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RESEARCH NOTE

Low and stable rates of antenatal syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study [version 1; peer review: 1 approved, 1 approved with reservations]

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V1 First published: 10 Jun 2014, 3:123
<https://doi.org/10.12688/f1000research.4190.1>

Latest published: 15 May 2015, 3:123
<https://doi.org/10.12688/f1000research.4190.2>

Abstract

Objective: The antenatal prevalence of syphilis and HIV/AIDS in migrants and refugees is poorly documented. The aim of this study was to audit the first year of routine syphilis screening in migrant and refugee women on the Thai Myanmar border.

Methods: From August 2012 to July 2013, 3600 pregnant women were screened for HIV (ELISA) and syphilis (VDRL with TPHA confirmation) at clinics along the Thai-Myanmar border.

Results: Seroprevalence for HIV 0.47% (95% CI 0.30-0.76) (17/3,599), and syphilis 0.39% (95% CI 0.23-0.65) (14/3,592), were low. Syphilis was significantly lower in refugees (0.07% 95% CI 0.01-0.38) (1/1,469), than in migrants (0.61% 95% CI 0.36-1.04) (13/2,123). The three active (VDRL $\geq$ 1:8 and TPHA reactive) syphilis cases with VDRL titres of 1:32 were easy to counsel and treat. Women with low VDRL titres ($>$ 75% were $<$ 1:8) and TPHA reactive results, in the absence of symptoms and both the woman and her husband having only one sexual partner in their lifetime, and the inability to determine the true cause of the positive results presented ethical difficulties for counsellors.

Conclusion: As HIV and syphilis testing becomes available in more and more settings, the potential impact of false positive results should be considered, especially in populations with low prevalence for these diseases. This uncertainty must be considered in order to counsel patients and partners accurately and safely about the results of these tests, without exposing women to increased risk for abuse or abandonment. Our findings highlight the complexities of counselling

Open Peer Review

Approval Status

	1	2
version 2		
(revision)		
15 May 2015
version 1
10 Jun 2014	view	view

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Any reports and responses or comments on the article can be found at the end of the article.

patients about these tests and the global need for more conclusive syphilis testing strategies.

Keywords

HIV syphilis pregnancy yaws refugees migrants Myanmar

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Competing interests: No competing interests were disclosed.

Grant information: This work was supported by a grant from the Wellcome Trust of Great Britain for the Thailand/Laos Major Overseas Programme 2010-2015 (Grant B9RTOZ2) jointly awarded to MORU and LOMRU. The Shoklo Malaria Research Unit is part of the Wellcome Trust Mahidol University Oxford Tropical Medicine (MORU) Research Programme.

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How to cite this article: McGready R, Kang J, Watts I *et al.* **Low and stable rates of antenatal syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study [version 1; peer review: 1 approved, 1 approved with reservations]** F1000Research 2014, **3**:123 <https://doi.org/10.12688/f1000research.4190.1>

First published: 10 Jun 2014, **3**:123 <https://doi.org/10.12688/f1000research.4190.1>

Introduction

The global health impact of sexually transmitted infections (STIs) including HIV/AIDS and syphilis is well recognized¹. Both syphilis and HIV/AIDS pose major health risks in the developing world, impacting maternal and infant health due to vertical transmission via congenital infection and/or through breastfeeding². This is estimated to cause over 500,000 adverse pregnancy outcomes per year, including stillbirth and congenital infection¹. Displaced populations of migrants and refugees within developing regions are particularly vulnerable to disease although data on the prevalence of infection is scarce³.

The Tak province on the Thai-Myanmar border is home to a diverse population comprised of local Thai and members of Thailand's ethnic minorities as well as foreign migrant workers and refugees of multiple ethnicities from Myanmar⁴. Members of the Karen ethnic group represent a large proportion of the ethnic minority people from both countries. The estimated 2 million displaced Burmese living in Thailand³ are vulnerable to STIs and HIV/AIDS⁵, due to the lack of access to health services, poor education and low income^{3,5,6}. In 2005, we reported on cross sectional surveys of HIV and syphilis in pregnant refugee and migrant women from the Thai-Myanmar border which showed low rates of HIV (0.4%) and syphilis (0.4%)⁷. While HIV screening in pregnancy was routine since the cross sectional surveys syphilis screening was only introduced when funding became available. The aim of this study was to audit the first year of routine syphilis screening in the same population and reassess the trends in HIV rates.

Methods

Study site and population

The Shoklo Malaria Research Unit (SMRU) provides health services and conducts research of relevance to the local population of migrants and refugees on the border between Thailand and Myanmar (www.shoklo-unit.com). As part of the efforts to reduce malaria-related maternal mortality⁸, pregnant women are encouraged to attend SMRU antenatal clinics (ANC) as frequently as every fortnight. For refugees the service has been available since 1986, and for migrant communities, since 1998. Three SMRU clinics operate in border communities north and south of the town of Mae Sot: Maela (MLA, 17°07'44"N 98°22'50"E) refugee camp (population circa 49,626) and in the migrant villages of Wang Pa (WPA, 16°49'42"N 98°32'25"E) and Mawker Tai (MKT, 16°19'37"N 98°40'12"E) (population circa 30,000).

Antenatal care

During the first antenatal visit, a dating ultrasound, routine screening blood tests (malaria smear, haematocrit, syphilis, HIV, full blood count) are taken, and medical and obstetric examinations are performed. Pre-test counselling, using an "opt-out" system, is provided to all women at their first antenatal visit before any screening blood tests are performed. Malaria smears are read promptly and positive cases are treated immediately. At all visits tablets of ferrous sulphate (200 mg daily), folic acid (5 mg weekly) and thiamine (vitamin B1 100 mg daily)⁹ are supplied to all pregnant women. Anaemic patients receive 800 mg of ferrous sulfate and 5 mg of folic acid daily, and a tetanus vaccination is

given to women who have not been previously immunized. The SMRU ANC program aims to provide integrated antenatal care for any medical or obstetric problem including treatment for HIV [life-long antiretroviral (ARV) triple therapy] or syphilis. ARV therapy was GPO-vir[®] (a combination of Stavudine (D4T) 30 mg, Lamivudine (3TC) 150 mg and Nevirapine (NVP) 200 mg) one tablet twice daily, for patients with low CD4 (<350/mm³) counts; and for late pregnancy presentation (34 weeks of more) or CD4 (≥350/mm³) then Zidovudine (AZT) 300 mg and Lamivudine (3TC) 150 mg as a combination tablet (ZilarVir) and Efavirenz (EFV) 600 mg taken in once dose once daily, is provided. Drug therapy for syphilis was benzathine penicillin G 2.4 million units by intramuscular injection.

Laboratory sampling

Point of care HIV testing is done using an on-site rapid diagnostic test (Core™ HIV 1&2, Core Diagnostics, UK). At the first antenatal visit the results of the screening test are explained to the patient and the sera of positive patients is transported to Mae Sot Hospital laboratory (30–60 km from the sites) for confirmation using an immunoassay (HIV Combi PT, cobas[®], Roche, Germany). Post-test counselling explaining the results of the confirmation test is provided the following week.

Syphilis testing is conducted at Mae Sot Hospital on samples taken at SMRU ANCs. The hospital's protocol¹⁰ uses the Venereal Disease Research Laboratory (VDRL) test (VDRL Carbon Particle Antigen Kit, Plasmatec, Lab21 part of Health Care Ltd, UK) and confirms positive VDRL results with *Treponema pallidum* haemagglutination (TPHA) assay (TPHA kit, Plasmatec, Lab21 part of Health Care Ltd, UK). If a screening using VDRL is negative, no further tests are performed. Counselling about the test results is provided by SMRU staff to all women at their next antenatal visit. A policy to treat all patients for whom both VDRL and TPHA were reactive with 2.4 million units penicillin IM weekly × 3 doses was employed. This simple regimen which should be effective for all stages of the disease and prevention of congenital syphilis was used due to the difficulties in determining the stage of infection in most of our patients who denied symptoms or exposure history. No further serological testing was carried out after treatment in line with current recommendations for resource-poor settings¹¹.

Ethical approval

Retrospective review of anonymized data from antenatal records was approved by the local Tak Community Advisory Board and the Oxford Tropical Research Ethics Committee (OXTREC 28-09).

Statistical analysis

Data were analysed using SPSS for Windows™ (Version 20, SPSS Inc.) (Dataset 1). Continuous normally distributed data were described by their means and compared with the students's *t* test, while non-normally distributed data were described by their median and compared with the Mann-Whitney U test. Percentages were calculated for categorical data, which were compared using the χ^2 test or Fisher's exact test. Factors associated with a positive syphilis status or a positive HIV status, were compared by univariate analysis and odds ratios (OR) were calculated with a 95% confidence interval.

HIV and syphilis antenatal screening data at SMRU 2012–13

1 Data File

<http://dx.doi.org/10.6084/m9.figshare.1044120>**Results**

From the 8th of August 2012, until the 7th of August 2013, there were 3,600 women who attended the SMRU antenatal clinics at least once. Most were regular attenders. The ethnic make-up of the refugee and migrant population was largely Karen and Burmese, and significant differences between baseline characteristics of refugee and migrant clinics and between the two migrant clinics were apparent (Table 1). Maela has the highest case load (1,477 ANC attenders), followed by Wang Pha (1,185) and then Maw Ker Thai

(954). Age and gravidity were similarly matched at all clinics, but women attending the migrant sites (WPA and MKT) had a significantly higher number of marriages and a shorter duration of residence at their current address when compared with MLA. Duration of residence and literacy was lowest in WPA. In this border population, country of residence differed significantly between sites, with only 8% of ANC patients in MLA reporting an address in Myanmar, compared with 34% in Maw Ker Thai and 67% in WPA. Finally, significant differences were seen in the ethnic makeup of the patient populations. Karen ethnicities account for 82% of MLA patients, but only around 30% of the patients in MKT and WPA. Muslim patients make up 12% of MLA's ANC attenders, but are less than 1% of the migrant populations. Around 40% of the migrant patients are ethnically Burmese, but less than 2% of the MLA patients report Burmese ethnicity. Other ethnic minorities comprise 10% of MKT's patients, 5% of WPA and only 2% of MLA.

Table 1. Baseline characteristics of pregnant refugees and migrants enrolled to SMRU antenatal clinics.

	Refugee	Migrant	
Characteristics	Maela N=1,477	Maw Ker Thai N=954	Wang Pha N=1,185
Age in years, mean $\pm$ standard deviation [range]	26.5 $\pm$ 7 [14–48]	26 $\pm$ 7 ^c [15–45]	27 $\pm$ 7 [14–46]
Gravidity, median [range]	2 [1–14]	2 [1–12]	2 [1–12]
Primigravidae, % (n)	30.9 (456)	32.0 (305)	30.1 (352)
Median number marriages per woman [range]	1 [1–3] ^{d,e}	1 [1–5]	1 [1–3]
Myanmar address, % (n)	8.1 (119) ^{e,f}	33.9 (323) ^e	66.8 (782)
Years at current address, median [range]	7 ^{e,f} [0–43]	3 ^c [0–42]	2 [0–40]
Literate, % (n)	64.1 (945) ^e	64.8 (618) ^e	51.1 (598)
Ethnic group ^a			
Sgaw Karen	73.1 (1078)	29.7 (283)	29.1 (341)
Mixed Karen (Sgaw and Poe)	2.2 (32)	3.7 (35)	2.9 (34)
Poe Karen	7.5 (111)	13.6 (130)	18.5 (217)
Muslim	11.9 (175)	0.4 (4)	0.2 (2)
Burmese	1.8 (27)	38.3 (365)	40.6 (476)
Mixed Karen and Muslim/ Burmese/Other	1.5 (23)	3.9 (38)	3.5 (42)
Other ^b Ethnic group e.g. Mon, Pa-Oh, Rakhine, Shan, Chin	2.0 (29)	10.2 (97)	4.9 (57)
Burmese and Muslim	0	0.2 (2)	0.2 (2)

^aEthnic group of the woman was derived from the ethnicity of the woman's parents. Sgaw Karen implies both parents were Sgaw Karen and so on. Muslim is used locally to define people who originated from Bangladesh or Rakhine state.

^bOther as in not one of the leading 3 ethnic groups (Karen, Burmese or Muslim)

^cP<0.05 significantly different Wang Pha;

^dP<0.05 significantly different Maw Ker Thai;

^eP<0.001 significantly different Wang Pha;

^fP<0.001 significantly different Maw Ker Thai

Syphilis

Syphilis was tested in 3,592 of 3,600 women (99.78%). The remaining 8 patients were not tested due to interruption of the usual screening process such as a patient actively miscarrying. Off-site testing found 0.50% (18/3,592) VDRL reactive of whom 22.2% (4/18) were TPHA non-reactive indicating biological false positive reactions. Prevalence of serological syphilis (VDRL and TPHA reactive sera) was 0.39% (95% CI 0.23–0.65) (14/3,592). Of these, the majority 78.6% (11/14) were low VDRL titres < 1:8 (three were 1:2; eight were 1:4) and the remaining three were all 1:32. Only two women were symptomatic, both at a titre of 1:32 and one of these women was also HIV positive. The proportion of serological syphilis in MLA, MKT and WPA was 0.07% (1/1,469), 0.73% (7/954) and 0.51% (6/1,169) respectively. Syphilis prevalence was significantly lower in MLA compared to MKT $P=0.008$ and WPA $P=0.049$, but there was no difference between the two migrant sites ($P=0.583$). The overall prevalence of syphilis was lower in refugees 0.07% (1/1,469) (95% CI 0.01–0.38) compared to migrants 0.61% (13/2,123) (95% CI 0.36–1.04), $P=0.011$.

All active syphilis cases found in this audit (titre $\geq 1:8$ and TPHA reactive) were in young migrant women who were also primigravidae and all were treated. Amongst their partners, one partner agreed to testing and treatment (HIV and syphilis positive case); one agreed to treatment but not to testing and one was not contactable. Amongst the 11 low titre couples: five husbands attended the clinic and all five were negative (VDRL titres in their wives were 1:4 (four cases) and 1:2 (one case)); the remaining six husbands did not get tested because they were away for work (five cases) and one woman never returned at all after the first consultation. Counselling couples with low VDRL titres who both reported to have one lifetime sexual partner was particularly challenging.

Treatment with IM Penicillin was given to 71% (10/14) of patients with serological syphilis (positive VDRL and TPHA reactive) and four low titre (2 with 1:2 and 2 with 1:4) women remained untreated. Three of these women had low risk histories (no history of symptoms and reporting only one lifetime sexual partner for both the woman and her husband) and one history was unknown as the woman never returned to ANC after the first visit.

HIV

A HIV test was performed on 3,599 of 3,600 women (99.9%) of whom 0.9% (34) were tested positive by a single on-site rapid diagnostic test (RDT). Off-site confirmation testing by double ELISA showed that 46.9% (95% CI 30.9–63.6%) (17/32) of these positive RDT results were false positives (including 2 cases for whom confirmation testing was initially indeterminate, but were ultimately negative on repeat samples). This high rate of RDT biological false positives is not unexpected in a low transmission setting as these tests are optimized for sensitivity at the expense of specificity¹². The confirmed HIV-positive rate in pregnancy was 0.47% (95% CI 0.30–0.76) (17/3,599). Lowest HIV rates were again observed in the refugee camp MLA 0.27% (4/1,474) compared to the migrant sites, MKT 0.52% (5/954) and WPA 0.68% (8/1,171). While MLA was significantly lower than WPA ($P=0.049$) no other significant differences were observed: MLA vs. MKT $P=0.329$, and MKT

vs. WPA $P=0.783$. The percentage of HIV cases in refugees was not significantly different from the combined percentage of the two migrant sites: 0.3% (95% CI 0.11–0.70) (4/1,474) vs. 0.61% (13/2,125) (95% CI 0.36–1.0), $P=0.215$. There were 82.4% (14/17) of HIV-positive women treated with ARVs following guidelines based on WHO recommendations. The three untreated women were all migrants: one decided to return to Burma; one miscarried with a very high CD4 count and was followed up with 6-monthly CD4 counts and one woman did not return for the result.

Trends over time

There has been no significant change in the prevalence of HIV and syphilis from 1997⁷ to 2013 in refugees, nor for syphilis⁷ in migrants 2005 to 2013. Data from Myanmar and Thailand (<http://aidsdatahub.org/Country-Reviews>) were included for comparison (Table 2).

Factors possibly associated with serological positive syphilis and HIV infection were examined by univariate analysis (Table 3). Further modelling was not done due to the low number of seropositive cases precluding meaningful conclusions.

Conclusions

There is limited research on the prevalence of HIV and syphilis in migrant and refugee pregnant populations, despite the vulnerability of these populations. Here we describe low and stable HIV and syphilis prevalence in three displaced populations near Mae Sot, on the Thai-Myanmar border. No statistically significant difference in HIV rates between refugees and migrants was observed while syphilis was almost absent in the refugees but prevalent in the migrant population with rates comparable to regional and world averages¹.

Univariate risk factor analysis demonstrated that age of 30 years or more, a history of remarriage, and non-Karen ethnicity, emerged as significant for both HIV and syphilis infection. However, unlike HIV, syphilis was significantly higher in the migrant population than the refugee population. Migration, and length of residence at the current address of < 6 months, was itself a risk factor. These findings suggest that the relatively stable social order in the refugee camp, compared with the more mobile migrant communities, may be protective against syphilis. Though the camp population is not fixed, local government, educational and religious institutions are well established, and largely controlled by a socially conservative Karen majority. Syphilis transmission differs from HIV transmission in that it is rarely transmitted during the chronic latent phase; the infection is passed most readily if the interval between partners is short¹³. HIV, on the other hand, can become increasingly infectious years after an untreated infection is established in one of the partners¹⁴. Karen culture, which does allow for remarriage in cases of divorce or death of a spouse, holds a strong taboo on multiple sexual partners or extramarital sex. This taboo may provide some protection in the Karen-dominated refugee camp and is supported by the ethnic trend shown in Table 1 and Table 3. Migrant communities contain more young men and women separated from their families and typical community support. High-risk sexual behaviours have been found to occur more frequently in migrant populations in Thailand than in non-migrants, possibly accounting for the higher prevalence of syphilis in this group.

Table 2. Trends in antenatal HIV and syphilis prevalence (95% CI) in migrant and refugee women at SMRU and in surrounding Thailand and Myanmar.

	Population	1997 Cross-sectional	2005 Cross-sectional	Aug-2012-Jul-2013 Population cohort
Syphilis	Refugee ^{a,b}	0 (0–0.9)% (0/404)	0.40 (0.1–1.2)% (3/741)	0.07 (0.01–0.38)% (1/1,469)
	Migrant ^{a,b}	n.a	0 (0–1.6) (0/234)	0.61 (0.36–1.04)% (13/2,123)
	Thailand ^c	n.a	0.13%	0.1%
	Myanmar ^c	n.a	2.0%	0.7%
HIV	Refugee ^b	0.2 (0–1.1)% (0/500)	0.40 (0.1–1.4)% (2/500)	0.27 (0.11–0.70)% (4/1,474)
	Migrant ^b	n.a	n.a	0.61 (0.36–1.04)% (13/2,125)
	Thailand ^c	1.75%	0.86%	0.59%
	Myanmar ^c	1.5%	1.3%	0.7%

^aSerological syphilis positive using the same criteria, and the same hospital for confirmatory testing at each survey time point; n.a. not available

^bData from refugee and migrant populations in 1997 and 2005 previously published in [Reference 7](#)

^cData on Thailand and Myanmar's infection rates provided for comparison from the Evidence To Action Website country profiles accessed Mar-2014 (<http://aidsdatahub.org/Country-Reviews>)

Table 3. Factors associated with antenatal syphilis and HIV, Thai-Myanmar border.

Variable		Syphilis ^a			HIV ^a		
		N	% (n)	OR (95% CI) P value	N	% (n)	OR (95% CI) P value
Group	Refugee	1469	0.1 (1)	Reference	1474	0.3 (4)	Reference
	Migrant	2123	0.6 (13)	9.045 (1.182–69.214) P=0.011	2125	0.6 (13)	2.262 (0.736–6.951) P=0.215
Marriage	Only 1	2813	0.2 (7)	Reference	2819	0.2 (6)	Reference
	> 1	779	0.9 (7)	3.635 (1.271–10.394) P=0.018	780	1.4 (11)	6.706 (2.472–18.192) P<0.001
Parity	Primipara	1112	0.4 (4)	Reference	1113	0.3 (3)	Reference
	Multipara	2480	0.4 (10)	1.121 (0.351–3.583) P=1.000	2486	0.6 (14)	2.095 (0.601–7.306) P=0.300
Literacy	Illiterate	1434	0.5 (7)	Reference	1439	0.4 (6)	Reference
	Literate	2158	0.3 (7)	0.663 (0.232–1.895) P=0.586	2160	0.5 (11)	1.223 (0.451–3.313) P=0.807
Age	< 30y	2408	0.2 (4)	Reference	2412	0.3 (7)	Reference
	≥ 30y	1184	0.8 (10)	5.119 (1.602–16.357) P=0.004	1187	0.8 (10)	2.919 (1.108–7.688) P=0.035
Parents	At least one Karen	2386	0.1 (3)	Reference	2392	0.2 (5)	Reference
	Neither Karen	1206	0.9 (11)	7.312 (2.036–26.258) P=0.001	1207	1.0 (12)	4.794 (1.685–13.639) P=0.003
Residence	Thailand	2370	0.3 (8)	Reference	2376	0.4 (10)	Reference
	Myanmar	1222	0.5 (6)	1.457 (0.504–4.208) P=0.573	1223	0.6 (7)	1.362 (0.517–3.587) P=0.609
Length residence current address	≥ 6mths	2965	0.2 (6)	Reference	2972	0.5 (14)	Reference
	< 6mths	627	1.3 (8)	6.374 (2.204–18.434) P=0.001	627	0.5 (3)	1.016 (0.291–3.545) P=1.000

^aOnly 1 woman had both HIV and syphilis so these were not compared as a risk factor for each other

A significant potential confounder to our analysis is the fact that existing serologic tests cannot differentiate between syphilis and yaws or other non-venereal treponematoses^{15,16}. Yaws is still included in Thailand's program of neglected tropical diseases indicating that total eradication may not have been achieved yet¹⁷. The last reported outbreak of yaws in Thailand was published in 1994 (within our patients' lifetime) and occurred in a remote village a few hundred kilometres south of the SMRU sites¹⁸. The last yaws-related publication from Myanmar was published in 1960¹⁹ on the proposed yaws national programme. Myanmar has been amongst the world's poorest 30 countries for decades, and populations on the borders, remote from central government, have had poor access to health services^{18,19}. If a national program has been implemented to eradicate Yaws, it is unlikely it has reached these communities. More than 75% of TPHA-reactive patients in our cohort had low VDRL titres <1:8¹⁷.

Amongst these women, all of the husbands who came to the clinic were negative and the couples presented low risk histories. Latent syphilis (acquired via sexual contacts not disclosed by the patients) cannot be ruled out but the picture is suggestive of an unidentified treponemal infection (such as yaws) causing false-positive results. Publicly available data of RPR or VDRL titres in pregnant women in Thailand (<http://aidsdatahub.org/Country-Reviews>) are similar to what was observed here and are in contrast to studies from Africa, where a greater proportion of high sera titres are reported^{20,21}. Counselling VDRL discordant couples with low risk histories where the wife has a very low VDRL titre presents an ethical challenge in this conservative culture. The potential for serious social consequences, such as abuse or abandonment, of giving false positive results to these couples should be considered. While the stable HIV prevalence in this population supports continuation of routine HIV screening for all pregnant women, a risk-factor-based screening approach for syphilis could be considered for the refugee camp.

An additional factor limiting the analysis of risk factors in this cohort is the small number of positive results. These numbers become even smaller if the low-titre syphilis patients are excluded.

Reports from 2011 estimate over 7 million people live in protracted refugee situations, and over 27 million are internally displaced persons

(<http://www.prspproject.org/protracted-refugee-situations/>). Contextual differences within such groups are highlighted here where differences were found in quite similar populations. While these results cannot be widely applied to other settings, the questions raised about unintended consequences of routine screening and the need for more conclusive syphilis testing strategies, have implications with global relevance. The overall cost-effectiveness and impact of syphilis serological testing in pregnancy in low prevalence areas requires more in-depth evaluation especially in settings where funding for the most basic health care needs remains precarious.

Data availability

figshare: HIV and syphilis antenatal screening data at SMRU 2012–13.

Doi: [10.6084/m9.figshare.10441202](https://doi.org/10.6084/m9.figshare.10441202)²²

Author contributions

RM and FH conceived the study. RM, METG, AMH, NWT, LK and FN designed the experiments. MEGT, AMH, NWT, LK and NC carried out the research. JK, IW, NC, and BM contributed to the design of experiments. IW, MBT, METG and RM prepared the first draft of the manuscript. RM, JK, IW, METG, MBT, BH, and FN contributed to the experimental design and preparation of the manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

This work was supported by a grant from the Wellcome Trust of Great Britain for the Thailand/Laos Major Overseas Programme 2010–2015 (Grant B9RTOZ2) jointly awarded to MORU and LOMRU. The Shoklo Malaria Research Unit is part of the Wellcome Trust Mahidol University Oxford Tropical Medicine (MORU) Research Programme.

Acknowledgments

We would like to thank the women who attended the antenatal clinics and the midwifery, counsellors, laboratory, pharmacy, IT and logistic staff who supported the work.

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Open Peer Review

Current Peer Review Status:

Version 1

Reviewer Report 16 September 2014

<https://doi.org/10.5256/f1000research.4486.r6142>

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Overall:

- This manuscript must be indexed subject to revisions/clarifications that are highlighted in specific sections mentioned below.

Strengths:

- The strengths of the study lay in its design, recruitment of displaced, vulnerable populations, and evaluation of rapid testing interventions (antenatal screening for HIV and Syphilis) with downstream implications for mother-to-infant transmission.
- Data on this population are sparse. Little is known about effectiveness of screening in migrant populations and actions taken to link them to care and prevention.

Limitations:

- A convenience sample is enrolled - leading to a biased sample of a migrant population whose primary study base is ill-defined. This limits generalizability of their findings.
- Confounding: a discussion is needed - especially because a multivariate analyses was not attempted.
- A small sample, and fewer infections detected in the small sample, limits a multivariate analysis.
- Two groups are compared with a null finding.

- A clear hypotheses, a clear primary objective and a clean sample size calculation based on that is needed.
- Implication section for policy and practice is missing.

Detailed suggestions are provided below:

Title:

- The title specifies the studied population, the location and the correct study design.
- A suggested alternative title could be: "Audit of the antenatal screening for syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study" for the following reasons:
 - The HIV and syphilis prevalence estimates obtained when screening the sampled population may not be a true reflection of the prevalence among the underlying source population (refer to the limitation in the discussion section below).
 - The rates of infections are not the only focus of the study. The study also explores counselling challenges following screening and some consequential considerations for future testing strategies; however these are not covered in the title.

Abstract:

- The abstract provides informative and balanced summary of the study.
- There is a discrepancy between the aim presented in the abstract and the one presented in the introduction. The aim of auditing the first year of the syphilis routine screening is mentioned in the abstract but not the one of reassessing the trends in HIV rates.

Introduction:

- The scientific background is provided and the rationale for the investigation was well explained: the 2 studied STIs present major health risks on maternal and child health (it would be useful to add the health risk on the woman and not only on the pregnancy outcomes). The pregnant woman is especially vulnerable to infection when displaced (low income was mentioned as a risk factor – along with low education and lack of access to health services – and it would be useful to explain the correlation). There is a large displaced population between Thailand and Myanmar and data on prevalence of infections among this population is scarce.
- The objective of the study is stated. The aim of auditing a screening program is quite ambitious (many of its facets are discussed which may be overwhelming to the reader).

Methods:

- The study design is overall well presented (including study site, data collection and laboratory testing, treatment plan and adequate statistical analysis plan).
- Regarding the study population, the eligibility criteria and the sample size considerations (sample should be large enough to reflect important variations) are not

discussed.

- Training and expertise of the people executing the screening tests is not mentioned. Authors should discuss the comparability of the testing methods in the three SMRU clinics included in the study and the quality assurance and control measures applied.

Results:

- The results section presents and adequately summarizes all relevant characteristics of the study participants (Table 1). However, it would be helpful to define the number of marriages that a woman has as the number of remarriages (which is explained in the discussion). Literacy should also be defined. Additionally, 2 MLA and 14 WPA patients are not segregated into the different ethnic groups and are therefore missing from this part of the table; this mismatch can be detected when computing the total number of participants from each of these two sites. Finally, it is advised to keep one of the two significance levels presented below the table ($P < 0.05$ or $P < 0.001$).
- The results on prevalence rates of syphilis and HIV are properly presented in Table 2. However, the data from other studies on prevalence rates in Myanmar and Thailand are not very informative given the fact that confidence intervals are not provided.
- The reasons for non-participation and missing data are provided for each of those who did not complete the screening. However, the authors should consider providing an explanation for the one instance where a partner was treated for syphilis without being tested first.
- A multivariate analysis would have been more informative than a univariate analysis in order to get a clearer understanding of the risk factors associated with contracting syphilis and HIV. But, as the authors mention, this type of analysis is not possible when having a small number of cases. The authors should consider adding the type of analysis in the title of Table 3. Also, the confidence interval of the odds ratio for syphilis in the migrant group (1.182 – 6.921 instead of 1.182– 69.214) A wide confidence interval could be due to small number of cases, and sampling variability issues - these could be acknowledged.

Discussion:

- The discussion summarises the key results. But the conclusion on the HIV rates does not accurately encapsulate what is presented in the results section. It is advised to state that no statistically significant difference in HIV rates is observed between the refugees and the combined migrant population attending both MKT and WPA sites (since it is mentioned in the results section that there is a statistically significant difference in HIV rates between MLA and WPA).
- The discussion is contextualized in relation to the studied population. The authors present sound explanations and interpretations of the results based on a good understanding of the cultural traits and traditions of the studied population.
- The authors discuss the clinical applicability of the study findings. It would be useful to further clarify the ethical difficulties faced and the challenges created during post-test counselling when a false positive syphilis result is undetected. For example, the authors can explain that a positive syphilis screening test does not necessarily confirm syphilis when titres are low and that yaws – which is not sexually transmitted – may instead be suspected.

This inability to determine the true cause of the positive result can lead to serious consequences when counselling a patient with low titres levels – as it may increase her risk of abuse and abandonment. It can also be specified that that yaws are transmitted through skin-to-skin contact and promoted by overcrowding and poor hygiene (which is very likely the case in the study population).

- The authors discuss limitations of the study. However, the convenience sampling of the study population is a limitation that is not mentioned in the discussion. There is a risk of selection bias since the study population consists of regular attendees of the SMRU antenatal clinics who may be very different from those who are not. For example, regular attendees of the clinic may be more health conscious – engage in less risky behaviors – and may have been more exposed to health recommendations and counselling than those who miss antenatal care visits.

- The generalizability of results (external validity) to the whole population of migrants and refugees in the studied location is difficult to establish given the risk of selection bias.

In conclusion, the study is scientifically sound however some editing is advised. It presents interesting data on HIV and syphilis prevalence for regular antenatal clinic attendees coming from a disadvantaged and understudied population of migrant and refugee at the Thai- Myanmar border.

It provides valuable ethical considerations and highlights a caveat pertaining to the current syphilis testing strategy and post-test counselling.

This review could help public health officials better understand the situation in regard to HIV and syphilis among the studied population in order to revise the routine screening program.

Competing Interests: No competing interests were disclosed.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response () 05 May 2015

Rose McGready, Mahidol University, Mae Sot, Thailand

We appreciate and would like to sincerely thank the significant effort of both reviewers in regards to this manuscript. We apologize for the tardiness of the response. We have provided a point by point response to the comments below.

Overall:

- **This manuscript must be indexed subject to revisions/clarifications that are highlighted in specific sections mentioned below.**

Strengths:

- **The strengths of the study lay in its design, recruitment of displaced, vulnerable populations, and evaluation of rapid testing interventions (antenatal**

screening for HIV and Syphilis) with downstream implications for mother-to-infant transmission.

- **Data on this population are sparse. Little is known about effectiveness of screening in migrant populations and actions taken to link them to care and prevention.**

Limitations:

- **A convenience sample is enrolled - leading to a biased sample of a migrant population whose primary study base is ill-defined. This limits generalizability of their findings.**

Thank you – we need to clarify. This is not a convenience sample but the whole population of pregnant women in well attended antenatal clinics. This point is similar to point 2 raised by reviewer one about the population. The methods (2nd paragraph) has been modified to better describe this population.

- **Confounding: a discussion is needed - especially because a multivariate analyses was not attempted.**

The original submissions did a univariate analysis (Table 3) and in the results a sentence was added “Further modelling was not done due to the low number of seropositive cases precluding meaningful conclusions.” At this reviewer’s request a multivariate analysis has been added here (next page) and as you can see the confidence intervals of the AOR are very large, which means the level of uncertainty are so high that we cannot confidently interpret the result. If the reviewer insists we can include the multivariate analysis in the main body of the paper with the appropriate changes to the methods section as well (included here).

Methods, statistical analysis: Factors associated with a diagnosis of syphilis or a diagnosis of HIV, were evaluated by univariate analysis; two logistic regression models were created using “syphilis (yes/no)” and “HIV (yes/no)” as dependent variables. All factors with a $P < 0.10$ in univariate analysis were entered in their respective stepwise forward logistic regression model, and were included in the relevant tables. Adjusted odds ratios (AOR) were given with their 95% confidence interval.

[see table 3 in new version - resubmission]

- **A small sample, and fewer infections detected in the small sample, limits a multivariate analysis.**

We have acknowledged this. The main reason to write this manuscript is not to explore risk factors but to question the prevalence at which syphilis testing is not viable for resource constrained settings.

- **Two groups are compared with a null finding.**

Yes – the incidence of HIV and syphilis is very low in both populations which is what we are trying to illustrate

- **A clear hypotheses, a clear primary objective and a clean sample size calculation based on that is needed.**

This is a non-selected inclusive cohort of all consecutively registered pregnant women so no sample size was provided. This has been clarified, 2nd paragraphs in the methods.

- **Implication section for policy and practice is missing.**

These implications are clarified in the paragraph starting at line 293.

Detailed suggestions are provided below:

Title:

- **The title specifies the studied population, the location and the correct study design.**
- **A suggested alternative title could be: “Audit of the antenatal screening for syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study” for the following reasons:**
 - **The HIV and syphilis prevalence estimates obtained when screening the sampled population may not be a true reflection of the prevalence among the underlying source population (refer to the limitation in the discussion section below).**
 - **The rates of infections are not the only focus of the study. The study also explores counselling challenges following screening and some consequential considerations for future testing strategies; however these are not covered in the title.**

We have amended the title in line with what has been suggested although we are confident that we have good coverage of the population. We agree with the second point.

Abstract:

- **The abstract provides informative and balanced summary of the study.**
There is a discrepancy between the aim presented in the abstract and the one presented in the introduction. The aim of auditing the first year of the syphilis routine screening is mentioned in the abstract but not the one of reassessing the trends in HIV rates.

Thank you for this comment and the aims are now aligned.

Introduction:

- **The scientific background is provided and the rationale for the investigation was well explained: the 2 studied STIs present major health risks on maternal and child health (it would be useful to add the health risk on the woman and not only on the pregnancy outcomes).**

We agree and a sentence added to the end of the first paragraph of the introduction.

The pregnant woman is especially vulnerable to infection when displaced (low income was mentioned as a risk factor – along with low education and lack of access to health services – and it would be useful to explain the correlation). There is a large displaced population between Thailand and Myanmar and data on prevalence of infections among this population is scarce.

Thank and this has been amended in the introduction (see end of the 2nd paragraph).

- **The objective of the study is stated. The aim of auditing a screening program is quite ambitious (many of its facets are discussed which may be overwhelming to the reader).**

Given the challenges we encountered, we found that such an audit (ambitious and complex as it is) is necessary to shed light on the issues faced in this context. It is our hope that the overwhelming experience of the reader will be lessened by the changes we have made in response to the general reviewer comments. No specific changes made to change the

objective.

Methods:

- **The study design is overall well presented (including study site, data collection and laboratory testing, treatment plan and adequate statistical analysis plan).**

OK

- **Regarding the study population, the eligibility criteria and the sample size considerations (sample should be large enough to reflect important variations) are not discussed**

Thank you. The sample is exhaustive and the study population is more clearly defined now in the methods section.

- **Training and expertise of the people executing the screening tests is not mentioned. Authors should discuss the comparability of the testing methods in the three SMRU clinics included in the study and the quality assurance and control measures applied.**

Thank you for this and the information has been added to the first paragraph of laboratory sampling.

Results:

- **The results section presents and adequately summarizes all relevant characteristics of the study participants (Table 1). However, it would be helpful to define the number of marriages that a woman has as the number of remarriages (which is explained in the discussion).**

Amended

Literacy should also be defined.

Amended: this was self-reported.

Additionally, 2 MLA and 14 WPA patients are not segregated into the different ethnic groups and are therefore missing from this part of the table; this mismatch can be detected when computing the total number of participants from each of these two sites.

Thank you for detecting this. It is an error and the numbers in the manuscript has been carefully reviewed in line with this finding.

Finally, it is advised to keep one of the two significance levels presented below the table ($P < 0.05$ or $P < 0.001$).

Amended: only $P < 0.05$ has been maintained.

- **The results on prevalence rates of syphilis and HIV are properly presented in Table 2. However, the data from other studies on prevalence rates in Myanmar and Thailand are not very informative given the fact that confidence intervals are not provided**

We think the comparative data compiled in one table is helpful to understand the situation of a population that is rarely provided with any type of sero-surveillance. We agree a better data source that provides confidence intervals would be useful but we are unable to find exact numbers for Thailand. We have expanded the paragraph in the results further and provided clearer reference material; including confidence intervals for the Myanmar data. **The reasons for non-participation and missing data are provided for each of those who did not complete the screening. However, the authors should consider providing an explanation for the one instance where a partner was treated for syphilis without**

being tested first.

High risk case and this has been added to the results section.

- **A multivariate analysis would have been more informative than a univariate analysis in order to get a clearer understanding of the risk factors associated with contracting syphilis and HIV. But, as the authors mention, this type of analysis is not possible when having a small number of cases. The authors should consider adding the type of analysis in the title of Table 3. Also, the confidence interval of the odds ratio for syphilis in the migrant group (1.182 – 6.921 instead of 1.182- 69.214) A wide confidence interval could be due to small number of cases, and sampling variability issues - these could be acknowledged.**

Analysis of risk factors is not the main objective of this manuscript, and the limitation of such an analysis due to low positivity is acknowledged in the original submission. We have clarified in the laboratory sampling section that sampling variability is minimized by regular quality control and standardization, and this is not a significant contributor to the wide confidence interval, unlike the small number of positive cases. The comment about the confidence interval of the odds ratio for syphilis is a little unclear to us, but the correct CI is as included in the table (1.182-69.214) i.e. it really is 69 and no 6.9.

Discussion:

- **The discussion summarises the key results. But the conclusion on the HIV rates does not accurately encapsulate what is presented in the results section. It is advised to state that no statistically significant difference in HIV rates is observed between the refugees and the combined migrant population attending both MKT and WPA sites (since it is mentioned in the results section that there is a statistically significant difference in HIV rates between MLA and WPA).**

Thank you for this suggestion and it has been amended as suggested.

- **The discussion is contextualized in relation to the studied population. The authors present sound explanations and interpretations of the results based on a good understanding of the cultural traits and traditions of the studied population.**
- **The authors discuss the clinical applicability of the study findings. It would be useful to further clarify the ethical difficulties faced and the challenges created during post-test counselling when a false positive syphilis result is undetected.**

For example, the authors can explain that a positive syphilis screening test does not necessarily confirm syphilis when titres are low and that yaws – which is not sexually transmitted – may instead be suspected. This inability to determine the true cause of the positive result can lead to serious consequences when counselling a patient with low titres levels – as it may increase her risk of abuse and abandonment. It can also be specified that that yaws are transmitted through skin-to-skin contact and promoted by overcrowding and poor hygiene (which is very likely the case in the study population).

We have amended the text as suggested.

- **The authors discuss limitations of the study. However, the convenience sampling of the study population is a limitation that is not mentioned in the discussion.**

There is a risk of selection bias since the study population consists of regular attendees of the SMRU antenatal clinics who may be very different from those who

are not. For example, regular attendees of the clinic may be more health conscious – engage in less risky behaviors – and may have been more exposed to health recommendations and counselling than those who miss antenatal care visits.

Sampling was exhaustive, it was not a convenience sample and we included women who came for only one ANC visit or arrived at the clinic for the first time while in labor.

- **The generalizability of results (external validity) to the whole population of migrants and refugees in the studied location is difficult to establish given the risk of selection bias.**

The sampling was exhaustive amongst consecutively enrolled pregnant women. The data is similar to previous surveys and consistent with other reports from the area suggesting the risk of selection bias is low. This has been better clarified in relation to the methods (the study population) and relation to other data sources included in the first paragraph of the discussion.

In conclusion, the study is scientifically sound however some editing is advised. It presents interesting data on HIV and syphilis prevalence for regular antenatal clinic attendees coming from a disadvantaged and understudied population of migrant and refugee at the Thai- Myanmar border.

It provides valuable ethical considerations and highlights a caveat pertaining to the current syphilis testing strategy and post-test counselling.

This review could help public health officials better understand the situation in regard to HIV and syphilis among the studied population in order to revise the routine screening program.

Competing Interests: no competing interests

Reviewer Report 27 June 2014

<https://doi.org/10.5256/f1000research.4486.r5072>

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R. Matthew Chico

Department of Disease Control, London School of Hygiene & Tropical Medicine, London, UK

Overall comment:

This is a well-written paper on an important topic, for which there is limited data: What is the prevalence below which routine screening of all pregnant women for HIV and, in particular, syphilis is no longer advisable?

Specific comments:

1. Syphilis is far more deleterious to birth outcomes than other bacterial sexually transmitted infections and, therefore, the potential risks associated with missed diagnoses should be made clearer in the paper. Among unscreened pregnant women in Tanzania, 51% of stillbirths, 24% of preterm live births, and 17% of all adverse pregnancy outcomes were attributable to maternal syphilis ¹. The authors should consider citing the comprehensive summary of the effect of curable STIs on birth outcomes by Chico *et al.* (Table 1. Effect of curable STIs/RTIs on pregnancy outcomes) ².
2. Clearly the rates of HIV and syphilis were low among the refugees and migrants tested along the Thai-Myanmar border. However, it is not clear in the manuscript (1) the proportion of pregnant women in these two populations who seek antenatal care services, and (2) the prevalence of syphilis and HIV in the two populations who do not seek ANC services. Are the pregnant women attending these health facilities healthier than the overall population? Pregnant women are encouraged to attend ANC clinics as frequently as every fortnight. This makes it more difficult to generalise results beyond the study population.
3. The refugee and migrant populations in this setting are unique for cultural reasons described in the paper. There should be some discussion about other contexts in which women are at elevated risk of HIV and syphilis infection, and that women may enter into transient marital relationships that are based in personal security, but expose them to other risks.
4. There should be some discussion about the use of rapid point of care (POC) tests for syphilis, in place of VDRL and TPHA assays. POC tests for syphilis simplify the screening and treatment procedures. The World Health Organization currently recommends the use of POC tests for syphilis in the antenatal care setting ³. Using POC tests will expedite case finding and treatment because results will be available during the same consultation. Although published results are not yet available, a combination HIV and syphilis POC test has recently been validated.
5. The paper would benefit from a table that delineates the demographic and birth-outcome data for the 14 women who were found to have syphilis. The risk profile in Table 3 suggests that (1) migrant women, (2) who have been married more than once, (3) who are above the age of 30, (4) whose parents are not Karen, and (5) who have lived at their present address less than six months, are most likely to have a syphilis infection. Considering these five risk factors, how many women had just one, or two, or three, or four, or all five?

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Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response () 05 May 2015

Rose McGready, Mahidol University, Mae Sot, Thailand

We appreciate and would like to sincerely thank the significant effort of both reviewers in regards to this manuscript. We apologize for the tardiness of the response. We have provided a point by point response to the comments below.

This is a well-written paper on an important topic, for which there is limited data: What is the prevalence below which routine screening of all pregnant women for HIV and, in particular, syphilis is no longer advisable?

Specific comments:

1.Syphilis is far more deleterious to birth outcomes than other bacterial sexually transmitted infections and, therefore, the potential risks associated with missed diagnoses should be made in clearer in the paper. Among unscreened pregnant women in Tanzania, 51% of stillbirths, 24% of preterm live births, and 17% of all adverse pregnancy outcomes were attributable to maternal syphilis ¹. The authors should consider citing the comprehensive summary of the effect of curable STIs on birth outcomes by Chico *et al.* (Table 1. Effect of curable STIs/RTIs on pregnancy outcomes) ².

We agree this is important and have amended the text as suggested in the 2nd paragraph of the introduction.

2.Clearly the rates of HIV and syphilis were low among the refugees and migrants tested along the Thai-Myanmar border. However, it is not clear in the manuscript (1) the proportion of pregnant women in these two populations who seek antenatal care services, and (2) the prevalence of syphilis and HIV in the two populations who do not seek ANC services. Are the pregnant women attending these health facilities healthier than the overall population? Pregnant women are encouraged to attend ANC clinics as frequently as every fortnight. This makes it more difficult to generalise results beyond the study population.

Thank you for pointing this out and this information has been added to the methods section.

1. We estimate the proportion at 90% - see 2nd paragraph of the methods section.

2. The “prevalence of syphilis and HIV in the two populations who do not seek ANC services” is impossible to answer. Data of HIV rates from the border wide camp Health information system suggest similarly low prevalence and this has been added

to the discussion first paragraph.

The ANC has always encouraged fortnightly voluntary visits (and care during childbirth in the clinic) and 4 or less antenatal visits in this setting has been associated with an increased risk of maternal death: AOR 2.50 (95%CI 1.41–4.43) (doi: 10.1371/journal.pone.0040244) and this detail has been added to the methods first paragraph.

3.The refugee and migrant populations in this setting are unique for cultural reasons described in the paper. There should be some discussion about other contexts in which women are at elevated risk of HIV and syphilis infection, and that women may enter into transient marital relationships that are based in personal security, but expose them to other risks.

This has been added into the discussion towards the end of the first paragraph in the conclusions.

4.There should be some discussion about the use of rapid point of care (POC) tests for syphilis, in place of VDRL and TPHA assays. POC tests for syphilis simplify the screening and treatment procedures. The World Health Organization currently recommends the use of POC tests for syphilis in the antenatal care setting ³. Using POC tests will expedite case finding and treatment because results will be available during the same consultation. Although published results are not yet available, a combination HIV and syphilis POC test has recently been validated.

We have not got experience with POC for syphilis. Our experience with POC for HIV (higher positivity rate than syphilis) has not been good as explained in the results – nearly ½ were false positive. As the incidence goes down the false positive rate goes up and this is one of the reasons we have not moved to POC tests for syphilis in this population. Currently the turn around time with the local Thailand hospital where the POC positive results are sent for confirmation and the distance involved is a minimum of 3 days (usually a week). This is very stressful for women. This has been added to the discussion. We are not against POC tests and use malaria POC testing frequently. POC tests have limitations in their own right and the limitations and advantages need to be determined locally.

On another note we have also found that hepatitis B POC tests also present us with a similar problem but to a lesser degree (the incidence of Hepatitis B in adults in this area approaches 10%). Approximately 10% of Hepatitis B Surface Ag POC positive tests turn out to be incorrect. This is not a problem when the point is to screen for healthy donors but it is a problem when you are telling an individual they have a chronic disease.

We would be delighted to be a site for testing sensitivity and specificity of such tests.

5.The paper would benefit from a table that delineates the demographic and birth-outcome data for the 14 women who were found to have syphilis. The risk profile in Table 3 suggests that (1) migrant women, (2) who have been married more than once, (3) who are above the age of 30, (4) whose parents are not Karen, and (5) who have lived at their present address less than six months, are most likely to have a syphilis infection. Considering these five risk factors, how many women had just one, or two,

or three, or four, or all five?

We appreciate this suggestion as a method to try to focus on at risk women. We have looked at this in 2 ways: scoring the number of risk factors a woman has (below)

We appreciate this suggestion as a method to try to focus on at risk women. We have looked at this in 2 ways: scoring the number of risk factors a woman has (below)

Score

Syphilis n=14

No syphilis n=3578

0

0 (0)

646 (100%)

1

2* (0.2%)

1082 (99.8%)

2

0 (0)

1032 (100%)

3

4 (0.7%)

1. 99.3%)

4

5 (2.3%)

216 (97.7%)

5

3 (10.0%)

27 (90.0%)

**Scored: one woman scored 1 because of 'migrant' status; and one woman scored 1 because of age ≥ 30 y.*

A risk factor score of ≥ 3 includes 1.44% (12/831) and a score <3 includes 0.07% (2/2762).

And trying to identify if a pattern of risk factors is common (below)

Finally as suggested by the 2nd reviewer we have run a multivariate analysis which can be found at the request of the 2nd reviewer (see comments). The main message of the manuscript is not to identify risk factors (which also does not seem practical given the low number of positive case).

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Competing Interests: no competing interests

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