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Prevalence and Practices of Unsafe Medical Injection and Infusion among People Living with HIV (PLWH) in Cambodia

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Keywords: injection, PLWH, unsafe injection, HIV, injection prevalence, injection practices

Abstract

Objectives: In late 2014, an outbreak of HIV due to having received medical injections from unlicensed medical providers in rural Cambodia highlighted the need to assess medical injection practices among those who are at risk of acquiring and/or transmitting HIV. This study examined medical injection/infusion behaviours among people living with HIV (PLWH) and those who were HIV-negative in Cambodia so that these behaviours can be properly addressed if they were to be quite prevalent, especially among the patients.

Design: A cross-sectional survey was conducted in order to examine injection behaviours and estimate the injection prevalence and injection rates by HIV status. Unsafe injections/infusions were those received from village providers who do not work at a health centre or hospital, or traditional providers at participant's (self-injection included) or provider's home. Logistic regression was performed to examine the relationship between unsafe injection/infusion and HIV, adjusting for sex, age, education, occupation, residence location, and other risk factors.

Setting: The survey was conducted in 10 HIV testing and treatment hospitals/clinics across selected provinces in Cambodia, from February to March, 2017.

Participants: A total number of 500 volunteers participated in the survey, 250 patients and 250 HIV-negative individuals.

Primary and secondary outcome measures: Measures of injection prevalence and other risk behaviour distribution were based on self-reports.

Results: Despite lower annual injection/infusion rates from all types of providers (three injections per person in PLWH vs four injections per person in HIV-negative), PLWH were more likely to have had an unsafe last injection/infusion, aOR=1.84 (95% CI: 0.71-4.80).

Conclusions: The inclination for medical injections and infusions (unsafe at times) among PLWH in Cambodia was a common practice and could possibly represent yet another opportunity for parenteral transmission outbreak.

Strengths and limitations of the study

- Our study's assessment of self-recall injection behaviours over 12 months could better reflect injection use and avoid capturing only certain fluctuations, as medical injections or infusions are relatively uncommon events. This, complemented with the questions on

the last injection received over the same period to capture a more recent behaviour helped complete the risk profile assessment.

- Our study captured 92% of PLWH had been diagnosed more than two years prior, therefore, prevalent cases, they were most likely got infected during the early 90's through unsafe sexual behaviours and not through unsafe injection practices, making reverse causation a weak case in our study.
- The study looked at not only the providers of the last injection or infusion (received within the past year), but also facility types at which these medical injections took place. These helped a more accurate assessment of formal vs. informal providers, especially in the Cambodian setting, where the majority of peddlers or village providers (not working in the hospitals) were likely unlicensed providers without proper medical training.
- The majority of these behaviours were based on self-reports, from the participants or patients, unfortunately; the assessment from the provider side could help to completely understand the injection practices and form a better-informed recommendation.

Introduction

The World Health Organization (WHO) considered over or unnecessary use of injections as unsafe injection practices, alongside the use of unsafe methods for injection, such as reusing syringe and needles [1, 2]. In some parts of the world, particularly in low- and middle-income countries (LMICs), this common medical procedure is being performed daily using unsafe (yet avoidable) injection practices which put both patients and communities at risk of bloodborne pathogen transmission [1-5]. In late 2014, a rural community in Cambodia had a large outbreak of human immunodeficiency virus (HIV) when an unlicensed medical practitioner infected 242 villagers aged between 2 and 89 years through his use of contaminated injection equipment [6, 7]. In early 2018, another two HIV outbreaks linked with unsafe injection practices occurred in India and Pakistan [3]. These incidents demonstrated the ongoing risk of outbreaks related to medical injection around the world, specifically in the LMICs.

In Cambodia, private health care providers are commonly sought for care. Although many of them are public healthcare workers who practice privately during off-working hours, there are also providers, mainly in rural areas, who are unlicensed private practitioners from whom the community seeks medical care including (but not limited) to injections and infusions.

This is not uncommon in some parts of LMICs in which a person without proper training or education in administering certain medical procedures provides medical injections [4].

The last Cambodia Demographic and Health Survey (CDHS 2014) assessed injection practices as part of their behavioural survey among the general population. According to their report, the prevalence of medical injection (having had any medical injections from health worker in the past 12 months) among the Cambodian population aged 15-49 was approximately 35% (or 37% and 27% among women and men, respectively) [8]. Previous studies on injection use and safety practices (including the DHS survey) in Cambodia usually focused on the general population [9]. These behavioural risk factors have not been studied among people living with HIV (PLWH), despite the fact that the risk of getting or transmitting bloodborne pathogens among this population are heavily shaped by these behaviours. We suspected that PLWH might be seeking medical injections at a higher rate than the general population for several reasons. First, being in regular care gives PLWH more opportunities to get diagnosed with various medical conditions and receive treatments. Second, PLWH often suffer from significantly more co-morbidities, such as age-related non-communicable diseases and mental or neurological

disorders, than the general population [10, 11]. For these reasons, PLWH might be in greater need of medical treatments, such as injections, than the general population.

Ever since the 2014 HIV outbreak in Roka village, there have been no other studies assessing injection behaviours among PLWH elsewhere; and the CDHS reported only medical injections given by health care workers. Without assessment of injection and infusion practices in people who are at risk of transmitting and acquiring HIV, it is challenging for public health professionals to advise or prepare public health measures which are both appropriate and efficient to address unsafe injection practices. Our study aims to primarily characterize injection practices among PLWH and those who were HIV-negative and determine whether the first group were at higher risk of seeking medical injections from informal providers.

Although when considering unsafe medical injections, people usually refer to used syringes and needles, we considered (in this paper) injections provided by unlicensed (medical) practitioners unsafe as well. Understanding these injection seeking behaviours among this population is helpful for planning necessary public health measures as well as improving access to formal healthcare facilities.

Methods

Study setting

Cambodians seeking HIV care or HIV testing were recruited for this study from HIV voluntary testing sites in Cambodia and HIV/AIDS treatment and care clinics (called Opportunistic Infections/Antiretroviral Therapy (OI/ART) sites). These sites are under the supervision of the National Centre for HIV/AIDS, Dermatology and STD (NCHADS) and there are 52 of them across Cambodia. These sites transmit their patients' follow-up visit information (for people in care) or new information (for newly-tested positive patients) to NCHADS database on a regular basis.

Inclusion and exclusion criteria

Participants were eligible if they were: at least 18 years of age on the day of interview, people who are living with HIV (PLWH), that is those who have known HIV+ status, or HIV- status (after having had their HIV test result) and are willing and able to provide written informed consent to take part in the study on the data collection day. Excluded were individuals who are not willing or able to complete the questionnaire or present any other condition that, in the opinion of the research or local healthcare staff, would preclude informed consent.

Study design, sampling and recruitment

We conducted a cross-sectional study comparing PLWH (n=250) who came to receive their HIV treatment care and those who came to have HIV testing and had a negative result (n=250) at selected HIV clinics in five provinces and the capital city of Cambodia, from early February to the end of March 2017. The sample size of 250 per group was calculated to provide 90% power to test the hypothesis using a two-sample comparison of proportions where the first proportion was set at 20% of injection use (HIV-negative participants) and the second proportion was set at 35% (HIV-positive participants. A two-stage sampling approach was employed for participant selection. First, we selected 10 sites and out of the 52 sites with joint testing/OI/ART services (meaning those with both testing and OI/ART services) using probability-proportional-to-size (PPS) method. Next, we consecutively sampled PLWH who came for their regular clinic visit or pharmacy refill at the selected sites. In a similar manner, HIV-negative individuals who came to selected sites for HIV testing who got a negative result were approached for recruitment. We compared these two groups of participants for their similar HIV behavioural risk profile. It should be noted that those who come to the HIV/AIDS clinics for (voluntary) HIV testing, more often than not, those who are part of the population who are at risk of getting HIV (Men who

have Sex with Men "MSM", Injection Drug Users "IDU" and Entertainment Workers "EW") and are regularly tested for HIV/AIDS.

Medical history and behavioural assessment

HIV-specific factors (HIV status and date of HIV test, WHO disease stage, etc.) were obtained from linkage with the NCHADS database. Behavioural data were collected using a Computer-Assisted Person Interview (CAPI) technique, administered via tablet and questions were guided by literature. Participants were asked to report on socio-demographic factors, such as date of birth, sex, education, marital status, occupation, general location of residence (village, community, district and province) and a wide range of behavioural factors including history of illicit injection drug use (IDU), alcohol and tobacco use, informal medical injection/infusion use, such as frequency, and type of provider.

Definition and classification

The outcome of interest, unsafe medical injection (or infusion), was defined as having received last injection or infusion (within the past year) at participant's or provider's home from village providers who do not work at health centre or hospital, traditional providers, or by self-injection. In Cambodia and especially in rural areas, these health workers might also provide

some basic medical services (including injections and infusions) at their patient's home or in private hospitals/clinics. Therefore, regardless of where the patients receive the injections, as long as they were provided by the providers who work at hospital or health centre, we considered these injections safe. Both intravenous and intramuscular injections were included in the questionnaire and reporting.

The prevalence of medical injections counted those who reported at least one injection or infusion (over the past year), but excluded vaccinations, non-medical injections and rare medical injections such as transfusion.

Statistical analysis

We computed percentages and means of the key characteristics by HIV status (Table 1). We first calculated the prevalence of having had at least one medical injection from health workers and from all provider types over the past year among the participants (by their HIV status). Chi-square and Exact tests were used for categorical variables and t-test for continuous variables. Next, the average number of past year's medical injections from each type of providers by HIV status was also computed and we reported the *P* derived from Poisson regression. Finally, to examine the relationship between unsafe medical injection practices and HIV status,

we performed a logistic regression, adjusting for sex, age, education, occupation, residence location, injection preference and other risk factors. All analyses were done in STATA 14.

Patient and public involvement

The patients, care givers and those who sought HIV testing but were negative participated in the data collection of the study. Preliminary results of the study had been presented at the University of Health Sciences at the 2018 Scientific Days among invited care givers, students and other invited guests and researchers.

Results

We presented key characteristics by HIV status in Table 1. [Insert Table 1 here] The socio-demographic factors are vastly different between the two groups in terms of age, marital status, educational background and occupation. PLWH appeared to be much older – mean age was 43 years (SD 9), of a lower educational background and married, while the majority of HIV-negative participants were younger – mean age was 31 years (SD 11), more educated and single. However, both groups were comparable in terms of their sex, income and residence location distribution. Female participants accounted for about 66% (n=164) of PLWH and 71% (n=177)

of those uninfected. The majority of participants from both groups were from the provinces, 91% (*n*=227) among PLWH and 93% (*n*=231) among the uninfected.

Table 1. Key characteristics of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Socio-demographics	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Gender					
Female	164	65.6	177	70.8	.21
Male	86	34.4	73	29.2	
Age[a] (Mean, SD)	(43.1, 9.0)		(30.6, 10.7)		<.001
Marital status					
Single	15	6.0	87	34.8	<.001
Married	140	56.0	141	56.4	
Divorced	41	16.4	15	6.0	
Widowed	54	21.6	7	2.8	
Education					
Secondary or higher	104	41.6	163	65.2	<.001
Primary or less	146	58.4	87	34.8	
Occupation[a]					
Unemployed	81	32.7	126	50.8	<.001
Self-employed/farmers	95	38.3	70	28.2	
Employed	72	29.0	52	21.0	
Household annual income[a,b] (USD)					
> 3,000	40	22.9	44	22.8	.48
1,800-3,000	45	25.7	42	21.8	
1,001-1,800	39	22.3	56	29.0	
≤ 1,000	51	29.1	51	26.4	
Current address[a]					
Province	227	90.8	231	92.8	.42

Phnom Penh	23	9.2	18	7.2	
Other behavioral risk factors[c]					
Smoke monthly or more often	30	12.0	13	5.2	<.01
Feeling drunk monthly or more often	45	18.0	63	25.2	.05
Contact with syringe and needle at workplace	8	3.2	36	15.5	<.01
Had at least one hospitalization	42	23.5	87	49.2	<.001

SD, Standard Deviation.

[a]Missing (HIV+, HIV-, respectively): age (*n*=5, *n*=5); occupation (*n*=2, *n*=2); other behavioral risk factors (*n*=75, *n*=57); current address (*n*=0, *n*=1).

[b]The categories for household income used quartiles to assure sufficient numbers in each category.

[c]Self-report over the past year.

Injection/infusion use

Injection and infusion practices are described in Table 2. [Insert Table 2 here] We found that the average annual number of injection/infusion from health workers was about three and four injections per person among PLWH and those who were HIV-negative, respectively (*P*<.001). The prevalence of any medical injection/infusion provided by health workers over the past year was higher among HIV-uninfected participants, 72% (*n*=153), compared to 40% (*n*=61) among those who were HIV-positive (*P*<.001). However, the prevalence of past year's injection/infusion from all providers between the two groups were comparable, 47% (*n*=66) among PLWH and 54% (*n*=110) among those uninfected (*P*=.24).

Table 2. Injection practices of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Injection and infusion practices	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Injection and infusion use					
Last injection/infusion within past year					
Given by relative/acquainted provider	51	23.0	50	22.8	.97
Recommended by provider	54	85.7	131	90.3	.33
Given at public hospital	35	44.9	97	54.5	.16
Given at private hospital/clinic	29	53.7	58	46.0	.35
Given at their own home	16	31.4	24	21.2	.16
Number of injections/infusions within past year					
More than last year	107	67.7	144	66.4	.78
From health workers (mean, SD)		(3.2, 7.5)		(4.3, 7.1)	<.001
From all providers (mean, SD)		(3.5, 7.1)		(4.4, 7.8)	<.001
At least one - health worker	61	40.4	153	72.5	<.001
At least one - all providers	66	47.5	110	53.9	.24
Prefer injection to other treatments[a]	124	49.6	145	58.0	.06
Injection and infusion safety					
Last injection within past year					
Unsafe[b] last injection	11	15.5	11	7.3	.06
Provider did not use new, unopened syringe/needle	0	0.0	6	3.8	.19
Last injection within past year					
Unsafe[b] last infusion	10	13.5	13	10.5	.52
Provider did not use new, unopened syringe/needle	0	0.0	3	2.5	.55

SD, Standard Deviation.

[a]The questions on this preference pertain to several tracer conditions (in which case medical injections are clearly unnecessary).

[b]Administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

When asked about the last injection/infusion they received within the past year, PLWH were more likely to report having received their last one(s) at a private hospital/clinic, 54 % (*n*=29), or at their own home, 31% (*n*=16), compared to a 46% (*n*=58) and 21% (*n*=24), respectively, reported by their HIV-negative counterparts. HIV-negative participants were more likely to have received their last injection/infusion at a public hospital, 54% (*n*=97), as opposed to 45% (*n*=35) of PLWH (*P*=.16). Figure 1 broke down last injection and infusion by facility types in more details. [Insert Figure 1 here]

Regardless of HIV status, public and private sector accounted for the majority of medical injection and infusion received. Although none of our PLWH reported having received their last injection or infusion at traditional healer's home, a substantial amount of them reported having received their last injection (15% (*n*=9)) and infusion (22% (*n*=14)) at their own home.

A large number of participants from both groups, 50% (*n*=124) of PLWH and 58% (*n*=145) of those uninfected, reported that they preferred injection/infusion to other forms of treatment when sick (*P*=.06). Moreover, more than 60% of participants from both groups

indicated that they had actually received more injections the past year than previous year. Similarly, over 80% of both PLWH and HIV-negative participants reported that their last injection was in fact recommended by their care provider.

Injection/infusion safety practices

About 4% (*n*=6) of HIV-negative participants reported that the provider for their last injection did not use a new, unopened package of syringe and needles while none of PLWH reported this practice (*P*=.06). Although the average annual injection/infusion rates from all provider types (including health workers) were slightly lower among PLWH (three injections per person) compared with those who were HIV-negative (four injections per person) (*P*<.001), we observed a slightly larger proportion of PLWH reported an unsafe last injection within the past year, 15% (*n*=11) vs 7% (*n*=11) reported by those who were HIV-negative (*P*=.06). Likewise, 13% (*n*=10) of PLWH reported an unsafe last infusion within the past year, compared to 10% (*n*=13) of HIV-uninfected participants (*P*=.52). Regardless of whether they live in the provinces or the capital city "Phnom Penh" (Figure 2), the majority of participants from both groups reported their provider recommended their last injection/infusion and more HIV- participants than PLWH received their last injection/infusion from health workers. [Insert Figure 2 here] In

figure 3, overall, we saw similar patterns across the country, except provinces in the central and north-eastern parts of Cambodia where injection/infusion use appeared the highest. [Insert Figure 3 here]

Association between unsafe medical injection/infusion and HIV

Table 3 presents the crude, adjusted OR and the 95% CI of the relationship between unsafe last medical injection and HIV status. [Insert Table 3 here] Before adjustment, only sex, occupation and presence of two or more risk behaviours were associated with having had unsafe last injection or infusion (Table 3). HIV status appeared to be positively associated with unsafe medical injection/infusion, cOR=1.45 (95% CI: 0.70-3.00). After adjusting for other covariates, PLWH were almost twice more likely to have had an unsafe last injection or infusion than those who were HIV-negative, aOR=1.84 (95% CI: 0.71-4.80).

Table 3. Association between getting unsafe medical injection and HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Outcome: unsafe injection/infusion	Crude OR	95 % CI	Adjusted OR[a]	95 % CI
HIV + (ref. HIV-)	1.45	0.70-3.00	1.84	0.71-4.80
Male (ref. female)	2.17	1.03-4.57	2.37	1.00-5.62
Age	1.00	0.97-1.03	0.98	0.94-1.02
Education (ref. secondary or higher)				

Primary or less	0.70	0.33-1.46	0.96	0.41-2.23
Occupation (ref. unemployed)				
Farmers and self-employed	0.91	0.41-2.01	0.83	0.36-1.91
Employed	0.48	0.17-1.36	0.59	0.20-1.72
Current address in Phnom Penh (ref. in provinces)	1.18	0.33-4.23	1.02	0.27-3.88
Prefer injection or infusion when sick (ref. no preference)	0.59	0.29-1.21	0.66	0.32-1.40
Had at least two risk behaviours[b]	0.67	0.19-2.33	0.47	0.13-1.75

CI, Confidence Interval.

Unsafe injection/infusion: last injection/infusion within the past year administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

[a]Adjusted for gender, age, education, occupation, residence location, injection or infusion preference, and presence of two or more risk behaviours.

[b]Combination of risk behaviours include: one or more hospitalization, contact with syringe and needle, smoking monthly or more often and feeling drunk monthly or more often in the past year.

Discussion

In our study, we found a high prevalence of medical injections (having had any medical injections in the past year from health workers) among the study participants in general (almost 60%), but PLWH were more likely to have had unsafe last injection or infusion (having received their last injection from informal providers), compared with those who were HIV-negative. Regardless of the reasons for medical injections (with few exceptions), this practice is very common, and should be addressed, whether it is the patients' false beliefs that injectable drugs

work better than oral ones for certain medical conditions or the tendency to over-prescribe these injectables.

According to the 2014 CDHS, there were great variations of injection prevalence (administered by health workers) across the provinces ranging from 12% to 45% among women and from 15% to 43% among men, and the average annual number of injections is between one to two per person [8]. We found a much higher prevalence among our study sample, our results were more in line with an article published in 2004 by Vong et al. that also looked at medical injections in Cambodia found a 40% of medical injection prevalence and average number of injection (over the past six months) of 5.9 per person [9]. It should be noted that both the 2004 study and the 2014 DHS examined the injection practices among the general population outside of HIV setting (treatment or testing), and that it was unclear in the CDHS if infusions were also counted for their injection reporting. Our study grouped infusions with injections when reporting prevalence, similar to the 2004 study (Vong et al), but our study reported the injection behaviours over the past year instead of over six months like Vong et al did. Several other factors such as limited education, tendency of prescribers to recommend and participant's personal preference of injection and the study population could be responsible for higher rates being

reported in our study compared with others. However, these seemed consistent with a recently published paper which found high Hepatitis C prevalence among Cambodian population that is likely due to medical injections [12]. Similarly, a review paper published in 2016 also reported a 12-month medical injection prevalence ranging from 30% to 68% across studies conducted in south Asia [13].

The older mean age of our patients might also explain the high prevalence of medical injections among them. The age distribution of PLWH in Cambodia is actually weighed down by those who had been infected in the early 90's; and as the HIV incidence had been decreasing since 2000, fewer people had become infected since then [14]. Because PLWH in the study were on average older, they could be sicker and, therefore, sought more medical procedures including injections.

The study should be interpreted with consideration to a number of limitations. First, our assessment of the outcome was based on self-recall over a relatively long period (12 months) which might cast some doubts over the accuracy of the answers given. However, to properly reflect on injection use and avoid capturing only certain fluctuations, a longer period recall is more reasonable. In addition, medical injections or infusions are generally uncommon events so

recalling them might not be too challenging. We also complemented this with the questions on the last injection received over the same period in order to capture a more recent behaviour. Second, cross-sectional design is known to obscure the outcome-exposure relationship in terms of their timing of occurrence. However, these PLWH were mostly prevalent cases – 92% of PLWH had been diagnosed more than two years prior (result not shown) – who were most likely got infected during the early 90's through unsafe sexual behaviours and not through unsafe injection practices. Lastly, because we took into account not only both provider of the last injection or infusion received within the past year, but also facility types at which these medical procedures were given in order to define unsafe injection/infusion practice, village providers were considered unsafe only if they performed injection/infusion at their home or patient's home. Although this might have underestimated the proportion of these unsafe medical procedures among our study participants (as we were not able to ascertain that all village providers or another person who offered medical injection/infusion in private settings – which we considered safe – had actually undergone proper medical training to provide such procedures), the combination of both provider and facility types still better captured the safety aspect of medical

injection/infusion than just considering each one of them separately. Besides, private clinics and hospitals in Cambodia are generally considered "formal" providers.

Implications on policy and practices

Better access to medical care is a challenge particularly in rural parts of LMICs and in Cambodia, it is no different. Our findings suggest the need to pull resources toward universal health coverage and educational programs on safe medical injection practices. Resources are always divided among many priorities in LMICs, therefore, support development partners and organizations play important roles in addressing these health needs. Besides these infrastructures for better healthcare access, other important programs or activities educating could be very beneficial for both patients and the general population. The care providers could be an important role models in enforcing correct practices when it comes to medical injection practices. In the setting of HIV/AIDS care in Cambodia, counsellors could potentially play that role. Several HIV health facilities offered a digital platform of communication, on a voluntary basis, to patients and care providers to interact with one another or with each other, on their HIV-related issues. These platforms could also be used as forums for speaking and educating our patients who are in care of safe injection practices. In addition to all of these, further investigations on the injection

practices from the care provider side and the benefits or usefulness of the above educational platforms would provide a more complete picture of the practices of medical injections in Cambodia and evidence as to whether they are beneficial or if additional programs are to be put in place.

Conclusions

The majority of Cambodian population, including those who are living with HIV, regard medical injections and infusions as a symbol for optimal medical care. This perception and injection seeking behaviours were as common in the provinces as in the capital city although provinces in the central and north-eastern parts of the country seemed to exhibit extremely high prevalence of unsafe medical injection practices. Although on average, they might have received slightly fewer number of annual injections, PLWH were more likely to have received unsafe last injection/infusion within the past year. This practice poses harms to themselves as well as their community and needs to be addressed among all stakeholders including providers who are able to prescribe medical injections including infusions. Our findings also suggested the need to evaluate and reinforce safe injection practices among our health workers for a complete assessment and understanding of medical injection education and practices in our health system.

Contributors

KS conducted literature search and data analysis, interpreted results, wrote the manuscript, and created figures. KK and KV conducted literature search, designed the study, collected the data and guided data interpretation. D.K. conducted literature search and collected the data. VS and PG conceptualized the study, conducted literature search, interpreted results and guided data interpretation. All authors provided critical feedback and shaped the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval

Written consent was obtained from each participant before the enrolment and interview process. All interviews were conducted in a private room at the health centres/clinics. All

instruments used for data collection were anonymous; no identifying information, such as name, address, telephone number, or date of birth was recorded. The HIV-related information, such as ART regimen and duration of HIV infection, were obtained from linking the patient's ART code to the national HIV database. The ART code for each patient is given by the HIV clinics once the patients are linked to care and is used as their identifier instead of their name in the national database. After the dataset had been linked, the ART code had been removed for all participants. The study data was stored on a personal computer, keyword-protected. The study protocol was approved by the University of California Los Angeles Institutional Review Board (UCLA-IRB# 16-000876) and the National Ethics Committee for Human Research (NECHR) of Cambodia (NECHR# 320) in 2016.

References

1. World Health Organization. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health care settings. Geneva: World Health Organization, 2016.

2. World Health Organization. Injection Safety: Questions and Answers. 2016. https://www.who.int/infection-prevention/publications/is_questions-answers.pdf?ua=1 (July 2020, date last accessed).

3. Altaf A. Unsafe Injection Practices by Medical Practitioners in South Asia Associated with Hepatitis and HIV Outbreaks. J Infectiology 2018;1(2):1-3.

4. Gupta E, Bajpai M, Sharma P, Shah A, Sarin S. Unsafe injection practices: a potential weapon for the outbreak of blood borne viruses in the community. Ann Med Health Sci Res. 2013;3(2):177-81.

5. World Health Organization. Make Smart Injection Choices: National Decision-Making for Safe and Appropriate Injections. 2017. https://www.who.int/infection-prevention/tools/injections/IS_medical-treatement_leaflet.pdf?ua=1 (July 2020, date last accessed).

6. Rouet F, Nouhin J, Zheng DP, Roche B, Black A, Prak S, et al. Massive Iatrogenic Outbreak of Human Immunodeficiency Virus Type 1 in Rural Cambodia, 2014-2015. Clin Infect Dis. 2018;66(11):1733-41.

7. Saphonn V, Fujita M, Samreth S, Chan S, Rouet F, Khol V, et al. Cluster of HIV Infections Associated With Unsafe Injection Practices in a Rural Village in Cambodia. J Acquir Immune Defic Syndr. 2017;75(3):e82-e6.

8. National Institute of Statistics; Directorate General for Health; and ICF International. Cambodia Demographic and Health Survey 2014. Phnom Penh, Cambodia, and Rockville, Maryland, USA: National Institute of Statistics; Directorate General for Health; and ICF International; 2015.

9. Vong S, Perz JF, Sok S, Som S, Goldstein S, Hutin Y, et al. Rapid assessment of injection practices in Cambodia, 2002. BMC public health. 2005;5:56.

10. amFAR. HIV and Comorbidities: The Foundation for AIDS Research (amFAR); 2020. https://www.amfar.org/hiv-and-comorbidities/ (July 2020, date last accessed).

11. World Health Organization. Chronic comorbidities and coinfections in PLHIV. https://www.who.int/hiv/topics/comorbidities/about/en/ (July 2020, date last accessed).

12. Pheng P, Meyer L, Segeral O, Chea P, Yi S, Tuot S, et al. Hepatitis C seroprevalence among people living with HIV/AIDS and pregnant women in four provinces in Cambodia: an integrated bio-behavioral survey. BMC Infect Dis. 2022;22(1):177. Epub 2022/02/24. doi: 10.1186/s12879-022-07163-2. PubMed PMID: 35193496; PubMed Central PMCID: PMCPMC8862396.

13. Janjua NZ, Butt ZA, Mahmood B, Altaf A. Towards safe injection practices for prevention of hepatitis C transmission in South Asia: Challenges and progress. World J Gastroenterol. 2016;22(25):5837-52.

14. Ministry of Health/National Center for HIV/AIDS, Dermatology and STDs (MOH/NCHADS). Annual Report 2016. National Center for HIV/AIDS, Dermatology and STDs. 2017.

Figure legends and captions

Figure 1

Caption: Figure 1. Injection and infusion use among study participants by types of facility.

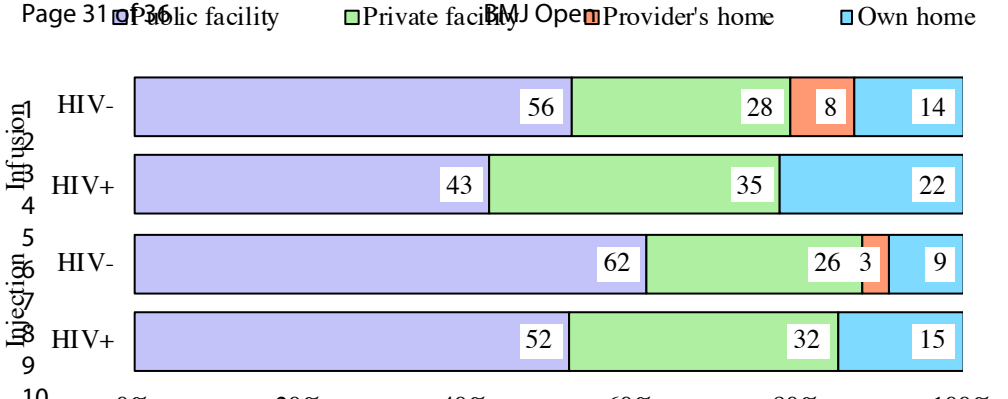
Figure 2

Caption: Figure 2. Injection and infusion use among study participants by residence location – Phnom Penh vs provinces

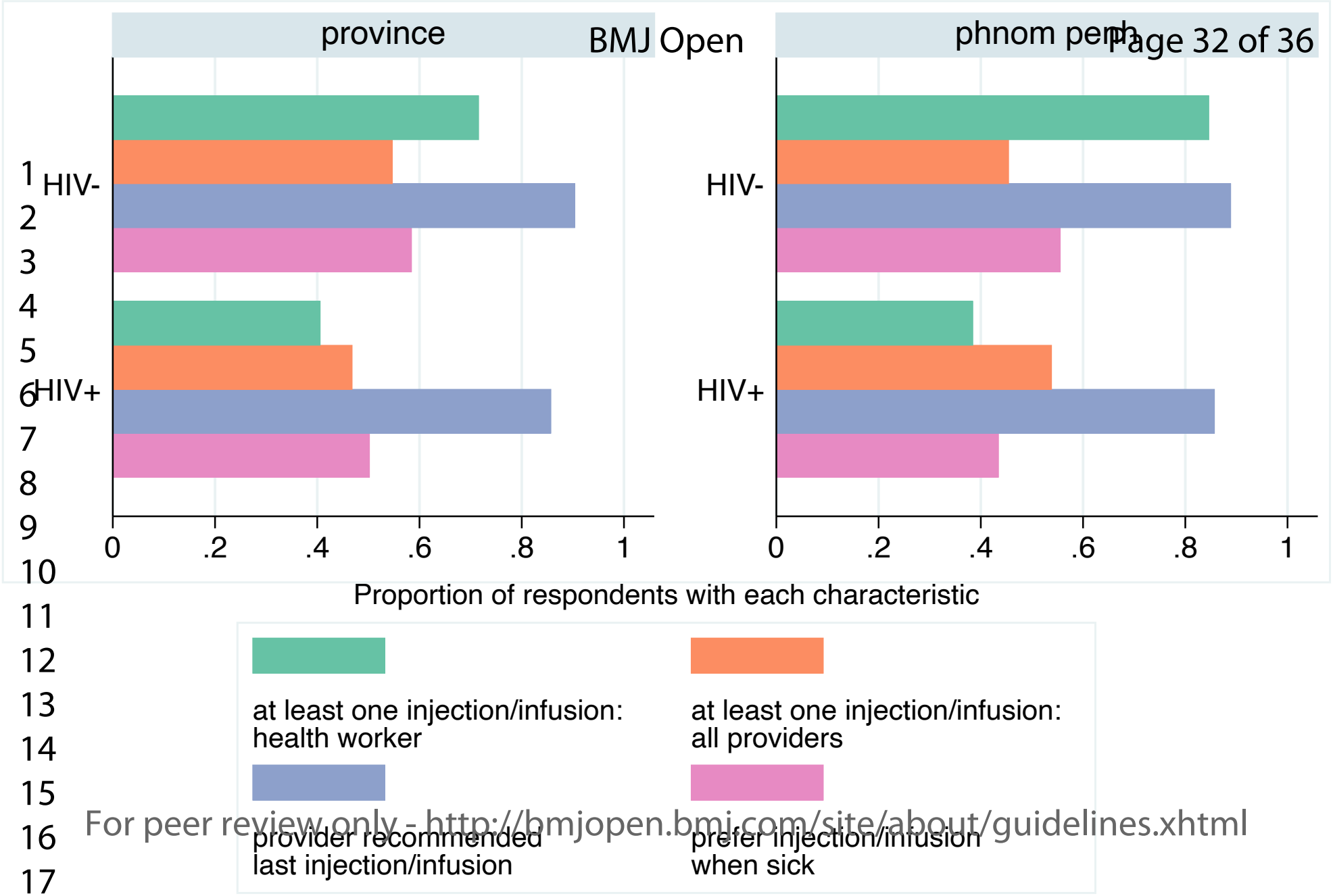
Figure 3

Legend: Note: West: Pursat; North-west: Siem Reap, Battambang, Odor Meanchey, Banteay Meanchey; South: Takeo, Kampot, Prey Veng; South-central: Phnom Penh, Kampong Speu; South-west: Sihanoukville, Koh Kong; East: Kratie, Mondulkiri; South-east: Tbong Khmum, Svay Rieng, Kampong Cham, Kandal; Central: Kampong Thom, Kampong Chhnang; North-east: Steung Treng; North: Preah Vihear

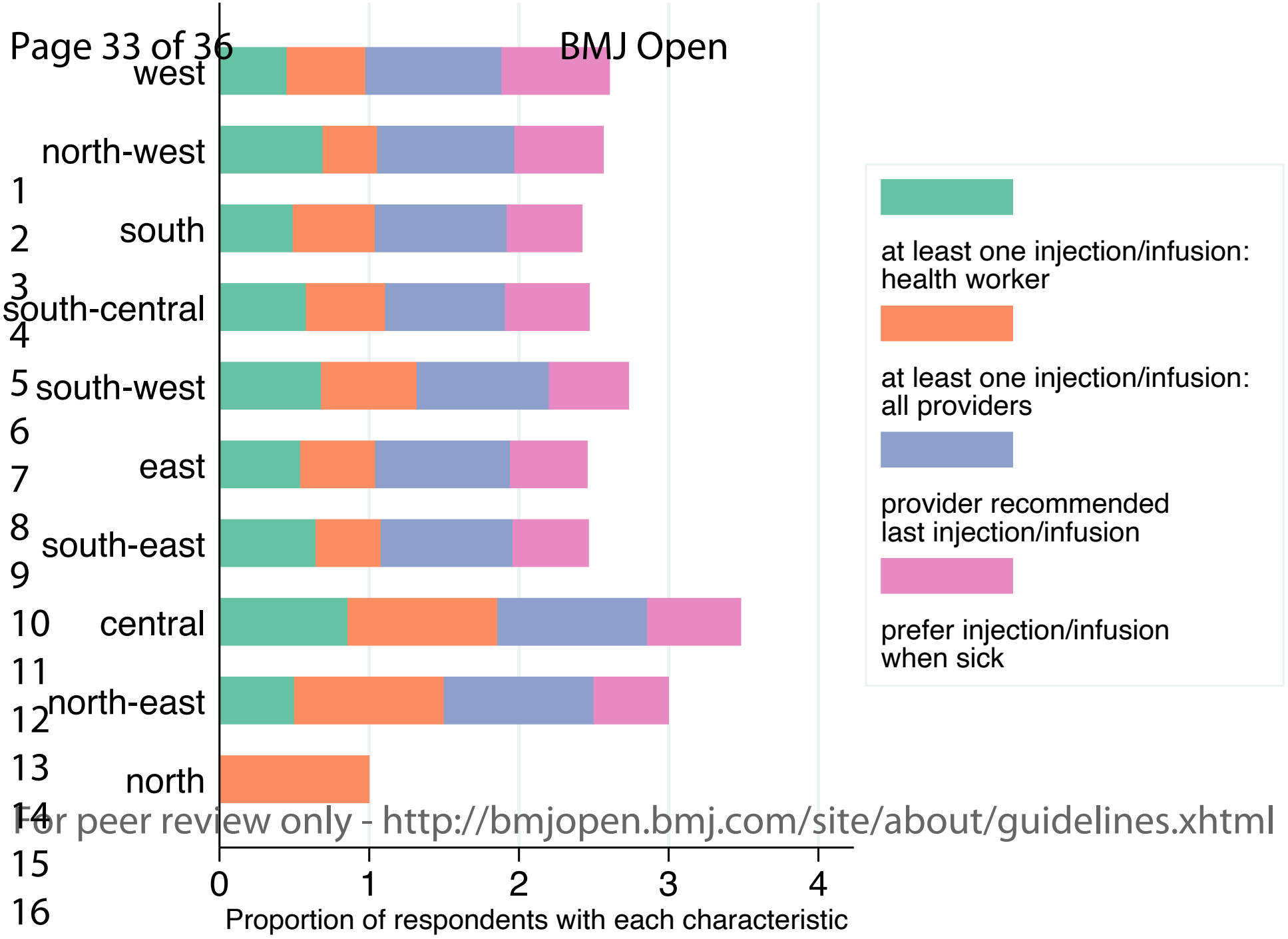
Caption: Figure 3. Injection and infusion use among study participants by geographic distribution.



Source: data from the 2017 Medical Injection Study (N=500), Cambodia



Source: data from the 2017 Medical Injection Study (n=500), Cambodia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Section in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract/Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background/Paragraph 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods/Study design, sampling and recruitment subheading/Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods/Study setting subheading/ Page 6
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods/Study design, sampling and recruitment subheading and Inclusion and exclusion criteria subheading/Page 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods/Definition and classification subheading/Page 8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods/page 8
Bias	9	Describe any efforts to address potential sources of bias	Discussion/Page 15-16
Study size	10	Explain how the study size was arrived at	Methods/Study design, sampling and recruitment subheading/Page 6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Results/Page 10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Method/Statistical analysis subheading/Page 8
		(*b*) Describe any methods used to examine subgroups and	N/A

interactions	
(*c*) Explain how missing data were addressed	Missingness occurred in less than 10% across the majority of variables (except income).
(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods/Study design, sampling and recruitment subheading/Page 5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Result/Page 7-8
		(b) Indicate number of participants with missing data for each variable of interest	Result/Page 8
		Cross-sectional study—Report numbers of outcome events or summary measures	Result/Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results/Page 13
		(*b*) Report category boundaries when continuous variables were categorized	Result/Page 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion/ Paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion/Page 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion/Paragraph 5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding/Page 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Behavioural Survey on Medical Injection and Infusion Practices among HIV-seronegative and People Living with HIV (PLWH) in 10 HIV Testing and Opportunistic Infections/Antiretroviral Therapy (OI/ART) Sites in Cambodia

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Behavioural Survey on Medical Injection and Infusion Practices among HIV-seronegative and People Living with HIV (PLWH) in 10 HIV Testing and Opportunistic Infections/Antiretroviral Therapy (OI/ART) Sites in Cambodia

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Keywords: injection, PLWH, unsafe injection, HIV, injection prevalence, injection practices

Abstract

Objectives: In late 2014, an HIV outbreak occurred in rural Cambodia among villagers who received medical injections from unlicensed medical providers, justifying the need to assess medical injection practices among those who are at risk of acquiring and/or transmitting HIV. This study examined medical injection/infusion behaviours among people living with HIV (PLWH) and those who were HIV-negative in Cambodia. These behaviours should be properly assessed, especially among PLWH, as their prevalence might influence a future risk of other outbreaks.

Design: A cross-sectional survey was conducted in order to examine injection behaviours and estimate the injection prevalence and injection rates by HIV status. Unsafe injections/infusions were those received from village providers who do not work at a health centre or hospital, or traditional providers at participant's (self-injection included) or provider's home. Logistic regression was performed to examine the relationship between unsafe injection/infusion and HIV, adjusting for sex, age, education, occupation, residence location, and other risk factors.

Setting: The survey was conducted in 10 HIV testing and treatment hospitals/clinics across selected provinces in Cambodia, from February to March, 2017.

Participants: A total number of 500 volunteers participated in the survey, 250 PLWH and 250 HIV-negative individuals.

Primary and secondary outcome measures: Measures of injection prevalence and other risk behaviour were based on self-reports.

Results: Although 47% of (*n*=66) PLWH reported comparable past year's injection/infusion use to the HIV-negative participants, 54% (*n*=110) (*P*=.24), 15% (*n*=11) of PLWH reported having received unsafe last injection compared to only 7% (*n*=11) of HIV-negative participants. In logistic regression, PLWH were more likely to have had an unsafe last injection/infusion, aOR=1.84 (95% CI: 0.71-4.80).

Conclusions: The inclination for medical injections and infusions (unsafe at times) among PLWH in Cambodia was a common practice and could possibly represent yet another opportunity for parenteral transmission outbreak.

Strengths and limitations of this study

- Medical injection and infusion practices assessed through self-reports could lead to bias.

- Only PLWH' injection and infusion practices had been assessed in this study, understanding the prescription tendencies of care providers would help complete the whole picture.
- Reverse causation, one of the biggest issues in cross-sectional study, is unlikely in our study.
- In Cambodian setting, injection and infusion practices need to account for the types of facility at which these practices are carried out in order to confirm the extent to which these practices could be interpreted as safe, which was exactly what we did in the study.

Introduction

The World Health Organization (WHO) considered over or unnecessary use of injections as unsafe injection practices, alongside the use of unsafe methods for injection, such as reusing syringe and needles [1, 2]. In some parts of the world, particularly in low- and middle-income countries (LMICs), this common medical procedure is being performed daily using unsafe (yet avoidable) injection practices which put both PLWH and communities at risk of bloodborne pathogen transmission [1-5]. In late 2014, a rural community in Cambodia had a large outbreak

of human immunodeficiency virus (HIV) when an unlicensed medical practitioner infected 242 villagers aged between 2 and 89 years through his use of contaminated injection equipment [6, 7]. In early 2018, another two HIV outbreaks linked with unsafe injection practices occurred in India and Pakistan [3]. In Iran, the behavioural survey among people who inject drugs (PWID) demonstrated a positive correlation between risky and unsafe injection and high prevalence of HIV among them [8]. These incidents and reports demonstrated the ongoing risk of outbreaks related to unsafe medical injection practices in many parts of the world. Additionally, a review article on injection practices worldwide published in 2000 reckoned that many injections are unsafe and unnecessary and that the region with the highest unsafe practice (reuse of injection materials) was indeed in South-East Asia [9].

In Cambodia, private health care providers are commonly sought for care. Although many of them are public healthcare workers who practice privately during off-working hours, there are also providers, mainly in rural areas, who are unlicensed private practitioners from whom the community seeks medical care including (but not limited) to injections and infusions. This is not uncommon in some parts of LMICs in which a person without proper training or education in administering certain medical procedures provides medical injections [4].

The last Cambodia Demographic and Health Survey (Cambodia DHS 2014) assessed injection practices as part of their behavioural survey among the general population. According to their report, the prevalence of medical injection (having had any medical injections from health worker in the past 12 months) among the Cambodian population aged 15-49 was approximately 35% (or 37% and 27% among women and men, respectively) [10]. Previous studies on injection use and safety practices (including the DHS survey) in Cambodia usually focused on the general population [11]. Moreover, although according to the 2019 review on injection practices using the DHS data from 40 countries reported reduced numbers of unsafe injections in 81% of the countries, the data used was from 2011-2015 [12], no other assessment had been reported since then. Until the present work, these behavioural risk factors have not been studied among people living with HIV (PLWH), despite the fact that the risk of getting or transmitting bloodborne pathogens among this population are heavily shaped by these behaviours. We hypothesized that PLWH might be seeking or receiving more medical injections (likely unnecessary and unsafe) than the general population for several reasons. First, being in regular care gives PLWH more opportunities to get diagnosed with various medical conditions and receive treatments. Second, PLWH often suffer from significantly more co-morbidities, such

as age-related non-communicable diseases and mental or neurological disorders, than the general population [13, 14]. For these reasons, PLWH might be in greater need of medical treatments, such as injections, than the general population.

Ever since the 2014 HIV outbreak in Roka village, there have been no other studies assessing injection behaviours among PLWH elsewhere; and the Cambodia DHS reported only medical injections given by health care workers. Without assessment of injection and infusion practices in people who are at risk of transmitting and acquiring HIV, it is challenging for public health professionals to advise or prepare public health measures which are both appropriate and efficient to address unsafe injection practices. Our study aims to primarily characterize injection practices among PLWH and those who were HIV-negative and determine whether the first group were more likely to seek unsafe or unnecessary medical injections.

Although when considering unsafe medical injections, people usually refer to used syringes and needles, we considered (in this paper) injections provided by unlicensed (medical) practitioners unsafe as well. Understanding these injection seeking behaviours among this population is helpful for planning necessary public health measures as well as improving access to formal healthcare facilities.

Methods

Study design and setting

We conducted a cross-sectional study among PLWH (n=250) who came to receive their HIV treatment care and those who came to have HIV testing and had a negative result (n=250) at 10 selected HIV clinics in five provinces and the capital city (Phnom Penh) of Cambodia, from early February to the end of March 2017. The sample size of 250 per group was calculated to provide 90% power to test the hypothesis using a two-sample comparison of proportions where the first proportion was set at 20% of injection use (HIV-negative participants) and the second proportion was set at 35% (HIV-positive participants). In Cambodia, HIV voluntary testing sites in Cambodia and HIV/AIDS treatment and care clinics (called Opportunistic Infections/Antiretroviral Therapy (OI/ART) sites) and are under the supervision of the National Centre for HIV/AIDS, Dermatology and STD (NCHADS); there are around 52 of them across Cambodia at the time of the study.

A two-stage sampling approach was employed for participant selection. We selected 10 sites and out of the 52 sites with joint testing/OI/ART services (meaning those with both testing and OI/ART services) using probability-proportional-to-size (PPS) method. Then, from each of

these 10 sites, we consecutively sampled 25 PLWH who came for their regular clinic visit or pharmacy refill. In a similar manner, HIV-negative individuals who came to each selected sites for HIV testing who got a negative result were approached for recruitment (25 per site).

Inclusion and exclusion criteria

Both PLWH and HIV-negative participants were eligible if they were at least 18 years old and were willing and able to provide written informed consent to take part in the study on the data collection day. Excluded were individuals who are not willing or able to complete the questionnaire, had undetermined test result, or presented any other condition that, in the opinion of the research or local healthcare staff, would preclude informed consent.

Medical history and behavioural assessment

HIV-specific factors (HIV status and date of HIV test, WHO disease stage, etc.) were obtained from linkage with the NCHADS database. Behavioural data were collected using a Computer-Assisted Person Interview (CAPI) technique, administered via tablet and questions were guided by literature. Participants were asked to report on socio-demographic factors, such as date of birth, sex, education, marital status, occupation, general location of residence (village, community, district and province) and a wide range of behavioural factors including history of

illicit injection drug use (IDU), alcohol and tobacco use, informal medical injection/infusion use, such as frequency, and type of provider.

Definition and classification

The outcome of interest, unsafe medical injection (binary outcome), was defined as having received last injection or infusion (within the past year) from village providers who do not work at health centre or hospital, from traditional providers, or by self-injection (other than diabetic medication) either at their own home or at the provider's home. In Cambodia and especially in rural areas, these health workers might also provide some basic medical services (including injections and infusions) at their patient's home or in private hospitals/clinics. Therefore, regardless of where the PLWH receive the injections, as long as they were provided by the providers who work at hospital or health centre, we considered these injections safe. Both intravenous and intramuscular injections were included in the questionnaire and reporting.

The prevalence of medical injections counted those who reported at least one injection or infusion (over the past year), but excluded vaccinations, non-medical injections and rare medical injections such as transfusion.

The HIV status was not assessed by the study team, those with known HIV-positive or HIV-negative result were informed of the present study and referred to study team for further information on the study and consent process from their care providers, we had no access to their HIV test or result.

Other risk behavioural assessment (alcohol and tobacco use, informal medical injection/infusion use, etc.) was based on participants' self-report.

Statistical analysis

We computed percentages and means of the key characteristics by HIV status. We calculated the prevalence of having had at least one medical injection from health workers and from all provider types over the past year among the participants (by their HIV status). Chi-square and Exact tests were used for categorical variables and t-test for continuous variables. Next, the average number of past year's medical injections from each type of providers by HIV status was also computed and we reported the *P* derived from Poisson regression. Finally, to examine the relationship between unsafe medical injection practices and HIV status, we performed a logistic regression, adjusting for sex, age, education, occupation, residence location, injection preference and other risk factors. Confounding variables were based on prior

knowledge and literature review on similar work previously conducted. All analyses were done in STATA 14.

Patient and public involvement

The PLWH, care givers and those who sought HIV testing but were negative participated in the data collection of the study. Preliminary results of the study had been presented at the University of Health Sciences at the 2018 Scientific Days among invited care givers, students and other invited guests and researchers.

Results

We presented key characteristics by HIV status in Table 1. [Insert Table 1 here] The socio-demographic factors are vastly different between the two groups in terms of age, marital status, educational background and occupation. PLWH appeared to be much older – mean age was 43 years (SD 9), of a lower educational background and married, while the majority of HIV-negative participants were younger – mean age was 31 years (SD 11), more educated and single. However, both groups were comparable in terms of their sex, income and residence location distribution. Female participants accounted for about 66% (n=164) of PLWH and 71% (n=177)

of those uninfected. The majority of participants from both groups were from the provinces, 91% (*n*=227) among PLWH and 93% (*n*=231) among the uninfected.

Table 1. Key characteristics of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Socio-demographics	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Gender					
Female	164	65.6	177	70.8	.21
Male	86	34.4	73	29.2	
Age[a] (Mean, SD)	(43.1, 9.0)		(30.6, 10.7)		<.001
Marital status					
Single	15	6.0	87	34.8	<.001
Married	140	56.0	141	56.4	
Divorced	41	16.4	15	6.0	
Widowed	54	21.6	7	2.8	
Education					
Secondary or higher	104	41.6	163	65.2	<.001
Primary or less	146	58.4	87	34.8	
Occupation[a]					
Unemployed	81	32.7	126	50.8	<.001
Self-employed/farmers	95	38.3	70	28.2	
Employed	72	29.0	52	21.0	
Household annual income[a,b] (USD)					
> 3,000	40	22.9	44	22.8	.48
1,800-3,000	45	25.7	42	21.8	
1,001-1,800	39	22.3	56	29.0	
≤ 1,000	51	29.1	51	26.4	
Current address[a]					
Province	227	90.8	231	92.8	.42

Phnom Penh (capital city)	23	9.2	18	7.2	
Other behavioural risk factors[c]					
Smoke monthly or more often	30	12.0	13	5.2	<.01
Feeling drunk at least once a month	45	18.0	63	25.2	.05
Contact with syringe and needle at workplace	8	3.2	36	15.5	<.01
Had at least one hospitalization	42	23.5	87	49.2	<.001

SD, Standard Deviation.

[a]Missing (HIV+, HIV-, respectively): age (*n*=5, *n*=5); occupation (*n*=2, *n*=2); current address (*n*=0, *n*=1).

[b]The categories for household income used quartiles to assure sufficient numbers in each category.

[c]Self-report over the past year.

Injection/infusion use

Injection and infusion practices are described in Table 2. [Insert Table 2 here] We found that the average annual number of injection/infusion from health workers was about three and four injections per person among PLWH and those who were HIV-negative, respectively (*P*<.001). The prevalence of any medical injection/infusion provided by health workers over the past year was higher among HIV-uninfected participants, 72% (*n*=153), compared to 40% (*n*=61) among those who were HIV-positive (*P*<.001). However, the prevalence of past year's injection/infusion from all providers between the two groups were comparable, 47% (*n*=66) among PLWH and 54% (*n*=110) among those uninfected (*P*=.24).

Table 2. Injection and infusion seeking behaviours of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Injection and infusion practices	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Injection and infusion received					
Last injection/infusion within past year					
Given by relative/acquainted provider	51	23.0	50	22.8	.97
Recommended by provider	54	85.7	131	90.3	.33
Given at public hospital	35	44.9	97	54.5	.16
Given at private hospital/clinic	29	53.7	58	46.0	.35
Given at their own home	16	31.4	24	21.2	.16
Number of injections/infusions within past year					
More than a year ago	107	67.7	144	66.4	.78
From health workers (mean, SD)		(3.2, 7.5)		(4.3, 7.1)	<.001
From all providers (mean, SD)		(3.5, 7.1)		(4.4, 7.8)	<.001
At least one - health worker	61	40.4	153	72.5	<.001
At least one - all providers	66	47.5	110	53.9	.24
Prefer injection to other treatments[a]	124	49.6	145	58.0	.06
Injection and infusion safety					
Last injection within past year					
Unsafe[b] last injection	11	15.5	11	7.3	.06
Provider did not use new, unopened syringe/needle	0	0.0	6	3.8	.19
Last injection within past year					
Unsafe[b] last infusion	10	13.5	13	10.5	.52
Provider did not use new, unopened syringe/needle	0	0.0	3	2.5	.55

SD, Standard Deviation.

[a]The questions on this preference pertain to several tracer conditions (in which case medical injections are clearly unnecessary).

[b]Administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

When asked about the last injection/infusion they received within the past year, PLWH were more likely to report having received their last one(s) at a private hospital/clinic, 54 % (*n*=29), or at their own home, 31% (*n*=16), compared to a 46% (*n*=58) and 21% (*n*=24), respectively, reported by their HIV-negative counterparts. HIV-negative participants were more likely to have received their last injection/infusion at a public hospital, 54% (*n*=97), as opposed to 45% (*n*=35) of PLWH (*P*=.16). Figure 1 broke down last injection and infusion by facility types in more details. [Insert Figure 1 here]

Regardless of HIV status, public and private sector accounted for the majority of medical injection and infusion received. Although none of our PLWH reported having received their last injection or infusion at traditional healer's home, about one-fourth of them reported having received their last injection (15% (*n*=9)) and infusion (22% (*n*=14)) at their own home.

A large number of participants from both groups, 50% (*n*=124) of PLWH and 58% (*n*=145) of those uninfected, reported that they preferred injection/infusion to other forms of treatment when sick (*P*=.06). Moreover, more than 60% of participants from both groups

indicated that they had actually received more injections the past year than previous year. Similarly, over 80% of both PLWH and HIV-negative participants reported that their last injection was in fact recommended by their care provider.

Injection/infusion safety practices

About 4% (*n*=6) of HIV-negative participants reported that the provider for their last injection did not use a new, unopened package of syringe and needles while none of PLWH reported this practice (*P*=.06). Although the average annual injection/infusion rates from all provider types (including health workers) were slightly lower among PLWH (three injections per person) compared with those who were HIV-negative (four injections per person) (*P*<.001), we observed a slightly larger proportion of PLWH reported an unsafe last injection within the past year, 15% (*n*=11) vs 7% (*n*=11) reported by those who were HIV-negative (*P*=.06). Likewise, 13% (*n*=10) of PLWH reported an unsafe last infusion within the past year, compared to 10% (*n*=13) of HIV-uninfected participants (*P*=.52). Regardless of whether they live in the provinces or the capital city "Phnom Penh" (Figure 2), the majority of participants from both groups reported their provider recommended their last injection/infusion and more HIV- participants than PLWH received their last injection/infusion from health workers. [Insert Figure 2 here] In

figure 3, overall, we saw similar patterns across the country, except provinces in the central and north-eastern parts of Cambodia where injection/infusion use appeared the highest. [Insert Figure 3 here]

Association between unsafe medical injection/infusion and HIV

Table 3 presents the crude, adjusted OR and the 95% CI of the relationship between unsafe last medical injection and HIV status. [Insert Table 3 here] Before adjustment, only sex, occupation and presence of two or more risk behaviours were associated with having had unsafe last injection or infusion (Table 3). HIV status appeared to be positively associated with unsafe medical injection/infusion, cOR=1.45 (95% CI: 0.70-3.00). After adjusting for other covariates, PLWH were almost twice more likely to have had an unsafe last injection or infusion than those who were HIV-negative, aOR=1.84 (95% CI: 0.71-4.80).

Table 3. Association between getting unsafe medical injection and HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Outcome: unsafe injection/infusion	Crude OR	95 % CI	Adjusted OR[a]	95 % CI
HIV + (ref. HIV-)	1.45	0.70-3.00	1.84	0.71-4.80
Male (ref. female)	2.17	1.03-4.57	2.37	1.00-5.62
Age	1.00	0.97-1.03	0.98	0.94-1.02
Education (ref. secondary or higher)				

Primary or less	0.70	0.33-1.46	0.96	0.41-2.23
Occupation (ref. unemployed)				
Farmers and self-employed	0.91	0.41-2.01	0.83	0.36-1.91
Employed	0.48	0.17-1.36	0.59	0.20-1.72
Current address in Phnom Penh (ref. in provinces)	1.18	0.33-4.23	1.02	0.27-3.88
Prefer injection or infusion when sick (ref. no preference)	0.59	0.29-1.21	0.66	0.32-1.40
Had at least two risk behaviours[b]	0.67	0.19-2.33	0.47	0.13-1.75

CI, Confidence Interval.

Unsafe injection/infusion: last injection/infusion within the past year administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

[a]Adjusted for gender, age, education, occupation, residence location, injection or infusion preference, and presence of two or more risk behaviours.

[b]Combination of risk behaviours include: one or more hospitalization, contact with syringe and needle, smoking monthly or more often and feeling drunk monthly or more often in the past year.

Discussion

In our study, we found a high prevalence of medical injections (having had any medical injections in the past year from health workers) among the study participants in general (almost 60%), but PLWH were more likely to have had unsafe last injection or infusion (having received their last injection from informal providers), compared with those who were HIV-negative. Regardless of the reasons for medical injections (with few exceptions), this practice is very common, and should be addressed, whether it is the PLWH's false beliefs that injectable drugs

work better than oral ones for certain medical conditions or the tendency to over-prescribe these injectables.

According to the 2014 CDHS, there were great variations of injection prevalence (administered by health workers) ranging from 12% to 45% and the average annual number of injections is one to two per person [10]. We found a much higher prevalence among our study sample, our results were more in line with an article published in 2004 by Vong et al. that also looked at medical injections in Cambodia found a 40% of medical injection prevalence and average number of injection (over the past six months) of 5.9 per person [11]. This is, in fact, consistent with findings from a review paper published in 2016 which found that 12-month medical injection prevalence ranged from 30% to 68% across studies conducted in south Asia [15]. It should be noted that both the 2004 study and the 2014 DHS examined the injection practices among the general population outside of HIV setting (treatment or testing), and that it was unclear in the CDHS if infusions were also counted for their injection reporting. Our study grouped infusions with injections when reporting prevalence, similar to the 2004 study (Vong et al), but our study reported the injection behaviours over the past year instead of over six months like Vong et al did. Several other factors such as limited education, tendency of prescribers to

recommend and participant's personal preference of injection and the study population could be responsible for higher rates being reported in our study compared with others. However, these seemed consistent with a recently published paper which found high Hepatitis C prevalence among Cambodian population that is likely due to medical injections [16]. High prevalence of medical injection (ranging from 30% to 68%) had also been reported across studies conducted in south Asia [15]. Although slightly different from our study, results from Kenyan survey published in 2016 reported a positive association between HIV and those who reported having received injection in the last 12 months [17]. The Kenyan study only reported injections from care providers and not traditional healers or other types of providers.

The older mean age of our PLWH might also explain the high prevalence of medical injections among them. Because PLWH in the study were on average older, they could be sicker and, therefore, sought more medical procedures including injections. The age distribution of PLWH in Cambodia is actually weighed down by those who had been infected in the early 90's; and fewer people had become infected since 2000 [18].

The study should be interpreted with consideration to a number of limitations. Our assessment of the outcome was based on self-recall which could result in misclassification of the

outcome measured. However, we have limited recalls to the past 12 months and reckon that to avoid capturing only certain fluctuations, a recall over 12 months appeared reasonable. Multiple studies used a 12-month timeframe for estimating prevalence (although they mainly assessed drug use) [19, 20]. Medical injections are generally also uncommon events, we, therefore, expected this misclassification, if any, to be minimal. By design, the outcome-exposure relationship in our study is obscure. However, our PLWH were mostly prevalent cases and older – 92% of PLWH had been diagnosed more than two years prior (result not shown) – who were most likely got infected during the early 90's through unsafe sexual behaviours and not through unsafe injection practices. Consecutive sampling among PLWH and HIV-negative participants could also affect our internal validity; however, the process of scheduling the appointment at each selected facility for both groups is already in itself a random process. There were also patients who just dropped in. In other words, there is no reason to believe that participants might differ in terms of injection use between the time of our data collection and any other time. This does, however, limit our own study findings' generalizability in a way that they might be applicable to only PLWH and HIV-negative population who come to receive care and seek HIV testing at the selected clinics and hospitals.

The strengths of our study included the fact that we took into account not only both provider of the last injection or infusion received within the past year, but also facility at which these medical procedures were given, the combination of both provider and facility types should be able to capture better the safety aspect of medical injection/infusion. It should be noted that private facilities in Cambodia are generally considered "formal" providers. Our work is one of the few studies which examined injection practices among PLWH over the past decade. Another study was conducted in 2016 (a year prior to when our study had started) [16]. Regardless, additional studies are necessary in order to confirm the findings from our work and understand the true underlying injection practices among PLWH.

Implications on policy and practices

Better access to medical care is a challenge particularly in rural parts of Cambodia. Our findings suggest the need to pull resources toward universal health coverage and educational programs on safe medical injection practices. Resources are always limited in LMICs; therefore, support development partners play important roles in addressing these health needs. Besides these, other important educational programs or activities directed at both PLWH and HIV-negative population also deemed beneficial. Care providers could be important role models in

enforcing correct practices of medical injection, particularly, counsellors in the setting of HIV/AIDS care here, could also play that role. Several HIV health facilities offered a digital platform of communication (Telegram group chat and Facebook Messenger chats are the most commonly used), on a voluntary basis, to PLWH and care providers to interact with one another or with each other, on their HIV-related issues. These platforms could also be used as forums for communicating correct safe injection practices to them. Of course, these types of programs would need further investigations in order to understand the population whom we could reach with these digital platforms. Regardless of HIV status, these educational programs and activities should be widely inclusive because use of medical injection seemed to be very common among both PLWH and those who were HIV-negative. Nevertheless, further investigations on the injection practices (among care provider) and the benefits of the aforementioned educational platforms would provide a more complete picture of the practices of medical injections in Cambodia and evidence as to whether they are beneficial or if additional programs are to be put in place.

Conclusions

The majority of Cambodian population, including those who are living with HIV, regard medical injections and infusions as a symbol for optimal medical care. Although on average, they might have received slightly fewer number of annual injections, PLWH were more likely to have received unsafe last injection/infusion within the past year. This practice poses harms to themselves as well as their community and needs to be addressed among all stakeholders including providers who are able to prescribe medical injections including infusions. Our findings suggested the need to evaluate and reinforce safe injection practices among our health workers for a complete assessment and understanding of medical injection education and practices in our health system.

Contributors

KS conducted literature search and data analysis, interpreted results, wrote the manuscript, and created figures. KK and KV conducted literature search, designed the study, collected the data and guided data interpretation. D.K. conducted literature search and collected the data. VS and PG conceptualized the study, conducted literature search, interpreted results and guided data interpretation. All authors provided critical feedback and shaped the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval

Written consent was obtained from each participant before the enrolment and interview process. All interviews were conducted in a private room at the health centres/clinics. All instruments used for data collection were anonymous; no identifying information, such as name, address, telephone number, or date of birth was recorded. The HIV-related information, such as ART regimen and duration of HIV infection, were obtained from linking the patient's ART code to the national HIV database. The ART code for each patient is given by the HIV clinics once the PLWH are linked to care and is used as their identifier instead of their name in the national database. After the dataset had been linked, the ART code had been removed for all participants. The study data was stored on a personal computer, keyword-protected. The study protocol was approved by the University of California Los Angeles Institutional Review Board (UCLA-IRB#

16-000876) and the National Ethics Committee for Human Research (NECHR) of Cambodia (NECHR# 320) in 2016.

References

1. World Health Organization. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health care settings. Geneva: World Health Organization, 2016.

2. World Health Organization. Injection Safety: Questions and Answers. 2016. https://www.who.int/infection-prevention/publications/is_questions-answers.pdf?ua=1 (July 2020, date last accessed).

3. Altaf A. Unsafe Injection Practices by Medical Practitioners in South Asia Associated with Hepatitis and HIV Outbreaks. J Infectiology 2018;1(2):1-3.

4. Gupta E, Bajpai M, Sharma P, Shah A, Sarin S. Unsafe injection practices: a potential weapon for the outbreak of blood borne viruses in the community. Ann Med Health Sci Res. 2013;3(2):177-81. Epub 2013/08/07. doi: 10.4103/2141-9248.113657. PubMed PMID: 23919185; PubMed Central PMCID: PMCPMC3728858.

5. World Health Organization. Make Smart Injection Choices: National Decision-Making for Safe and Appropriate Injections. 2017. https://www.who.int/infection-prevention/tools/injections/IS_medical-treatement_leaflet.pdf?ua=1 (July 2020, date last accessed).

6. Rouet F, Nouhin J, Zheng DP, Roche B, Black A, Prak S, et al. Massive Iatrogenic Outbreak of Human Immunodeficiency Virus Type 1 in Rural Cambodia, 2014-2015. Clin Infect Dis. 2018;66(11):1733-41. Epub 2017/12/07. doi: 10.1093/cid/cix1071. PubMed PMID: 29211835; PubMed Central PMCID: PMCPMC5963970.

7. Saphonn V, Fujita M, Samreth S, Chan S, Rouet F, Khol V, et al. Cluster of HIV Infections Associated With Unsafe Injection Practices in a Rural Village in Cambodia. J Acquir Immune Defic Syndr. 2017;75(3):e82-e6. Epub 2017/01/28. doi: 10.1097/QAI.0000000000001295. PubMed PMID: 28129255; PubMed Central PMCID: PMCPMC6814627.

8. Esmaeili A, Shokoohi M, Danesh A, Sharifi H, Karamouzian M, Haghdoost A, et al. Dual Unsafe Injection and Sexual Behaviors for HIV Infection Among People Who Inject Drugs in Iran. AIDS and behavior. 2019;23(6):1594-603. Epub 2018/11/22. doi: 10.1007/s10461-018-2345-5. PubMed PMID: 30460664; PubMed Central PMCID: PMCPMC6527484.

9. Hutin YJFH, Anja M; Armstrong, Gregory L. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. Bmj. 2003. doi: 10.1136/bmj.327.7423.1075.

10. National Institute of Statistics; Directorate General for Health; and ICF International. Cambodia Demographic and Health Survey 2014. Phnom Penh, Cambodia, and Rockville, Maryland, USA: National Institute of Statistics; Directorate General for Health; and ICF International; 2015.

11. Vong S, Perz JF, Sok S, Som S, Goldstein S, Hutin Y, et al. Rapid assessment of injection practices in Cambodia, 2002. BMC public health. 2005;5:56. Epub 2005/06/03. doi: 10.1186/1471-2458-5-56. PubMed PMID: 15929800; PubMed Central PMCID: PMCPMC1173117.

12. Hayashi T, Hutin YJ, Bulterys M, Altaf A, Allegranzi B. Injection practices in 2011-2015: a review using data from the demographic and health surveys (DHS). BMC Health Serv Res. 2019;19(1):600. Epub 2019/08/29. doi: 10.1186/s12913-019-4366-9. PubMed PMID: 31455315; PubMed Central PMCID: PMCPMC6712605.

13. amFAR. HIV and Comorbidities: The Foundation for AIDS Research (amFAR); 2020. https://www.amfar.org/hiv-and-comorbidities/ (July 2020, date last accessed).

14. World Health Organization. Chronic comorbidities and coinfections in PLHIV. https://www.who.int/hiv/topics/comorbidities/about/en/ (July 2020, date last accessed).

15. Janjua NZ, Butt ZA, Mahmood B, Altaf A. Towards safe injection practices for prevention of hepatitis C transmission in South Asia: Challenges and progress. World J Gastroenterol. 2016;22(25):5837-52. Epub 2016/07/20. doi: 10.3748/wjg.v22.i25.5837. PubMed PMID: 27433097; PubMed Central PMCID: PMCPMC4932219.

16. Pheng P, Meyer L, Segeral O, Chea P, Yi S, Tuot S, et al. Hepatitis C seroprevalence among people living with HIV/AIDS and pregnant women in four provinces in Cambodia: an integrated bio-behavioral survey. BMC Infect Dis. 2022;22(1):177. Epub 2022/02/24. doi: 10.1186/s12879-022-07163-2. PubMed PMID: 35193496; PubMed Central PMCID: PMCPMC8862396.

17. Kimani D, Kamau R, Ssempijja V, Robinson K, Oluoch T, Njeru M, et al. Medical injection use among adults and adolescents aged 15 to 64 years in Kenya: results from a national survey. J Acquir Immune Defic Syndr. 2014;66 Suppl 1:S57-65. Epub 2014/01/15. doi: 10.1097/QAI.0000000000000106. PubMed PMID: 24413041; PubMed Central PMCID: PMCPMC4794988.

18. Ministry of Health/National Center for HIV/AIDS, Dermatology and STDs (MOH/NCHADS). Annual Report 2016. National Center for HIV/AIDS, Dermatology and STDs. 2017.

19. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health. 2017;5(12):e1192-e207. Epub 2017/10/28. doi: 10.1016/S2214-109X(17)30375-3. PubMed PMID: 29074409; PubMed Central PMCID: PMCPMC5683738.

20. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Methodological Guidelines to Estimate the Prevalence of Problem Drug Use on the Local Level. Lisbon: EMCDDA, December 1999.

Figure legends and captions

Figure 1

Caption: Figure 1. Injection and infusion use among study participants by types of facility.

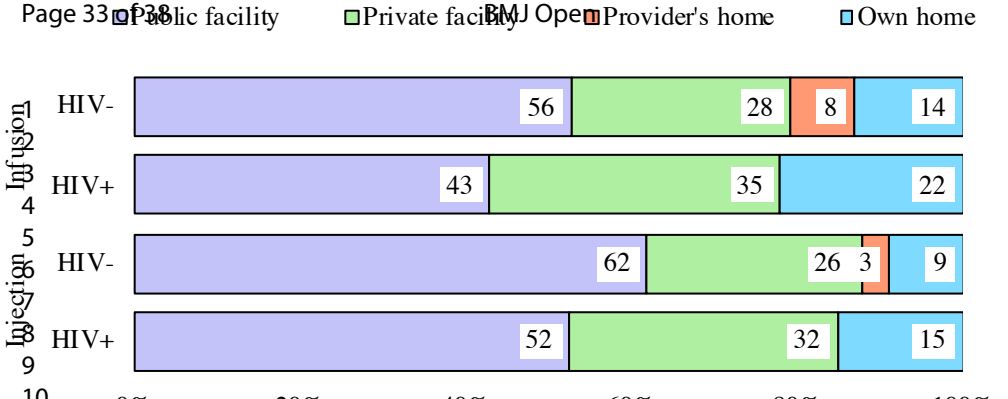
Figure 2

Caption: Figure 2. Injection and infusion use among study participants by residence location – Phnom Penh vs provinces

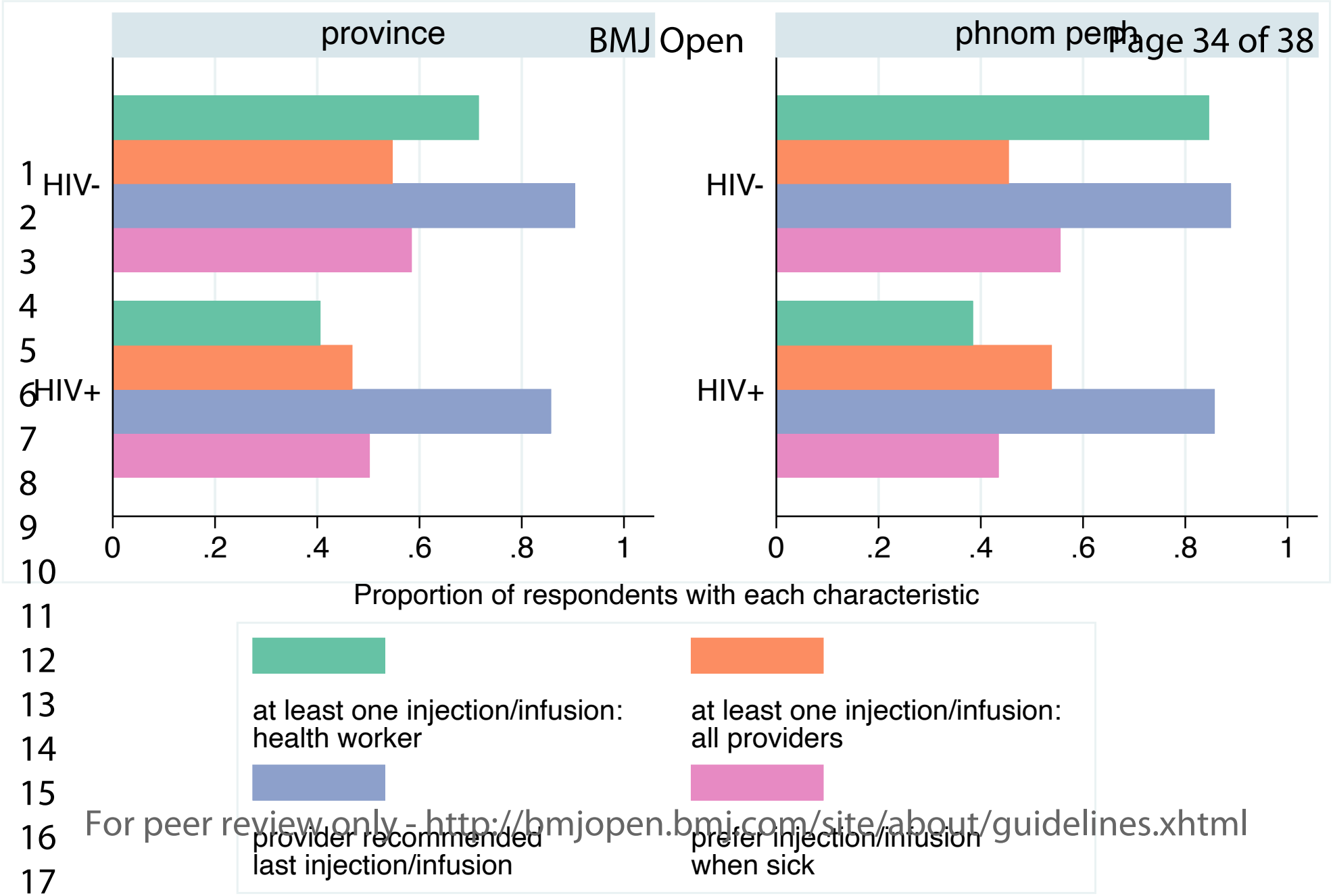
Figure 3

Legend: Note: West: Pursat; North-west: Siem Reap, Battambang, Odor Meanchey, Banteay Meanchey; South: Takeo, Kampot, Prey Veng; South-central: Phnom Penh, Kampong Speu; South-west: Sihanoukville, Koh Kong; East: Kratie, Mondulkiri; South-east: Tbong Khmum, Svay Rieng, Kampong Cham, Kandal; Central: Kampong Thom, Kampong Chhnang; North-east: Steung Treng; North: Preah Vihear

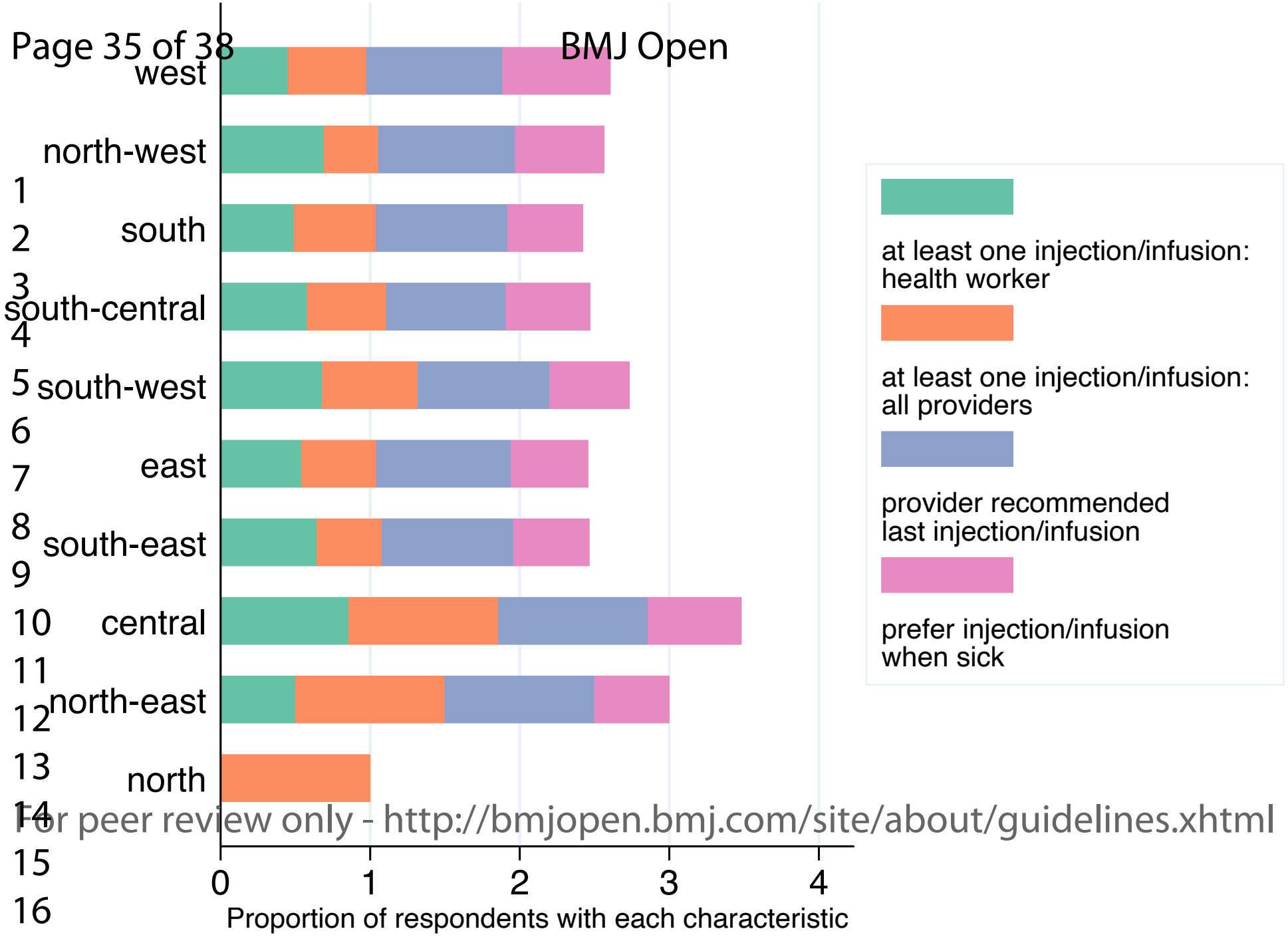
Caption: Figure 3. Injection and infusion use among study participants by geographic distribution.



Source: data from the 2017 Medical Injection Study (N=500), Cambodia



Source: data from the 2017 Medical Injection Study (n=500), Cambodia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Section in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract/Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background/Paragraph 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods/Study design and setting subheading/Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods/Study design and setting subheading/Page 6
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods/ Study design and setting and Inclusion and exclusion criteria/Page 6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods/Definition and classification subheading/Page 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods/Medical history and behavioural assessment/page 7
Bias	9	Describe any efforts to address potential sources of bias	Discussion/Page 15-16
Study size	10	Explain how the study size was arrived at	Methods/Study design and setting subheading/Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Results/Page 9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Method/Statistical analysis subheading/Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	Missingness occurred in less than 10% across the majority of

	variables (except income).
(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods/Study design, sampling and recruitment subheading/Page 5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Result/Page 7-8
		(b) Indicate number of participants with missing data for each variable of interest	Result/Page 8
		Cross-sectional study—Report numbers of outcome events or summary measures	Result/Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results/Page 13
		(*b*) Report category boundaries when continuous variables were categorized	Result/Page 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion/ Paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion/Page 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion/Paragraph 5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding/Page 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Medical injection and infusion practices among HIV-seronegative people and people living with HIV: a behavioural survey of ten HIV testing and opportunistic infections/antiretroviral therapy sites in Cambodia

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Medical injection and infusion practices among HIV-seronegative people and people living with HIV: a behavioural survey of ten HIV testing and opportunistic infections/antiretroviral therapy sites in Cambodia

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Keywords: injection, PLWH, unsafe injection, HIV, injection prevalence, injection practices

Abstract

Objectives: In late 2014, an HIV outbreak occurred in rural Cambodia among villagers who received medical injections from unlicensed medical providers, justifying the need to assess medical injection practices among those who are at risk of acquiring and/or transmitting HIV. This study examined medical injection/infusion behaviours among people living with HIV (PLWH) and those who were HIV-negative in Cambodia. These behaviours should be properly assessed, especially among PLWH, as their prevalence might influence a future risk of other outbreaks.

Design: A cross-sectional survey was conducted in order to examine injection behaviours and estimate injection prevalence and rates by HIV status. Unsafe injections/infusions were those received from village providers who do not work at a health centre or hospital, or traditional providers at participant's (self-injection included) or provider's home. Logistic regression was performed to examine the relationship between unsafe injection/infusion and HIV, adjusting for sex, age, education, occupation, residence location, and other risk factors.

Setting: The survey was conducted in 10 HIV testing and treatment hospitals/clinics across selected provinces in Cambodia, from February to March, 2017.

Participants: A total number of 500 volunteers participated in the survey, 250 PLWH and 250 HIV-negative individuals.

Outcome measures: Measures of injection prevalence and other risk behaviour were based on self-reports.

Results: Both groups of participants reported similar past year's injection/infusion use, 47% (*n*=66) among PLWH and 54% (*n*=110) HIV-negative participants (*P*=.24). However, 15% (*n*=11) of PLWH reported having received unsafe last injection compared to only 7% (*n*=11) of HIV-negative participants. In logistic regression, this association remained numerically positive, but was not statistically significant (adjusted odds ratio 1.84 [95% CI: 0.71-4.80]).

Conclusions: The inclination for medical injections and infusions (unsafe at times) among PLWH and the general population in Cambodia was common and could possibly represent yet another opportunity for parenteral transmission outbreak.

Strengths and limitations of this study

- By accounting for the types of facilities at which injections and infusions were carried out, as we have done in our study, we were able to ascertain that the outcome of the study

(the extent to which these injections/infusions could be interpreted as safe or unsafe) was measured reasonably accurately.

- One of the biggest issues in any cross-sectional studies is reverse causation; however, this was highly unlikely in our study.
- Medical injection and infusion practices were assessed through self-reports, which could lead to bias.
- In order to have a complete understanding of the injection and infusion practices, the prescription tendencies of care providers should have also been assessed, but our work was only able to assess these practices among PLWH and those who were HIV-negative across the 10 selected study sites.

Introduction

The World Health Organization (WHO) considered over or unnecessary use of injections as unsafe injection practices, alongside the use of unsafe methods for injection, such as reusing syringe and needles [1, 2]. In some parts of the world, particularly in low- and middle-income countries (LMICs), this common medical procedure is being performed daily using unsafe (yet

avoidable) injection practices which put both PLWH and communities at risk of bloodborne pathogen transmission [1-5]. In late 2014, a rural community in Cambodia had a large outbreak of human immunodeficiency virus (HIV) when an unlicensed medical practitioner infected 242 villagers aged between 2 and 89 years through his use of contaminated injection equipment [6, 7]. In early 2018, another two HIV outbreaks linked with unsafe injection practices occurred in India and Pakistan [3]. In Iran, the behavioural survey among people who inject drugs (PWID) demonstrated a positive correlation between risky and unsafe injection use and the prevalence of HIV [8]. These incidents and reports demonstrated the ongoing risk of outbreaks related to unsafe medical injection practices in many parts of the world. Additionally, a review article on injection practices worldwide published in 2000 reckoned that many injections are unsafe and unnecessary and that the region with the highest unsafe practice (reuse of injection materials) was indeed in Southeast Asia [9].

In Cambodia, private health care providers are commonly sought for care. Although many of them are public healthcare workers who practice privately during off-working hours, there are also providers, mainly in rural areas, who are unlicensed private practitioners from whom the community seeks medical care including (but not limited) to injections and infusions.

This is not uncommon in some parts of LMICs in which a person without proper training or education in administering certain medical procedures provides medical injections [4].

The last Cambodia Demographic and Health Survey (Cambodia DHS 2014) assessed injection practices as part of their behavioural survey among the general population. According to their report, the prevalence of medical injection (having had any medical injections from health worker in the past 12 months) among the Cambodian population aged 15-49 was approximately 35% (or 37% and 27% among women and men, respectively) [10]. Previous studies on injection use and safety practices (including the DHS survey) in Cambodia usually focused on the general population [11]. Moreover, although according to the 2019 review on injection practices using the DHS data from 40 countries reported reduced numbers of unsafe injections in 81% of the countries, the data used was from 2011-2015 [12], no other assessment had been reported since then. Until the present work, these behavioural risk factors have not been studied among people living with HIV (PLWH), despite the fact that the risk of getting or transmitting bloodborne pathogens among this population are heavily shaped by these behaviours. We hypothesized that PLWH might be seeking or receiving more medical injections (likely unnecessary and unsafe) than the general population for several reasons. First, being in

regular care gives PLWH more opportunities to get diagnosed with various medical conditions and receive treatments. Second, PLWH often suffer from significantly more co-morbidities, such as age-related non-communicable diseases and mental or neurological disorders, than the general population [13, 14]. For these reasons, PLWH might be in greater need of medical treatments, such as injections, than the general population.

Ever since the 2014 HIV outbreak in Roka village, there have been no other studies assessing injection behaviours among PLWH elsewhere; and the Cambodia DHS reported only medical injections given by health care workers. Without assessment of injection and infusion practices in people who are at risk of transmitting and acquiring HIV, it is challenging for public health professionals to advise or prepare public health measures which are both appropriate and efficient to address unsafe injection practices. Our study aims to primarily characterize injection practices among PLWH and those who were HIV-negative and determine whether the first group were more likely to seek unsafe or unnecessary medical injections.

Although when considering unsafe medical injections, people usually refer to used syringes and needles, we considered (in this paper) injections provided by unlicensed (medical) practitioners unsafe as well. Understanding these injection seeking behaviours among this

population is helpful for planning necessary public health measures as well as improving access to formal healthcare facilities.

Methods

Study design and setting

We conducted a cross-sectional study among PLWH (n=250) who came to receive their HIV treatment care and those who came to have HIV testing and had a negative result (n=250) at 10 selected HIV clinics in five provinces and the capital city (Phnom Penh) of Cambodia, from early February to the end of March 2017. The sample size of 250 per group was calculated to provide 90% power to test the hypothesis using a two-sample comparison of proportions where the first proportion was set at 20% of injection use (HIV-negative participants) and the second proportion was set at 35% (HIV-positive participants). In Cambodia, HIV voluntary testing sites in Cambodia and HIV/AIDS treatment and care clinics (called Opportunistic Infections/Antiretroviral Therapy (OI/ART) sites) and are under the supervision of the National Centre for HIV/AIDS, Dermatology and STD (NCHADS); there are around 52 of them across Cambodia at the time of the study.

A two-stage sampling approach was employed for participant selection. We selected 10 sites and out of the 52 sites with joint testing/OI/ART services (meaning those with both testing and OI/ART services) using probability-proportional-to-size (PPS) method. Then, from each of these 10 sites, we consecutively sampled 25 PLWH who came for their regular clinic visit or pharmacy refill. In a similar manner, HIV-negative individuals who came to each selected sites for HIV testing who got a negative result were approached for recruitment (25 per site).

Inclusion and exclusion criteria

Both PLWH and HIV-negative participants were eligible if they were at least 18 years old and were willing and able to provide written informed consent to take part in the study on the data collection day. Excluded were individuals who were not willing or able to complete the questionnaire, had undetermined test result, or presented any other condition that, in the opinion of the research or local healthcare staff, would preclude informed consent.

Medical history and behavioural assessment

HIV-specific factors (e.g. HIV status, date of HIV test, WHO disease stage, etc.) were obtained from linkage with the NCHADS database. Behavioural data were collected using a Computer-Assisted Person Interview (CAPI) technique, administered via tablet and questions were guided

by the literature. Participants were asked to report on socio-demographic factors, such as date of birth, sex, education, marital status, occupation, general location of residence (village, community, district and province) and a wide range of behavioural factors including history of illicit injection drug use (IDU), alcohol and tobacco use and informal medical injection/infusion use (frequency, and type of provider).

Definition and classification

The outcome of interest, unsafe medical injection (binary outcome), was defined as having received the last injection or infusion (within the past year) from village providers who do not work at a health centre or hospital, from traditional providers, or by self-injection (other than diabetic medication) either at their own home or at the provider's home. In Cambodia and especially in rural areas, these health workers might also provide some basic medical services (including injections and infusions) at their patient's home or in private hospitals/clinics. Therefore, regardless of where the PLWH received the injections, as long as they were provided by the providers who worked at a hospital or health centre, we considered these injections safe. Both intravenous and intramuscular injections were included in the questionnaire and reporting.

The prevalence of medical injections included those who reported at least one injection or infusion (over the past year), but excluded vaccinations, non-medical injections and rare medical injections such as transfusion.

The HIV status was not assessed by the study team, those with known HIV-positive or HIV-negative results were informed of the present study and referred by their care providers to the study team for further information on the study and consent process. We had no access to their HIV test or result.

Other risk behavioural assessment (alcohol and tobacco use, informal medical injection/infusion use, etc.) was based on participants' self-report.

Statistical analysis

We computed percentages and means of the key characteristics by HIV status. We calculated the prevalence of having had at least one medical injection from health workers and from all provider types over the past year among the participants (by their HIV status). Chi-square and Fishers' exact tests were performed for categorical variables and t-tests for continuous variables. Next, the average number of past year's medical injections from each type of providers by HIV status was also computed and we reported the *P* derived from Poisson regression. Finally, to

examine the relationship between unsafe medical injection practices and HIV status, we performed logistic regression, adjusting for sex, age, education, occupation, residence location, injection preference and other risk factors. Confounding variables were based on prior knowledge and literature review on similar work previously conducted [12, 15, 16]. All analyses were done in STATA 14.

Patient and public involvement

The PLWH, care givers and those who sought HIV testing but were negative participated in the data collection of the study. Preliminary results of the study had been presented at the University of Health Sciences at the 2018 Scientific Days among invited care givers, students and other invited guests and researchers.

Results

We presented key characteristics by HIV status in Table 1. The socio-demographic factors are vastly different between the two groups in terms of age, marital status, educational background and occupation. PLWH appeared to be much older – mean age was 43 years (standard deviation [SD] 9), of a lower educational background and married, while the majority of HIV-negative participants were younger – mean age was 31 years (SD 11), more educated and single.

However, both groups were comparable in terms of their sex, income and residence location distribution. Female participants accounted for about 66% (*n*=164) of PLWH and 71% (*n*=177) of those uninfected. The majority of participants from both groups were from the provinces, 91% (*n*=227) among PLWH and 93% (*n*=231) among the uninfected.

Table 1. Key characteristics of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Socio-demographics	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Gender					
Female	164	65.6	177	70.8	.21
Male	86	34.4	73	29.2	
Age[a] (Mean, SD)	(43.1, 9.0)		(30.6, 10.7)		<.001
Marital status					
Single	15	6.0	87	34.8	<.001
Married	140	56.0	141	56.4	
Divorced	41	16.4	15	6.0	
Widowed	54	21.6	7	2.8	
Education					
Secondary or higher	104	41.6	163	65.2	<.001
Primary or less	146	58.4	87	34.8	
Occupation[a]					
Unemployed	81	32.7	126	50.8	<.001
Self-employed/farmers	95	38.3	70	28.2	
Employed	72	29.0	52	21.0	
Household annual income[a,b] (USD)					
> 3,000	40	22.9	44	22.8	.48

1,800-3,000	45	25.7	42	21.8	
1,001-1,800	39	22.3	56	29.0	
≤ 1,000	51	29.1	51	26.4	
Current address[a]					
Province	227	90.8	231	92.8	.42
Phnom Penh (capital city)	23	9.2	18	7.2	
Other behavioural risk factors[c]					
Smoke monthly or more often	30	12.0	13	5.2	<.01
Feeling drunk at least once a month	45	18.0	63	25.2	.05
Contact with syringe and needle at workplace	8	3.2	36	15.5	<.01
Had at least one hospitalization	42	23.5	87	49.2	<.001

SD, standard deviation.

[a]Missing (HIV+, HIV-, respectively): age (*n*=5, *n*=5); occupation (*n*=2, *n*=2); current address (*n*=0, *n*=1).

[b]The categories for household income used quartiles to assure sufficient numbers in each category.

[c]Self-report over the past year.

Injection/infusion use

Injection and infusion practices are described in Table 2. We found that the average annual number of injection/infusion from health workers was about three and four injections per person among PLWH and those who were HIV-negative, respectively (*P*<.001). The prevalence of any medical injection/infusion provided by health workers over the past year was higher among HIV-uninfected participants, 72% (*n*=153), compared to 40% (*n*=61) among those who were HIV-positive (*P*<.001). However, the prevalence of past year's injection/infusion from all providers

between the two groups were comparable, 47% (*n*=66) among PLWH and 54% (*n*=110) among those uninfected (*P*=.24).

Table 2. Injection and infusion seeking behaviours of study participants by HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Injection and infusion practices	HIV+ (*n*=250)		HIV- (*n*=250)		*P*
	n	%	*n*	%	
Injection and infusion received					
Last injection/infusion within past year					
Given by relative/acquainted provider	51	23.0	50	22.8	.97
Recommended by provider	54	85.7	131	90.3	.33
Given at public hospital	35	44.9	97	54.5	.16
Given at private hospital/clinic	29	53.7	58	46.0	.35
Given at their own home	16	31.4	24	21.2	.16
Number of injections/infusions within past year					
More than a year ago	107	67.7	144	66.4	.78
From health workers (mean, SD)		(3.2, 7.5)		(4.3, 7.1)	<.001
From all providers (mean, SD)		(3.5, 7.1)		(4.4, 7.8)	<.001
At least one - health worker	61	40.4	153	72.5	<.001
At least one - all providers	66	47.5	110	53.9	.24
Prefer injection to other treatments[a]	124	49.6	145	58.0	.06
Injection and infusion safety					
Last injection within past year					
Unsafe[b] last injection	11	15.5	11	7.3	.06
Provider did not use new, unopened syringe/needle	0	0.0	6	3.8	.19
Last injection within past year					
Unsafe[b] last infusion	10	13.5	13	10.5	.52

Provider did not use new, unopened syringe/needle	0	0.0	3	2.5	.55

SD, standard deviation.

[a]The questions on this preference pertain to several tracer conditions (in which case medical injections are clearly unnecessary).

[b]Administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

When asked about the last injection/infusion they received within the past year, PLWH were more likely to report having received their last one(s) at a private hospital/clinic, 54 % (*n*=29), or at their own home, 31% (*n*=16), compared to a 46% (*n*=58) and 21% (*n*=24), respectively, reported by their HIV-negative counterparts. HIV-negative participants were more likely to have received their last injection/infusion at a public hospital, 54% (*n*=97), as opposed to 45% (*n*=35) of PLWH (*P*=.16). Figure 1 broke down last injection and infusion by facility types in more details. [insert Figure 1 here]

Regardless of HIV status, public and private sector accounted for the majority of medical injection and infusion received. Although none of our PLWH reported having received their last injection or infusion at traditional healer's home, about one-fourth of them reported having received their last injection (15% (*n*=9)) and infusion (22% (*n*=14)) at their own home.

A large number of participants from both groups, 50% (n=124) of PLWH and 58% (n=145) of those uninfected, reported that they preferred injection/infusion to other forms of treatment when sick (P=.06). Moreover, more than 60% of participants from both groups indicated that they had actually received more injections the past year than previous year. Similarly, over 80% of both PLWH and HIV-negative participants reported that their last injection was in fact recommended by their care provider.

Injection/infusion safety practices

About 4% (n=6) of HIV-negative participants reported that the provider for their last injection did not use a new, unopened package of syringe and needles while none of PLWH reported this practice (P=.06). Although the average annual injection/infusion rates from all provider types (including health workers) were slightly lower among PLWH (three injections per person) compared with those who were HIV-negative (four injections per person) (P<.001), we observed a slightly larger proportion of PLWH reported an unsafe last injection within the past year, 15% (n=11) vs 7% (n=11) reported by those who were HIV-negative (P=.06). Likewise, 13% (n=10) of PLWH reported an unsafe last infusion within the past year, compared to 10% (n=13) of HIV-uninfected participants (P=.52). Regardless of whether they live in the provinces or the capital

city “Phnom Penh” (Figure 2), the majority of participants from both groups reported their provider recommended their last injection/infusion and more HIV-negative participants than PLWH received their last injection/infusion from health workers. [insert Figure 2 here] In figure 3, overall, we saw similar patterns across the country, except provinces in the central and north-eastern parts of Cambodia where injection/infusion use appeared the highest. [insert Figure 3 here]

Association between unsafe medical injection/infusion and HIV

Table 3 presents the crude odds ratio (cOR), adjusted OR (aOR) and the 95% CIs of the relationship between unsafe last medical injection and HIV status. Before adjustment, only sex, occupation and presence of two or more risk behaviours were associated with having had unsafe last injection or infusion (Table 3). The association between unsafe medical injection/infusion and HIV status was numerically positive but was not statistically significant (cOR=1.45 [95% CI: 0.70-3.00]). After adjusting for other covariates, the aOR was 1.84 (95% CI: 0.71-4.80), remaining statistically non-significant.

Table 3. Association between getting unsafe medical injection and HIV status, Informal Medical Injection Study (*n*=500), Cambodia, 2017

Outcome: unsafe injection/infusion	Crude OR	95 % CI	Adjusted OR[a]	95 % CI
HIV + (ref. HIV-)	1.45	0.70-3.00	1.84	0.71-4.80
Male (ref. female)	2.17	1.03-4.57	2.37	1.00-5.62
Age	1.00	0.97-1.03	0.98	0.94-1.02
Education (ref. secondary or higher)				
Primary or less	0.70	0.33-1.46	0.96	0.41-2.23
Occupation (ref. unemployed)				
Farmers and self-employed	0.91	0.41-2.01	0.83	0.36-1.91
Employed	0.48	0.17-1.36	0.59	0.20-1.72
Current address in Phnom Penh (ref. in provinces)	1.18	0.33-4.23	1.02	0.27-3.88
Prefer injection or infusion when sick (ref. no preference)	0.59	0.29-1.21	0.66	0.32-1.40
Had at least two risk behaviours[b]	0.67	0.19-2.33	0.47	0.13-1.75

OR, odds ratio. CI, confidence interval.

Unsafe injection/infusion: last injection/infusion within the past year administered at participant's or provider's home by village providers who do not work at health centre or hospital, traditional providers, or self-injection.

[a]Adjusted for gender, age, education, occupation, residence location, injection or infusion preference, and presence of two or more risk behaviours.

[b]Combination of risk behaviours include: one or more hospitalization, contact with syringe and needle, smoking monthly or more often and feeling drunk monthly or more often in the past year.

Discussion

In our study, we found a high prevalence of medical injections (having had any medical injections in the past year from health workers) among the study participants in general (almost 60%), but PLWH were more likely to have had unsafe last injection or infusion (having received

their last injection from informal providers), compared with those who were HIV-negative. Regardless of the reasons for medical injections (with few exceptions), this practice is very common, and should be addressed, whether it is the PLWH's false beliefs that injectable drugs work better than oral ones for certain medical conditions or the tendency to over-prescribe these injectables.

According to the 2014 CDHS, there were great variations of injection prevalence (administered by health workers) ranging from 12% to 45% and the average annual number of injections is one to two per person [10]. We found a much higher prevalence among our study sample, our results were more in line with an article published in 2004 by Vong et al. that also looked at medical injections in Cambodia found 40% of medical injection prevalence and average number of injection (over the past six months) of 5.9 per person [11]. This is, in fact, consistent with findings from a review paper published in 2016 which found that the 12-month medical injection prevalence ranged from 30% to 68% across studies conducted in South Asia [17]. It should be noted that both the 2004 study and the 2014 DHS examined the injection practices among the general population outside of HIV setting (treatment or testing), and that it was unclear in the CDHS if infusions were also counted for their injection reporting. Our study

grouped infusions with injections when reporting prevalence, similar to the 2004 study (Vong et al), but our study reported the injection behaviours over the past year instead of over six months like Vong et al did. Several other factors such as limited education, tendency of prescribers to recommend and participant's personal preference of injection and the study population could be responsible for higher rates being reported in our study compared with others. However, these seemed consistent with a recently published paper which found high Hepatitis C prevalence among Cambodian population that is likely due to medical injections [16]. High prevalence of medical injection (ranging from 30% to 68%) had also been reported across studies conducted in south Asia [17]. Results from Kenyan survey published in 2016 suggested a positive association between HIV and those who reported having received injection in the last 12 months [18]. Although it should be noted that the Kenyan study only reported injections from care providers and not traditional healers or other types of providers.

The older mean age of our PLWH might also explain the high prevalence of medical injections among them. Because PLWH in the study were on average older, they could be sicker and, therefore, sought more medical procedures including injections. The age distribution of

PLWH in Cambodia is actually weighed down by those who had been infected in the early 90's; and fewer people had become infected since 2000 [19].

The study should be interpreted with consideration to a number of limitations. Our assessment of the outcome was based on self-recall which could result in misclassification of the outcome measured. However, we have limited recalls to the past 12 months and reckon that to avoid capturing only certain fluctuations, a recall over 12 months appeared reasonable. Multiple studies used a 12-month timeframe for estimating prevalence (although they mainly assessed drug use) [20, 21]. Medical injections are generally also uncommon events, we, therefore, expected this misclassification, if any, to be minimal. By design, the outcome-exposure relationship in our study is obscure. However, our PLWH were mostly prevalent cases and older – 92% of PLWH had been diagnosed more than two years prior (result not shown) – who were most likely got infected during the early 90's through unsafe sexual behaviours and not through unsafe injection practices. Consecutive sampling among PLWH and HIV-negative participants could also affect our internal validity; however, the process of scheduling the appointment at each selected facility for both groups is already in itself a random process. There were also patients who just dropped in. In other words, there is no reason to believe that participants might

differ in terms of injection use between the time of our data collection and any other time. This does, however, limit our own study findings' generalizability in a way that they might be applicable to only PLWH and HIV-negative population who come to receive care and seek HIV testing at the selected clinics and hospitals.

The strengths of our study included the fact that we accounted for not only both the provider of the last injection or infusion received within the past year, but also the facility at which these medical procedures were given. The combination of both provider and facility types should be able to capture better the safety aspect of medical injection/infusion. It should be noted that private facilities in Cambodia are generally considered "formal" providers. Our work is one of the few studies which examined injection practices among PLWH over the past decade. Another study was conducted in 2016 (a year prior to when our study had started) [16]. Regardless, additional studies are necessary in order to confirm the findings from our work and understand the true underlying injection practices among PLWH.

Implications on policy and practices

Better access to medical care is a challenge particularly in rural parts of Cambodia. Our findings suggest the need to pull resources toward universal health coverage and educational programs on

safe medical injection practices. Resources are always limited in LMICs; therefore, support development partners play important roles in addressing these health needs. Besides these, other important educational programs or activities directed at both PLWH and HIV-negative population are also deemed beneficial. Care providers could be important role models in enforcing correct practices of medical injection, particularly counsellors in the setting of HIV/AIDS care here could also play that role. Several HIV health facilities offered a digital platform of communication (Telegram group chat and Facebook Messenger chats are the most commonly used), on a voluntary basis, to PLWH and care providers to interact with one another on their HIV-related issues. These platforms could also be used as forums for communicating correct safe injection practices to them. Of course, these types of programs would need further investigations in order to understand the population whom we could reach with these digital platforms. Regardless of HIV status, these educational programs and activities should be widely inclusive because use of medical injection seemed to be very common among both PLWH and those who were HIV-negative. Nevertheless, further investigations on the injection practices (among care provider) and the benefits of the aforementioned educational platforms would

provide a more complete picture of the practices of medical injections in Cambodia and evidence as to whether they are beneficial or if additional programs are to be put in place.

Conclusions

The majority of the Cambodian population, including those who are living with HIV, regard medical injections and infusions as a symbol for optimal medical care. Although on average, they might have received slightly fewer number of annual injections, PLWH were as likely to have received unsafe last injection/infusion within the past year as those who were HIV-negative. This practice poses harms to themselves as well as their community and needs to be addressed among all stakeholders including providers who are able to prescribe medical injections including infusions. Our findings suggested the need to evaluate and reinforce safe injection practices among health workers for a complete assessment and understanding of medical injection education and practices in the health system.

Contributors

KS conducted literature search and data analysis, interpreted results, wrote the manuscript, and created figures. KK and KV conducted literature search, designed the study, collected the data and guided data interpretation. D.K. conducted literature search and collected the data. VS and

PG conceptualized the study, conducted literature search, interpreted results and guided data interpretation. All authors provided critical feedback and shaped the final manuscript.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval

Written consent was obtained from each participant before the enrolment and interview process. All interviews were conducted in a private room at the health centres/clinics. All instruments used for data collection were anonymous; no identifying information, such as name, address, telephone number, or date of birth was recorded. The HIV-related information, such as ART regimen and duration of HIV infection, were obtained from linking the patient's ART code to the national HIV database. The ART code for each patient is given by the HIV clinics once the PLWH are linked to

care and is used as their identifier instead of their name in the national database. After the dataset had been linked, the ART code had been removed for all participants. The study data was stored on a personal computer, keyword-protected. The study protocol was approved by the University of California Los Angeles Institutional Review Board (UCLA-IRB# 16-000876) and the National Ethics Committee for Human Research (NECHR) of Cambodia (NECHR# 320) in 2016.

References

1. World Health Organization. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health care settings. Geneva: World Health Organization, 2016.

2. World Health Organization. Injection Safety: Questions and Answers. 2016. https://www.who.int/infection-prevention/publications/is_questions-answers.pdf?ua=1 (July 2020, date last accessed).

3. Altaf A. Unsafe Injection Practices by Medical Practitioners in South Asia Associated with Hepatitis and HIV Outbreaks. J Infectiology 2018;1(2):1-3.

4. Gupta E, Bajpai M, Sharma P, Shah A, Sarin S. Unsafe injection practices: a potential weapon for the outbreak of blood borne viruses in the community. Ann Med Health Sci Res. 2013;3(2):177-81. Epub 2013/08/07. doi: 10.4103/2141-9248.113657. PubMed PMID: 23919185; PubMed Central PMCID: PMCPMC3728858.

5. World Health Organization. Make Smart Injection Choices: National Decision-Making for Safe and Appropriate Injections. 2017. https://www.who.int/infection-prevention/tools/injections/IS_medical-treatement_leaflet.pdf?ua=1 (July 2020, date last accessed).

6. Rouet F, Nouhin J, Zheng DP, Roche B, Black A, Prak S, et al. Massive Iatrogenic Outbreak of Human Immunodeficiency Virus Type 1 in Rural Cambodia, 2014-2015. Clin Infect Dis. 2018;66(11):1733-41. Epub 2017/12/07. doi: 10.1093/cid/cix1071. PubMed PMID: 29211835; PubMed Central PMCID: PMCPMC5963970.

7. Saphonn V, Fujita M, Samreth S, Chan S, Rouet F, Khol V, et al. Cluster of HIV Infections Associated With Unsafe Injection Practices in a Rural Village in Cambodia. J Acquir Immune Defic Syndr. 2017;75(3):e82-e6. Epub 2017/01/28. doi: 10.1097/QAI.0000000000001295. PubMed PMID: 28129255; PubMed Central PMCID: PMCPMC6814627.

8. Esmaeili A, Shokoohi M, Danesh A, Sharifi H, Karamouzian M, Haghdoost A, et al. Dual Unsafe Injection and Sexual Behaviors for HIV Infection Among People Who Inject Drugs in Iran. AIDS and behavior. 2019;23(6):1594-603. Epub 2018/11/22. doi: 10.1007/s10461-018-2345-5. PubMed PMID: 30460664; PubMed Central PMCID: PMCPMC6527484.

9. Hutin YJFH, Anja M; Armstrong, Gregory L. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. Bmj. 2003. doi: 10.1136/bmj.327.7423.1075.

10. National Institute of Statistics; Directorate General for Health; and ICF International. Cambodia Demographic and Health Survey 2014. Phnom Penh, Cambodia, and Rockville, Maryland, USA: National Institute of Statistics; Directorate General for Health; and ICF International; 2015.

11. Vong S, Perz JF, Sok S, Som S, Goldstein S, Hutin Y, et al. Rapid assessment of injection practices in Cambodia, 2002. BMC public health. 2005;5:56. Epub 2005/06/03. doi: 10.1186/1471-2458-5-56. PubMed PMID: 15929800; PubMed Central PMCID: PMCPMC1173117.

12. Hayashi T, Hutin YJ, Bulterys M, Altaf A, Allegranzi B. Injection practices in 2011-2015: a review using data from the demographic and health surveys (DHS). BMC Health Serv Res. 2019;19(1):600. Epub 2019/08/29. doi: 10.1186/s12913-019-4366-9. PubMed PMID: 31455315; PubMed Central PMCID: PMCPMC6712605.

13. amFAR. HIV and Comorbidities: The Foundation for AIDS Research (amFAR); 2020. https://www.amfar.org/hiv-and-comorbidities/ (July 2020, date last accessed).

14. World Health Organization. Chronic comorbidities and coinfections in PLHIV. https://www.who.int/hiv/topics/comorbidities/about/en/ (July 2020, date last accessed).

15. Janjua NZ, Akhtar S, Hutin YJ. Injection use in two districts of Pakistan: implications for disease prevention. Int J Qual Health Care. 2005;17(5):401-8. Epub 2005/05/11. doi: 10.1093/intqhc/mzi048. PubMed PMID: 15883127.

16. Pheng P, Meyer L, Segeral O, Chea P, Yi S, Tuot S, et al. Hepatitis C seroprevalence among people living with HIV/AIDS and pregnant women in four provinces in Cambodia: an integrated bio-behavioral survey. BMC Infect Dis. 2022;22(1):177. Epub 2022/02/24. doi: 10.1186/s12879-022-07163-2. PubMed PMID: 35193496; PubMed Central PMCID: PMCPMC8862396.

17. Janjua NZ, Butt ZA, Mahmood B, Altaf A. Towards safe injection practices for prevention of hepatitis C transmission in South Asia: Challenges and progress. World J Gastroenterol. 2016;22(25):5837-52. Epub 2016/07/20. doi: 10.3748/wjg.v22.i25.5837. PubMed PMID: 27433097; PubMed Central PMCID: PMCPMC4932219.

18. Kimani D, Kamau R, Ssempijja V, Robinson K, Oluoch T, Njeru M, et al. Medical injection use among adults and adolescents aged 15 to 64 years in Kenya: results from a national survey. J Acquir Immune Defic Syndr. 2014;66 Suppl 1:S57-65. Epub 2014/01/15. doi: 10.1097/QAI.0000000000000106. PubMed PMID: 24413041; PubMed Central PMCID: PMCPMC4794988.

19. Ministry of Health/National Center for HIV/AIDS, Dermatology and STDs (MOH/NCHADS). Annual Report 2016. National Center for HIV/AIDS, Dermatology and STDs. 2017.

20. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. Lancet Glob Health. 2017;5(12):e1192-e207. Epub 2017/10/28. doi: 10.1016/S2214-109X(17)30375-3. PubMed PMID: 29074409; PubMed Central PMCID: PMCPMC5683738.

21. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Methodological Guidelines to Estimate the Prevalence of Problem Drug Use on the Local Level. Lisbon: EMCDDA, December 1999.

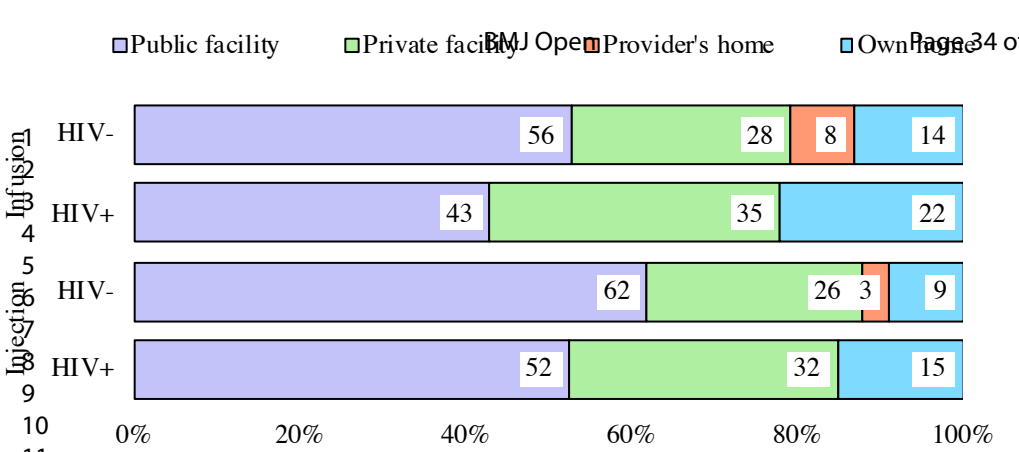
Figure titles and legends

Figure 1. Injection and infusion use among study participants by types of facility

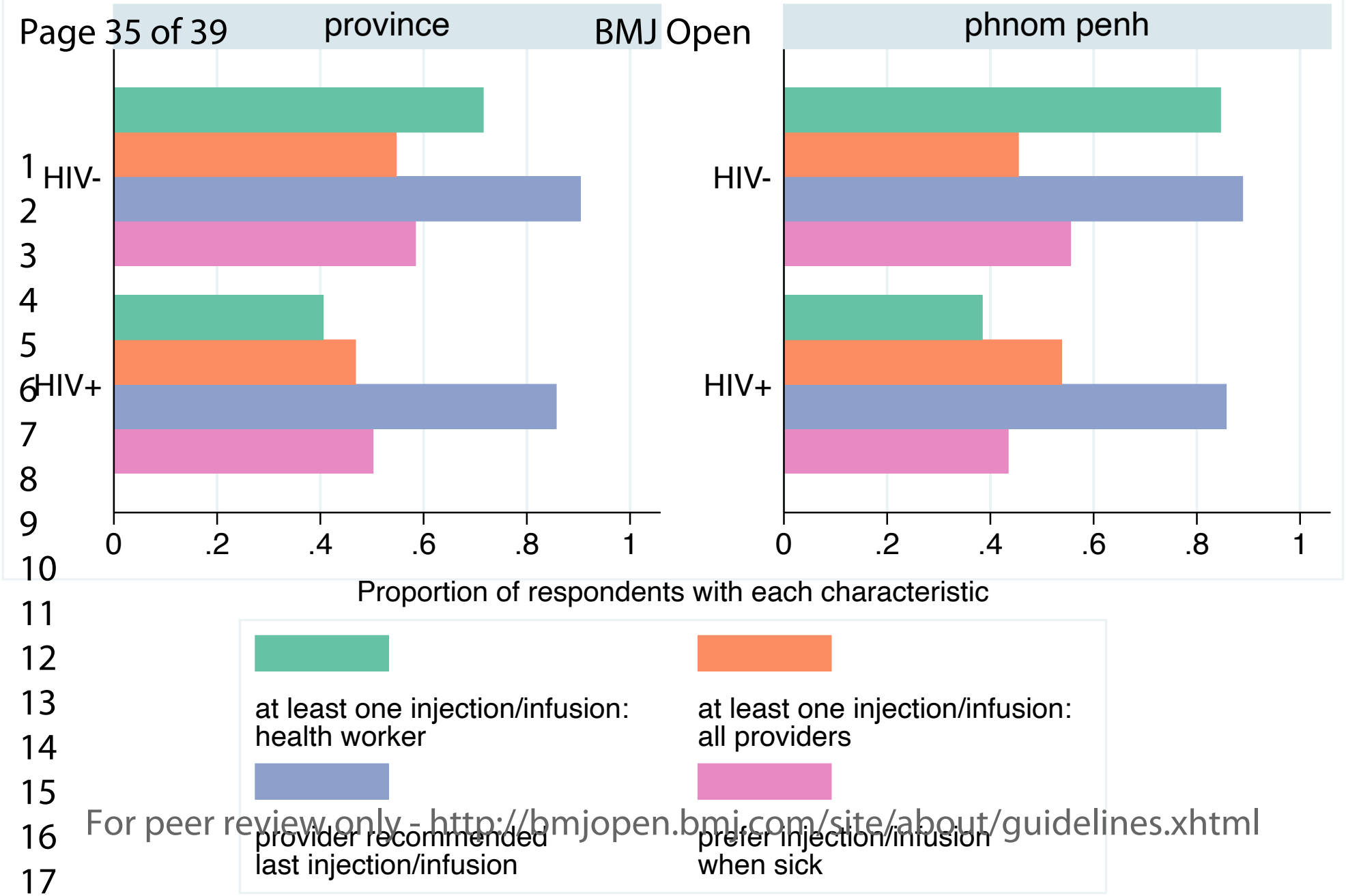
Figure 2. Injection and infusion use among study participants by residence location – Phnom Penh vs provinces

Figure 3. Injection and infusion use among study participants by geographic distribution

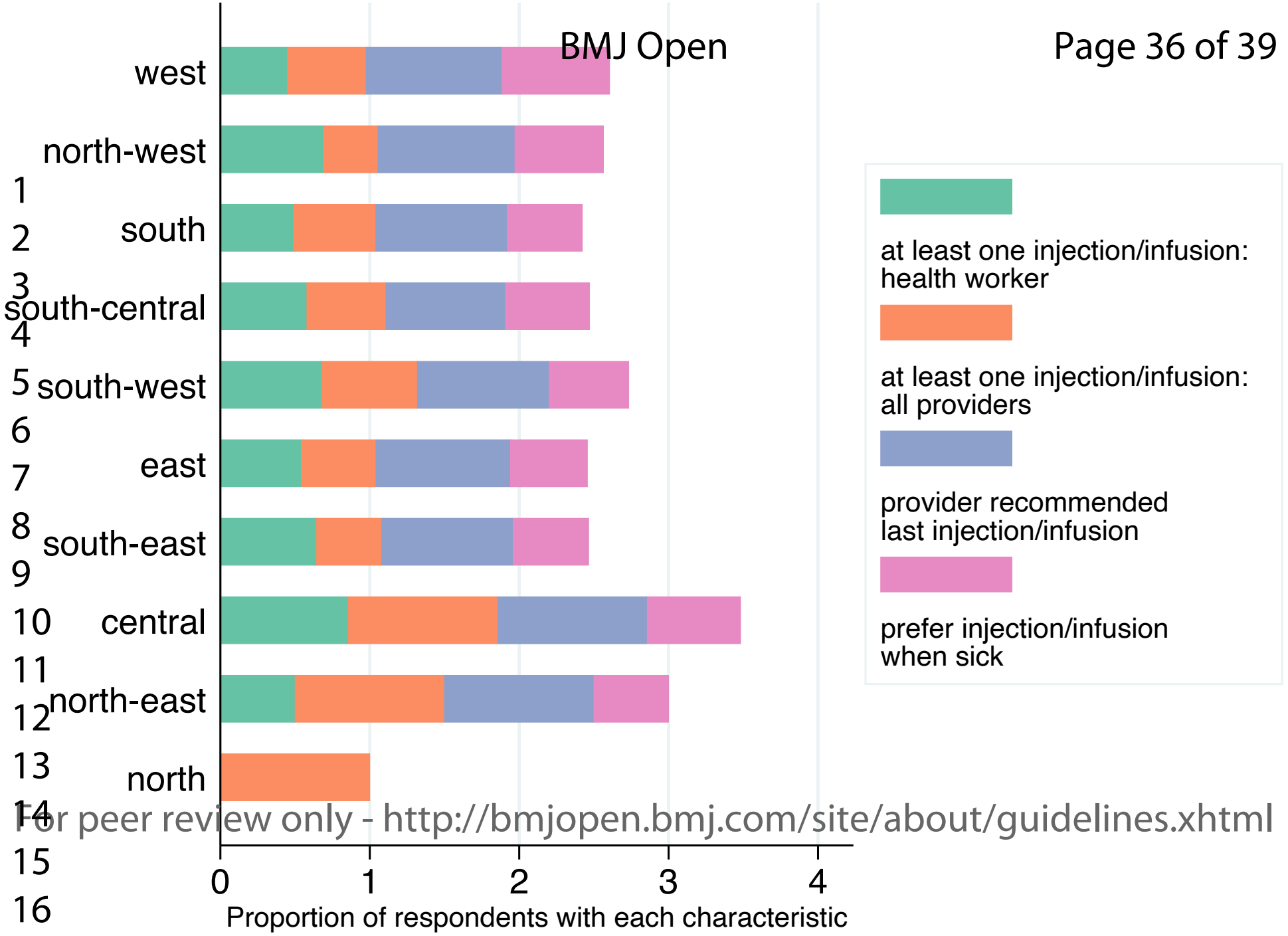
Note: West: Pursat; North-west: Siem Reap, Battambang, Odor Meanchey, Banteay Meanchey; South: Takeo, Kampot, Prey Veng; South-central: Phnom Penh, Kampong Speu; South-west: Sihanoukville, Koh Kong; East: Kratie, Mondulkiri; South-east: Tbong Khmum, Svay Rieng, Kampong Cham, Kandal; Central: Kampong Thom, Kampong Chhnang; North-east: Steung Treng; North: Preah Vihear



Source: data from the 2017 Medical Injection Study (N=500), Cambodia



Source: data from the 2017 Medical Injection Study (n=500), Cambodia



STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Section in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Abstract/Methods
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background
Objectives	3	State specific objectives, including any prespecified hypotheses	Background/Paragraph 5
Methods			
Study design	4	Present key elements of study design early in the paper	Methods/Study design and setting subheading/Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods/Study design and setting subheading/Page 6
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Methods/ Study design and setting and Inclusion and exclusion criteria/Page 6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods/Definition and classification subheading/Page 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods/Medical history and behavioural assessment/page 7
Bias	9	Describe any efforts to address potential sources of bias	Discussion/Page 15-16
Study size	10	Explain how the study size was arrived at	Methods/Study design and setting subheading/Page 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Results/Page 9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Method/Statistical analysis subheading/Page 8
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	Missingness occurred in less than 10% across the majority of

	variables (except income).
(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
(*e*) Describe any sensitivity analyses	N/A

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Methods/Study design, sampling and recruitment subheading/Page 5
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Result/Page 7-8
		(b) Indicate number of participants with missing data for each variable of interest	Result/Page 8
		Cross-sectional study—Report numbers of outcome events or summary measures	Result/Page 9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results/Page 13
		(*b*) Report category boundaries when continuous variables were categorized	Result/Page 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion/ Paragraph 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion/Page 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion/Paragraph 5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding/Page 19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at

http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.