



## RESEARCH NOTE

# **REVISÉD** Audit of antenatal screening for syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study [version 2; referees: 2 approved]

**Previously titled:** Low and stable rates of antenatal syphilis and HIV in migrant and refugee women on the Thai-Myanmar border: a descriptive study

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## 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 the same population and reassess the trends in HIV rates.

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

## Open Peer Review

Referee Status:

Invited Referees	
1	2
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**REVISED Amendments from Version 1**

We thank the reviewers for their comments which have significantly improved the message of this manuscript. We have responded to both reviewers comments in the new manuscript and explained the context in more detail. The second reviewer was worried that the sampling was convenience however we have clarified that is more likely to represent the population. The difficulty of antenatal screening tests in a low endemic and resource poor setting with low literacy rates remains the focus of the redrafted manuscript. The added **supplementary materials** explore the risk factors associated with serological positive syphilis on univariate analysis with a view to considering risk factor based screening. In addition, the surname of one of the authors (previously Mary Ellen Gilder) has been changed due to marriage.

**See referee reports**

## Introduction

The global health impact of sexually transmitted infections (STIs) including HIV/AIDS and syphilis is well recognized<sup>1</sup>. 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 breastfeeding<sup>2</sup>. This is estimated to cause over 500,000 adverse pregnancy outcomes per year, including stillbirth and congenital infection<sup>1</sup>. Syphilis more than any other bacterial and curable sexually transmitted infection, has greater potential to cause adverse birth outcomes when the diagnosis is missed<sup>3</sup>. This was demonstrated in an area with a high rate of syphilis (7.7% amongst 19,878 women screened by RPR testing at antenatal clinic (ANC)) where, 51% of stillbirths, 24% of preterm live births, and 17% of all adverse pregnancy outcomes in unscreened women were attributable to maternal syphilis<sup>4,5</sup>. For the mother, untreated syphilis and HIV can cause multiple medical problems including death, and the open sores of syphilis increase the risk of human immunodeficiency virus (HIV) infection.

Displaced populations of migrants and refugees within developing regions are particularly vulnerable to disease although data on the prevalence of infection is scarce<sup>6</sup>.

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 Myanmar<sup>7</sup>. 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 Thailand<sup>6</sup> are vulnerable to STIs and HIV/AIDs<sup>8</sup>, due to the lack of access to health services, poor education and low income<sup>6,8,9</sup>. In a cross-sectional study conducted amongst female sex-workers in 2009 in the major cities of Myanmar 18.4% of 136 participants tested positive for HIV and economic reasons were recognized as compelling to not use condoms with clients<sup>10</sup>.

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%)<sup>11</sup>. While HIV screening in pregnancy has been 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](http://www.shoklo-unit.com)). As part of the efforts to reduce malaria-related maternal mortality<sup>12</sup>, pregnant women are encouraged to attend SMRU antenatal clinics (ANC) as frequently as every fortnight. Indeed low attendance, or fewer than four antenatal visits (equivalent to the number of antenatal malaria screens) is a risk factor for maternal mortality in this setting<sup>12</sup>. 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 42,000)<sup>13</sup>. A recent publication using the WHO Safe Motherhood Needs Assessment of the quality of care at the facility recognized that the essential elements of ANC were all provided except syphilis testing<sup>14</sup>.

These antenatal clinics are well attended and in the only formal survey undertaken more than 90% of women in refugee camps were found to be attending SMRU ANC<sup>15</sup>. For migrants, a more mobile population, based on village population lists (42,000) and with no reason to believe birth rates would differ in migrants and refugees we suspect that ANC is equally well attended by this population<sup>13</sup>. Antenatal clinic attendance and births in SMRU centres continues to increase yearly in the migrant population (WPA and MKT). Women are accepted anytime including at the time of birth, although the majority of women have already booked with the antenatal clinic. This audit was a non-selected inclusive cohort of all consecutively registered pregnant women in a one year period.

### 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)<sup>16</sup> 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/mm<sup>3</sup>) counts; and for late pregnancy presentation (34 weeks of more) or CD4 (≥350/mm<sup>3</sup>) 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). The HIV rapid detection test (RDT) was carried out by SMRU laboratory technicians whose practice is standardized by regular quality control across the 3 SMRU sites by one of the authors (LK), and who have significant expertise on use of RDTs in malaria<sup>17</sup>. At the first antenatal visit the results of the screening test are explained to the patient and the sera of positive RDT cases is transported to Mae Sot Hospital laboratory (30–60 km from the sites) for confirmation using an immunoassay (HIV Combi PT, Cobas®, Roche, Germany). Mae Sot Hospital is the main Government Hospital for the Province of Tak and their practice is certified by Thailand Department of Public Health. Post-test counselling explaining the results of the confirmation test is provided the following week.

Syphilis testing is conducted at Mae Sot Hospital on a fee for service basis, on samples taken at SMRU ANCs. The hospital's protocol<sup>18</sup> 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 settings<sup>19</sup>.

### Factors associated with serological positive syphilis and HIV

Factors possibly associated with serological positive syphilis and HIV infection were examined by univariate and multivariate analysis (Table 3). The small number of cases makes the confidence intervals on univariate and multivariate analysis wide. The serological positive syphilis risk factor were examined in detail to determine if a risk factor based screening would be possible (see [supplementary materials](#)).

### 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  $\chi^2$  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. Factors associated with a diagnosis of syphilis, and 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 value <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.

### 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 8<sup>th</sup> of August 2012, until the 7<sup>th</sup> 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 (1,475 ANC attenders), followed by Wang Pha (1,171) 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 remarriages and a shorter duration of residence at their current address when compared with MLA. Duration of residence and literacy (self-reported ability to read) 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 MKT and 67% in WPA. Finally, significant differences were seen in the ethnic makeup of the populations. Karen ethnicities account for 82% of MLA patients, but only around 30% of the patients in MKT and WPA. Burmese 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 Burman, but less than 2% of the MLA patients report Burman ethnicity. Other ethnic minorities comprise 10% of MKT's patients, 5% of WPA and only 2% of MLA.

### 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

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

	Refugee	Migrant	
Characteristics	Maela N=1,475	Maw Ker Thai N=954	Wang Pha N=1,171
Age in years, mean $\pm$ standard deviation [range]	26.5 $\pm$ 7 [14–48]	26 $\pm$ 7 <sup>c</sup> [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] <sup>c,d</sup>	1 [1–5]	1 [1–3]
Myanmar address, % (n)	8.1 (119) <sup>c,d</sup>	33.9 (323) <sup>c</sup>	66.8 (782)
Years at current address, median [range]	7 <sup>c,d</sup> [0–43]	3 <sup>c</sup> [0–42]	2 [0–40]
Literate, % (n)	64.1 (945) <sup>c</sup>	64.8 (618) <sup>c</sup>	51.1 (598)
Ethnic group <sup>a</sup>			
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)
Burman Muslim	11.9 (175)	0.4 (4)	0.2 (2)
Burman	1.8 (27)	38.3 (365)	40.6 (476)
Mixed Karen and Burman Muslim/Burman/Other	1.5 (23)	3.9 (38)	3.5 (42)
Other <sup>b</sup> Ethnic group e.g. Mon, Pa-Oh, Rakhine, Shan, Chin	2.0 (29)	10.2 (97)	4.9 (57)
Burman and Burman Muslim	0	0.2 (2)	0.2 (2)

<sup>a</sup>Ethnic 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. Burman Muslim is used locally to define people who originated from Bangladesh or Rhakine state.

<sup>b</sup>Other as in not one of the leading 3 ethnic groups (Karen, Burman or Burman Muslim)

<sup>c</sup>P<0.05 significantly different Wang Pha;

<sup>d</sup>P<0.05 significantly different Maw Ker Thai;

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 (n=3) 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 (his wife had a titre of 1:32 and one marriage) 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 specificity<sup>20</sup>. 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% (5/594) 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 Myanmar; 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 1997<sup>7</sup> to 2013 in refugees, nor for syphilis<sup>7</sup> in migrants 2005 to 2013. While data from Thailand<sup>21</sup> is reported for comparison we were unable to obtain the raw data for confidence interval analysis (Table 2). For Myanmar<sup>22</sup> it was possible to obtain raw data for the whole country combined and by location, so Myawaddy data, from the Burmese town opposite Mae Sot, Thailand, was included. The data were collected from 1st Mar–31st May 2012 from 35 sentinel sites with a projected sample size of 400 from each site. Of note is the higher rate in Myawaddy than all Myanmar combined

for HIV and syphilis. A comment from the report: “syphilis prevalence was highest among pregnant women in age group 40–44 as 0.6% (4/492)” was similar to observations in the SMRU data.

Factors possibly associated with serological positive syphilis and HIV infection were examined by univariate and multivariate analysis (Table 3). The small number of cases makes the confidence intervals on univariate and multivariate analysis wide. On multivariate analysis, older maternal age and a short history of residence at the current address were risk factors for syphilis; and remarriage and non-Karen parentage were risk factors for HIV; however more data is required to confirm this.

### 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 refugees over a 15–16 year period, on the Thai-Myanmar border. This is supported by low published rates in refugees from the same area resettled in new countries<sup>23</sup>. The data for migrants is newly available and while no statistically significant difference in HIV rates was observed between refugees and the combined migrant population, HIV rates were higher in the migrant group situated closer to the Mae Sot and Myawaddy townships. Syphilis was almost absent in the refugees and prevalence in the migrants on a par with data from Myanmar<sup>22</sup> and comparable to regional and world averages<sup>1</sup>. The data presented here are contextual

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

	Population	1997 Cross-sectional	2005 Cross-sectional	Aug-2012–Jul-2013 Population cohort
Syphilis	Refugee <sup>a,b</sup>	0 (0–0.9)% (0/404)	0.40 (0.1–1.2)% (3/741)	0.07 (0.01–0.38)% (1/1,469)
	Migrant <sup>a,b</sup>	n.a	0 (0–1.6) (0/234)	0.61 (0.36–1.04)% (13/2,123)
	Thailand <sup>c</sup>	n.a	0.13%	0.1%
	Myanmar <sup>c</sup>	n.a.	2.0%	0.32 (0.24–0.43)% (45/13,995)
	Myawaddy <sup>c</sup>			0.50 (0.14–0.18)% (2/400)
HIV	Refugee <sup>b</sup>	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 <sup>b</sup>	n.a	n.a.	0.61 (0.36–1.04)% (13/2,125)
	Thailand <sup>c</sup>	1.75%	0.86%	0.59%
	Myanmar <sup>c</sup>	1.5%	1.3%	0.80 (0.67–0.96)% (112/13,995)
	Myawaddy <sup>c</sup>			1.5 (0.39–2.54)% (4/400)

<sup>a</sup>Serological syphilis positive using the same criteria, and the same hospital for confirmatory testing at each survey time point; n.a. not available

<sup>b</sup>Data from refugee and migrant populations in 1997 and 2005; published in reference<sup>7</sup>

<sup>c</sup>Data for Thailand from reference<sup>21</sup> and Myanmar from reference<sup>22</sup>

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

Variable	Syphilis <sup>a</sup>				HIV <sup>a</sup>			
	N	% (n)	OR (95% CI) P value	AOR (95% CI) P value	N	% (n)	OR (95% CI) P value	AOR (95% CI) P value
Group								
Refugee	1,469	0.1 (1)	Reference	Reference	1,474	0.3 (4)	Reference	Reference
Migrant	2,123	0.6 (13)	<b>9.045 (1.182–69.214)</b> <b>P=0.034</b>	3.461 (0.407–29.454) P=0.256	2,125	0.6 (13)	2.262 (0.736–6.951) P=0.15	Not included
Marriage								
Only 1	2,813	0.2 (7)	Reference	Reference	2,819	0.2 (6)	Reference	Reference
>1	779	0.9 (7)	<b>3.635 (1.271–10.394)</b> <b>P=0.016</b>	2.507 (0.851–7.391) P=0.096	780	1.4 (11)	<b>6.706 (2.472–18.192)</b> <b>P&lt;0.001</b>	<b>5.497 (1.982–15.247)</b> <b>P&lt;0.001</b>
Parity								
Primipara	1,112	0.4 (4)	Reference	Reference	1,113	0.3 (3)	Reference	Reference
Multipara	2,480	0.4 (10)	0.122 (0.351–3.583) P=0.847	Not included	2,486	0.6 (14)	2.095 (0.601–7.306) P=0.246	Not included
Literacy (self-reported)								
Literate	2,158	0.3 (7)	Reference	Reference	1,439	0.4 (6)	Reference	Reference
Illiterate	1,434	0.5 (7)	1.507 (0.528–4.307) P=0.444	Not included	2,160	0.5 (11)	0.818 (0.302–2.217) P=0.693	Not included
Age								
<30 y	2,408	0.2 (4)	Reference	Reference	2,412	0.3 (7)	Reference	Reference
≥30 y	1,184	0.8 (10)	<b>5.119 (1.602–16.357)</b> <b>P=0.006</b>	<b>4.632 (1.417–15.139)</b> <b>P=0.011</b>	1,187	0.8 (10)	<b>2.919 (1.108–7.688)</b> <b>P=0.030</b>	2.094 (0.0777–5.648) P=0.144
Parents								
At least 1 Karen	2,386	0.1 (3)	Reference	Reference	2,392	0.2 (5)	Reference	Reference
Neither Karen	1,206	0.9 (11)	<b>7.312 (2.036–26.258)</b> <b>P=0.002</b>	3.799 (0.997–14.681) P=0.052	1,207	1.0 (12)	<b>4.794 (1.685–13.639)</b> <b>P=0.003</b>	<b>4.514 (1.581–12.887)</b> <b>P=0.005</b>
Residence								
Thailand	2,370	0.3 (8)	Reference	Reference	2,376	0.4 (10)	Reference	Reference
Myanmar	1,222	0.5 (6)	1.457 (0.504–4.208) P=0.487	Not included	1,223	0.6 (7)	1.362 (0.517–3.587) P=0.532	Not included
Length residence								
≥6mths	2,965	0.2 (6)	Reference	Reference	2,972	0.5 (14)	Reference	Reference
<6mths	627	1.3 (8)	<b>6.374 (2.204–18.434)</b> <b>P=0.001</b>	<b>4.220 (1.471–13.297)</b> <b>P=0.008</b>	627	0.5 (3)	1.016 (0.291–3.545) P=1.000	Not included

OR=Odds ratio; AOR=adjusted odds ratio

<sup>a</sup>1 woman had both HIV and syphilis; including HIV in the syphilis model; or syphilis in the HIV model did not change the AOR values

and are not presented to detract from the vulnerability of refugee and migrant women who are at increased risk of HIV and syphilis infection, due to transient marital relationships based on personal security or unwanted sexual attacks<sup>24</sup>. Rather, to question the prevalence at which routine screening of all pregnant women for HIV and, in particular, syphilis is no longer advisable<sup>25</sup> and to describe the situation from a low prevalence, low resource setting. In addition and for clarity for the reader, while the distinction between refugee and migrant women is reasonable, publications from this border do not usually try to distinguish migrants from urban Mae Sot and those from the rural areas of Tak province<sup>26</sup>. In this publication the MKT population is about 60 km from Mae Sot and the WPA population only 30 km from Mae Sot. Rural, predominantly agricultural workplaces are likely to present less risk from sexually transmitted infections than urban occupations including domestic and services work and factory jobs. It would be useful to make a more formal comparison of these risks in the future as these could affect the recommendations for antenatal screening.

Very little confidence can be placed in the multivariate analysis and it is questionable whether it should be presented at all given the low number of cases and subsequently wide confidence intervals. Somewhat reassuring in terms of data robustness is the association of HIV with the number of remarriages, similar to the number of partners in other settings, and a risk factor typically described in HIV epidemiology<sup>27</sup>. There is an association suggesting protection from HIV with Karen parentage. 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 populations in the refugee camp and is supported by the ethnic trend shown in [Table 1](#) and [Table 3](#).

Older age of women as a risk factor for syphilis is consistent with the Myanmar National AIDS Programme report<sup>22</sup>. This is also suggestive of another confounder to our analysis, the fact that existing serologic tests cannot differentiate between syphilis and yaws or other non-venereal treponematoses<sup>28,29</sup>. Yaws is still included in Thailand's program of neglected tropical diseases indicating that total eradication may not have been achieved yet<sup>30</sup>. 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 sites<sup>31</sup>. The last yaws-related publication from Myanmar was published in 1960<sup>32</sup> on the 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<sup>31,32</sup>. 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 <1:8 and the active cases were in all in younger women<sup>30</sup>. Amongst these low titre 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 VDRL titres in pregnant women in Thailand

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<sup>5,33</sup>. Counselling VDRL discordant couples with low risk histories, where the woman has a very low VDRL titer presents an ethical challenge in this conservative culture. The potential for serious social consequences, such as abuse or abandonment, from false positive results in such couples should be considered.

While the stable HIV prevalence in this population supports continuation of routine HIV screening for all pregnant women, the cost-effectiveness of the syphilis screening in the refugee population is unclear and this would be an area of valuable future research. Donor funds for these screening programs remain precarious and increasingly difficult to sustain as highlighted by Spiegel *et al.*,<sup>34</sup> and as organizations realign services with funding constraints, it is the least cost-effective that will be the first to be abandoned. In low prevalence settings where routine syphilis screening is carried out, healthcare workers should be prepared to counsel low risk couples with discordant screening results, and such counselling should include an explanation of the possibility of false-positive results due to exposure to yaws or other non-venereal treponematoses in countries where the disease has been or remains endemic<sup>30</sup>.

There are limitations with this data series. There are women, estimated at less than 10% of all pregnant women in the catchment area, who do not attend antenatal or delivery care, and obviously we cannot know their status to determine whether they are more or less at risk than women who attended antenatal care. In some viewpoints the lack of point of care (POC) tests, promoted by WHO as the way forward to eliminate maternal transmission of HIV and syphilis, would be considered a limitation<sup>35</sup>. The experience at SMRU has only been with POC for HIV (higher positivity rate than syphilis) and their performance is not encouraging as nearly half were false positives. As the incidence goes down the performance of POC tests likewise falls. Currently maternal distress while waiting for confirmation of a positive POC test for HIV which is sent to the local Thailand Government hospital is a minimum of 3 days. Syphilis, with a lower prevalence than HIV, is likely to have a higher rate of false positive POC tests and for this reason have not been introduced<sup>36</sup>.

Reports from 2011 estimate over 7 million people live in protracted refugee situations, and over 27 million are internally displaced persons<sup>37</sup> and 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.1044120](https://doi.org/10.6084/m9.figshare.1044120)<sup>38</sup>



### Author contributions

RM and FH conceived the study. RM, MEGT, 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, MEGT and RM prepared the first draft of the manuscript. RM, JK, IW, MEGT, 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

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### 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.

## Supplementary materials

Each woman in the database was scored with a one for each of the following risk factors: migrant, age  $\geq 30$  years, history of remarriage, neither parent of the pregnant woman was of the Karen ethnic group and residence of  $< 6$  months at the current address, otherwise the woman was given a score of zero. The five risk factors were tallied for each woman. Most women with syphilis had a score of three or more and accounted for 1.45% (12/830) of all women with a score of three or more. Women with syphilis and a score of less than three included 0.07% (2/2762). Limiting screening to a risk factor score of 3 or more would include less than  $\frac{1}{4}$  of women attending ANC 23% (830/3600), and omit approximately 14.3% (2/14) of cases.

Score	Syphilis n=14	No syphilis n=3578
0	0 (0)	646 (100%)
1	2* (0.2%)	1082 (99.8%)
2	0 (0)	1032 (0%)
3	4 (0.7%)	575 (99.3%)
4	5 (2.3%)	216 (97.7%)
5	3 (10.0%)	27 (90.0%)

\*Score of one obtained in one case due to 'migrant' status, and in the other case because the woman was  $\geq 30$  years old.

Another attempt to identify risk factors was to identify a pattern of risk factors and this is shown in the table below.

Risk factors	Status	Age	Remarriage*	Ethnic group <sup>^</sup>	Residence
1	Refugee	$\geq 30$	1	Karen	$\geq 6$ mths
1	Migrant	$< 30$	1	Karen	$\geq 6$ mths
3	Migrant	$< 30$	1	not Karen	$< 6$ mths
3	Migrant	$\geq 30$	1	not Karen	$\geq 6$ mths
3	Migrant	$\geq 30$	1	not Karen	$\geq 6$ mths
3	Migrant	$\geq 30$	$> 1$	Karen	$\geq 6$ mths
4	Migrant	$< 30$	$> 1$	not Karen	$< 6$ mths
4	Migrant	$< 30$	$> 1$	not Karen	$< 6$ mths
4	Migrant	$\geq 30$	1	not Karen	$< 6$ mths
4	Migrant	$\geq 30$	1	not Karen	$< 6$ mths
4	Migrant	$\geq 30$	$> 1$	not Karen	$\geq 6$ mths
5	Migrant	$\geq 30$	$> 1$	not Karen	$< 6$ mths
5	Migrant	$\geq 30$	$> 1$	not Karen	$< 6$ mths
5	Migrant	$\geq 30$	$> 1$	not Karen	$< 6$ mths

\*one of the partners with more than one marriage

<sup>^</sup>Karen = at least one of the pregnant woman's parents of Karen ethnicity

**Conclusion:** there is insufficient data on which to base a protocol of risk factor based screening.

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[Data Source](#)

# Open Peer Review

Current Referee Status:



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## Version 2

Referee Report 26 August 2015

doi:10.5256/f1000research.6971.r10130



**Nitika Pant Pai**

Division of Clinical Epidemiology, Department of Medicine, Royal Victoria Hospital, McGill University Health Centre, Montreal, QC, Canada

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

**Competing Interests:** No competing interests were disclosed.

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## Version 1

Referee Report 16 September 2014

doi:10.5256/f1000research.4486.r6142



**Nitika Pant Pai<sup>1</sup>, Jana Daher<sup>2</sup>**

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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 ( $P < 0.005$  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.

**We have read this submission. We 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.**

**Competing Interests:** No competing interests were disclosed.

Author Response ( Member of the F1000 Faculty ) 05 May 2015

**Rose McGready**, Tropical Medicine Division, Shoklo Malaria Research Unit, 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 (2<sup>nd</sup> 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 if 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, 2<sup>nd</sup> 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 2<sup>nd</sup> 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 ( $P < 0.005$  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 not 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

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**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 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 <sup>1</sup>. 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) <sup>2</sup>.
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<sup>3</sup>. 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?

## References

1. Watson-Jones D, Chanhalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, Whitehouse A, Balira R, Todd J, Ngeleja D, Ross D, Buvé A, Hayes R, Mabey D: Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. *J Infect Dis*. 2002; **186** (7): 940-947 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
2. Chico RM, Hack BB, Newport MJ, Ngulube E, Chandramohan D: On the pathway to better birth outcomes? A systematic review of azithromycin and curable sexually transmitted infections. *Expert Rev Anti Infect Ther*. 2013; **11** (12): 1303-1332 [PubMed Abstract](#) | [Free Full Text](#) | [Publisher Full Text](#) | [Reference Source](#)
3. World Health Organization: The use of rapid syphilis tests: Geneva:WHO. 2006. [Reference Source](#)

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

**Competing Interests:** No competing interests were disclosed.

Author Response ( *Member of the F1000 Faculty* ) 05 May 2015

**Rose McGready**, Tropical Medicine Division, Shoklo Malaria Research Unit, 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<sup>1</sup>. 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)<sup>2</sup>.**

We agree this is important and have amended the text as suggested in the 2<sup>nd</sup> 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 2<sup>nd</sup> 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 THPA 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 <sup>3</sup>. 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  $\geq 30$  y.*

A risk factor score of  $\geq 3$  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 2<sup>nd</sup> reviewer we have run a multivariate analysis which can be found at the request of the 2<sup>nd</sup> 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).

## References

1. Watson-Jones D, Chanhalucha J, Gumodoka B, Weiss H, Rusizoka M, Ndeki L, Whitehouse A, Balira R, Todd J, Ngeleja D, Ross D, Buvé A, Hayes R, Mabey D: Syphilis in pregnancy in Tanzania. I. Impact of maternal syphilis on outcome of pregnancy. *J Infect Dis.* 2002; **186** (7): 940-947 [PubMed Abstract](#) | [Publisher Full Text](#) | [Reference Source](#)
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3. World Health Organization: The use of rapid syphilis tests: Geneva:WHO. 2006. [Reference Source](#)

**Competing Interests:** no competing interests