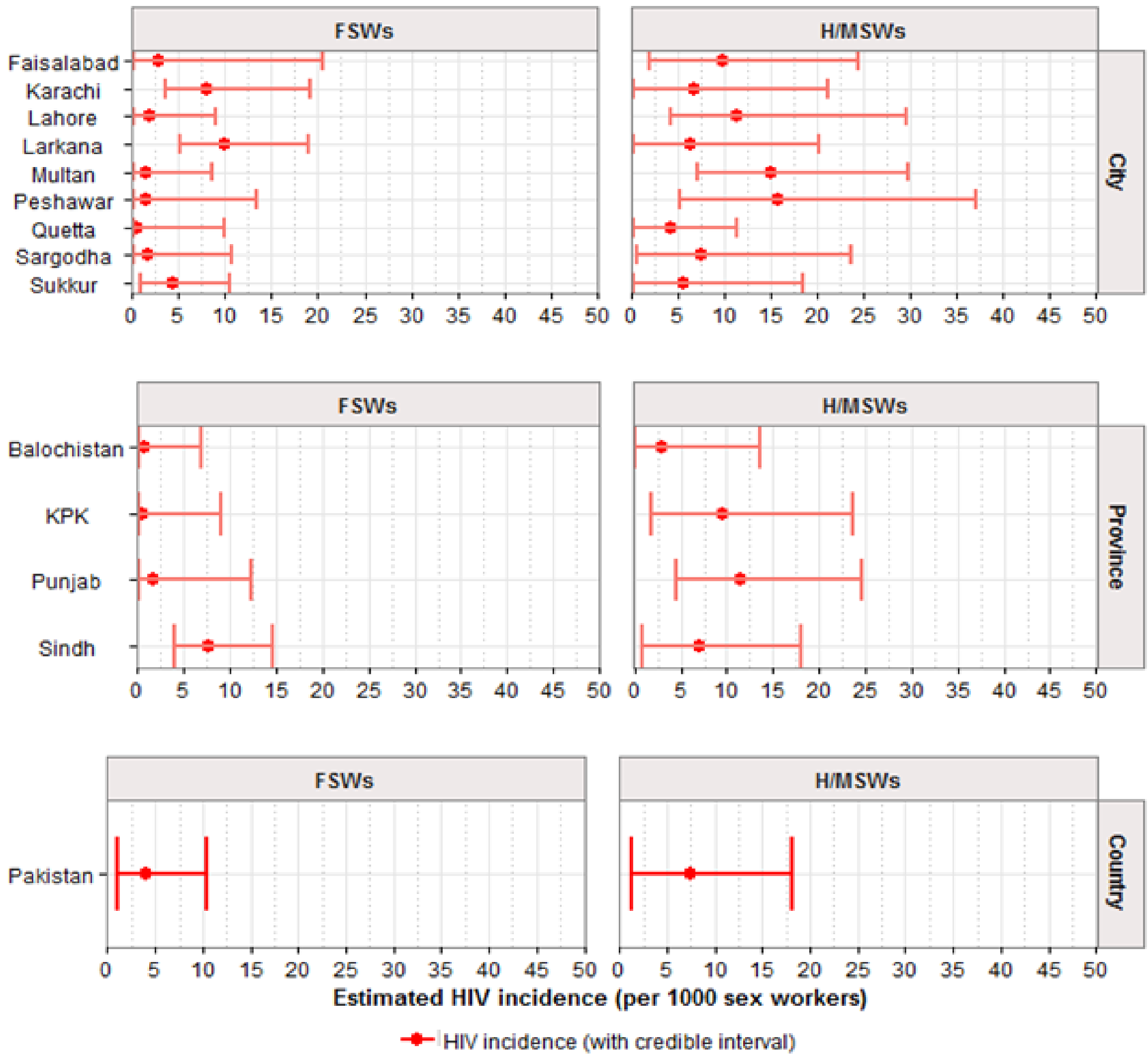
Note that estimates are for FSWs and H/MSWs who had sex with PWIDs and tested HIV negative in 2011.
SWs = sex workers; FSWs = female sex workers, H/MSWS = Hijra/male/transgender sex workers;
PWIDs = people who inject drugs; KPK = Province of Khyber Pakhtunkhwa.
For FSWs, city- and provincial-specifc estimations were made only for Sindh Province and the cities within (i.e., Karachi, Larkana and Sukkur).

Figure 5.2 Estimated proportion of HIV transmission through sex with PWIDs and outside of sexual interaction by sex worker group, city, province, and in Pakistan



Bars refer estimates of credible intervals obtained from 95% confidence interval of transmission coefficients.
SWs = sex workers; FSWs = female sex workers; H/MSWs = hijra/male/transgender sex workers;
PWIDs = people who inject drugs; KPK = Province of Khyber Pakhtunkhwa.
Note that, for FSWs, city- and provincial-specifc estimations were made only for Sindh Province and the cities within (i.e., Karachi, Larkana and Sukkur).

Figure 5.3 Estimated overall incidence of HIV among SWs who had sex with PWIDs in six months period, 2011/2012



Bars refer estimates of credible intervals obtained from 95% confidence interval of transmission coefficients.
SWs = sex workers; FSWs = female sex workers; H/MSWs = hijra/male/transgender sex workers;
PWIDs = people who inject drugs; KPK = Province of Khyber Pakhtunkhwa.

6 SUMMARY

6.1 SUMMARY OF FINDINGS

The overall goal of this research was to utilize epidemiological and mathematical modeling methods to explore the complex social and sexual networking among KPs in Pakistan, with a focus on elucidating pathways leading to heterogeneity in HIV transmission dynamics. Specifically, we focused on determining the factors associated with the overlapping HIV risk among SWs, estimating and projecting the current and future status of HIV epidemics among KPs, determining the KPs that may drive new HIV infections within each city, understanding heterogeneity in the emerging trends of HIV epidemics among KPs and the role of sexual networking among KPs in HIV transmission.

In order to achieve this goal, four related studies were conducted. In these studies, combined with epidemiological analyses, mathematical models were adapted, validated and utilized to improve our understanding of geographical variations in the trends of HIV epidemics, variations in the KPs that drive new HIV infections, and how HIV sub-epidemics among KPs have evolved over time in Pakistan. Following an in-depth mapping exercise performed to determine the size and distribution of KPs at highest risk of HIV acquisition, four rounds of cross-sectional IBBS conducted among KPs between 2005-2011 were used for epidemiological and modeling analyses.

Consistent with the pattern of HIV epidemics in other countries in Asia, whereby HIV transmission begins among PWID and subsequently spreads to SWs and their clients, the HIV epidemic in Pakistan is fuelled by PWIDs and the epidemics among SWs has emerged and continues to rise; and the upsurge of the epidemics among SWs is perhaps relate to the social and sexual networking between PWIDs and SWs. The epidemics in Pakistan is perhaps part of a sub-regional pattern that includes Iran and Afghanistan; it is most concentrated among KPs, and predominantly driven by PWIDs in part due to interconnected drug trade routes between countries.

The studies demonstrate that the HIV epidemics started to emerge and continue to rise among SWs in most cities, first started among H/MSWs followed by FSWs. Furthermore, there is geographical variation in the sexual networking structure among KPs that may be driving the increasing epidemics among SWs. Most importantly, this research highlights that, in Pakistan, a significant proportion of sexually transmitted HIV infections among SWs likely spilled over from PWIDs as a result of sexual networking among the two KPs, suggesting that sexual transmission of HIV is likely one of the key transmission routes driving the emerging trends of HIV sub-epidemics among SWs; however, results vary substantially by city, province and SW group. The Province of Sindh has the highest proportion of sexually transmitted infections among SWs, followed by Punjab.

The study presented in Chapter 2 demonstrates that there is heterogeneity in the overlapping patterns of HIV risk behavior between SWs and PWIDs. Results indicate that SWs who sexually interacted with PWID have higher odds of exposure to drug injection, suggesting that SWs who had sex with PWID can be expected to be at a higher risk of HIV infection due to overlapping vulnerabilities (i.e. the risk of injection and/or having sex with PWID). This overlapping risk, however, varies among KPs. We found that HSWs were more likely to be engaged in overlapping risk behavior than other SW populations, likely due to stigma, social discrimination, low literacy, established social and sexual networking structures for the exchange of sex for money and/or drugs, and a range of other societal, legal, and structural factors. Thus, given that the HIV epidemic is driven by PWID in Pakistan, HSWs might be at a higher risk of HIV transmission compared to other SW groups.

Findings from the studies presented in Chapters 3 and 4 indicate that Pakistan is experiencing an increase in HIV infections among KPs, particularly among SWs, suggesting HIV might be spreading from PWIDs to the rest of the population through sexual networks. The epidemic continues to vary considerably by KP and city, highlighting multiple interconnected sub-epidemics within the country. PWIDs, followed by H/MSWs, remain the most severely affected groups, with nearly 1 in every 2 PWIDs and 1 in every 5 H/MSWs projected to be living with HIV by 2020. Karachi is currently experiencing escalated HIV incidence among KPs, largely due to a rapid upsurge of new infections among both H/MSWs and FSWs in the past decade. Faisalabad is similar to Karachi in terms of experiencing a relatively high burden HIV epidemic, but largely due to increased incidence among PWIDs followed by H/MSWs. The upsurge of new infections in Larkana is likely to remain mostly among FSWs and H/MSWs, while the epidemics in Quetta may largely be driven by H/MSWs. HIV incidence in Lahore, Multan and Peshawar likely to remain driven by PWIDs, followed by H/MSWs.

Building on the previous three studies, the study presented in Chapter 5 shows that sexual networking is likely to play a significant role in HIV transmission between KPs, particularly from PWIDs to SWs. Nearly one-in-five HIV infections among both FSWs and H/MSWs who had sex with PWIDs is caused by sexual transmission from PWIDs. The province of Sindh has relatively the highest proportion of sexually transmitted infections among SWs (more than 60% and nearly 75% of sexually transmitted infections among FSWs and H/MSWs, respectively) in Pakistan caused by sexual networking with PWIDs, followed by Punjab. The study demonstrated considerable variations by city and SW group. More than half of HIV infections in the City of Sukkur among FSWs is likely due to sexual networking with PWIDs, while the highest proportion of sexually transmitted infections among H/MSWs may be in Peshawar.

In summary, though the HIV epidemics in Pakistan is predominantly driven by PWIDs, sub-epidemics among SWs has emerged in most regions and continues to rise. In the short term, SWs from Sindh province are likely to be disproportionately affected by the new upsurge of SW sub-epidemics. The epidemics in Pakistan is heterogenous, comprised of multiple sub-epidemics among KPs, with substantial variations in HIV risk vulnerabilities and geographical trends. It is likely that social and sexual networking among KPs plays a key role in the emergence, persistence and spread of HIV among SWs.

6.2 IMPLICATIONS OF FINDINGS

This research found robust evidence for HIV sub-epidemics among SWs in multiple regions in Pakistan, most of which have emerged only recently and continue to grow and potentially the overlap in sexual networking between PWIDs and SWs played a role for the emergence and spread of HIV from PWIDs to SWs. This research has provided key information that can be used for: national and regional level resource mobilization, national and regional level target setting, and geographical prioritization of the response, through local level programme planning, target setting and monitoring, and advocacy.

We profiled the HIV epidemics in Pakistan, with details on information relevant to inform policy and guide the design of effective intervention strategies. Geographical comparisons on a disaggregate level, which are not common in literature, provided insights into further understanding of the variations in underlying epidemiological drivers of epidemics and proximal sources of new HIV infections.

Evidence presented about the role of the complex social and sexual interactions between PWIDs and SWs in HIV transmission also has global implications; it is relevant to HIV prevention organizations working with marginalized populations elsewhere. As far as the typology of KPs in any concentrated epidemics are concerned, the evidence from this research also calls for a more robust epidemic appraisal for KPs that takes into account the overlapping of HIV risk vulnerabilities as key epidemiological driver.

6.2.1 RECOMMENDATIONS

We recommend that:

- Pakistan evaluates national and regional policy guidelines to ensure a strategic approach to evaluating and monitoring of emerging and rising HIV sub-epidemics among SWs is included. There is an urgent need to expand the provision, scope, and coverage of HIV interventions among SWs to be ahead of the emerging and growing HIV epidemics. Any recommendation to prioritize particular KPs in Pakistan should consider the emerging sub-epidemics among SWs.
- Pakistan continues to investigate the complex social and sexual mixing patterns between PWIDs and SWs and underlying structural factors to fully understand epidemiological drivers of sub-epidemics at a local level.
- Pakistan coordinates with all stakeholders at different levels to developing frameworks to support and customize new planning and improving intervention strategies, including scaling up priority HIV interventions and resource allocation to maximize population-level impact. Context-specific interventions and service delivery approaches, customized to local sub-epidemics, are highly recommended.

Aside from direct implications for policy setting and public health practice, the studies included in this thesis added new knowledge to the HIV research field. This research:

- is novel that it quantifies the proportional contribution of sexual transmission of HIV from PWIDs to SWs in a context of concentrated epidemics largely driven by PWIDs, including the scale and comparative analysis between cities; and
- suggests that currently available HIV epidemic appraisal approaches for concentrated epidemics are not robust, and thus indicates the need for developing new methods that account for the potential impact of social and sexual networking within and between KPs in order to accurately quantify the distribution of incident infections.

6.3 FUTURE RESEARCH

There are opportunities to extend this research further on many dimensions. First, data obtained from this research heavily relied on four rounds of IBBS data conducted among KPs. Although these IBBS are wide-ranging and comprehensively examine risk behaviors, network configuration and environments that each KP is embedded within, model estimations and predictions of epidemics could be improved by using more rounds of prevalence data among KPs and sexual clients of SW, as well as by incorporating information on programs and services (such as condom distribution, ART coverage, harm reduction, clean needle distribution, etc.). Methodologically rigorous studies on underlying structural factors along the pathway to HIV risk among KPs and the general population will be useful for epidemic appraisal so as to set policies and design more effective intervention strategies.

Second, the model we constructed and utilized to estimate the proportional contribution of transmission among SWs attributed to sex with PWIDs can be further extended to incorporate transmission through drug injection. Despite the proportion of SWs who inject drugs in Pakistan being relatively small compared to those who sexually interact with PWIDs, further research on the proportional transmission of HIV to SWs attributed to drug injection is warranted for a complete understanding of the impact of overlapping risk behaviours within and between KPs in HIV transmission dynamics. Such results will have significant implications for epidemic appraisals in concentrated epidemics.

Lastly, it would be worthwhile to further extend this modeling exercise and explore the key mathematical modeling parameters analytically such as using the basic reproduction number when information on mean duration of infection becomes available. This helps to better understand whether sexual transmission between KPs and/or sharing of needles/syringe within and between KPs can sustain the epidemics, particularly in a context of concentrated epidemic where it is largely driven by PWIDs. Note that the basic reproduction number, which can be computed as a product of infection rate and the mean duration of the infection (period of infectiousness), is the expected number of secondary cases produced by a typical infective individual over the course of its infectious period in an entirely susceptible population.

7 APPENDICES

7.1 APPENDIX A

7.1.1 DATA SOURCES AND COLLECTION METHODS

In addition to details provided in each study, this section provides a general overview of the study sites, populations, and methods used for mapping, sampling and data collection. A total of four rounds of IBBS data among KPs in 20 major cities in Pakistan were collected and used in this research. Data was collected between 2005 and 2011. All KPs were surveyed in each round, except FSWs in round 3 because of the very low prevalence observed from the second-round IBBS[1, 2]. Data from MSWs and HSWs was also collected as combined, except the fourth round in 2011 that they were surveyed separately.

Description of key populations

The description and characterization of each KP is consistent in all rounds of IBBS data and with the UNAIDS guidelines[3].

PWIDs – any person who has been injecting drugs regularly for non-therapeutic reasons, and often characterized by sharing used needles for injection.

FSWs – biologically female person who receive money or goods in exchange for sexual services, either regularly or occasionally, regardless of the site of operation. FSW typologies captured in the IBBS include street –, home –, *kothi-khana* –, and brothel – based FSWs. Note that *kothi-khana* – based FSWs are those who live and operate out of small premises/houses rented by network operators (or pimps).

MSWs – any male person who provide sexual services to another male person in return for money or other financial benefits. They identify themselves according to their sexual behaviors rather than by sexual identity, and often do not operate through networks rather operate independently to solicit clients, such as in public places.

HSWs – any transgender individual who undertakes sexual activity with a man in return for money or other financial benefits. H*ijras* are biologically male persons and form a distinct sociocultural group unique to South Asia, and considered to be a third gender[4-6]. Most h*ijras* are transgender individuals who are born males and often cross-dress in feminine attire, only a few having been born with intersex variations, and some having undergone surgical sex change[4-6]. Many *hijras* often operate out of *deras* – houses, operated and supervised by gurus (also known as teachers, spiritual leaders, or "retired" HSWs), where a number of student *hijras* live[1, 2, 7, 8].

Study sites, mapping and populations

A total of 20 cities, all from four provinces in Pakistan (Sindh, Punjab, Baluchistan and KPK), were surveyed in four rounds, though the KPs that were surveyed varies in each round (Table 7.1). Cities were selected based on prior knowledge about high risk activities and HIV prevalence, and geographical accessibility of the area. Each round IBBS data were collected following in-depth network mappings of KPs; mapping aimed to estimate the size, distribution and basic operational typology of SWs in each targeted city selected for survey. The mapping exercise encompasses identifying high risk behaviours to describe the KPs, quantifying number of settings or hot spots where KPs commonly congregate and/or engage in high risk activities.

Table 7.1 Cities surveyed in each of the four IBBS rounds, 2005-2011

Geography		KPs surveyed in each round of IBBS											
		2005			2006/7			2008/9			2011		
Province	City	PWIDs	FSWs	H/MSWs	PWIDs	FSWs	H/MSWs	PWIDs	FSWs	H/MSWs	PWIDs	FSWs	H/MSWs
Punjab	Lahore	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Multan	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Faisalabad	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Sargodha				✓	✓	✓	✓					
	Gujranwala				✓	✓	✓						
	D.G Khan							✓			✓	✓	
	Gujrat										✓		
	RY Khan										✓		
	Pakpattan										✓		
	Rawalpindi											✓	✓
Sindh	Karachi		✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Hyderabad	✓	✓	✓	✓	✓	✓	✓		✓			
	Sukkur	✓	✓	✓	✓	✓	✓				✓	✓	✓
	Larkana				✓	✓	✓	✓		✓	✓	✓	✓
	Dadu										✓		
KPK	Peshawar	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
	Bannu				✓	✓	✓						
	Haripur										✓	✓	✓
Balochistan	Quetta	✓	✓	✓	✓	✓	✓				✓	✓	✓
	Turbat										✓		

IBBS = integrated biological and behavioural surveillance; SWs = sex workers; PWIDs = people who inject drugs; FSWs = female sex workers; H/MSWs = hijra/ transgender/male sex workers; KPK = Khyber Pakhtunkhwa; RY Khan = Rahim Yar Khan; DG Khan = Dera Ghazi Khan
Stands for the city, KP group and year IBBS data was collected.

Mapping involved systematically identifying key informants, contact tracing, and triangulating of results done through a process of validating identified hot spots and estimated number of KPs in each hotspot. Estimates sizes of each KP in each city were obtained by combining estimates obtained from all validated spots. Mapping exercise was performed in all rounds except round 3 in 2008/09. A mapping result obtained in round 2 in 2006/07 was used to develop sampling frame for the third-round survey conducted in 2008/09 due to short time interval between the two surveys.

Following mapping, a representative sample of each KP was drawn from estimated population sizes of each KP in each city. In cities with relatively large size of KPs, the sample size ranges from 350-400. Various sampling techniques were utilized to recruit a representative of each KP in each city. MSWs were recruited through multistage cluster sampling, while HSWs were recruited through network mapping of *gurus* to gather information on both home- and *dera*- based HSWs. Street-based FSWs were recruited using time-location cluster sampling, while brothel-, home- and *koth-kana* – based FSWs were recruited through systematic random sampling. PWIDs were recruited using multistage cluster sampling. Further details on methods used to collect data in each round can be found in previous reports[1, 2, 7, 8].

Data collection strategies

Data was collected by trained interviewers using structured questionnaires. Survey questionnaires were prepared in English, but were translated and administered in Urdu, Pakistan's national language. Inclusion criteria for MSWs and HSWs were being men aged 13 and 15 or older, respectively, and FSWs were being women of age 15 or older, selling sex for men in exchange for money or other financial benefits. Inclusion criteria for PWIDs were being a person aged 18 or above who had injected drugs for non-therapeutic purposes in the past six months. Table 7.2 presents the average age distribution of KPs surveyed in each round. PWIDs were the older KPs, while H/MSWs were younger KPs surveyed.

Table 7.2 Mean and standard deviation of age among KPs surveyed in each round

Year of data collection	mean(SD) of age in each key population		
	PWIDs	FSWs	H/MSWs
Round 1: 2005	33.7 (8.5)	27.6 (6.8)	24.3 (6.4)
Round 2: 2006/07	32.3 (7.6)	27.3 (6.7)	24.3 (6.4)
Round 2: 2008/9	33.2 (8.9)	**	24.5 (6.3)
Round 4: 2011	31.5 (8.7)	27.6 (5.9)	24.7 (6.5)

**Survey was not conducted; KPs = key populations; PWIDs= people who inject drugs; FSWs = female sex workers; H/MSWs = hijra/transgender/male sex workers; SD = standard deviations.

Informed consent was obtained from each participant of the study prior to interview, followed by interviews conducted by trained field workers. Information on demographic characteristics, such as sexual and drug injection behaviors, networking structure within and between KPs, access to services, migration and sex work experience, condom and clean needle use practices, number of sexual clients and knowledge of STIs, was collected from each participant.

All participants received honorariums for their time and were referred for voluntary counselling, and provided with HIV prevention and services information. Each participant was further asked for HIV test, and data on HIV test result were collected from all who volunteered and consented for the test. HIV test results were linked to the corresponding data by an encrypted unique identifier; no personal identifying information accompanied the data.

In order to determine HIV status, capillary blood was collected for dried blood spot sampling and stored at room temperature. Samples were transported weekly to the reference laboratories for enzyme immunoassay screening (HIV Genetic Systems rLAV ELISA/EIA, Bio-Rad, United States) and positive tests were confirmed in duplicate with an alternative enzyme immunoassay (Vironostika HIV Uni-Form II EIA, Biomeriux, The Netherlands). Indeterminate results were resolved using Genetic Systems HIV-1 Western Blot (Bio-Rad, United States).

All rounds of surveys received ethical approval from HOPE International and Public Health Agency of Canada. Further details of exposition of the methodology on mapping, and on how the IBBS was conducted, including sampling techniques, study participants recruitment, and data collection procedures has been described previously[1,2,7,8].

7.2 APPENDIX B

7.2.1 STATISTICAL ANALYSES (CHAPTER 2)

Study measures

The aim of this study was to examine overlapping HIV risk among SWs that would link them with PWID populations; that is, through sex with PWID and/or drug injection in the past 6 months. The outcome variable was the variable describing drug injection experience among SWs. In addition to socio-demographic characteristics of each SW groups, Table 7.5 presents the list of variables used to describe SWs in terms of high risk behavior that they used to interact with PWID. Only the 2011 IBBS data was utilized for this study because the previous IBBS data sets did not have data from all three SW groups: FSWs, MSWs and HSWs. Note that FSWs were not surveyed in round 3 because of the very low prevalence observed from the second-round IBBS[1, 2]. Data from MSWs and HSWs was also collected as combined, except the fourth round in 2011 that they were surveyed separately.

Table 7.3 List of variables explored for analysis in Chapter 2

Variables		Description
Socio-demographic	age	age at interview
	Income (in rupees)	Income per month
	Education level	Education level of the person
	Current marital	Current marital status (married, not married)
	city	8 major cities with data available among all KPs
Biological	HIV status	HIV test results (either positive or negative)
Behavioral	Duration in practicing high-risk behavior (years)	Time since a SW started engaging with high risk behaviors (practicing sex work or drug injection)
	Condom use	Condom use in the last sex with a paying client
	KPs	Either FSWs, HSWs, MSWs and PWIDs
	Sex with PWID	Sexually contacted a PWIDs in the past 6 months (yes, no, do not know)
	Drug injection [outcome variable]	Injected drug in the past 6 months (yes, no)
Structural	Usual means of soliciting clients	How and where SWs used to solicit their clients (through mediator, mobile phone, old client, roaming)

Statistical analysis

In Chapter 2, a statistical modeling analysis was performed to explore heterogeneity among SWs in relation to their overlapping risk interactions with PWIDs. HIV prevalence of each KP was estimated from the number of HIV-infected people divided by the total number of people surveyed in each of the respective KPs. Bivariate logistic regression was used to identify factors for multivariable analyses that may be significantly related to drug injection. Wald tests were used to select factors that may be associated with drug injection at a significant level of $p<0.10$. Multivariable logistic regression analyses were performed to examine the impact of identified variables on the likelihood of injecting drugs after adjusting for covariates. These variables were selected based on literature and epidemiological evidence. Only variables with less than 1% missing data were included in the multivariable analyses. In all analyses, sampling weights based on the respective estimated population sizes of each KP obtained from mapping in each city was utilized. Weighting was identified as described in literature[10-12].

7.3 APPENDIX C

7.3.1 MATHEMATICAL MODELLING (CHAPTERS 3 AND 4)

For studies in Chapter 3 and 4, the UNAIDS Estimation and Projection Package model (EPP)[13], a deterministic mathematical modeling, was adapted and used to estimate and project HIV prevalence overtime[13-15]. EPP is a built-in model designed to estimate the trend in HIV prevalence over time by fitting the model to the empirical prevalence of HIV obtained from surveillance data. The HIV epidemics of Pakistan is comprised of multiple sub-epidemics, and therefore, the EPP models were fit to empirically estimated HIV prevalence among each KP within each city. Description of our modeling process are discussed in detail in each methods' section of Chapters 3 and 4. Further details about the EPP model and its fitting procedure can also be found elsewhere[13-15]. In addition to the empirically estimated prevalence of HIV, data information from IBBS and mapping were used as input parameters. Demographic information about Pakistan, obtained from Pakistan's Bureau of Statistics and the UN, were also utilized in the modeling exercise as appropriate. Table 7.4 presents summary of compartments of populations and sources of data used in modeling.

Table 7.4 Compartments of populations and sources of data used in modeling

Subpopulation	Data source
PWIDs	Four rounds of IBBS, 2005-2011
FSWs	Three rounds of IBBS, 2005-2011
H/MSWs	Four rounds of IBBS, 2005-2011
Clients for H/MSWs	Estimated using IBBS data, 2005-2011
Clients of FSWs	Estimated using IBBS data, 2005-2011
Male remaining subpopulation	Pakistan Bureau of Statistics[16] and population growth estimates from UN[17]
Female remaining subpopulation	Pakistan Bureau of Statistics[16] and population growth estimates from UN[17]

The combined data of MSWs and HSWs were used for analysis because MSWs and HSWs are similar in terms of their bilogy, both born as biological males and have male clients; however, HSWs are transgender.
In addition, data among these two KPs (i.e., HSWs and MSWs) were collected as combined, except the last IBBS round in 2011, and thus we combine them for consistency of analysis.
PWIDs = people who inject drugs; FSWs = female sex workers; H/MSWs=hijra/trangender/male sex workers; IBBS = integrated biologuical and behavioural surveillance; UN = United Nations.

The sizes of each KP of all rounds were obtained from mapping exercises conducted before data collection (Table 7.5). The population sizes of sexual clients of each SW groups were estimated from IBBS data, using responses to the survey question asking the number of clients that each respondent had sex with in the past month[1,2,7,8].

Table 7.5 Sample size, and mean (SD) of duration of time engaging in high risk activity

Key population	Year IBBS was conducted								Over all*
	Round 1, 2005		Round 2, 2006/7		Round3, 2008/9		Round 4, 2011		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	Mean(SD)
PWIDs	2417	5.9 (5.2)	4003	5.4 (4.7)	2958	4.6 (3.9)	4935	4.6 (4.4)	5.1 (4.5)
FSWs	3013	5.5 (4.5)	4513	5.2 (4.3)	**	**	4282	5.3 (4.1)	5.3 (4.3)
H/MSWs	3258	7.7 (5.9)	4284	8.2 (5.9)	2362	8.7 (6.1)	7363	8.6 (5.2)	8.4 (5.6)

*Weighted means and pooled variance techniques were used to determine the overall mean and standard deviation for each key population. **Data was not collected because of very low HIV prevalence found in the previous round. IBBS = integrated biological and behavioural surveillance; PWIDs= people who inject drugs; FSWs = female sex workers; H/MSWs = hijra/transgender/male sex workers; SD = standard deviations.

EPP varies four parameters in order to fit to the empirically estimated HIV prevalence; it fits to prevalence data points by minimizing the least squares difference between the fitted curve and the full set of data points. These included: the start year of the epidemic, the rate of growth of the epidemic – determined by the rate of spread of the epidemic or reproduction potential (and directly proportional to the basic reproduction number or potential), the peak prevalence – obtained by the proportion of the population who are at risk of infection at the start of the epidemic, and the recruitment rate or the rate at which at risk people who die due to AIDS or otherwise leave are replaced by new at-risk people. The goodness-of-fit procedure used by the mathematical model fits to the empirical point estimates of HIV prevalence. However, there is uncertainty in the underlying prevalence in each KP, and thus a 95% confidence intervals of HIV prevalence, in addition to point estimates, was used.

In addition, mathematical model projections are uncertain due to the uncertainty surrounding the value of the true prevalence for the years in which empirical estimates of prevalence was made. Therefore, a range of plausible HIV epidemic trends were examined as follows. Year-specific point estimates of empirical prevalence were used to fit the model, and for this initially the EPP model with many LHS intervals were simulated as recommended by UNAIDS. However, the model was also fit to each scenario – each city and KP, using sample intervals of 100. These intervals produced more variance in the estimated HIV epidemic and thus produced a range of possible HIV epidemics. Any model estimated epidemic was considered plausible if it fit through at least two of the 95% confidence intervals of empirically estimated prevalence for the respective KP in each city.

For each scenario, EPP generates an estimated prevalence by combining each sub-populations' and cities' estimate prevalence, and therefore, a combined prevalence was used to display as the estimated and projected prevalence of HIV in Pakistan. The range of estimated prevalence of HIV in Pakistan was obtained from the combined prevalence estimates of these three scenarios. Note that these estimated numbers were obtained together with the estimated size of total population for respective years. A standard method of estimating incidence was then used to estimate the incidence rate of HIV per person-years from a number of estimated parameters including number of people living with HIV, number of people died from HIV and population size of people without HIV in respective years.

Sensitivity analysis

The estimated duration of time, which refers to the number of years a KP was engaged in high-risk behavior[18], was used to set scenarios and fit models. A survey question asking how long the respondent was involved in sex work for FSWs, HSWs and MSWs and drug injection for PWIDs was used to estimate the mean duration of time KP are likely to be involved in high risk activity. Averaging the survey question response likely results in an estimated duration that is biased downward since those interviewed are still members of the risk group at the time of survey. However, a bias upward also exists because those with very short durations in the respective risk group are less likely to have been captured in the survey. We, therefore, conducted sensitivity analyses, in which we varied the mean duration spent in risky behavior, to assess its impact on model-estimated prevalence and incidence trends.

Because of the variation in the number of years spent in a KP across cities, mean number of years spent in risky exposure obtained from each round and KP was used to estimate the overall mean number of years of at-risk prior to turnover for each KP. Weighted means and pooled variance techniques were used to determine the overall mean and standard deviation for each key population. Our "minimum" estimate (or short duration) was assumed to be the weighted mean duration that survey respondents had been working as SW or injecting drugs at the time of the survey. The overall mean duration plus standard deviation was assumed as medium duration for each respective KP. We used expertise opinion to assume the long duration. Table 7.6 presents the three model scenarios constructed to explore on uncertainty surrounding the mean duration that SWs and PWIDs were involved in sex work and drug injection respectively.

Table 7.6 Scenarios based on duration of time KPs were engaged in high-risk activity

Duration of time	Key population			Data source
	PWIDs	FSWs	H/MSWs	
Scenario 1: Short duration	5.1	5.4	8.3	IBBS, 2005-2011
Scenario 2: Medium duration	11.0	8.5	12.0	IBBS, 2005-2011
Scenario 3: Long duration	15.0	11.0	17.0	Assumed

IBBS = integrated biological and behavioural surveillance; PWIDs= people who inject drugs; FSWs = female sex workers; H/MSWs = hijra/transgender/male sex workers.

7.4 APPENDIX D

7.4.1 MATHEMATICAL MODELLING (CHAPTER 5)

Because the EPP model lacks flexibility, a deterministic model was designed to accommodate the context of overlapping risk vulnerability to HIV transmission due to sexual mixing between SWs and PWIDs. The model was contextualized and fitted to the 2011 IBBS data collected among KPs in Pakistan. We used information on HIV status and duration of sexual mixing among KPs to estimate the probability of SWs getting infected from PWIDs through sex. With the assumption that MSWs and HSWs have same biological susceptibility, the two KPs were combined for modeling analysis. Model compartments were constructed based on individual's gender (males vs. female), high-risk behavior KPs engaged (sex work vs. drug injection) and the sexual link between KPs (insertive vs. receptive and vaginal vs. anal) during their interaction.

The model discussed in this chapter is based on the following inclusion/exclusion criteria, and assumptions made based on epidemiological contexts and availability of data for analysis.

- As identified in the IBBS 2011 data, SWs who had engaged in sex with someone from a different transmission risk groups ((i.e., SWs with PWIDs, or conversely, PWIDs with SWs) were used to explore HIV transmission from PWIDs to SWs. A question asking whether SWs had sex with a person who inject drugs in the past 6 months preceding the interview date. Those who responded "yes" to the question were assumed as SWs who had sexual interaction with PWIDs.
- We excluded KPs for which HIV status were missing or indeterminate.

- FSWs were all females and their interactions with PWIDs were considered as receptive vaginal sex. No information was captured in the IBBS data about FSWs having anal sex specifically with PWIDs.
- H/MSWs were all men and their interactions with PWIDs were considered as receptive anal sex. No information was captured in the IBBS data about H/MSWs having insertive anal sex specifically with PWIDs.
- PWIDs were all men and their interactions with SWs was considered as insertive vaginal sex with FSWs and insertive anal sex with H/MSWs. No information was captured about PWIDs having receptive anal sex specifically with H/MSWs.
- We excluded PWIDs who were females. Female PWIDs were less than 0.1% of the total PWIDs.
- We assumed no PWID-SW sexual interaction for SWs who did not know whether or not they had sex with PIWDs.
- We assumed no sexual interaction within and between SWs and H/MSWs.
- For each KP, infectious individuals depart the group for reasons other than developing AIDS (such as non-AIDS related death) at a rate μ are assumed to be immediately replaced by susceptible KPs.
- Guided by the objective of the study, we only used sexual behaviour as the link between PWIDs and SWs. It is worth mentioning that there is descriptive information showing the fraction of SWs injecting drugs; however, behavioural data was not available to characterize this fraction of SWs further in terms of their needle-sharing behaviour within and/or between SWs and PWIDs. Therefore, in this modeling exercise, we did not attempt to quantify HIV transmission through injection within SWs who perhaps injected drugs or from PWIDs to SWs through sharing needles.

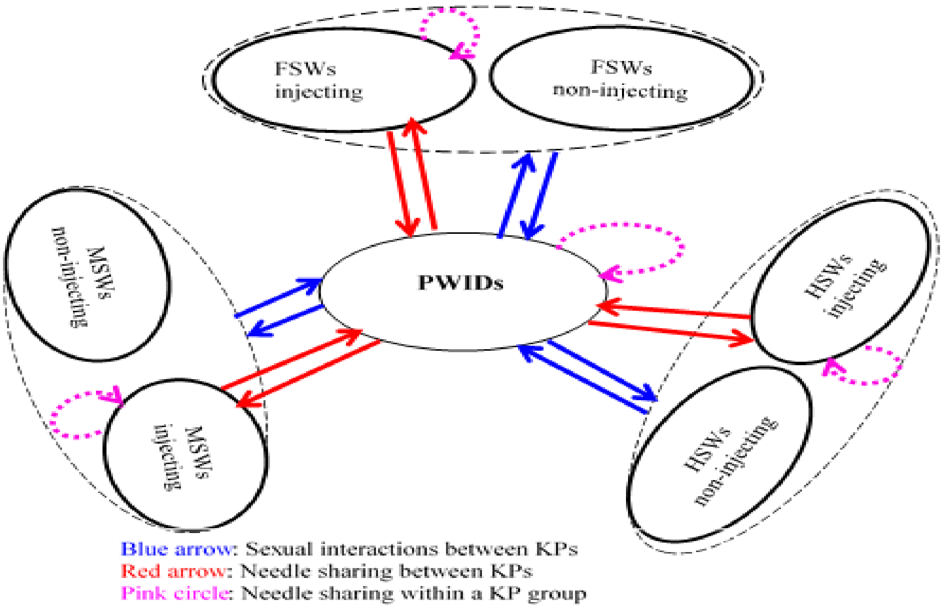
We assumed all individuals in a compartment are homogenous in all the parameters used to compartmentalize the total population. There exists a homogenous and constant population that the death or turnover of susceptible and infectious individual is immediately compensated by the new susceptible KP coming into the compartment[19].

In order to explore the level of behavioral complexity required to realistically simulate the transmission of HIV amongst KPs, context-specific models were constructed and each model was fit to the observed epidemiological IBBS data. The risk of HIV acquisition varies widely, dependent on many individual factors, by condom use[20], male-circumcision [21-24], antiretroviral treatment initiation[25], use of sterilized needle during needle-sharing, and STI infection[26-28]. However, only condom use and male-circumcision – to account for reduced risk of transmission and STI infection – to account for increased risk were incorporated into built models. Data on viral load and ART were not incorporated due to lack of data.

Model formulation

The disease process is modelled using an SI (susceptible-infected) – basic transmission model framework. Each SW group divide their PWID sexual contacts as identified in the IBBS data. In order to determine newly infected individuals (i.e., people who transferred from S to I state), input parameters such as probability of infection through a specific route of transmission, HIV prevalence in each subpopulation, frequency of partners with which individuals interact per specified time, and co-factors such as condom use, level of STIs and male-circumcision were utilized. Though there is evidence to suggest that viral load is related to the likelihood of transmission, we did not stratify infected individuals to reflect variations in infectivity due to lack of limited data on viral load. The IBBS data only captures possible interaction between SWs and PWIDs that might have in the past 6 months, and thus model was constructed to yield short term estimation (only six months period).

Figure 7.1 Schematic diagram showing complex and overlapping interactions between KPs



The schematic diagram in Figure 7.1 depicts the complex interaction within and between KPs is more general, constructed by taking future research prospects into account.

Interacting populations

The total population of included KPs, denoted by N(t), was subdivided into three mutually-exclusive compartments based on their risk behavior as identified in the IBBS data (drug injection vs. sex work) and gender (biologically male vs. female). Then, the total population under study becomes:

$$N(t) = \sum\nolimits_{k} N^{k}(t)\,;\; k = d, f \; and \; m,$$

where $k = d, f \; and \; m$ represents PWIDs, FSWs and H/MSWs, respectively.

Population states: Each interacting SW groups and PWIDs is stratified by HIV status, and compartmentalized as susceptible (denoted by S) and infected (denoted by I) individuals. The total population in each KP becomes:

$$N^k(t) = \sum_k S^k\,(t) + \sum_k I^k\,(t), k = d, f, m.$$

Each KP group can further be characterized by behavioral co-factors such as condom use, level of STI infection, and male-circumcision as appropriate. Therefore, input parameters of these co-factors can be incorporated to correct the infection rate.

Infection rate: HIV infection through sex with an infected partner is formulated to incorporate the effective contact rate for HIV transmission, also known as probability of transmission per sexual contact. This parameter was estimated by fitting to IBBS data. The number of new infections due to sexual contact is calculated based on the infection rate:

- the prevalence in the partner population,
- the mixing relations - the proportion of the total desired partners belonging to a group,
- the frequency of sexual partners per specified time,
- the probability of HIV transmission per sexual act (or sexual contact),
- protective measures that reduce the risk of transmission (such as consistent use of condoms and male-circumcision) - accounted as co-factors using parameters to correct the transmission probability, and
- the possible impact of the presence of other STIs - accounted by adding a co-factor that increases the effective transmission probability by fixed amount.

Mortality: Natural mortality occurs in all compartments of KPs at a rate of μ. KPs in the AIDS stage suffer an additional disease-induced death at a rate of σ. All KPs with HIV were assumed to have similar disease-induced death rate.

KPs turnover rate: KPs were allowed to move only between compartments of S and I as a result of infection. An individual leaving a compartment was assumed to be going for good and not coming back into its KP group due AIDS (at a probability of γ; defined as unity divided by 10) or non-AIDS related deaths (at a rate of μ). KPs could also turn over totally from high risk activity (quit) at some rate. Without loss of generality, we assumed constant size of each KP that KPs who moved out or quit from high-risk activity are replaced by new KPs at the same rate.

Partnership turnover rate: The desired turnover rate of sexual partners is estimated from IBBS data, and it refers to the total number of desired sexual partners from PWIDs per specified time. Due to lack of specific information about PWIDs as sexual clients to SWs, it was estimated from a response about total number of partners in a month, but independent of the partners' age.

Partnership mixing patterns: Sexual partnership among SWs with PWIDs is assumed fractional mixing. In general, the fractional mixing matrix (independent of age preference) is supplied as a generic mixing range. KPs being compartmentalized by risk behaviour and gender, we assumed no sexual mixing within each KP and between FSWs and H/MSWs.

Derivation of transmission probability *per sexual act*

In order to mathematically describe this, let us assume the probability of transmission of HIV to a completely susceptible person of KP k from an infected partner per sex act is ϕ^k. Then, the probability of NOT being infected per sex act per partnership is:

$$(1-\phi^k) \times \ldots \times (1-\phi^k) = (1-\phi^k)^{\Psi^k},$$

where Ψ^k is the number of sex acts per partner per unit time. However, because we do not have data on number of sex acts per partnership, we assume the probability of transmission per partnership instead of per sex act, and thus $\Psi^k = 1$.

Therefore, the probability of infection, also known as coefficient of transmission per partnership, through sex becomes:

$$\beta_s^k = 1 - (1-\phi^k)^{\Psi^k} = \phi^k.$$

If, for instance, we incorporate the protective effect of condom use, we have:

$$\beta_s^k = (1-\epsilon_c \eta^k)\phi^k.$$

The parameter ϕ^kvaries depending on the role in sexual intercourse (insertive vs. receptive), gender (male vs. female) of the susceptible individual having sex with an infected partner.

Note that the protective effect of consistent condom use is incorporated to account for the reduction in infection rate by a factor of $(1-\epsilon_c\eta^k);\ k = d, f, m,$ where ϵ_c $(0 < \epsilon_c < 1)$ and η $(0 < \eta < 1)$ represent the protective effect of consistent condom use and fraction of susceptible KP groups who used condom respectively. The value of η was estimated using IBBS data from a question asking KPs about their condom use experience with their paying sexual clients. Those who responded as “Sometimes’ or “Never” were considered as “inconsistent” users whereas those responded as “Always” were assumed KPs who consistently used condom per specified time.

Other co-factors which increase or decrease the risk of transmission such as male-circumcision and STI infection of the susceptible person can also be incorporated in a similar fashion as appropriate.

Model equations

In order to formulate mathematical equations, we assumed there are four interacting KPs groups in each SW group vs. PWIDs mixing patterns, stratified by HIV status. KPs are defined by hierarchical stratification of three levels: gender, sexual behaviour and injection behavior. PWIDs are all men who inject drugs, but stratified by their sexual interaction behaviour with SWs. All SWs are linked with PWIDs by sex, and each of FSWs and H/MSWs had specified number of sexual partners at specified time interval. The sexual mixing matrices serve to allocate sexual partnership; they specify who have sex with whom. Without loss of generality, we assumed no sexual interaction between FSWs and H/MSWs. It should be mentioned that fraction of SWs are also linked with PWIDs through injection drugs, but there is no information to further characterize SWs about their needle-sharing within and between SWs, and those with PWIDs. For instance, no data was captured about the frequency of needle sharing within and/or between SWs who inject drugs. Therefore, this modeling exercise was formulated based on available behavioural information about sexual interaction between SWs and PWIDs.

SWs sexually interacting with PWIDs: infections from PWIDs to SWs

The rate of change of the population of susceptible ($S_s^{f,m}; s\ for\ sex, f = FSWs\ and\ m = H/MSWs$) to become infected/infectious ($I_s^{f,m};\ s\ for\ sex, f = FSWs\ and\ m = H/MSWs$) through sex (heterosexual transmission for FSWs and homosexual for H/MSWs) is give by:

$$\frac{dI_s^{f,m}}{dt} = \lambda_s^{f,m}\ c_s^{f,m} S_s^{f,m} - \gamma I_s^{f,m} - \mu I_s^{f,m} \ldots\ldots\ldots\ldots\ldots (1)$$

where $c_s^{f,m}$ is the rate of change of sexual partners per FSW or H/MSW, μ is the non-AIDS mortality rate, $\lambda_s^{f,m}$is the probability of being infected from heterosexual transmission per FSW or homosexual transmission per H/MSWs.

The rate of infection, λ_s^f, equals to the PWIDs -to-FSW heterosexual transmission efficiency per partnership provided that PWID is infected ($\beta_{m\to f}^f$) multiplied by the weighted prevalence ($\sum_i M^f(s,i;t) P_s^d(i,t)$; where $M^f(s,i;t)$ is the probability that a FSW has a sexual partnership with a male partner from subgroup i (i.e., a PWID) at time t). Note that $P_s^d(i,t)$ is the weighted prevalence of HIV among PWIDs who had sex with FSWs.

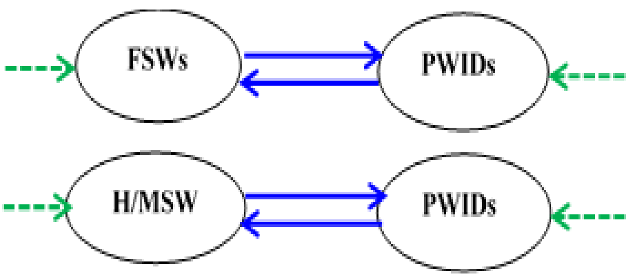
Similarly, the parameter λ_s^m, defined as the probability of being infected from homosexual transmission per H/MSW, equals the PWIDs -to-H/MSWs transmission efficiency per partnership provided that the PWID partner is infected ($\beta_{m\to m}^m$) multiplied by the weighted prevalence ($\sum_i M^m(s,i;t) P_s^d(i,t)$; where $M^m(s,i;t)$ is the probability that a H/MSW has a sexual partnership with a male sexual partner from subgroup i (i.e., a PWID) at time t). Note that $P_s^d(i,t)$ is the prevalence among PWIDs who had sex with H/MSWs, and it is necessarily the same prevalence discussed above in relation to PWIDs who had sex with FSWs.

The parameters $\gamma \; and \; \mu$ refers to the rate of movement from infected to AIDS compartment (i.e., unity divided by average duration of stay in the infected/infectious compartment) and non-AIDS-related death, respectively.

Proportional infections

In order to estimate proportional transmission through sex from PWIDs to SWs, we assumed two key sources of infections: sexual transmission occurring between KPs and transmission occurring outside of sexual interaction between KPs (hereafter called transmission from outside).

Figure 7.2 A simple schematic diagram showing sexual transmission between KPs



Blue arrow: Sexual transmission between SWs and PWIDs
Green Arrow: Transmission through outside of sexual interaction between SWs and PWIDs

Figure 2 presents a schematic diagram representing routes of HIV transmission between SWs and PWIDs. The solid blue arrows represent transmission through sexual interaction between SWs and PWIDs, while the broken green arrows represent the transmission from outside of sexual interaction between SWs and PWIDs (such as through drug injection, sex with non-PWIDs sexual clients of SWs, non-PWIDs spouses of SWs if married, or non-SW spouses of PWIDs if married). Note the likelihood of transmission in the sexual interaction between SWs and PWIDs and risk environment for KPs to get infected from outside varies. Sexual interaction between FSWs and PWIDs in this figure is assumed through vaginal sex, while sexual transmission between H/MSWs and PWIDs is through anal sex. PWIDs = people who inject drugs; FSWs=female sex workers; H/MSWs=hijra/transgender/male sex workers.

It is important to note that transmission from outside may include transmission through drug injection, sex with non-PWIDs sexual clients of SWs, non-PWIDs spouses of SWs (if married), or non-SW spouses of PWIDs (if married). Based on HIV status, each PWID and SW groups can be compartmentalized into four mutually exclusive pairs of groups:

$\{PWID_{-}, FSWs_{-}\}$, $\{PWID_{+}, FSW_{-}\}$, $\{PWIDs_{-}, FSW_{+}\}$, or $\{PWID_{+}, FSW_{+}\}$, and

$\{PWID_{-}, H/MSWs_{-}\}$, $\{PWID_{+}, H/MSW_{-}\}$, $\{PWID_{-}, H/MSW_{+}\}$, or $\{PWID_{+}$, $H/MSWs_{+}\}$, where + and - refers to HIV status in respective KPs.

Therefore, the probability that an infection occurs through any of the two routes of transmission (i.e., through sex or outside of sexual interaction) to a randomly selected KP is a function of the hazard of infection through that route of infection, denoted by $\lambda^{k} = \beta P^{k'}$, defined as the rate of new infections per susceptible person in a KP group k per specified time, where β is the effective contact rate of transmission (also knows as transmissibility coefficient) and $P^{k'}$, is the weighted population prevalence in the opposite KP group k'. The parameter β is also a function of other parameters such as type of relationship between any two randomly interacting KPs of different groups (vaginal vs. anal sex) and role in sexual interaction (i.e., insertive vs. receptive), and the parameter itself can be determined when fitting the hazard of infection to the biological and behavioural data obtained from IBBS. This yields a total of four transmission coefficients for any two randomly interacting KPs of different groups (k and k'), specifically transmission coefficient during sexual interaction by positive partner (β_s^d and β_s^k ; s for sexual interaction, d for *PWID*, and k for *f=FSW* or *m=H/MSW* and from outside of sexual interaction partner (β_o^d and β_o^k ; o for outside of sexual interaction, d for PWID, and k for *f=FSW* or *m=H/MSW*). Note that the indices in the transmission coefficient of β_s^k stands for heterosexual (resp: homosexual) transmission for *f=FSWs* (resp: H/MSWs) due to sex with PWIDs, while β_o^k , stands for transmission though a transmission route outside of sexual interaction between SWs and PWIDs.

We used estimates of coefficients of transmission, $\beta_{s,o}^k$ (with 95% confidence interval), of each route of transmission obtained from fitted IBBS data to estimate the probability that new infections occur among SWs through sex from PWIDs or outside of sexual interaction with PWIDs in the 6 months period. The total number of susceptible SWs is as identified in the IBBS data weighted to the size of SWs obtained from mapping.

Example – Estimating infection rate

A simplified example of the model utilized in this study may help to clarify the method used to estimate infection rate: assume that SWs have just two potential sources of infection – infection from sex with a PWID or infection from sex with non-injecting client. In fact, SWs can get infected in more than two sources such as through injecting drugs themselves, or through sex with non-clients. However, this example assumes a more simplified 2-source scenario in the PWID-FSW sexual interaction. In this scenario, we utilize several parameters to estimate the infection rate among SWs:

- Probability of transmission per 6-month time period if partner is HIV infected (pt)
- Probability of consistent condom use (pc)
- Factor reducing HIV transmission probability among women with consistent condom use in the PWIDs-FSWs sexual interaction (fc)
- Probability of male-circumcision (pcc)

- Factor reducing HIV transmission probability due to male-circumcision in the PWID-FSWs sexual interaction (fcc). All male sexual partners assumed as circumcised.
- Probability of infection with another STI (ps)
- Factor increasing HIV transmission probability among women infected with other STI (fs)
- Probability of sexual interaction with PWIDs in the past 6 months (pp)
- Probability that injecting client or partner (PWIDs) is HIV infected (pi)
- Probability that non-injecting client is HIV infected (prevalence among non-injecting clients) (pni).

The 6-month infection rate from non-injecting clients among SWs in this simplified example would be as follows.

Infection rate from a PWID sexual client to FSW would be:

$$Rate\ (infection\ from\ PWID) \coloneqq \lambda^{f}_{s,PWID\rightarrow FSW} = \beta^{f}_{s,PWID\rightarrow FSW}\ {P_s}^{k'}$$

$$= pt * pp * (pc * fc * (pcc * fcc) * ((ps * fs + (1 - ps)) * pi) + ((1 - pc) * ((ps * fs + (1 - ps)) * pi))$$

Infection rate from non-injecting sexual client (denoted by $nonPWID$) to FSW would be:

$$Rate\ (infection\ from\ nonPWID\ client) \coloneqq \lambda^{f}_{o,nonPWID\rightarrow FSW} = \beta^{f}_{o,nonPWID\rightarrow FSW}\ P^{gen.pop}$$

$$= pt * (pc * fc * (pcc * fcc) * ((ps * fs + (1 - ps)) * pni) + ((1 - pc) * ((ps * fs + (1 - ps)) * pni))$$

The overall infection rate would be:

$$
\begin{aligned}
&Rate\ (infection\ overall) \\
&\qquad = Rate\ (infection\ from\ PWID) + Rate\ (infection\ from\ nonPWID) \\
&\qquad - [Rate\ (infection\ from\ PWID) \times Rate\ (infection\ from\ nonPWID)]
\end{aligned}
$$

Therefore, the proportion of infections attributable to sexual transmission from PWID that would not have occurred otherwise would be:

$$
\begin{aligned}
&Rate\ (attributable\ to\ sex\ with\ PWID) \\
&\qquad = Rate\ (infection\ overall) - Rate\ (infection\ from\ nonPWID).
\end{aligned}
$$

Note that $P^{k'}$ and $gen.pop$ stands for weighted prevalence of HIV among PWID and the general population respectively. Note that the effect of ART or viral load among infectious KPs were not considered due to lack of data.

Table 7.7 Definitions of biological and behavioural parameters

Parameter		Parameter definition	Value	Reference
Biological	Probability of acquiring HIV from an infected source, (%)			
	ϕ_s^f	Receptive vaginal intercourse: PWID-to-FSW	0.08 (95%CI: 0.06-0.11)	[27]
	ϕ_s^m	Insertive vaginal intercourse: FSW-to-PWID	0.04 (95%CI: 0.01-0.14)	[27]
	ϕ_s^m	Receptive anal intercourse: PWID-to-H/MSW	1.38 (95% CI: 1.02-1.86)	[27]
	ϕ_s^d	Insertive anal intercourse: H/MSW-to-PWID	0.11 (95% CI: 0.04-0.28)	[27]
	φ_j^k	Needle sharing for drug injection (k for KP group)	0.63 (95% CI: 0.41-0.92)	[27]
Behavioural	π^k	Inflow of KP k (k for KP groups)	*Varies by region and KP	IBBS 2011/09
	η^k	Fraction of susceptible SWs using condom consistently	*Varies by region and KP	IBBS 2011
	θ^k	Fraction of susceptible KPs suffered from STI	*Varies by region and KP	IBBS 2011
	c_s^f	Sex partners to FSWs	*Varies by region and KP	IBBS 2011
	c_s^m	Sex partners to H/MSWs	*Varies by region and KP	IBBS 2011
	c_j^d	Needle-sharing partners to PWIDs	*Varies by region and KP	IBBS 2011
	c_s^d	Sex partners to PWIDs	*Varies by region and KP	IBBS 2011
Epidemiological	γ	Disease progression rate (= (rate from infectiousness to AIDS)$^{-1}$)	1.0 (SD = 0.85)	[31]
	ϵ_c^f	Condom effectiveness in heterosexual intercourse	0.80 (95% CI: 0.53-0.92)	[27, 32]
	ϵ_c^m	Condom effectiveness in homosexual intercourse	0.70 (95% CI: 0.58-0.80)	[33]
	δ	AIDS-related death rate: (=(mean adult survival time)$^{-1}$)	0.1	[31]
Co-factors modifying HIV transmission risk	$\psi_{m\to f}^f$	increased risk of transmission due to STIs	2.65 (95% CI: 1.35-5.19)	[34]
	$\psi_{m\to m}^m$	increased risk of transmission due to STIs	3.63 (95% CI: 1.6-8.1)	[35]
	Male-circumcision (heterosexual partners): FSWs vs. PWIDs			
	$\varrho_{d\to f}^f$	Receptive partner is HIV-uninfected (female)	0.8 (95% CI: 0.53-1.36)	[27]
	$\varrho_{f\to d}^d$	Insertive partner is HIV-uninfected (male)	0.5 (95% CI: 0.34-0.72)	[27, 36]
	Male-circumcision (homosexual): H/MSWs vs. PWIDs			
	$\varrho_{d\to m}^m$	Receptive partner is HIV-uninfected	0.86 (95% CI: 0.70-1.06)	[36]
	$\varrho_{m\to d}^d$	Insertive partner is HIV-uninfected	0.27 (95% CI: 0.17-0.44)	[27]
	μ	Non-AIDS related death rate (age: 15-60)	0.08	[17]

KPs = key populations; IBBS=integrated biological and behavioural surveillance; STI: sexually transmitted infections, FSWs =female sex workers; H/MSWs=hijra/transgender/male sex workers;
*Behavioural paramaters extracted from IBBS data varies by city and key population.
Note that iconstant KP

Table 7.8 State variables

Key Population	Variables	Definition
FSWs	N_s^f	Total population of FSWs who had sex with PWIDs
	S_s^f	Susceptible FSWs who had sex with PWIDs
	I_s^f	Infected/infectious FSWs who had sex with PWIDs
	A_s^f	Infected FSWs who had sex with PWIDs at AIDS stage
H/MSWs	N_s^m	Total population of H/MSWs who had sex with PWIDs
	S_s^m	Susceptible H/MSWs who had sex with PWIDs
	I_s^m	Infected/infectious H/MSWs who had sex with PWIDs
	A_s^m	Infected H/MSWs who had sex with PWIDs at AIDS stage
PWIDs	N_s^d	Total population of PWIDs who had sex with SWs
	N_i^d	Total population of PWIDs who had no sex with SWs
	S_s^d	Susceptible PWIDs who had sex with SWs
	S_i^d	Susceptible PWIDs who had no sex with SWs
	I_s^d	Infected/infectious PWIDs who had sex with SWs
	I_i^d	Infected/infectious PWIDs who had no sex with SWs
	A_s^d	Infected PWIDs who had sex with SWs at AIDS stage
	A_i^d	Infected PWIDs who had no sex with SWs at AIDS stage

KPs =key populations; PWIDs = people who inject drugs; SWs = sex workers; FSWs = female sex workers; H/MSWs = hijra/transgender/male sex workers.

Note that the KPs in the study that new infections were estimated from are those who had sex with one another in the past 6 months.

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7.6 APPENDIX E

7.6.1 ETHICS APPROVAL FROM UNIVERSITY OF MANITOBA

University of Manitoba | Research Ethics and Compliance

Research Ethics - Bannatyne
P126-770 Bannatyne Avenue
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HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION/DEPARTMENT:	ETHICS #:
Dessalegn Melesse	U of M/Centre for Global Health	HS19303 (H2016:030)
HREB MEETING DATE (If applicable):	**APPROVAL DATE:** January 15, 2018	**EXPIRY DATE:** <u>**January 26, 2019**</u>
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Dr. James Blanchard		

PROTOCOL NUMBER:	PROJECT OR PROTOCOL TITLE:
NA	Understanding Heterogeneity in HIV Transmission Dynamics Among Key Populations at Highest Risk of Acquisition: A Mathematical Modeling Approach
SPONSORING AGENCIES AND/OR COORDINATING GROUPS: U of M - Supervisor Resaerch Assistantship	

Submission Date of Investigator Documents:	HREB Receipt Date of Documents:
January 2, 2018	January 2, 2018

REVIEW CATEGORY OF ANNUAL REVIEW: **Full Board Review** ☐ **Delegated Review** ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name(if applicable)	Version(if applicable)	Date

Annual approval
Annual approval implies that the most recent <u>HREB approved</u> versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc are approved.

<u>**Consent and Assent Form(s):**</u>

CERTIFICATION
The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this ***Certificate of Annual Approval*** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION
The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

Research Ethics and Compliance is a unit of the Office of the Vice-President (Research and International)

umanitoba.ca/research

QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. <u>**This approval is valid until the expiry date noted on this certificate of annual approval.**</u> **A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form**.
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,

[redacted]

Chair, Health Research Ethics Board
Bannatyne Campus