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Case-control study of risk factors for incident syphilis infection among men who have sex with men in Tokyo, Japan

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Introduction: In Japan, syphilis notifications have increased. Men who have sex with men (MSM) in Tokyo have contributed substantially to the increase in syphilis notifications. We thus aimed to determine the correlates of incident syphilis among them.

Methods: MSM who attended a Tokyo clinic that serves sexual minorities were recruited in a case-control study in 2015. A case was seropositive for primary/secondary/asymptomatic syphilis at enrolment visit and seronegative at prior visit or had oral ulcers positive for *Treponema pallidum* DNA at enrolment. For each case, two controls seronegative at enrolment and prior visit were selected. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to assess for correlates of case status.

Results: Among 35 cases, the median age was 37 (range = 21–63) years and was similar to the 71 controls. Among HIV-positive participants (26 cases and 67 controls), cases were independently associated with higher frequency of anal or oral sex (OR = 3.4; 95% CI = 1.4–8.6; increase per category from < 1/month, ≥ 1/month but < 1/week, to ≥ 1/week) and no or inconsistent condom use during anal or oral sex (OR = 3.0; 95% CI = 1.1–8.3; increase per category from using every time, occasionally, to never), adjusted for residency and time between visits.

Discussion: Modifiable behaviours were associated with incident syphilis, and dissemination of prevention messages are needed.

Syphilis, a nationally notifiable infectious disease in Japan, has seen a considerable rise in the number of notifications,[1,2] similar to many other countries globally,[3,4] including within the Western Pacific Region.[5–7] In Japan, while more recent increases in syphilis have been among heterosexual men and women,[8] during 2013–2014, this increase was predominantly associated with men who have sex with men (MSM).[1,2] The number of notifications among MSM remained high through 2018. Notably, both the absolute number of reported MSM and heterosexual syphilis cases and the notification rate per population have been highest in Tokyo (4 cases per 100 000 persons-years during 2012–2016), contributing one third of the national cases.[8,9]

Recent studies among MSM have reported that factors associated with syphilis were low educational attainment, sex with casual partners without a condom and coinfection with other sexually transmitted infections (STIs).[10–13] Using mobile phone applications and the Internet to seek partners has also been reported as a potential risk factor for STIs, including syphilis, among MSM.[14–16] While these and other practices have been suggested as possible contributors to the recent rise of syphilis notifications in Japan, very few studies have evaluated potential predictors for syphilis acquisition in Japan. Recently, there was a cohort study analysing the risk factors of incident syphilis infection among HIV-positive MSM in Japan,[17] but behavioural factors were not assessed. To better understand the syphilis outbreak

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among MSM in Tokyo, we conducted a clinic-based case-control study based on a self-administered questionnaire to assess the potential risk factors, including modifiable behavioural factors, for incident syphilis.

MATERIALS AND METHODS

Study design and setting

We conducted a case-control study at Shirakaba Clinic, a clinic that serves sexual minority populations. The clinic is located in the urban area of Tokyo, and most of the patients are MSM from Tokyo and its neighbouring areas. Annually, the clinic serves about 500 HIV-positive patients, and patients with HIV-infection are advised to visit the clinic for antiretroviral therapy treatment and checkup about every three months. Other patients may make a visit if they have signs/symptoms or have concerns regarding STI acquisition.

Sampling and study population

Sampling

Persons who visited Shirakaba Clinic from 1 January to 31 November 2015 and received a syphilis test based on the clinician's evaluation were recruited. Eligible subjects were Japanese males who self-reported as MSM, aged ≥18 years and with sexual activity (anal and/or oral sex) with another male in the six months before study entry. Based on the recent findings from Champenois et al.,[11] assuming 62% exposure in the controls (e.g. for unprotected sex), we estimated that a total sample size of 105 participants with a case-to-control ratio of one to two would be able to detect an odds ratio (OR) of 4.8 with 80% power.[11]

Case subjects

A case was defined as an eligible subject with evidence of recent syphilis infection. For syphilis infection, one of the following conditions based on clinical examination and laboratory evaluation was required: (1) seropositivity by nonspecific (i.e. rapid plasma reagin [RPR]) and specific (i.e. *Treponema pallidum* latex agglutination [TPLA]) treponemal tests for primary, secondary or asymptomatic syphilis[18,19] at a clinic visit at the time of study entry and seronegative based on a nonspecific treponemal test at prior visit; (2) a syphilitic lesion testing positive for *T. pallidum* DNA (*polA*/*TpN47* genes) by polymerase chain reaction (PCR)[20,21] at the enrolment visit (PCR method available on a limited basis for research). We excluded late stage and neurosyphilis cases because they likely would not reflect recent infection, and sexual activity within the recent six months would not be causally related to such infections.

Control subjects

A control was defined as an eligible subject without evidence of recent syphilis infection. Control subjects were seronegative by nonspecific treponemal test for syphilis at both the most recent clinic visit (i.e. time of study entry) and prior visit. For each case, two controls who visited the clinic at the time closest to the time of case detection (within a month) were selected; this was done to recruit controls in a systematic manner and to ensure the same distribution of recruitment time as cases.

Data collection

The following data were collected from the self-administered questionnaire: (1) socio-demographic characteristics, (2) health conditions including past STI history, and (3) sexual activities in the past six months. Pre-exposure prophylaxis for HIV was not available in Japan at the time and thus not included. The questionnaire was developed based on those from recent studies[10,11] and adapted to the Japanese context. Before conducting the study, we performed a pilot study[22] to pretest and improve the questionnaire tool. The questionnaire was completed by the respondent in a private location to reduce social desirability bias. In addition, the following data were collected from the patients' medical charts: (1) clinical data including the stage of syphilis (primary, secondary or asymptomatic); (2) syphilis serology; and (3) HIV-related data. Participants received an STI prevention packet as compensation.

Laboratory testing

Shirakaba Clinic tested serum for syphilis by using the RPR test and TPLA test. The diagnosis of seropositive syphilis was based on both serum RPR value and positive TPLA result.[23] For those highly suspected to be primary stage syphilis based on clinical diagnosis, the clinic sent samples of the syphilitic lesions from those patients to the National Institute of Infectious Diseases (NIID) in Japan

(*1*) where PCR was performed.[20,21] Patients were notified of the results in seven days, and they received empirical treatment for syphilis while waiting for the results. Patients were notified of their test results in person or by phone and offered appropriate treatment and follow-up with post-test counselling. The clinic also tested subjects' serum for HIV by using a fourth-generation combined enzyme immunoassay and antigen screening tests.

Statistical analysis

Descriptive analyses were conducted to assess the distribution of characteristics among cases and controls. To compare distributions, the Student's *t*-test or the Mann–Whitney U test was used for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Using univariate logistic regression with odds ratios and the associated 95% confidence intervals, we assessed the association between syphilis infection and sociodemographic characteristics, health conditions including past STI history and recent sexual activities. Potential risk factors for incident syphilis hypothesized a priori based on a conceptual model (e.g. condom use, frequency of sex) were considered for inclusion in a multivariable model for risk factors adjusted for duration between entry visit and prior visit. Variables with a notably large or small OR in the univariate analysis were also considered in further exploratory analyses. Statistical significance was defined as two-sided P-values < 0.05. All statistical analyses were performed with the Statistical Package for Social Sciences Ver.18.0 (SPSS Inc., Chicago, Illinois, USA).

Ethics

This study was approved by the ethics committee of the NIID in Japan (approval no: NIID-564) and was implemented in accordance with the provisions of the Declaration of Helsinki.[24] Informed consent was obtained from all participants in the study.

RESULTS

Description of syphilis cases and controls

During the study period, a total of 123 participants (41 cases and 82 controls) agreed to participate and were enrolled in the study. Twelve subjects agreed to participate but did not respond to the questionnaire; based on the questionnaire responses, five additional subjects were excluded because they provided discrepant answers from the recruitment screening (i.e. they denied having sex in the past six months in the questionnaire). The remaining 106 participants (35 cases and 71 controls) were enrolled for analysis (**Fig. 1**). The sexual identity of all participants was confirmed to be MSM based on self-reporting. One case was married to a woman, and one control was divorced.

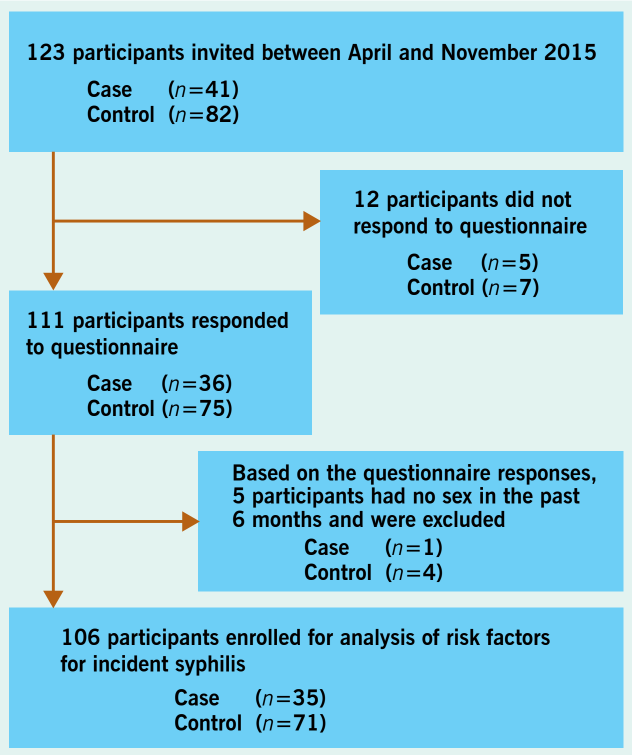
Among cases, the median age at study entry was 37 (range: 21–63) years, and the median age for first sex with a male was 18 (range: 10 –25) years, both of which were similar to those of controls (**Table 1**). For stage of syphilis, three (8.6%) were primary, 13 (37.1%) were secondary and 19 (54.3%) were asymptomatic. Among the symptomatic primary/secondary cases, 12 (34.3%) presented with rash, three (8.6%) with chancre and one (2.9%) with oral ulcer. Thirty-two (91.4%) cases, including all asymptomatic cases, were diagnosed by serology, while all three (8.6%) cases with primary syphilis were diagnosed by PCR. The median duration between study entry visit and prior visit was 3.7 (IQR: 2.5–6.1) months among cases compared to 2.6 (IQR: 2.0–3.0) months among controls ($P < 0.01$).

Correlates of incident syphilis infection, univariate analysis

Compared to controls, cases were more likely to have resided in Tokyo (OR = 3.5; 95% CI = 1.1–11.1) and have a past history of syphilis (OR = 2.7; 95% CI = 1.1–6.2) (**Table 1**). Cases were also more likely to have a past history of STIs other than syphilis or HIV (OR = 5.4; 95% CI = 1.7–16.8); specifically, cases had a higher odds of having a past history of gonorrhea infection and anogenital human papillomavirus (HPV) infection (**Table 1**).

In contrast, while most cases and controls were infected with HIV, a lower proportion of the cases were infected with HIV relative to controls (26 cases [74.3%] versus 67 controls [94.4%]; OR = 0.2; 95% CI = 0.1–0.6) (**Table 1**). Among the HIV-positive participants, 24 cases (92.3%) and 64 controls (95.6%) were receiving antiretroviral therapy (ART) at the time of study entry and HIV-RNA was well suppressed in both cases and controls, with a median CD4 count (cell/μL) of 603 (IQR: 195–1206) in cases and 655 (IQR: 482–778) in controls. HIV-positive MSM had a shorter interval period between study entry and prior visit (median: 2.8 months;

Fig. 1. **Participant enrolment process**



IQR: 2.1–3.5) compared to HIV-negative MSM (median: 4.9 months; IQR: 2.2–10.7). Intervals were similar for HIV-positive (median: 2.7 months) and HIV-negative (median: 2.6 months) controls, but only four out of 13 HIV-negative MSM were controls. While the majority of the HIV-positive cases were asymptomatic (18/26 cases), among the nine HIV-negative cases, six were secondary, two were primary, and one was asymptomatic for stages of syphilis.

Cases were significantly associated with both the number of sex partners and average frequency of sex (anal or oral) in the past six months compared to controls with a dose-response relationship of increased odds of case status with increase in either of these factors (**Table 2**). Cases were also associated with alcohol intake and sex toy use during sex (anal or oral). In addition, cases had a greater odds of no or inconsistent condom use during sex. While there was a greater magnitude of association for anal than oral sex, there was a dose-response trend for both; combined as a single variable (i.e. complete, occasional or no condom use based on either sex act),

Table 1. **Socio-demographic and sexually transmitted infection status characteristics of study participants and association with incident syphilis by univariate analysis**

	Cases (*n* = 35), *n* (%)*		Controls (*n* = 71), *n* (%)		OR	(95% CI)	*P*-value
Socio-demographic characteristics							
Median age, years (range)	37 (21–63)		37 (23–57)				0.79
Duration between entry visit and prior visit, median month (IQR)	3.7 (2.5–6.1)		2.6 (2.0–3.0)				<0.01
Residence							
Outside Tokyo	4	(11.4)	22	(31.0)	Ref		
Tokyo	31	(88.6)	49	(69.0)	3.5	(1.1–11.1)	0.03
Education background							
College or university	26	(74.3)	55	(77.5)	Ref		
High school and below	9	(25.7)	16	(22.5)	1.2	(0.5–3.0)	0.72
Employment status							
Full time	30	(85.7)	63	(88.7)	Ref		
Non-full time	5	(14.3)	8	(11.3)	1.3	(0.4–4.4)	0.66
Median age at the first sex with male (range)	18 (10–25)		19 (9–30)				0.11
History of sex with female	16	(45.7)	21	(29.6)	2.0	(0.9–4.6)	0.10
Median age at the first sex with female (range)	19 (15–25)		20 (15–30)				0.32
STI status							
Past syphilis	24	(68.6)	32	(45.1)	2.7	(1.1–6.2)	0.02
HIV seropositive	26	(74.3)	67	(94.4)	0.2	(0.05–0.6)	0.01
Past STIs other than syphilis or HIV	31	(88.6)	42	(59.2)	5.4	(1.7–16.8)	<0.01
Gonorrhoea	9	(25.7)	7	(9.9)	3.2	(1.1–9.4)	0.03
Chlamydia	5	(14.3)	15	(21.1)	0.6	(0.2–1.9)	0.40
Genital herpes	3	(8.6)	4	(5.6)	1.6	(0.3–7.4)	0.68
Hepatitis B	13	(37.1)	18	(25.4)	1.7	(0.7–4.2)	0.21
Anogential HPV	15	(42.9)	16	(22.5)	2.6	(1.1–6.2)	0.03
Amebiasis	3	(8.6)	3	(4.2)	2.1	(0.4–11.1)	0.39

**n* (%) unless indicated as otherwise for age, duration between study visits

STI, sexually transmitted infection; OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; ART, antiretroviral therapy; IQR, interquartile range; HPV, human papillomavirus.

Table 2. **Participant characteristics regarding sexual activities in the past six months before study entry and association with incident syphilis by univariate analysis**

	Cases (*n* = 35), *n* (%)		Controls (*n* = 71), *n* (%)		OR	(95% CI)
Number of sex partners						
1–5	11	(31.4)	40	(56.3)	Ref	
6–15	16	(45.7)	22	(31.0)	2.6	(1.0–6.7)
≥ 16	8	(22.9)	9	(12.7)	3.2*	(1.0–10.3)
Partner type						
Steady	1	(2.9)	8	(11.3)	Ref	
Casual	34	(97.1)	63	(88.7)	4.3	(0.5–36.0)
Method of seeking sex partners†						
Cruising spot	23	(65.7)	47	(66.2)	1.0	(0.4–2.3)
Internet	16	(45.7)	28	(39.4)	1.3	(0.6–2.9)
Mobile phone applications	19	(54.3)	37	(52.1)	1.1	(0.5–2.5)
Average frequency of sex (anal or oral)						
< 1/month	4	(11.4)	24	(33.8)	Ref	
≥ 1/month but < 1/week	21	(60.0)	40	(56.3)	3.2	(1.0–10.3)
≥ 1/week	10	(28.6)	7	(9.9)	8.6*	(2.0–35.9)
Alcohol intake during sex (anal or oral)						
No	16	(45.7)	47	(66.2)	Ref	
Yes	19	(54.3)	24	(33.8)	2.3	(1.0–5.3)
Recreational drug use during sex (anal or oral)						
No	30	(85.7)	61	(85.9)	Ref	
Yes	5	(14.3)	10	(14.1)	1.0	(0.3–3.2)
Sex toy use during sex (anal or oral)						
No	24	(68.6)	60	(85.7)	Ref	
Yes	11	(31.4)	10	(14.3)	2.8	(1.0–7.3)
Condom use during anal sex‡						
Every time	9	(25.7)	35	(50.0)	Ref	
Occasionally use	18	(51.4)	26	(37.1)	2.7	(1.0–6.9)
No use	8	(22.9)	9	(12.9)	3.5	(1.0–11.5)
Condom use during oral sex‡						
Every time	12	(34.3)	32	(45.7)	Ref	
Occasionally use	8	(22.9)	20	(28.6)	1.1	(0.4–3.1)
No use	15	(42.9)	18	(25.7)	2.2	(0.9–5.8)
Condom use during anal or oral sex‡						
Every time	3	(8.6)	22	(31.4)	Ref	
Occasionally use	27	(77.1)	45	(64.3)	4.4	(1.2–16.1)
No use	5	(14.3)	3	(4.3)	12.2*	(1.9–79.4)

*Significant for trend.
†Includes multiple responses
‡Data for 1 control not available for analysis
OR, odds ratio; CI, confidence interval

there was a more than 10-fold increase in odds for those that did not use condoms at all relative to those who used them every time for either sex act (**Table 2**). Although the difference was not statistically significant, cases had a four-fold higher odds of having sex with a casual partner compared to controls; all nine participants who reported a steady partner were HIV-positive, and eight of them were controls. There were no differences between cases and controls in the method of seeking partners (cruising spot, Internet or mobile phone applications) (**Table 2**). In addition to type of method, no differences were detected when comparing the number of methods used in seeking sex partners. Although there were no differences between cases and controls in the method of seeking partners, all four HIV-negative controls used mobile phone applications compared to 67% (45/67) of the HIV-positive controls.

Identification of potential risk factors among HIV-positive cases and controls by multivariable analysis

Given that there were only 13 HIV-negative subjects (9/35 cases and 4/71 controls) and HIV-positive subjects differed in health-care access behaviour (e.g. shorter time between visits), the main analysis was restricted to HIV-positive cases (n = 26) and controls (n = 67). Results from univariate analysis for this restricted population were similar, with case status remaining strongly associated with the following:

- Tokyo residency (OR = 3.5; 95% CI = 1.0–13.0);
- past history of syphilis (OR = 4.9; 95% CI = 1.7–14.5);
- past history of STIs other than syphilis or HIV (OR = 5.5; 95% CI = 1.5–20.1);
- number of sex partners (relative to 1–5 partners, OR = 2.1 [95% CI = 1.1–3.9] for 6–15 partners, and OR = 4.2 [95 %CI = 1.2–14.8] for ≥ 16 partners);
- average frequency of sex (relative to < 1/month, OR = 4.8 [95% CI = 1.0–23.0] for ≥ 1/month but < 1/week, and OR = 15.3 [95% CI = 2.6–91.9) for ≥ 1/week]; and

- no or inconsistent condom use during anal or oral sex (relative to using every time, OR = 2.9 [95% CI = 0.8–11.1] for occasional use and OR = 8.9 [95% CI = 1.3–61.1) for no use]).
- While not significant, case status also remained associated with alcohol intake (OR = 2.0; 95% CI 0.8–5.1) and sex toy use (OR = 2.8; 95% CI = 0.9–8.4).

Number of sex partners, past syphilis infection, past STIs other than syphilis or HIV, alcohol intake and sex toy use did not remain significant, and the association with case status was reduced when adjusted for average frequency of sex (anal or oral), an a priori hypothesized strong risk factor for incident infection. In multivariable analysis, average frequency of sex (anal or oral) and no or inconsistent condom use during either anal or oral sex both independently remained significantly associated with incident syphilis, with both having a three-fold increase in odds for increase per category, adjusted for Tokyo residency and duration between entry visit and prior visit (**Table 3**).

DISCUSSION

Our case-control study found that no or inconsistent condom use during anal or oral sex and higher frequency of sex were potential risk factors for incident syphilis infection among HIV-positive MSM in Tokyo with a dose–response trend. As most of the participants were HIV-positive MSM (87.8% [93/106]), and as HIV-positive patients were believed to differ from HIV-negative patients as a population, the primary analysis was restricted to the former. As HIV patients are requested to visit this clinic on a regular basis (usually every three months, including for ART and laboratory testing), we found that the interval between visits was short among HIV-positive participants, thus increasing the likelihood of categorizing them as a control due to more frequent outcome detection. Furthermore, although the majority of the HIV-positive cases were detected as asymptomatic, the majority of HIV-negative cases were detected as having secondary syphilis; given the more routine visits among HIV-positive cases, HIV-negative cases appeared to be detected at a later, symptomatic stage of syphilis. This restriction was thus deemed important to reduce sparse data bias and detection-related bias.

Although past studies from other countries have reported similar findings,[10–13] to our knowledge, this is the first study in Japan to assess for modifiable behaviours for incident syphilis infection among HIV-positive MSM. Similar to a recent case-control study in France[11] that found unprotected oral sex to be a potential risk factor for incident syphilis among MSM, we also found unprotected sex to be associated with greater odds of incident syphilis; importantly, we found a strong dose–response relationship and the association to be strongest when there was no condom use for either oral or anal sex. Although there were only 13 HIV-negative participants, none of the nine cases used condoms at every sexual encounter while two of the four controls used them consistently, indicating a similar direction of risk with unprotected sex. As the majority of HIV-negative participants were also detected at the secondary stage with longer duration between visits, encouraging more routine testing among this subpopulation would be important to consider.

Our study showed that Tokyo residency was marginally associated with incident syphilis. Tokyo has been the epicentre of the syphilis outbreak in Japan with both the highest absolute number of cases and the highest notification rate in Japan.[2] As Tokyo residency remained associated with case status adjusted for frequency of sex, we considered that one of the possible reasons might be due to the syphilis status of the partner he would have encountered in Tokyo. As the syphilis notification rate has been highest in Tokyo, the prevalence would also be expected to be high, and, all else being equal, the risk of syphilis infection might be higher when encountering a “new partner” in Tokyo. New partner acquisition has been associated with incident STI such as anogential HPV.[25]

This study has several important limitations. First, this study was conducted at a single clinic in Tokyo, and generalizability of findings may be limited. However, this clinic reported the largest number of syphilis cases in Tokyo, representing 18% (76/417 cases) of cases notified from Tokyo in 2013.[26] The clinic-based controls also accounted for biases associated with health care–seeking behaviours and helped ensure that cases and controls arose from the same population. While restriction to HIV-positive patients was deemed important to prevent detection-related biases, our interpretations are limited to HIV-positive MSM, and the small number of HIV-negative

Table 3. **Multivariable analysis of factors associated with incident syphilis among HIV-positive participants, *n* = 93**

	Cases (*n* = 26), *n* (%)*		Controls (*n* = 67), *n* (%)		OR	(95% CI)
Tokyo residency	23	(88.5)	46	(68.7)	3.1	(0.8–12.4)
Average frequency of sex (anal or oral)						
< 1/month	2	(7.7)	23	(34.3)	3.4**	(1.4–8.6)
≥ 1/month but < 1/week	16	(61.5)	38	(56.7)		
≥ 1/week	8	(30.8)	6	(9.0)		
Condom use during oral or anal sex†						
Every time	3	(11.5)	20	(30.3)	3.0**	(1.1–8.3)
Occasionally use	19	(73.1)	43	(65.2)		
No use	4	(15.4)	3	(4.5)		
Duration between entry visit and prior visit, median month (IQR)	3.2	(2.5–5.8)	2.7	(2.0–3.0)	1.0***	(0.9–1.1)

**n* (%) except for duration between study visits, as indicated.
**Odds ratio represents increase per category.
***Odds ratio represents increase per month.
†Data for 1 control not available for analysis.
OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range.

patients precluded reliable assessments for effect modification. Second, this study may be affected by residual or unmeasured confounding, such as that due to sex with a new partner. Third, we could not evaluate temporality of events given the interval-censored nature of the data collected; although we assessed sexual activity in the six months before incident infection detection, it is not possible to determine the specific timing of sexual activity that would have been causally related to the acquisition of syphilis. Lastly, because cases and controls were aware of their syphilis infection status at the time of the survey, such knowledge could have affected the reporting behavior differently between cases and controls.

This study was the first case-control study to evaluate potential behavioural risk factors for incident syphilis infection in Japan. In addition to locations in the Region reporting a high burden of syphilis.[5] These findings may be of particular relevance for Member States where a high syphilis burden has been found in HIV-positive MSM.[27] Although previous studies have pointed out that consistent condom use may protect against syphilis infection,[10–13] this study was the first from Japan to evaluate such practices and found that consistent condom use was associated with lower odds of incident syphilis in the current outbreak. Conversely, higher frequency of sex was associated with incident syphilis. These findings are important for making informed, evidence-based recommendations regarding syphilis prevention among MSM in Japan. Feedback of the preliminary findings to stakeholders, including the MSM community, has taken place, and reporting of HIV status became required for national syphilis surveillance in January 2019; however, concerns remain as syphilis notifications among MSM remain high. To tackle the syphilis outbreak, targeted STI prevention education (including condom use), risk communication and outreach for testing and further investigations are needed among MSM in Tokyo, particularly among non-HIV-positive MSM where information is limited. Tokyo prefecture has enhanced STI education and awareness activities, and several local jurisdictions in Japan have initiated active contact-tracing investigations and partner notifications. With the upcoming Tokyo Olympic/Paralympic Games in 2020, a major global event with a potentially unprecedented number of visitors to enter Japan, continued syphilis prevention and control will be important.

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Field epidemiology training programmes in the Asia-Pacific: what is best practice for supervision?

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Introduction: Field epidemiology training programmes (FETPs) emphasize competency-based training and learning by doing. Supervision of FETP trainees is critical for programmes to achieve learning outcomes. We sought to address a knowledge gap regarding what constitutes effective FETP supervision.

Methods: We investigated FETP supervision using a mixed-methods approach. Quantitative data were collected through a survey of FETP directors. Qualitative data included written feedback from the survey and a focus group discussion (FGD) conducted with FETP supervisors at the 8th South-East Asia and Western Pacific Bi-regional TEPHINET Conference. FGD questions focused on effective supervisory qualities and activities and challenges to effective supervision. We calculated descriptive statistics for quantitative data and analysed qualitative data using a deductive content analysis approach.

Results: Eleven FETP directors responded to the survey and 23 participated in the FGD. Overall, supervision was seen as very important for trainee outcomes. Participants identified the different roles of academic and field supervisors but emphasized the importance of an enabling and supporting attitude towards trainees. Soft skills and interpersonal abilities were among the most important qualities identified for effective supervision. Key challenges identified included a lack of consistency in supervisors' technical knowledge and the difficulty of finding candidate supervisors with sufficient interest, availability and motivation for supervision.

Discussion: Several practical recommendations arose from this study for supervision in FETPs, including recruiting and training supervisors with a more holistic range of skills. Our findings also provide key points for current FETP supervisors to consider to improve their own practice.

Field epidemiology is defined as the "the practice of epidemiology in real time and real place, which in turn involves both science and art".[1] Field epidemiology is a key component of the response to some of the world's major public health problems; it has been vital to detecting and controlling such large-scale outbreaks as the 2014 outbreak of Ebola virus disease in West Africa, the 2009 H1N1 influenza pandemic and the 2003 multicountry outbreak of severe acute respiratory (SARS). Adequate training of field epidemiologists is an indicator of country capacity in implementing the International Health Regulations (2005).[2]

Field epidemiologists are frequently trained in dedicated on-the-job training programmes called field epidemiology training programmes (FETPs).[3] FETPs aim to build the capacity of public health systems in the countries where they are implemented. They do this by recruiting health-care workers, scientists and others and building their competence in field epidemiology through on-the-job mentorship, supervision and training. Several practices distinguish these programmes from academic education in public health. FETPs use a service-based approach (where trainees support the host organization's priorities), implementing competency-based training under the supervision of qualified mentors/supervisors and strengthening systems capacity using a learning-by-doing approach.[3] Following the establishment of the United States Epidemic Intelligence Service as one of the first formal FETPs in 1951, other FETPs have been established worldwide.[4] The Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) reports that there are now 71 FETPs operating in more than 100 countries globally.[5]

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Supervision of trainees in the field is a core component of FETPs and one that is thought to facilitate learning and the application of that learning to promote and protect public health. Supervisory structures vary according to the model of the FETP, the organization delivering the programme and the context. The FETP handbook identifies supervision as the responsibility of both technical leaders (typically resident advisers) and field supervisors.[3] Within this handbook, supervision is described as involving consultation on epidemiology methods, monitoring and evaluating trainee activities and mentoring and troubleshooting trainee projects. While terminology and models of supervision differ among programmes, it is typical for trainees to have a workplace or field supervisor who is based in their host organization in addition to an academic or programme supervisor who is a subject matter specialist affiliated with the FETP. For example, in many United States Centers for Disease Control and Prevention (CDC) programmes that provide support for FETPs, resident advisers (CDC epidemiologists employed to provide technical support to FETPs) and other programme staff provide additional scientific support to trainees, complementing day-to-day field supervision by a senior colleague in the workplace.[3] (Note that throughout this paper we use the term supervisor for anyone in a designated supervisory role of the trainee, whether this be a workplace/field supervisor or academic/programme supervisor. We recognize that in many programmes the term mentor is more frequently used for people in this role. Trainees also have many other names, but we have used trainees throughout.)

Despite the central role of supervision in FETPs, there is little published evidence on best practice in FETP supervision. Existing FETP guidelines largely focus on the logistical aspects of supervision with limited consideration of the broader qualities and activities that are important for effective supervision.[3,6] Programme experiences from the Asia-Pacific and other regions highlight issues related to FETP supervision such as a lack of adequate epidemiology knowledge among workplace supervisors,[6,7] and the interest in professional training in supervisory techniques.[7] A more comprehensive body of peer-reviewed evidence exists for other professions where supervision is a key component, such as health-care worker training that takes place in clinical settings.[8,9] Some of this literature may also be applicable to the FETPs, including the importance of integrating theoretical knowledge with practical experience[10] and recognizing the value of a holistic supervisory role, including interpersonal skills, nurturing and guiding alongside teaching specific skills and content knowledge.[8] However, none of the literature captures the particular needs and expectations of FETP supervisors.

Therefore, we undertook a mixed-methods study to determine the components and characteristics of effective supervision in the FETP context from the perspective of experienced FETP staff in the Asia-Pacific region. Our aim was to provide information on best practice in FETP supervision to further strengthen FETPs and the response to public health problems and threats.

METHODS

Study design

This study employed a mixed-methods design, combining focus group discussions (FGDs) and a cross-sectional survey.

Study population and data collection

FGD were held at a workshop for FETP supervisors titled "How to improve field epidemiology training in the Asia-Pacific" at the 8th South-East Asia and Western Pacific Bi-regional TEPHINET Conference, in Siem Reap, Cambodia from 28 November to 2 December 2016. The workshop was advertised as "of interest to FETP staff and supervisors" via materials sent to all attendees before the conference. Two experienced facilitators from Australia presented a summary of the literature on FETP supervision, including knowledge gaps; then, the facilitators guided FGD on the key themes outlined in **Box 1**. These discussions were documented in detailed notes.

To obtain quantitative insights on different aspects of the key topic areas, FETP directors attending the same TEPHINET conference were invited to provide their views in a survey on various aspects of FETP supervision. The survey included 16 open- and closed-ended questions about FETP supervision including the differing roles of programme and field supervisors, effective supervisory qualities and activities, and challenges to supervision. Survey questions were based on key themes and findings about supervision in the literature review and informed by reports from the investigators who are experienced FETP supervisors.[8,9,11]

Data analysis

Qualitative data from the workshop were analysed using a deductive content analysis approach.[12] Quantitative survey data were analysed using descriptive statistics. We calculated numbers and proportions of positive responses for questions with binary responses; Likert scale questions were calculated using the numbers and proportions of positive, negative and neutral responses. Data from open-ended questions were coded according to the framework of themes developed from workshop data (**Box 1**).

Consent

Participants at the workshop signed consent forms to participate in the workshop and have the findings published. FETP directors provided implied consent by responding to the survey and were informed that the results of the survey would be published.

Ethics statement

Ethics approval for this study was provided by the Australian National University (protocol 2016/420) and the University of New South Wales Human Research Ethics Committees (protocol 15571).

RESULTS

Results are organized into themes addressing the key study questions, shown in **Box 1**. Quantitative results from the survey are presented in **Tables 1 to 4**. Qualitative analyses of workshop discussions are available in **Box 2**. The majority of survey and FGD questions did not distinguish between field and programme supervisors. Other than in **Table 2**, results describe a general perspective on good practice in supervision without reference to specific supervisory roles.

Participation in the survey and workshop

Twenty-three participants attended the workshop. Of the 19 total member countries represented in the Western Pacific and South-East Asia regions of TEPHINET, participants were associated with programmes in 13 countries and identified themselves as supervisors, mentors and resident advisers.

Box 1. **Key themes addressed in the workshop and survey**

- What are the roles of a Field Epidemiology Training Programme (FETP) supervisor?
- What makes a good FETP supervisor?
- What are the challenges to supervision?

Directors from 11 of these TEPHINET programmes responded to the survey (response rate of 58%). Of these, 91% (n = 10) had a programme duration of 13–24 months. The majority of programmes (73%, n = 8) had been established for more than 10 years, 18% (n = 2) for 6–10 years and 9% (n = 1) for 4–5 years.

What are the roles of an FETP supervisor?

Survey

Overall, FETP directors appeared to have a high degree of recognition of the value of supervisors for effective FETP training. The majority of FETP directors (55%) perceived the role of the supervisor as being “very effective” in facilitating the development of competent field epidemiologists; the remainder rated the supervisor’s role as “effective”.

A wide range of activities were considered to be part of the supervisory role (**Tables 1 and 2**). The activities rated as most important for effective supervision were those that emphasized an interpersonal connection between the supervisor and trainee to learn practical skills, including logistical arrangements to support these activities. Comparing the roles of field and programme supervisors, the field supervisor was seen as having a more holistic role with more than 50% of participants rating each of the 18 activities outlined in **Table 2** as part of the field supervisor’s role. In contrast, many participants perceived the programme supervisor to have a more defined role that focused on transfer of technical skills and knowledge. One survey participant indicated that “daily discussions on outbreak investigation and feedback to the trainee” were a particularly effective supervisory activity, reflecting the strong emphasis on the value of interpersonal contact and soft skills developed through regular contact with field supervisors (**Table 2**).

Box 2. **Key findings arising from the discussion on FETP supervision at the 8th South-East Asia and Western Pacific Bi-regional TEPHINET Conference workshop, 2016**

What are the roles of a field epidemiology training programme (FETP) supervisor?

1. Helping trainees meet programme requirements, including:
    - Logistical support
        - *directing trainees to appropriate projects*
        - *arranging access to data and appropriate resources, including people*
    - Providing feedback
      helping trainees improve their performance and ultimately meet their programme requirements
    - Teaching and training
      supporting the trainee to learn by doing rather than teaching didactically
2. Different roles in different settings
   instructive, technical support in the classroom and more pragmatic, personal support in the field
3. Helping the trainee to develop a professional network
   supporting trainees to build networks within public health and epidemiology communities
4. Holistic support of the trainee
   assisting trainees to develop skills and face challenges in both work and life and overall supporting an enriching trainee experience

What makes a good FETP supervisor?

1. Skills and qualities
   interpersonal skills, mentoring and leadership skills, patience, commitment and motivation in supervision, empathy for trainees, role modelling and guidance
2. Availability
   easily available and approachable, with plenty of time made for trainees
3. Professional background
   having a health-related profession and training to confer technical knowledge and credibility
4. Understanding of FETP requirements
   having a sound understanding of programme requirements and expectations of trainees
5. Different styles for different settings
   being able to adapt supervisory style according to trainee needs and contextual demands

What are the challenges to supervision?

1. Time and availability
   supervisors lacking time and availability is a major barrier to positive trainee outcomes
2. Differing expectations from different supervisors
   when supervisors disagree and particularly when they give diametrically opposite feedback, this can be very challenging for both trainees and supervisors
3. Cultural and language issues
   for supervisors and trainees working in cross-cultural environments, there can be challenges around expectations of interactions and how feedback is given and received
4. Organizational barriers and issues
   issues can arise when trainees are in employed positions and have a workplace supervisor who may not understand FETP projects and deliverables and may also want the trainee to do other work
5. Doing rather than enabling
   trying to didactically teach trainees the right way to do something can be a frustrating and time-consuming process, rather than supporting them to guide their own learning needs

Workshop

A key theme from the workshop was that the primary role of the supervisor was not to teach didactically, but instead to facilitate the trainee's learning and to guide the trainee to ask the right questions. This was seen as fitting under the overall ethos of FETPs, facilitating learning by doing, and was exemplified by one participant's analogy of the supervisor as a midwife: the supervisor coaches and provides encouragement and expertise, but in the end, it is the trainee who has to do the work.

Another key theme from the workshop was the different supervisory roles played by programme and field supervisors. Several participants highlighted that, in the classroom, supervisors should act mainly as instructors in specific technical areas. In the field, however, their role was to supervise the work of the trainee in outbreak investigations and to provide technical support, if needed. It was suggested that these differences could limit the capacity for programme supervisors to provide support on more holistic or interpersonal matters, while field supervisors held greater responsibility for supporting development of a different set of skills such as leadership and communication.

Table 1. **FETP directors' ratings of effectiveness of different supervisory activities (n = 11)**

Supervisory activities	Rated "effective" or "very effective" n(%)	Rated "neither effective nor ineffective" n(%)	Rated "ineffective" or "very ineffective" n(%)
Ensuring the trainee has adequate exposure to outbreaks and other public health events	11 (100%)	0 (0%)	0 (0%)
Teaching specific techniques and concepts, e.g. teaching how to write a questionnaire	10 (91%)	1 (9%)	0 (0%)
Ensuring the trainee has appropriate level of responsibility	10 (91%)	1 (9%)	0 (0%)
Ensuring the trainee has an adequate amount of time to complete work	10 (91%)	1 (9%)	0 (0%)
Regular one-on-one meetings with formal feedback	10 (91%)	0 (0%)	1 (9%)
Informal on-the-job feedback	9 (82%)	2 (18%)	0 (0%)
Observation by the trainee of the supervisor conducting outbreak investigations	9 (82%)	1 (9%)	1 (9%)
Giving advice on professional development	9 (82%)	2 (18%)	0 (0%)
Observation by the supervisor of the trainee conducting outbreak investigations	9 (82%)	2 (18%)	0 (0%)
Feedback on written work	8 (73%)	3 (27%)	0 (0%)

What makes a good FETP supervisor?

Survey

FETP directors perceived the supervisor's level of public health knowledge as the most critical quality for effective supervision (**Table 3**). Similarly, their technical skills were also seen as highly important along with a range of more holistic qualities including enthusiasm, interpersonal skills, approachability and availability.

Workshop

The workshop discussion highlighted that good interpersonal skills, particularly mentoring and leadership skills, as well as high levels of patience were particularly important for effective supervision. Good supervisors were seen as being committed and having passion and motivation to supervise. Other participants viewed the supervisory relationship as a type of parental role in which the supervisor cared about and guided the trainee in a range of areas. Workshop participants identified a supervisor's level of availability and approachability as critical characteristics.

In addition to their personal and interpersonal traits, the training background of the supervisor – specifically having a health-related profession – was seen as important. In addition to presumably conferring technical knowledge, having a health-related background was seen to confer credibility to the supervisor. It was also seen as critical that supervisors had a sound understanding of programme requirements so they knew what the trainee was expected to achieve.

What are the challenges to supervision?

Survey

A lack of interest in supervision and insufficient skills to provide effective feedback were perceived to be the greatest challenges to effective supervision (**Table 4**). A survey participant noted that "not all can effectively teach, even though they may be able/competent", suggesting that aptitude for and interest in supervision are important along with a supervisor's level of knowledge and experience.

A lack of technical skills and relevant knowledge was seen as the next most critical barrier to good supervision (**Table 4**). A supervisor's lack of time was also noted as a challenge, and comments from survey participants also stated that supervisors often lacked time to support trainees. Other comments identified the remoteness of programme supervisors and their lack of time spent face to face with

Table 2. **FETP directors' ratings of key supervisory activities for field and programme supervisors**

Supervisory activity	Rated positive for field supervisors, *n* (%), *n* = 11	Rated positive for programme supervisors, *n* (%), *n* = 10
To teach the trainee interpersonal skills (i.e. teamwork)	11 (100%)	4 (40%)
To help the trainee negotiate organizational/logistical issues	10 (100%)*	4 (44%)*
To help the trainee develop professional networks	10 (100%)*	7 (78)*
To provide opportunities for the trainee to develop technical skills (i.e. data analysis) but not directly teach these	10 (91%)	8 (80%)
To provide opportunities for the trainee to develop interpersonal skills (such as teamwork) but not directly teach these	10 (91%)	6 (60%)
To monitor the trainee's progress	10 (91%)	5 (56%)*
To provide feedback to the trainee on their progress	10 (91%)	6 (60%)
To ensure the quality of outbreak investigations undertaken by the trainee	10 (91%)	7 (70%)
To motivate the trainee	9 (90%)*	5 (56%)*
To identify projects for the trainee	9 (90%)*	6 (67%)*
To inspire the trainee	8 (80%)*	5 (50%)
To provide emotional support to the trainee	8 (80%)*	4 (40%)
To help the trainee recognize their strengths and weaknesses	8 (80%)*	7 (78%)*
To teach the trainee technical skills (i.e. data analysis)	8 (73%)	8 (80%)
To teach the trainee management skills (i.e. managing staff)	8 (73%)	5 (50%)
To ensure the quality of other public health work undertaken by the trainee	8 (73%)	6 (60%)
To provide opportunities for the trainee to develop management skills (i.e. managing staff) but not directly teach these	7 (64%)	5 (50%)
To help the trainee develop a career plan	6 (55%)	5 (50%)

* = 1 response missing for this item

Table 3. **FETP directors' ratings of the importance of selected supervisor qualities and skills (*n* = 11)**

Supervisor qualities and skills	Rated "somewhat important" or "very important", *n* (%)	Rated "neither important nor unimportant", *n* (%)	Rated "not very important" or "not at all important", *n* (%)
Public health knowledge	11 (100%)	0 (0%)	0 (0%)
Technical skills	10 (91%)	1 (9%)	0 (0%)
Enthusiasm for public health	10 (91%)	1 (9%)	0 (0%)
Interpersonal skills	10 (91%)	1 (9%)	0 (0%)
Approachability	10 (91%)	1 (9%)	0 (0%)
Availability	10 (91%)	1 (9%)	0 (0%)
Enthusiasm for teaching	9 (82%)	2 (18%)	0 (0%)
Empathy	8 (73%)	3 (27%)	0 (0%)
Seniority	5 (45%)	6 (55%)	0 (0%)

Table 4. **FETP directors' ratings of important challenges to supervision (n = 11)**

Challenges to supervision	Rated "somewhat important" or "very important", *n* (%)	Rated "neither important nor unimportant", *n* (%)	Rated "not very important" or "not at all important", *n* (%)
Supervisor lacks interest in supervision	11 (100%)	0 (0%)	0 (0%)
Supervisor lacks skills and knowledge on how to give effective feedback	11 (100%)	0 (0%)	0 (0%)
Supervisor lacks technical skills and knowledge in public health	10 (91%)	1 (9%)	0 (0%)
Supervisor lacks time to devote to supervision	9 (82%)	2 (18%)	0 (0%)
Supervisor is an inappropriately senior person within the organization	8 (73%)	1 (9%)	2 (18%)

trainees as a barrier to teaching technical competencies. The supervisor's degree of seniority was seen as less important, with only 27% (***n*** = 3) identifying this as a "very important" challenge for effective supervision (**Table 4**).

Workshop

It was deemed important to engage committed and motivated supervisors. However, identifying and finding these people was perceived to be challenging. This was linked to the issues of time and availability, as people who would make good supervisors may lack the time required for hands-on supervision.

Differing expectations between supervisors across contexts was a commonly reported issue. It was acknowledged that having multiple supervisors is sometimes necessary, but when supervisors disagree, it can be challenging for both trainees and supervisors. Different expectations of the trainees can also be an issue when trainees are in employed positions and report to a superior who is not FETP trained and who may not fully understand the trainees' projects and deliverables.

Participants identified various barriers and challenges to giving effective feedback to trainees. These included different expectations between supervisors and trainees, cultural and language barriers, availability of trainees and supervisors for meetings due to physical locations and time available from other responsibilities. Professional reflective learning, clear expectations about required programme standards as well as operating within a trusting supervisory relationship were seen as important in trying to manage these barriers and challenges.

DISCUSSION

Workshop and survey results indicated that FETP directors and supervisors had a high level of confidence in the value and effectiveness of FETP supervisors. Participants identified several key components to effective supervision, including interpersonal and communication abilities, relevant training background and technical skills and time and availability for frequent in-person contact with trainees. We found several areas to improve the structure and practice of supervision in FETPs.

Existing FETP guidelines often focus on the specific logistical and didactic responsibilities of supervisors and emphasize the need for strong technical skills.[3,13] Our results highlighted the importance of a holistic role for the supervisor, which includes mentoring the trainee in interpersonal and communication skills, alongside technical competencies and knowledge. These findings are consistent with the literature from other field-based training such as clinical settings where priority is placed on supervisor reassurance, role modelling, empathy and interpersonal skills (in addition to technical skills);[8,14] the literature on academic supervision also emphasizes the importance of soft skills such as encouragement, empathy and supportiveness.[15]

The survey results highlighted important differences in the perceived roles of programme and field supervisors. One person can sometimes perform both roles and/or the roles may overlap; however, in our findings, the role of programme supervisor was seen to be more specific to teaching technical skills and knowledge. On the other hand, field supervisors were expected to provide practical, motivational and emotional support in addition to supporting learning. The many supervisory priorities reflect and are likely guided by existing FETP guidelines that outline the different roles of supervisor.[3,13] However, the most critical activity for both types of supervisor was viewed as supporting the trainees to develop their own knowledge and abilities rather than trying to make them learn the right way. While this reflects a key ethos of FETPs, i.e. learning by doing, it also reflects literature on best practice supervision in other areas. Academic supervision literature provides similar guidance, suggesting the value of letting supervision be driven by the trainee's needs[15] and striking a balance between direction and self-direction based on a trainee's level of familiarity and expertise.[16] The literature on clinical supervision provides a similar view, suggesting that as trainees develop expertise they may benefit from independently directing their own learning and contribute to their own professional growth.[9] Overall, our study findings suggest that a key contribution of the supervisor is to enable trainees to identify and pursue areas for their own development, giving them opportunities to direct their own learning and to apply theoretical knowledge in practical scenarios[10] rather than taking a purely instructive approach.

Our study participants identified a variety of challenges to effective field epidemiology supervision, including: a lack of commitment and interest in being a supervisor; and ineffective communication skills, including the inability to provide constructive feedback. Another key challenge identified was that workplace supervisors could lack sufficient technical skills and knowledge, limiting their ability to provide adequate technical supervision. These experiences echo those reported from other programmes where poor training outcomes were reported from field supervisors who lacked any relevant background in public health or epidemiology.[6,7]

Our findings on both the challenges of supervision as well as the role and quality of good supervision have practical implications. They suggest that the ideal supervisor has a relevant background; well-developed technical skills; good programme knowledge; is interested, warm, motivated and committed to FETP supervision; and has sufficient time to dedicate to these tasks. While this ideal may not be frequently realized, it is worthwhile for programmes to consider some of these qualities in supervisor recruitment. Programmes should also consider these traits when conducting orientation and training of supervisors; such training should cover programme requirements and operation but also help supervisors improve technical competencies.[7,17] As suggested in the clinical supervision literature,[9] supervisor training should also include opportunities to assess and train new supervisors in areas of effective communication, giving feedback, building trusting relationships and empathetic mentoring with trainees. The similarities of good supervisors alongside the challenges of supervision were remarkably similar between the programmes represented in this study, suggesting the value of inter-FETP collaboration to develop role descriptions and training for FETP supervisors. These could then be adapted to the local context and be included in programme curricula and guidelines for each country to enable supervisors to have greater understanding and expectations of their role.

A limitation to this study was that our sample was small and purposive. Given the specific nature of our research question, this was deemed the most feasible and appropriate study design. We did not collect data from the participants to assess the extent to which each participant was involved with direct supervision. However, individuals in the director role would typically have frequent contact with programme supervisors and substantial exposure to supervision practices. Another limitation was that we only considered the views of supervisors rather than trainees and that we relied on self-reported subjective data. While this method is commonly used to assess the effectiveness of supervision across a range of settings, more objective evidence could be obtained by targeting evaluation at the level of subsequent trainee behaviour in the workplace or public health outcomes resulting from the work of FETP graduates.[18] Studies of supervision in other contexts have assessed efficacy using measures such as trainees' publication rates and job attainment in relevant specialist fields, which could be explored in developing indicators of supervisor performance in FETPs.[19] Given the study's sample from Western Pacific and South-East Asian FETPs, this may limit the generalizability of our findings to other regions, though comparison with other findings from African and Asia-Pacific FETPs indicates similar experiences and challenges with regards to supervision.[6,7]

To conclude, supervision is a core component of FETPs, and this study has identified some of the key elements and challenges of effective supervision in these programmes. Our findings provide the basis for practical recommendations for FETP supervisory recruitment and training. The findings also provide material for FETP supervisors to consider in their own reflective practice, including practising empathy towards their trainee's overall professional and personal development and being responsive to both their practical and emotional needs. To better understand what and how effective supervision occurs, it would be worthwhile conducting further research in this area, particularly incorporating trainee viewpoints as well as evaluating supervision via FETP trainee outcomes.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Original Research

Meteorological factors associated with hand, foot and mouth disease in a Central Highlands province in Viet Nam: an ecological study

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Background: Hand, foot and mouth disease (HFMD) is a public health problem in Viet Nam, and studies have reported seasonal fluctuation in the occurrence of HFMD. This study sought to describe the occurrence of HFMD and its associated meteorological factors in Dak Lak province, Viet Nam.

Methods: Monthly data on HFMD cases were collected from all commune health stations in Dak Lak province from 2012 through 2013. An HFMD case was defined as a brief febrile illness accompanied by a typical skin rash with or without mouth ulcers. Average temperature, maximum temperature, minimum temperature, humidity, rainfall, evaporation, sunshine duration and wind speed were recorded monthly at five local meteorological stations throughout Dak Lak.Data were aggregated at the district level, and the association between these meteorological factors and HFMD cases were examined by Poisson regression.

Results: In 2012 through 2013, there were 7128 HFMD patients in Dak Lak. The number of HFMD cases increased during the rainy season. An increased risk of HFMD was associated with higher average temperature (risk ratio and 95% confidence interval: 1.06; 1.03–1.08 per 1 °C increase), higher rainfall (1.19; 1.14–1.24 per 200 mm increase) and longer sunshine duration (1.14; 1.07–1.22 per 60 hours increase). The risk of HFMD was inversely associated with wind speed (0.77; 0.73–0.81 per 1 m/s increase).

Conclusion: This study suggests that there is a significant association between HFMD occurrence and climate. Temperature, rainfall, wind speed and sunshine duration could be used as meteorological predictors of HFMD occurrence in Viet Nam's Central Highlands region. Intensified surveillance for HFMD during the rainy season is recommended.

Hand, foot and mouth disease (HFMD) is an acute enterovirus infectious disease. HFMD has no vaccine or specific therapy thus far. Early detection of outbreaks, early recognition of severe HMFD and timely supportive treatment are among the key principles applied to minimize the burden of disease.[1] HFMD is a major health problem in many countries, notably in the World Health Organization's (WHO) Western Pacific Region, including Viet Nam.[1–3] In Viet Nam, the first HFMD epidemic was reported in Ho Chi Minh City in 2003,[4] it then gradually spread around the country until multiple significant outbreaks in 2010 caused national concern. Since 2011, HFMD has been included in the National Communicable Disease Surveillance System. According to data from the Viet Nam Ministry of Health in 2012, HFMD had the highest mortality among the notifiable communicable diseases under the General Department of Preventive Medicine, Ministry of Health, with 157 391 cases and 45 deaths.[5]

Certain meteorological factors have been found to be associated with the occurrence of HFMD. Temperature had a positive association with the number of HFMD cases in studies.[6–9] In Japan, the weekly number of HFMD cases rose by 11.2% when average temperatures increased 1 °C.[10] The relationship with humidity was inconsistent; some studies showed the risk of HFMD increased 0.51–4.7% when relative humidity elevated 1%,[6,8–10] while other studies reported that HFMD and humidity were not associated.[11,12] The relationship between HFMD and rainfall is also inconsistent. A study in Guangdong supported a positive association between

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rainfall and HFMD,[6] while two studies from Guangdong found a non-significant association.[8,9] In China, when wind speed increased 1 m/s, the risk of HFMD increased 4.01%.[9] A study in Hong Kong SAR (China) also demonstrated that wind speed was positively associated with HFMD consultation rates.[11] Most studies denoted positive associations with evaporation and sunshine and HFMD occurrence.[6,11,13]

In Viet Nam, the association between HFMD and climate parameters has not been well examined. A model including climate parameters could be used as an early surveillance system to predict annual HFMD epidemics.[14] This study aimed to describe the occurrence of HFMD, and its association with meteorological factors in Dak Lak province in the Central Highlands region of Viet Nam.

METHODS

Study setting

An ecological study was conducted using data from January 2012 through December 2013 in Dak Lak province (total population: ~1.8 million). Dak Lak is located between 12°09′–13°25′ north latitudes and 107°28′–108°59′ east longitudes and shares a border with Cambodia (**Fig. 1**). The terrain is mainly relatively flat highland with an average altitude of about 500 m above sea level. Dak Lak has a tropical monsoon climate with two distinct seasons: the rainy season is usually from May through October and the dry season is from November through April. The rainy season typically receives 90% of the annual rainfall. The annual average rainfall is about 2000 mm, and the annual average temperature ranges between 23 °C and 24 °C. (**Table 1**)

HFMD prevention and control activities in Dak Lak province were carried out under an unofficial multisectoral committee. Key activities included surveillance of HFMD with routine weekly reports, laboratory-based sentinel surveillance and monitoring of environmental risk factors for HFMD epidemics.

Data collection

The number of HFMD cases was collected from the Center for Disease Control of Dak Lak Province. These data were obtained through the Communicable Disease Surveillance System in Viet Nam from 2012 through 2013.[15] Circular 54/2015/TT-BYT mandates the reporting of HFMD by all levels of health care, from the commune health station to the national level.

According to the Viet Nam Ministry of Health protocol,[15] mainly based on WHO recommendations,[1] individuals suspected of having HFMD were those who meet the case definition as a brief febrile illness accompanied by a typical skin rash with or without mouth ulcers. Once identified, a patient was treated at the nearest health facility or transferred, depending on the severity of the condition, to a district or provincial hospital for further diagnosis and treatment. Total numbers of HFMD cases were recorded monthly during the surveillance period from 2012 through 2013. Meteorological data were provided by the hydro-meteorological forecast station of Dak Lak province.[16] Average/maximum/minimum temperature (°C), relative humidity (%), amount of rainfall (mm), amount of evaporation (mm), duration of sunshine (hours) and average wind speed (m/s) were recorded daily from five stations of meteorology throughout Dak Lak province and averaged for each month.

Data analysis

The main aim of the data analysis was to determine if an association exists between the number of HFMD cases and the meteorological parameters. The outcome was the monthly number of HFMD cases in each district. The predictive variables were average temperature, maximum temperature, minimum temperature, humidity, rainfall, evaporation, sunshine duration and wind speed.

The study assumed that the distribution of HFMD cases followed the Poisson distribution as the number of HFMD cases was relatively small compared to the provincial population. Poisson regression was used to model the associations between the meteorological factors and the distribution of HFMD cases. Due to a variation of meteorological factors in season and location, in subsequent analyses, time (month, year) and area (district) were considered simultaneously in a multivariable model. The effects of meteorological variables were modelled as follows:

$$\lambda_t = exp(\beta_0 + \beta_1 X_{t1} + \beta_2 X_{t2} + \ldots + \beta_p X_{tp})$$

where $\boldsymbol{\beta}_0, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, \ldots, \boldsymbol{\beta}_p$, are regression coefficients related to variables $\boldsymbol{x}_{t0}, \boldsymbol{x}_{t1}, \boldsymbol{x}_{t2}, \ldots, \boldsymbol{x}_{tp}$, respectively (with $\boldsymbol{x}_{t0} = \mathbf{0}$), and $\boldsymbol{\lambda}_t$ denoted the number of HFMD cases at month t. The regression coefficients were estimated by the

Figure 1. **Map of Viet Nam showing Dak Lak province (in dark green area)**

Disclaimer: The boundaries shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. White lines on maps represent approximate border lines for which there may not yet be full agreement.

method of maximum likelihood by using the R program package.[17]

Ethics statement

The study was approved by the Scientific Committee of the University of Medicine and Pharmacy at Ho Chi Minh City, Viet Nam as Decision No. 66/YTCC-DT dated 25 March 2014.

RESULTS

In 2012 through 2013, the National Disease Surveillance System reported there were 7128 HFMD patients in Dak Lak: 5191 patients in 2012 (incidence rate: 289 per 100 000 population) and 1937 patients in 2013 (186 per 100 000 population).

Although HFMD patients were reported throughout the year, the number of HFMD cases increased from April through May and September through October (**Fig. 2**), accounting for about 50% of total HFMD cases. The average number of patients per month was 25 in the rainy season (from May through October) and 15 in the dry season (from November through April of the next year). Compared to the dry season, on average, there were 10 more patients per month in the rainy season (95% CI: 4–15) cases ($P < 0.005$).

Data analysis showed that the number of HFMD cases was associated with climate factors (**Tables 2 and 3**). Due to multicollinearity among average temperature, maximum temperature and minimum temperature of these variables, only average temperature and humidity were included in the final model. The correlation coefficients (r) of average temperature with maximum and minimum temperature were 0.77 and 0.82, respectively; between humidity and evaporation, the correlation coefficient (r) of humidity and evaporation was 0.87.

Results of univariate analysis showed a significant increase in the risk of HFMD when average temperature, humidity and rainfall were elevated. The study found a

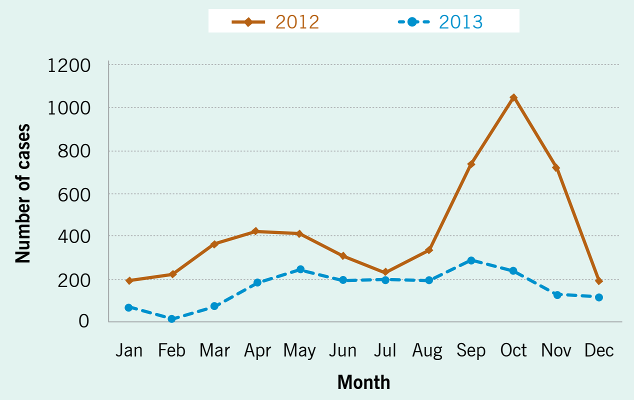
Table 1. **Climate change and occurrence of hand, foot and mouth disease cases stratified by month, Dak Lak province, Viet Nam, 2012–2013**

Month	No. of cases (a)	Average temperature (°C) (b)	Maximum temperature (°C) (b)	Minimum temperature (°C) (b)	Humidity (%) (b)	Rainfall (mm) (b)	Evaporation (mm) (b)	Sunshine (hours) (b)	Wind speed (m/s) (b)
January	261	20.8	29.9	15.2	82.0	15.4	96.1	198.1	2.9
February	239	22.5	33.1	16.5	79.0	9.4	105.0	224.5	2.7
March	436	24.3	34.0	16.8	76.7	50.9	124.4	248.4	2.4
April	604	25.5	34.6	20.0	79.1	170.5	101.1	233.4	1.7
May	658	25.6	33.5	20.3	81.5	193.7	89.5	252.9	1.4
June	504	24.7	31.4	20.7	85.7	223.4	68.1	163.1	2.1
July	427	24.2	31.5	19.7	86.8	206.2	65.5	163.8	1.8
August	527	24.2	31.5	20.2	85.3	184.8	73.5	166.3	2.4
September	1017	23.7	31.1	20.0	88.0	525.3	52.0	131.9	1.8
October	1285	23.2	30.2	18.0	84.8	163.1	69.4	182.9	1.8
November	849	23.2	30.6	17.6	85.3	97.5	72.8	188.9	2.3
December	321	20.9	29.2	14.9	82.7	16.6	87.0	202.1	2.5

a Data are total number of cases tallied from 2012 through 2013.

b Data are averages across two years (2012–2013).

Figure 2. **Distribution of hand, foot and mouth disease cases by month, Dak Lak province, Viet Nam, 2012–2013**



reverse association between HFMD and sunshine duration and wind speed. In the multivariable Poisson regression model, results indicated that average temperature, rainfall and sunshine duration had significantly positive effects on the number of HFMD cases. The risk of HFMD, however, reduced when wind speed increased. Humidity was not significantly associated with HFMD case counts in the multivariable model.

DISCUSSION

The present study demonstrated a seasonal pattern of HFMD occurrence in a Central Highlands province of with a higher number of cases occurring in the rainy season. This was one of a few studies examining the association between meteorological factors and HFMD occurrence in Viet Nam. Our finding is consistent with what has been reported in a previous study conducted in southern Viet Nam.[4] However, exact reasons for the relationship between weather and HFMD are limited. Meteorological factors could affect occurrences of infectious disease via survival and transmission of pathogens in the environment as well as population activities and behaviour.[18–20]

Pathophysiology of enteroviruses was found to be affected by temperature, humidity and surface of fomites.[19] This study found that within the range of average temperatures in the region, a one-degree higher average temperature was associated with an increase of 6% in the number of HFMD cases. Studies from Hong Kong SAR (China) and Japan revealed similar findings: a positive association between average temperature and number of HFMD cases.[7–11,20–22] Moreover, a study in Hong Kong SAR (China) showed that warm weather in winter might increase the number of HFMD cases.[23] High temperatures could increase the growth of enteroviruses and also interfere with inactivation and recovery of enteroviruses.[24,25]

HFMD has seasonality. In temperate regions, the number of patients who are infected with enteroviruses rises in summer.[11,25,26] In subtropical and tropical regions, enteroviruses circulate throughout the year and elevate during the rainy season.[1] This study found each 200 mm increase in rainfall was associated with a 19% increased risk of HFMD onset. This finding is also consistent with that found in previous studies from other countries.[6,28,29] A possible explanation is that high rainfall makes soil moist, which may facilitate viral persistence and spreading.[25,30] In contrast, some studies in China did not support the association between rainfall and HFMD.[8,9]

Although some previous studies suggested that humidity was associated with HFMD,[6–8,10,11] the current study did not find a statistically significant association between humidity and the number of HFMD cases each month. The difference between the current study and previous studies that showed a positive effect was the use of monthly data. Another study using monthly data also concluded no association with the number of HFMD cases.[28]

Table 2. **Risk factors for hand, foot and mouth disease in Dak Lak province: univariate analysis**

Risk factor	Unit of comparison	Risk ratio (95%CI)	p-value
Average temperature	Per 1 °C increase	1.18 (1.16 – 1.21)	< 0.001
Humidity	Per 5% increase	1.14 (1.11 – 1.18)	< 0.001
Rainfall	Per 200 mm increase	1.26 (1.23 – 1.29)	< 0.001
Sunshine	Per 60 hours increase	0.95 (0.91 – 0.98)	< 0.001
Wind speed	Per 1 m/s increase	0.66 (0.63 – 0.69)	< 0.001

Table 3. **Risk factors for hand, foot and mouth disease in Dak Lak province: multivariable analysis**

Risk factor	Unit of comparison	Risk ratio (95%CI)	p-value
Average temperature	Per 1 °C increase	1.06 (1.03 – 1.08)	< 0.001
Humidity	Per 1% increase	1.06 (0.99 – 1.12)	0.053
Rainfall	Per 200 mm increase	1.19 (1.14 – 1.24)	< 0.001
Sunshine	Per 60 hours increase	1.14 (1.07 – 1.22)	< 0.001
Wind speed	Per 1 m/s increase	0.77 (0.73 – 0.81)	< 0.001

In agreement with results from other studies that showed the effect of increased sunshine,[12,31] our findings showed that the risk of HFMD increased by 14% per 60 hours of increase in sunshine duration. However, another study showed a negative correlation between sunshine duration and HFMD infection;[2] this disparity needs further researches to provide more evidence. For wind speed, this study denoted a negative association with the number of HFMD cases: 1 m/s increase in wind speed leads to a decrease of 23% in the risk of HFMD. A possible reason is that months with higher wind speed in Dak Lak were often from December through February, which is the dry season with lower temperature. These factors could have an effect on the dispersal and persistence of pathogens in the environment.

The current study had some limitations: HFMD epidemics have been shown to occur in two- to three-year cycles,[31] and the two-year period in our study might not be adequate to identify the cycle of enteroviruses and the effects of climate change on HFMD in an ecological analysis. It would be useful to conduct a longer study and conduct time series analysis to detect the natural cycle of HFMD outbreaks in this region. Data based on surveillance systems might be underestimated. To our knowledge, there were several HFMD patients treated in private clinics that were not recorded. In addition, HFMD patients with mild self-limiting or unclear symptoms were not diagnosed as HFMD and were not notified to the HFMD surveillance system.

CONCLUSION

HFMD is a seasonal health-related challenge in Dak Lak province and other geographical areas with the same climatic characteristics. Understanding the association between HFMD and meteorology is important to predict epidemic trends. Future studies should explore the association between other meteorological factors and the incidence of HFMD to provide more evidence for new policies to be developed. Health departments should use more meteorological data to predict the number of HFMD cases, to identify periods of high risk for HFMD outbreaks and increase health communications during outbreaks. The data also suggest that the occurrence of HFMD in this region is likely the result of multiple causes that remain to be delineated; we recommend that research be conducted to describe a more complete picture of risk factors for HFMD development.

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Conflicts of interests

The authors declare that they have no competing interests. Every author was involved in drafting the article and revising its intellectual content.

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Screening for latent tuberculosis infection by an Aboriginal Community Controlled Health Service, New South Wales, Australia, 2015

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Objective: Ongoing transmission of tuberculosis (TB) continues in Indigenous communities in New South Wales (NSW), Australia. In a pilot project, a Public Health Unit TB team partnered with an Aboriginal Community Controlled Health Service (ACCHS) in a community with a cluster of TB to augment screening for latent TB infection (LTBI) using interferon-gamma release assay (IGRA). This study examined screening data and programme outcomes at 12 months post hoc to advise practice and policy formulation.

Methods: We conducted a retrospective, cross-sectional analysis of demographic and clinical data of ACCHS patients, stratified by IGRA testing status. Differences in sex and age distribution between the groups and cases of a genetically and epidemiologically linked TB cluster in Aboriginal people in NSW were assessed using non-parametric tests.

Results: Of 2019 Aboriginal and Torres Strait Islander people seen by general practitioners during the study period, 135 (6.7%) participated in the screening. Twenty-four (17.8%) participants were IGRA positive. One person was diagnosed with active TB. Twelve participants received a chest X-ray at the time of the positive test, and six participants had an additional chest X-ray within 12 months. None commenced preventive treatment for LTBI.

Discussion: ACCHS screening for LTBI reached individuals in the age group most commonly affected by TB in these Aboriginal communities. No conclusions can be made regarding the population prevalence due to the low screening rate. Further strategies need to be developed to increase appropriate follow-up and preventive treatment.

Tuberculosis (TB) is a major public health issue and a leading cause of death worldwide.[1] Despite the low incidence of TB in Australia (5.7 cases per 100 000 population in 2014), TB is still endemic in Indigenous communities.[2] Sociocultural factors and individual risk factors for infection contribute to ongoing TB transmission in Australian Indigenous communities.[3]

LTBI is infection with *Mycobacterium tuberculosis,* in the absence of clinical signs or symptoms of active TB.[4] The lifetime risk of TB reactivation is 5–10%, with most developing active TB in the first five years after infection.[5] Treating LTBI decreases the risk of active TB by 60–90%.[6] The most commonly used treatments for LTBI are six- or nine-month courses of isoniazid.[7]

The World Health Organization (WHO) set the goal of TB elimination by 2050 and initiated the End TB strategy in 2014.[8] In Australia, the National Tuberculosis Advisory Committee (NTAC) guidelines assist TB services with achieving programme targets. Indigenous Australians are included in the populations WHO and NTAC recommends for targeted testing and treatment for LTBI.[8,9]

There is no gold standard for the diagnosis of LTBI. The two tests currently used are the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). While TST involves two encounters with specialized staff 48–72 hours apart, IGRA is a one-visit, whole-blood test that measures the immune response to antigens of *M. tuberculosis*. WHO recommends either TST or IGRA to test for

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LTBI.[10] At the time of this project, NTAC recommended TST to diagnose LTBI, but "IGRAs may be a preferred option where resources, distance or other factors make TST impractical to administer;"[11] IGRA was only funded under Medicare in Australia for immunocompromised patients. In 2017 the NTAC position statement was revised and now recommends "either TST or IGRA for the investigation of LTBI in most circumstances".[12]

Since 2000, 48 genetically and epidemiologically linked cases of active TB (mycobacterial interspersed repetitive units [MIRU] pattern 23'3425153322) have been diagnosed in Aboriginal people. Many of these patients resided in an Aboriginal Community Controlled Health Service (ACCHS) catchment area in northern New South Wales (NSW), Australia. TB transmission has occurred despite implementation of TB control measures such as household contact tracing and community-based screening events using TST.[13]

With concerns about ongoing TB transmission and after consultations with Aboriginal people of the affected communities and TB expert committees, the local Public Health Unit (PHU) collaborated with the ACCHS in a pilot project to offer screening for LTBI and to provide preventive therapy.

To eliminate TB, the support of primary care providers who care for high-risk populations is essential.[7] Previous collaborations between ACCHS and NSW Ministry of Health highlight the benefits of partnerships.[14]

The overall objectives of the ongoing project include: to better understand the epidemiology of LTBI in the communities served by the ACCHS; to identify who is reached by the ACCHSs offering screening; to strengthen the partnership between the ACCHS and PHU TB Team; to raise TB awareness in the ACCHS setting; and to advise practice and policy formulation, including IGRA funding and incorporation of TB screening in annual health assessment in at-risk communities.

We describe a retrospective epidemiological analysis of data from the IGRA screening project with the following aims:

1. assess the reach of this model of TB screening for a rural Australian Aboriginal population;
2. compare the demographic characteristics of people in the project with the general ACCHS patient population and those in the TB MIRU pattern 23'3425153322 cluster in NSW; and
3. evaluate the TB screening outcomes at 12 months.

METHODS

General practitioners (GPs) and all clinical staff working for the ACCHS providing services in three Aboriginal communities in northern NSW received basic TB training and were encouraged to screen for TB and offer IGRA testing to their patients who presented for medical consultations at the central or one of the two outreach clinics between 3 June 2013 and 27 January 2015. The decision to test with IGRA was intended to treat those with TB as identified by the GPs and the PHU TB team (TB doctors, TB nurses and Aboriginal TB Community Engagement Officers). All patients were eligible for testing; however, testing was offered as part of a GP consultation; therefore, study inclusion was at the GP's discretion.

The IGRA used in this project was Quantiferon TB Gold (QIAGEN GmbH, Hilden, Germany). Trained nurses at the ACCHS or at a private pathology service collected the samples, which were then sent to Brisbane for incubation and analyses within 16 hours.

Patients provided verbal consent to participate in the project, which included consent for sharing of their demographic and TB-related clinical data (IGRA, chest X-ray and sputum test results) with the PHU TB team. At the time of blood collection, nurses ensured that patients understood they were having an IGRA test, and patients provided signed consent to proceed.

Participants were questioned about active TB symptoms (cough, night sweats, weight loss). Participants' data were recorded in their medical files at the ACCHS and in the Notifiable Conditions Information Management System (NCIMS) database, administered by NSW Health Ministry.

ACCHS doctors notified all participants of their results. If the IGRA test was positive or there were clinical concerns, participants were referred for a chest X-ray (at a private radiology service in the town of the main ACCHS clinic), sputum test for acid-fast bacilli (AFB) with smear, polymerase chain reaction (PCR) and culture (at a private pathology service) and to a TB specialist clinician to explore treatment options. The PHU TB team contacted all referred patients and offered a range of support services for further assessment and preventive TB treatment. When preventive treatment was declined or deemed inappropriate, the referring GP was informed and a repeat chest X-ray was offered to the patient 12 months after the positive IGRA result.

Case definitions

We defined LTBI as a positive IGRA test in the absence of clinical manifestations of active TB based on symptoms, radiology and sputum test results.

The TB cluster cases are 37 epidemiologically linked, active TB cases in Aboriginal people in NSW with the MIRU pattern 23'3425153322 diagnosed between October 2000 and February 2015. Cluster cases diagnosed outside NSW and diagnosed after the study period were not included in the analysis.

Data collection

We compared non-identifiable data retrieved from NCIMS and ACCHS. Demographic data including age, sex, Indigenous status and resident postcode of people screened with IGRA and people within the TB cluster were retrieved from NCIMS. Only Indigenous people were included in the study. Variables used for the outcome analysis of the people who screened positive for LTBI (IGRA result, sputum test results, chest X-ray at 0 and 12 months and TST results from previous screening) were also extracted from NCIMS.

Demographic data of patients presenting to the ACCHS between 3 June 2013 and 27 January 2015 were requested from the Executive Officer of the ACCHS and extracted from Medical Director software using the PenCat tool.[15]

Data analysis

We undertook a descriptive analysis on the screening outcomes data. All data used were from people identifying as Aboriginal and Torres Strait Islander. Data from non-Indigenous people accessing the ACCHS were excluded. We compared the demographic characteristics of the ACCHS's patient population, the individuals screened by IGRA and the individuals within the TB cluster cases in NSW. χ^2 tests were used to assess differences in sex distribution between four groups (ACCHS patients, IGRA screening participants, IGRA screening participants who tested positive for LTBI and TB cluster cases). A non-parametric Kruskal–Wallis test and Mann–Whitney U post hoc tests were used to compare median ages. Further analysis was undertaken to describe the outcomes of the IGRA screening project 12 months later, using the clinical data extracted from NCIMS.

Ethics

This study was approved by the Aboriginal Health and Medical Research Council (1093/15) with a waiver of informed consent, the North Coast NSW Ethics Committee (NCNSW HREC No LNR 121) and received a Site Specific Assessment Approval (LNRSSA/15/NCC).

RESULTS

Between 3 June 2013 and 27 January 2015, 2019 Aboriginal and Torres Strait Islander peoples presented to the ACCHS for a GP consultation.

A total of 135 individuals (61 males [45%] and 74 females [55%]) were screened for TB using IGRA, or 6.7% of all Indigenous-patient GP presentations in this period. We do not have data on how many patients declined IGRA screening. Overall, 24 of the 135 participants tested (17.8%) were IGRA positive; one (4.2%) was diagnosed with active TB.

Between October 2000 and February 2015, 37 epidemiologically linked TB MIRU pattern 23'3425153322 cluster cases in Aboriginal people were diagnosed in NSW; these individuals were not necessarily patients of the ACCHS.

Gender and median age comparison

The gender and median ages of the ACCHS clinic patients, IGRA participants and patients of the TB cluster are presented in **Table 1**.

No statistically significant difference in sex distribution was found between ACCHS patients and patients

Table 1. **Sex and median age comparison with ACCHS attendees as the reference group**

	ACCHS patients *n* = 2019	Patients screened for TB by IGRA *n* = 135	*P*-value	IGRA positive *n* = 24	*P*-value	TB cluster cases	*P*-value
Sex*	-	-	0.740	-	0.626	-	<0.01
Male	942 (47%)	61 (45%)	-	10 (42%)	-	28 (76%)	-
Female	1077 (53%)	74 (55%)	-	14 (58%)	-	9 (24%)	-
Median age** (years)							
Male	20	44	<0.01	48	<0.01	41	<0.01
Female	24	43	<0.01	49	<0.01	41	<0.01
Range age (years)	0–88	3–75	-	19–66	-	0–65	-

* Pearson's chi-squared test for gender comparison

** Mann-Whitney U post hoc test for median age comparison

screened by IGRA (χ^2 = 0.11, P = 0.74) and IGRA participants who screened positive for LTBI (P = 0.63). Significantly more of the cases within the TB cluster were among men (76%) compared to all ACCHS attendees (47%, $P \leq 0.01$), all IGRA participants (45%, $P \leq 0.01$) and IGRA participants who screened positive for LTBI (42%, $P \leq 0.01$).

The median ages of patients tested by IGRA (male 44 years/female 43 years; range 3 to 75 years), those who were IGRA positive (male 48 years/female 49 years; range 19 to 66 years), and those within the TB cluster (male 41 years/female 41 years; range 0 to 65 years) were significantly higher compared to the general ACCHS patient population (male 20 years/female 24 years; range 0 to 88 years; $P \leq 0.01$ for all groups and both sexes.)

Outcome analysis

Out of 135 IGRA tests, 102 (75.6%) were negative, nine (6.7%) were indeterminate and 24 (17.8%) were positive for TB. In this report, indeterminate test results were not included in the screening outcome analysis.

Positive IGRA tests

Of the 24 people who tested IGRA positive, 13 (54.2%) were newly diagnosed with LTBI and one (4.2%) was diagnosed with active TB. The other 10 (41.7%) participants with LTBI had positive TSTs before the IGRA screening documented in the NCIMS database, but the TST results were not documented in the ACCHS medical records and had not been disclosed by the participants at the time of IGRA screening.

Eight of the 24 participants who were IGRA positive (33.3%) reported having a cough; one participant reported cough, weight loss and night sweats, and one participant reported general malaise. All 24 participants who were IGRA positive were referred for chest X-ray and sputum testing for AFB.

Sixteen participants (64%) had a chest X-ray. Eleven (68.8%) were reported as normal and five (31.3%) were abnormal (reported findings were atelectasis, chronic obstructive pulmonary disease, pulmonary nodules and pleural effusion, consolidation and bilateral consolidation).

Five of the 24 participants (20.8%) had sputum tested for AFB. The sputum of one participant was smear and PCR positive for AFB and culture positive for *M. tuberculosis*. This participant had reported night sweats and weight loss, and active TB was considered at the time of presentation. The participant completed treatment for active TB.

In summary, of the 24 IGRA positive participants referred for sputum testing and chest X-ray 21 (87.5%) had a chest X-ray and/or sputum tested. One participant had chest X-ray and sputum testing resulting in a diagnosis of active TB, 16 had chest X-ray only; 4 had sputum testing only; and 3 did not have chest X-ray or sputum testing. The active TB case was the participant with TB-like symptoms and consolidations on chest X-ray.

12 months follow-up

Twelve of the 14 participants (85.7%) with a new positive TB screening result (13 LTBI and 1 active TB) had a chest X-ray at the time of the positive test, and 6 of these 12 (50%) had a repeat chest X-ray at 12 months. One person died of other causes before the scheduled chest X-ray at 12 months. Four participants (40%) of the 10 who tested IGRA positive with a previous positive TST had a chest X-ray at the time of their positive IGRA test but did not have a repeat chest X-ray at 12 months.

Referral for preventive treatment and assessment of previous TB contact and counselling was offered to all patients with newly diagnosed LTBI; however, none who had LTBI detected by IGRA screening commenced preventive treatment for LTBI. The patient diagnosed with active TB completed treatment for TB.

DISCUSSION

This screening project involving 135 participants reached both males and females. The median age for patients tested with IGRA was 44 years for males and 43 years for females. Twenty four of the 135 (18%) screened by IGRA had positive tests. Twenty one (87.5%) of those who tested positive had chest X-ray and/or sputum testing. One case of active TB was diagnosed. None of those with positive IGRA results that were interpreted as indicative of latent TB infection initiated treatment.

Of the 2019 ACCHS presentations, 135 (7%) participated in the IGRA screening. It is unknown how many patients were offered IGRA; however, the participating GPs reported that most patients accepted it. Symptoms reported by participants can create selection bias, but we did not assess how these reports influenced GPs' decisions to offer screening. Other biases that potentially increased screening included GP awareness of TB in the household or other TB contact (unknown to the patient), knowledge of lifestyle factors (such as smoking and drug use), the patient's living circumstances and GP's TB knowledge. Both providers and participants may have been influenced by their awareness of TB in local communities or the diagnosis of a case of active TB at the ACCHS. We tried to mitigate bias by providing basic TB training and TB screening instructions to all clinical staff at the ACCHS before commencement of this project. Research into what encourages provider and patient participation in TB screening in this setting is required.

The screening project reached both males and females, including men in the age group most affected by TB in the MIRU pattern 23'3425153322 cluster.[13] Previous informal reviews of TB screening activities by the PHU TB team displayed a disproportional low participation rate among men. We believe that the established doctor–patient relationship between the GPs offering IGRA screening to their male patients contributed to our results. Furthermore, unpublished research involving interviews with Aboriginal men affected by TB suggest TB screening in the annual Aboriginal and Torres Strait Islander Health Assessment at the ACCHS would further enhance participation. A formal comparison of outcomes from contact screening in this setting with the IGRA project would assist in adapting targets and interventions to local epidemiology as recommended by WHO.[16]

We found that 17.8% of the people screened were infected with *M. tuberculosis*. This result should be interpreted with caution as only 7% of the target population was screened; therefore, population prevalence cannot be inferred from this study. The median estimated population prevalence for LTBI in Australia is between 0% and 10%, which is lower than our findings.[17] Follow-up studies are needed to make conclusions about the TB prevalence in this community.

Access to specialized TST and LTBI follow-up services are limited for the widely dispersed rural Aboriginal communites in northern NSW. TST has proven insufficient for preventing ongoing TB transmission in these communites. We believe IGRA offered in ACCHSs with the support of a specialized TB service would further understanding of the prevalence of TB and allow screening in communities that may have high infection rates.

Medicare funding for IGRA has increased since implementation of this pilot project, but it only covers screening if a patient is a contact of an active case, even in groups with higher TB notification rates. Indigenous peoples are a "vulnerable and hard-to-reach group" as defined by WHO, and interventions must be designed to increase access to TB services.[16] Medicare-funded IGRA is required for ACCHSs to provide autonomous services to identify, treat and manage LTBI. The number of indeterminate IGRA test results reinforced that IGRA screening must include staff training on specimen collection, particularly on proper processing time frames and storage of specimens.

The participation rate for sputum collection for AFB, smear and culture (20.8%) might have been influenced by low rates of cough and by the logistics of sputum collection and delivery to the private pathology laboratory. On-the-spot sputum collection in the ACCHS setting and transport to the laboratory is being promoted to increase the number of people who have at least one sputum specimen tested for AFB.

Early diagnosis of active TB is a valuable tool for TB prevention.[18] Improving the rate of sputum collection and follow-up chest X-ray at 12 months can enhance the diagnosis of early TB. CXRs to diagnose active TB were obtained from 85.7% of the participants with newly diagnosed LTBI, and 50% repeated a chest X-ray 12 months later. Identifying and addressing Aboriginal and Torres Strait Islander peoples' concerns regarding radiological testing may improve follow-up rates.

LTBI treatment reduces the risk of progression to active disease for high-risk individuals.[16] A population-based study with Indigenous populations in the United States of America, Greenland and Canada found LTBI screening and treatment were associated with significant decreases in TB notification rates.[19] In our study, none of the participants with newly diagnosed LTBI were treated for latent TB despite a range of patient-centred services offered by the ACCHS and the PHU TB team. Aboriginal health workers facilitated communication between the patient, GP and the PHU TB Team and provided care coordination and emotional support to the patient. Convenient appointment times during business hours, and transport to specialist appointments were also offered. It is likely that health service and patient influences were barriers to treatment for LTBI, including treatment length, presence of contraindicating medical conditions, the potential for adverse medication reactions and access to specialist TB services, which have been shown in previous studies.[20,21] Health services must elicit and be receptive to Aboriginal and Torres Strait Islanders peoples' views on LTBI treatment and find a way forward together to prevent TB. Regularly providing TB specialist services at the ACCHS could improve follow-up, strengthen the ACCHS-TB Team partnership, increase TB knowledge in GPs, and contribute to two-way learning with Aboriginal and Torres Strait Islander peoples.

Since the start of the pilot project, many Aboriginal and Torres Strait Islander people have requested further information on TB or referred someone they knew with a history of TB to the ACCHS. The PHU TB team, respiratory medical specialists and GPs with TB knowledge and experience continue to provide outreach and education support for TB to ACCHS staff, including the doctors working in this community.

Limitations

We could not estimate LTBI prevalence because only 7% of the target population was screened. Financial support for the IGRA tests was limited and we were unable to continue to offer screening. The study design with a discretionary, GP-led approach to offering IGRA screening does not allow any conclusions regarding the reasons for or against participation by the patient. Furthermore, we are unable to comment on the reasons or restraints to offering IGRA by the GP. A structured approach for IGRA screening (for example in the annual health assessment) as well as documented reasons as to why a patient declined the offered screening will improve evaluations of this model of care. Limited data were available to compare participant characteristics. This study was not able to compare the IGRA screening outcomes with those for routine TB screening methods.

CONCLUSION

TB incidence for the Australian Aboriginal and Torres Strait Islander population is significantly higher than the Australian-born non-Indigenous population,[2] and accessible and socioculturally appropriate health services are required to support the unique structures and care needs of Aboriginal communities. Two of the main limiting factors of this pilot project were the costs of IGRA and a discretionary approach to screening. Further research, with a structured approach, needs to further evaluate the effectiveness of this model of care. We recommend that IGRA becomes accessible under Medicare for Aboriginal and Torres Strait Islander people and for TB screening to be incorporated into the annual health assessment as a routine screening.

Ongoing community engagement and collaboration is necessary to develop TB elimination strategies for vulnerable and hard-to-reach groups. Increasing access to screening and specialist care through the ACCHS will support this. This project identified policy and practice issues that need to be addressed to implement a sustainable TB screening programme with IGRA in an ACCHS.

Conflict of interest

None.

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Spatial distribution of tuberculosis in a rural region of Western Province, Papua New Guinea

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Introduction: There is a high burden of tuberculosis (TB) in the Western Province, Papua New Guinea. This study aims to describe the spatial distribution of TB in the Balimo District Hospital (BDH) catchment area to identify TB patient clusters and factors associated with high rates of TB.

Methods: Information about TB patients was obtained from the BDH TB patient register for the period 26 April 2013 to 25 February 2017. The locations of TB patients were mapped, and the spatial scan statistic was used to identify high- and low-rate TB clusters in the BDH catchment area.

Results: A total of 1568 patients were mapped with most being from the Balimo Urban (n = 252), Gogodala Rural (n = 1010) and Bamu Rural (n = 295) local level government (LLG) areas. In the Gogodala region (Balimo Urban and Gogodala Rural LLGs), high-rate clusters occurred closer to the town of Balimo, while low-rate clusters were located in more remote regions. In addition, closer proximity to Balimo was a predictor of high-rate clustering.

Discussion: There is heterogeneity in the distribution of TB in the Balimo region. Active case-finding activities indicated potential underdiagnosis of TB and the possibility of associated missed diagnoses of TB. The large BDH catchment area emphasizes the importance of the hospital in managing TB in this rural region.

Western Province in Papua New Guinea (PNG) has a very high burden of tuberculosis (TB) with a case notification rate of 674 per 100 000 people in 2016.[1] TB is known to cause a high burden of disease in Balimo and the Gogodala region of the Middle Fly District; the average reported incidence of TB at Balimo District Hospital (BDH) was 727 cases per 100 000 people per year from 2014 to 2016 for people in the combined Balimo and Gogodala local level government (LLG) areas.[2] Furthermore, rates of paediatric and extrapulmonary TB have been identified as very high, with 25.0% of patients aged 0–14 years, and 77.1% of patients diagnosed with extrapulmonary TB infection.[2]

BDH is the primary facility providing TB diagnosis and DOTS-based treatment in the Gogodala region. Other smaller health facilities, including health clinics and aid posts, can provide limited TB services such as clinical extrapulmonary TB diagnosis and treatment and pulmonary TB services when a sputum sample is not able to be transferred to the town of Balimo.[2] Given the high burden of TB reported at BDH, there is a need to understand the distribution of TB in the Balimo region. Such analysis will provide insight into areas with high and low rates of TB as well as evidence to support the focused delivery of TB services. This study used spatial epidemiology techniques to (1) define the catchment area of BDH, (2) identify clustering of TB in the BDH catchment area and (3) investigate factors associated with high rates of TB. The approach aimed to illustrate the local TB burden in the context of the geography of this remote region of PNG, using mapping to illustrate the results as a complement to the underlying quantitative spatial analysis.

STUDY POPULATION AND METHODS

Study setting and patient cohort

Patient data were obtained from the BDH TB patient register, which includes all patients diagnosed and commenced on TB treatment at BDH, as described previ-

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ously.[2] TB patients may be bacteriologically confirmed using smear microscopy or diagnosed clinically as occurs for the majority of cases in the Balimo region, in accordance with the World Health Organization (WHO) case definitions and PNG National Tuberculosis Management Protocol.[2–4] In this study, patient locations were identified as the first village recorded as a residential address for each patient. Out of 1614 TB patients registered from 26 April 2013 to 25 February 2017, 1568 were mapped after excluding patients from outside Western Province (n = 13) and those for whom a residential address could not be determined (n = 33).

Geographic and population data

This study focused on the Balimo Urban (population 4394), Gogodala Rural (population 33 033) and Bamu Rural (population 13 432) LLG areas. In PNG, LLG areas are subdivided into rural wards and urban areas and further subdivided into census units. For this study, each patient's location was matched to a census unit and from there to an electoral ward based primarily on PNG census data or, alternatively, on the 2012 and 2017 PNG government election polling schedules.[5,6] Instances of alternate local names were checked and confirmed locally.

Provincial, district and LLG boundary data and latitude and longitude coordinates of census units were obtained from the PNG National Statistical Office and census data. For coordinates that could not be obtained from census data, alternate sources including ArcGIS Online (Esri, Redlands, CA, USA) and a 2018 Google search were used. Population data for electoral wards used the 2011 national census figures[7] to describe the underlying population at risk in the cluster analyses and logistic regression. Population size was not projected to later years as ward-level population growth data were not available.

Mapping and cluster analyses

The residential locations of TB patients diagnosed at BDH were mapped to identify the BDH catchment area (i.e. the region served by the hospital as defined by the origins of TB patients who have travelled to the hospital). Mapping of residential locations was primarily based on census unit-level coordinates. However, patients from some locations were mapped based on the average coordinates of a combination of census units as the precise census unit was rarely known for these patients. Average ward coordinates were calculated using the Geographic Midpoint Calculator available in 2017. There were four locations where all census units within a ward were averaged and four locations where the averaged coordinates included several census units within a ward. Towns and villages are depicted in Figures 1 to 3 spatially as dots as we did not have access to georeferenced boundaries at the ward level for this region of PNG.

Cluster analyses were undertaken separately for the Gogodala and Bamu regions using averaged ward-level coordinates and ward-level population data. The Gogodala region included the 39 Gogodala Rural LLG wards plus Balimo Urban LLG; the Bamu region included the 19 Bamu Rural LLG wards.[7] Eleven patients located within Western Province but outside the Gogodala and Bamu regions were excluded from the cluster analyses.

Cluster analyses based on paediatric and extrapulmonary TB cases were undertaken to compare clusters in these patient groups to the overall cluster analysis. These subanalyses used the same underlying population and coordinate data but with case data restricted to patient subgroups in the Gogodala region only. Age-stratified population data were not available for the wards in this region, so geographic differences in age distribution were not taken into account in the overall analysis.

The spatial scan statistic was calculated using SaTScan™ (version 9.6) (SaTScan, Boston, MA., USA).[8]

A discrete Poisson probability model was used because occurrence of the disease is rare.[9,10] The data were scanned for areas with either high- or low-rate clusters. A circular spatial window was used, and the maximum spatial cluster size was set at the default size of 50% of the population at risk. The analyses were run with the default 999 replications with statistical significance set at $P < 0.05$. Secondary clusters that were significant were non-overlapping Gini clusters. These clusters are selected to maximize the Gini index, which is a measure of statistical dispersion, and which can provide evidence of the best non-overlapping clusters to report from one larger cluster or multiple smaller clusters.[10,11] Shapefiles depicting cluster areas were generated using SaTScan™. All maps were created using ArcGIS ArcMap 10.4.1(Esri, Redlands, CA., USA) and used the World Topographic Map basemap layer provided within the ArcGIS Online package.

Investigation of high-rate TB clusters

For wards in the Gogodala region, univariate and multivariate logistic regression were used to investigate the relationship between ward-level demographic and geographic variables and the occurrence of wards in significant high-rate TB cluster areas. Based on ward-level population data, the predictor variables included gender ratio (total males/total females), housing density (total ward population/total number of households in the ward) and distance from Balimo (distance in kilometres from the averaged Balimo coordinates to the averaged ward coordinates). Distance was calculated using the National Hurricane Center Latitude/Longitude Distance Calculator.[12] Statistical analyses were performed using Stata/IC version 14 (StataCorp LLC, College Station, TX., USA).

ETHICS APPROVAL

This study received local approval from the Middle Fly District Health Service and the Evangelical Church of PNG Health Service. Human research ethics approval was received from the James Cook University Human Research Ethics Committee (H6432) and the PNG Medical Research Advisory Committee (MRAC No. 17.02).

RESULTS

The 1568 TB patients were identified at 90 localities across Western Province. These locations, shown in **Fig. 1**, are based on census unit-level coordinates (averaged where relevant; see methods) and delineated by the LLG boundaries of Western Province. The catchment area is depicted with the majority of patients originating from the Balimo Urban (n = 252) and Gogodala Rural (n = 1010) LLG areas with a large number also in Bamu Rural LLG (n = 295). Eleven patients were located in other LLGs in Western Province.

Cluster analyses

High- and low-rate TB clusters are described in **Table 1**, and depictions in **Fig. 2** (for the Gogodala region, n = 1262) and **Fig. 3** (for the Bamu region, n = 295) are based on the ward-level population and TB patient data. Cluster numbers included in **Table 1** correspond to the cluster numbers depicted in **Fig. 2** and **3**. The optimal Gini coefficients were found at 20% of the population in the Gogodala region and at 10–12% of the population in the Bamu region; paediatric TB and extrapulmonary TB subgroups were at 12% and 20%, respectively. Only clusters with less than these proportions of the population at risk were reported for each region. In the Gogodala region, high-rate clusters were generally identified closer to Balimo, while low-rate clusters were seen on the outskirts of the region (**Fig. 2**). This trend continued to be evident for the paediatric (n = 283) and extrapulmonary TB (n = 978) subgroups (**Fig. 2**). In the Bamu region, three high-rate clusters were identified in the lower regions of the Bamu and Gama Rivers; low-rate clusters were identified further along the Gama River and in the far north of the Bamu Rural LLG (**Fig. 3**).

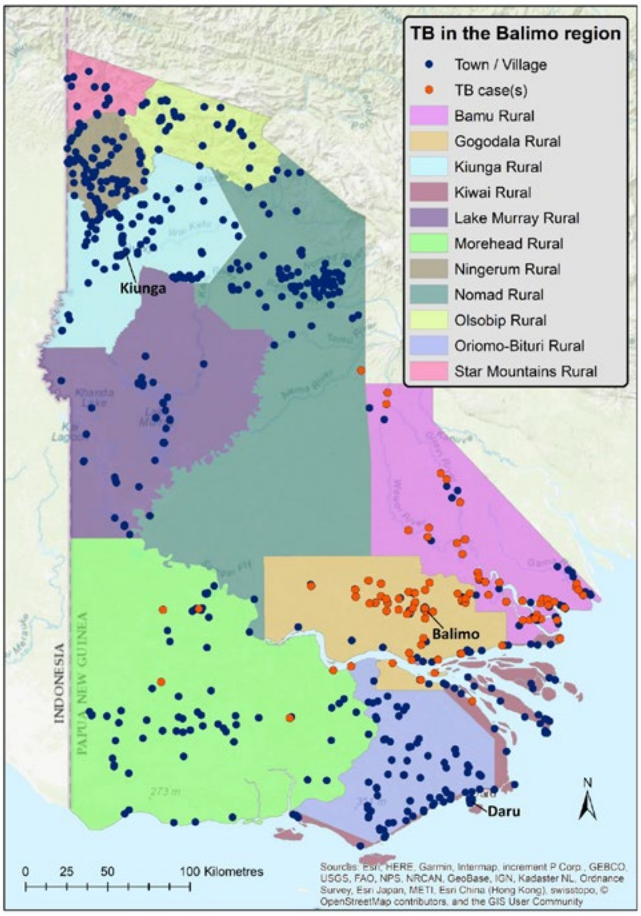
The logistic regression results for predictors of ward-level high-rate TB clusters are summarized in **Table 2**. In both the univariate and multivariate analyses, wards in high-rate TB clusters were associated with closer proximity to Balimo. Housing density had an odds ratio of 0.63 (95% CI: 0.34–1.20) in the univariate analysis, while the odds ratio in the multivariate analysis was 1.26 (95% CI: 0.55–2.90), suggesting confounding between housing density and distance from Balimo in this analysis.

DISCUSSION

This study examined the spatial distribution of TB patients diagnosed at BDH. The extensive hospital catchment area highlights the considerable distance that people travel to seek care for TB symptoms; however, the capacity to travel may help define and explain the lower case numbers in communities located further away from a health centre. In the Gogodala and Bamu regions, both high- and low-rate TB clusters were identified, illustrating the heterogeneity of reported TB burden across the region with a substantially higher TB burden evident in closer proximity to Balimo.

Most villages in the Gogodala Rural LLG had TB cases identified during the study period. Villages with no reported TB patients were predominantly located south of Balimo near the Fly River. Geographic challenges may be particularly important for people from this area as travel to either Balimo or Daru is lengthy, and fuel to travel by motorized boat to Daru is expensive. However, some patients were reported from the Gogodala region between Balimo and the Fly River, which may reflect a choice to travel to Balimo or, potentially, referral from a peripheral health facility in the region. Overall, villages

Fig. 1. Map of Western Province, Papua New Guinea, with orange dots representing towns and villages (at the census unit level) where tuberculosis patients were identified in this study, differentiated by local level government area.



Map of Western Province, Papua New Guinea, with orange dots representing towns and villages (at the census unit level) where tuberculosis patients were identified in this study, differentiated by local level government area.

with no or low rates of TB should be noted for future investigation to identify people symptomatic for TB and describe treatment-seeking practices.

In this study, low-rate clusters occurred in more remote areas, while closer proximity to Balimo was a predictor of a ward located in a high-rate TB cluster. This association is potentially linked with underdiagnosis of TB in more remote areas as less arduous travel will promote better access to care. If villages in high-rate TB clusters reflect accurate rates of TB for the region more generally, villages with low rates of TB may indicate underdiagnosis of TB and are sites where active TB investigations should be undertaken. This finding is important as other research from our group has described potential underdiagnosis of TB in the Balimo region.[13]

Table 1. High- and low-rate tuberculosis clusters identified in wards in the Gogodala and Bamu regions of Western Province, Papua New Guinea using the spatial scan statistic

No.	Locations in cluster	Pop	Obs	Exp	RR	p
Gogodala region (Balimo Urban and Gogodala Rural LLG areas)						
1	↑ Kimama	704	162	23.74	7.68	< 0.01
2	↓ Lewada, Dede, Konedobu, Tapila, Dewala, Pagona, Duaba	5854	20	197.39	0.09	< 0.01
3	↑ Bamustu, Uladu, Kewa, Kotale, Tai, Balimo Urban	7351	429	247.87	2.11	< 0.01
4	↓ Urio, Kenewa, Waya, Ugu, Kawiapo, Aduru, Baramula	6970	116	235.02	0.44	< 0.01
5	↓ Awaba	1646	6	55.50	0.10	< 0.01
6	↓ Ali, Makapa, Sialoa	4147	68	139.83	0.46	< 0.01
7	↑ Pisi	1119	73	37.73	1.99	< 0.01
8	↑ Ike, Yau, Aketa, Adiba, Kawito Station, Dadi	4801	212	161.88	1.37	0.01
Bamu region (Bamu Rural LLG area)						
1	↑ Sisiami	331	37	7.27	5.68	< 0.01
2	↑ Bamio	741	54	16.27	3.84	< 0.01
3	↓ Samakopa	1292	2	28.38	0.06	< 0.01
4	↓ Kawalasi	654	2	14.36	0.13	< 0.01
5	↑ Nemeti	229	15	5.03	3.09	0.02
6	↓ Ukusi	293	0	6.44	0.00	0.03
7	Garu	549	3	12.06	0.24	0.09
8	Ibuo	385	2	8.46	0.23	0.27
9	Gagoro	184	8	4.04	2.01	0.92
10	Miruwo	789	22	17.33	1.29	1.00

LLG: local level government; Pop: population; Obs: observed cases; Exp: expected cases; RR: relative risk; TB: tuberculosis

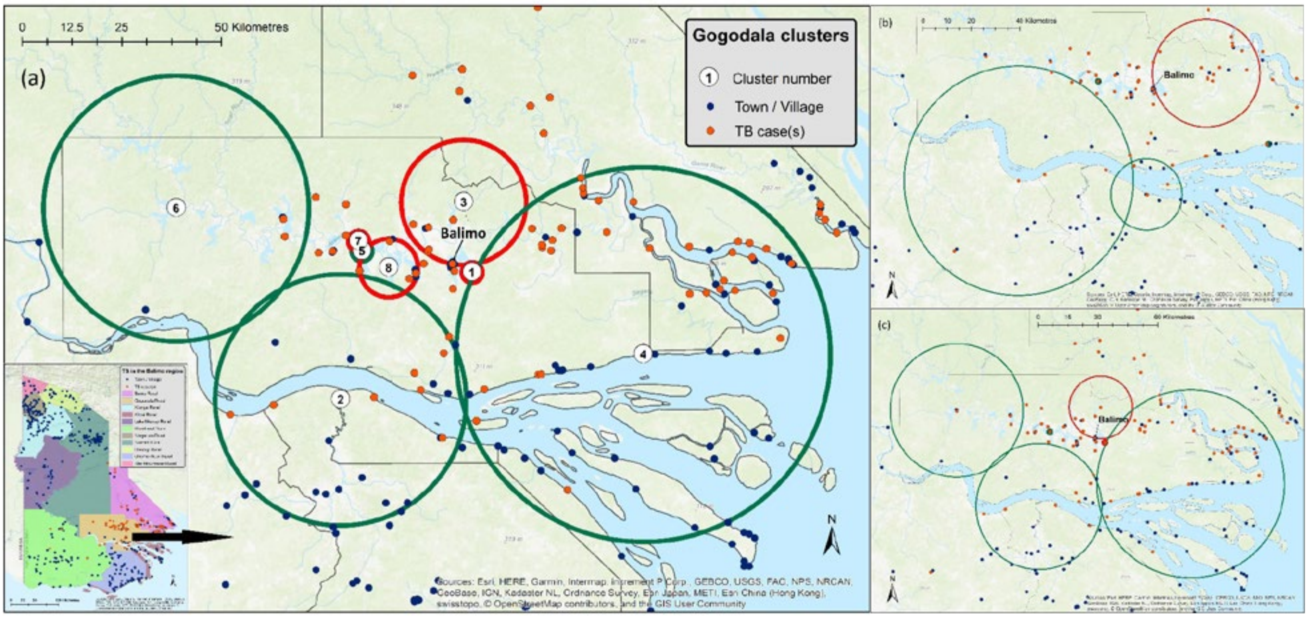
Statistical significance was set at $P < 0.05$. High- and low-rate clusters that were significant are denoted with up- and down-arrows, respectively. The number of observed cases of TB are all those diagnosed for the cluster locations over the study period (26 April 2013 – 25 February 2017)

Table 2. Univariate and multivariate logistic regression examining ward-level predictors of high-rate TB clustering in the Gogodala region

Predictor variables	n	Univariate OR (95% CI)	Univariate p	Multivariate OR (95% CI)	Multivariate p
Gender ratio*	40	0.77 (0.00–242.74)	0.93	-	-
Housing density†	40	0.63 (0.34–1.20)	0.14	1.26 (0.55–2.90)	0.58
Distance from the town of Balimo‡	40	0.87 (0.79–0.95)	< 0.01	0.86 (0.77–0.96)	< 0.01

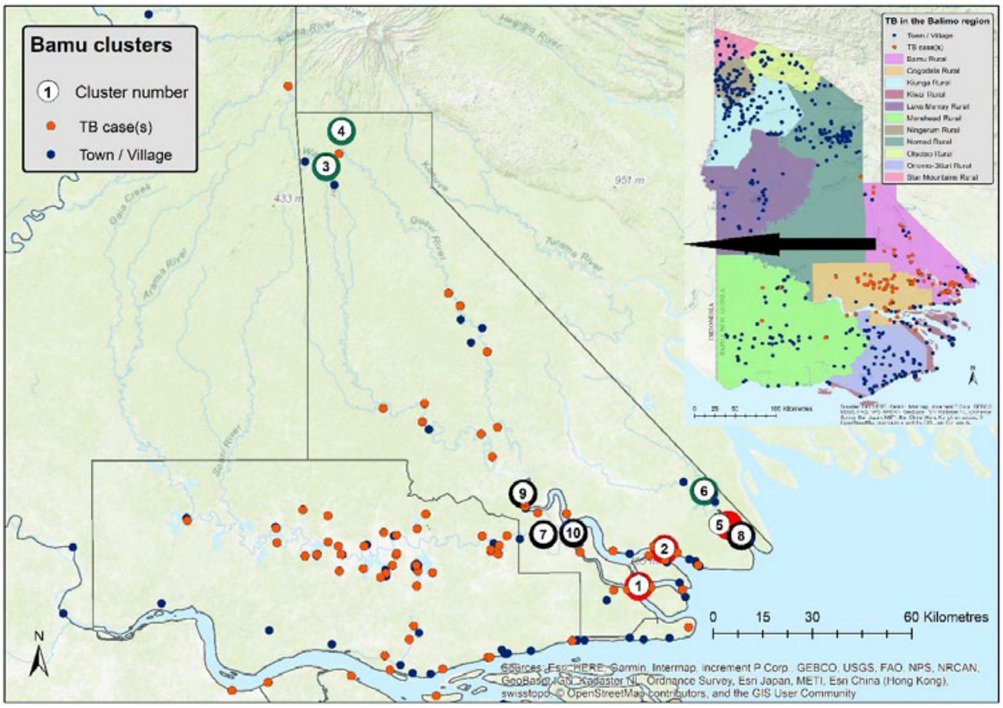
CI: confidence interval; OR: odds ratio
*Gender ratio is defined as total males/total females.
†Housing density is defined as number of persons/number of households.
‡Distance from the town of Balimo is based on distance between average ward coordinates in kilometres.

Fig. 2. **Geographic distribution of high-rate (red circles) and low-rate (green circles) tuberculosis clusters identified in the analysis of wards in the Gogodala region in Western Province, Papua New Guinea. Cluster analyses are depicted for (a) all patients, (b) paediatric TB patients and (c) extrapulmonary TB patients.**



Orange dots represent locations where TB patients were identified and may include multiple TB patients. (Map sources: Esri, HERE, Garmin, Intermap, increment P Corp., GEBCO, USGS, FAO, NPS, NRCAN, GeoBase, IGN, Kadaster NL, Ordnance Survey, Esri Japan, METI, Esri China (Hong Kong Special Administrative Region), swisstopo, © OpenStreetMap contributors and the GIS User Community)

Fig 3. **Geographic distribution of high-rate (red circles) and low-rate (green circles) tuberculosis clusters identified in the analysis of wards in the Bamu Rural local level government area in Western Province, Papua New Guinea.**



Clusters that were not statistically significant are shown as black circles. Orange dots represent locations where TB patients were identified and may include multiple TB patients. (Map sources: Esri, HERE, Garmin, Intermap, increment P Corp., GEBCO, USGS, FAO, NPS, NRCAN, GeoBase, IGN, Kadaster NL, Ordnance Survey, Esri Japan, METI, Esri China (Hong Kong Special Administrative Region), swisstopo, © OpenStreetMap contributors and the GIS User Community)

The possibility of underdiagnosis of TB was emphasized by results from the cluster analysis for the Bamu Rural LLG region. The high-rate clusters in three of these wards are the result of non-routine active case-finding activities. During an eight-day period in March 2016, 96 patients from eight villages in the Bamu Rural LLG region, including villages in these three high-rate cluster wards, were diagnosed with TB. By comparison, only 31 patients from these eight villages were diagnosed over the remainder of the study period. These diagnoses demonstrate the potential of an even higher burden of TB in remote and difficult-to-reach locations, reflecting people who may not otherwise have been diagnosed with TB. The geographically distant low-rate clusters seen in the Bamu Rural LLG likely reflect a combination of access challenges and the possibility of travel by patients to health centres other than BDH for TB care.

Other studies have described higher TB density in regions with closer proximity to urbanized areas and delayed treatment-seeking in people who travelled to a health facility by foot, while increased distance and poorer access to health facilities have been associated with diagnostic delay in some resource-limited settings.[14–17] In addition, urbanization has been associated with higher rates of TB as a result of factors such as overcrowding and increased TB transmission risk;[18,19] however, it is notable that housing density in Balimo was below average for the 40 Gogodala region wards (density of 6.9 people per household compared to an average of 7.4). Previous research in PNG has noted the importance of challenging travel in the context of TB care, including in the Gogodala region where travel is primarily by boat or by foot.[20,21] In addition, where travel by boat is possible, socioeconomic factors and affordability of fuel will play a role in the ability to travel.[20] Other factors, including proximity to a health facility, health worker training and local TB awareness activities have been associated with increased TB notifications.[22–25] In the Gogodala region, possible reasons for locations with high case density include the presence of an actively staffed aid post or health clinic that regularly refers presumptive TB patients or increased case-finding or awareness activities.

High rates of paediatric and extrapulmonary TB have previously been identified in the Balimo region.[2] Separate cluster analysis of these patient subgroups identified similar patterns to the overall distribution of TB in the Gogodala region. This finding may indicate similar TB transmission patterns across the region as well as consistency in the approach to identifying TB in a region where diagnoses are predominantly based on clinical signs and symptoms.

Awaba has the largest health centre in the Gogodala region outside of Balimo. The low-rate cluster identified in the Awaba ward is due to registration of TB patients diagnosed and started on TB treatment at the Awaba Health Centre instead of at BDH. The Awaba TB register was not available for this study, although TB incidence at the centre was estimated to be 381 cases per 100 000 people per year in a 2011 Western Province TB evaluation study.[26]

In our study, the 11 patients from within Western Province but outside the Gogodala and Bamu regions may be important when considering importation of TB into the Gogodala region. Seven of these patients had alternative addresses recorded within the Gogodala and Bamu regions, including two at logging camps and one at a school. This suggests mobility of people in the region, particularly in the context of education and employment, which is important when considering that schools and workplaces can be important sites of TB transmission.[27,28]

In this analysis, it was assumed that a TB patient's first recorded address was where they were living at the time of registration. However, people with more than one address recorded may be more mobile, particularly if travelling between their residential and home villages (i.e. place of birth or family village) or workplace. Thus, some patient locations may not have reflected the location where TB infection occurred. An unknown number of TB patients were registered at smaller health facilities in the Balimo region. Although such patient numbers are likely to be low, these facilities will have influenced the analyses to an unknown extent. In addition, the TB patients identified and described here will not include Balimo-region patients diagnosed and commenced on treatment in the provincial capital of Daru. Finally, this analysis was based on population data collected in the 2011 PNG census. Thus TB rates may have been inaccurate for wards that experienced unusually high or low growth in the time before and during our study period of 2013 to 2017.

CONCLUSIONS

This analysis provides insight into TB distribution in the BDH catchment area. The results provide baseline data about TB distribution across the region as well as targeted information that points to the need for village- and ward-specific TB investigations. In this region, TB clustering likely reflects the ease with which people can travel and seek treatment, demonstrating the importance of access to health services. However, investigation of high-rate TB clusters, as well as diagnoses resulting from targeted case-finding activities, emphasize the high potential for missed TB diagnoses in the region. The potentially substantial burden of undiagnosed TB in the extensive catchment area of BDH indicates an urgent need for active case-finding activities both to reduce TB disease burden and prevent ongoing transmission of TB in the region. This study may help focus a more targeted active TB case detection programme. Furthermore, these results emphasize the importance of targeted investment in resources and facilities in the Middle Fly District to improve and strengthen the provision of TB care in Western Province.

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Gap in measles vaccination coverage among children aged 9 months to 10 years in Ho Chi Minh City, Viet Nam, 2014

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Introduction: When Viet Nam launched the Expanded Programme on Immunization in 1981, it covered six vaccines, including measles. Subsequently, Viet Nam experienced a marked reduction in measles infections. A nationwide measles epidemic occurred in April 2014 and an investigation found that 86% of affected children aged 9 months to 10 years were not fully vaccinated; therefore, understanding the reasons for not vaccinating could improve vaccination coverage.

Method: We performed a cross-sectional study to determine vaccination coverage and reasons for non-vaccination among children aged 9 months to 10 years in six districts in Ho Chi Minh City with the highest number of measles cases in 2014. Measles vaccination status of the youngest child in each household was determined and reasons for non-vaccination were investigated. A χ^2 test and multiple logistic regression were used to identify independent predictors of full vaccination.

Results: In total, 207 children were enrolled during the study period in 2014. Full measles vaccination coverage was 55% in these households, and 73% of parents were aware of the importance of measles vaccination to protect their children. We found that the father's education level (under high school versus high school and above) and the site where the survey was conducted were significantly associated with vaccination status.

Conclusion: The vaccination coverage was lower than the coverage reported by district preventive medicine centres of the seven study wards. Lack of the second vaccination was a key obstacle to eliminating the vaccination gap. A catch-up mass vaccination campaign or health promotion of measles vaccination directed towards parents should be considered to improve vaccination coverage.

The World Health Organization (WHO) has developed plans to eliminate measles in the Western Pacific Region, which includes Viet Nam.[1] However, recent measles outbreaks throughout the world, including in the United States of America, the Netherlands, Australia, China, the Philippines, Indonesia and Viet Nam have highlighted the challenges in achieving this goal.[2–5] In May 2014, more than 3900 confirmed measles cases and 133 deaths were reported in Viet Nam, a large increase in cases compared to 2012 (637 cases) and 2013 (1233 cases).[6–8] The Ministry of Health in Viet Nam introduced the Expanded Programme on Immunization (EPI) in 1981 with the support of WHO and the United Nations Children's Fund (UNICEF). EPI provides immunization services through community health centres (CHCs) that dedicate one or two days per month to this service. In 2009, measles vaccination was administered at the ages of 9 months and 6 years; in 2011, the second dose administration was brought forward to 18 months of age. If children miss any of the measles vaccine doses, immunization services are tasked to administer the missed dose. Viet Nam has conducted periodic measles vaccine campaigns targeting children aged 9 months to 10 years at CHCs to address gaps in coverage among young children; however, according to the 2014 outbreak report, 82% of measles cases occurred in children under the age of 10, and 86% of the infected children were not fully vaccinated or had unknown vaccination status.[9,10] The proportion of the measles cases occurred in persons known to have no previous measles vaccines was 3%. The proportion in those who had only one dose was 3%. The proportion in those with unknown vaccination status was 6%

Ho Chi Minh City (HCMC), the largest municipality in Viet Nam, is subdivided into 19 urban districts and

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five rural districts. Urban districts are further divided into wards and rural districts into towns and communes. HCMC covers an area of 2061.4 km^2 with a population of about 8.6 million people. With a population density of 4.2 persons per km^2, there is a high risk of infectious disease transmission.[11] In 2013–2014, an outbreak of measles occurred in southern Viet Nam; a total of 3486 cases were reported, including 1023 cases in HCMC. This outbreak started in HCMC and spread to neighbouring provinces.[10]

The aims of this study were to describe measles vaccination coverage among children aged from 9 months to 10 years living in HCMC and to identify individual factors associated with and reasons for non-vaccination.

METHODS

Study design and sample size

In June 2014, we conducted a cross-sectional study in the seven wards of HCMC with the highest number of measles cases, which were located in six different districts of HCMC (**Table 1**).

The formula to calculate sample size was: $n = 4$ (r) (1-r) (f) (1.1)/(e^2) (p) (n_h).[13] We planned to recruit 210 children into the study based on the estimated vaccination coverage (r = 98%) reported by the EPI in Viet Nam, taking into account the design effect (f = 1.5f), the proportion of children under 10 years old (P = 7.5%), the average household size (n_h = 4) and given $\alpha = 0.05$ and 95% confidence interval.[14]

Sampling and data collection

We selected study households using a cluster sampling method described by the Johns Hopkins Bloomberg School of Public Health.[15] Out of 259 wards with an average population of 24 000 people each (range: 10 000–61 000), the seven wards with the highest number of cases during the 2014 measles epidemic were selected. Questionnaires were collected in a designated facility in each ward, followed by randomly selected door-to-door visits to 30 households in each ward. We interviewed the parents or principal caregivers of the youngest child face-to-face using a standard questionnaire describing the child's vaccination history. Vaccination status was determined by reviewing the child's vaccination cards and through parental recall. The study excluded children who were not permanent residents of the ward. We confirmed the child's residence status using household registration books. Lastly, we retrieved the previous year's (2013) population-level vaccination coverage in the seven study wards from the district preventive medicine centres (DPMC).

Data analysis and management

The analysis took into account the cluster design of the study. Study factors included demographic information such as age, gender, parents' education level and employment; the number of children in each house; and the distance from the household to the closest vaccination site. We examined the relationship between study factors and vaccination status weighted by the number of children in each age group residing in each ward. Vaccination coverage was categorized into three groups: no vaccination, one-dose vaccination and two-dose vaccination. We then created a variable that reflected whether a child was fully vaccinated and used it as the outcome with two levels: fully vaccinated and not fully vaccinated. Fully vaccinated was defined as a child who either (1) was aged 18 months or older and had received two doses of measles vaccine or (2) was aged 9–18 months and had received one dose of measles vaccine. Not fully vaccinated was defined as partial or non-vaccination, including children of any age who had either not received any measles vaccine or children aged ≥18 months old who had received only one dose of measles vaccine. The study population for the analysis also included the children ≥ 18 months of age who did not receive at least one dose of measles vaccine. A χ^2 test, unadjusted and adjusted logistic regression models were computed by R statistical software (version 3.3.0, R Foundation for Statistical Computing, Vienna, Austria) to explore associated factors of vaccination. The R package BMA was used to conduct Bayesian model averaging approach, which not only accounts for the uncertainty in variable selection by averaging over the best models but also combines estimate and prediction.[16] For the multivariable analysis, variables were selected by univariate analysis of each variable using a p-value cut-off point of 0.25. Variables were also selected that were previously known to be important risk factors, such as parental awareness, parents' level of education and fear of adverse reactions. Models

Table 1. **Weighted vaccination coverage among children aged 9 months to 10 years in seven wards of six districts in Ho Chi Minh City, Viet Nam, 2014[12]**

Community	Number of children	Weight	Surveyed immunization coverage weighted by population		Reported immunization coverage weighted by population	
			Full (%)	Not full (%)	Full (%)	Not full (%)
Ward 8, District 8	281	4.1%	5 (20.0)	20 (80.0)	216 (76.9)	65 (23.1)
Phuoc Loc Ward, Nha Be District	294	4.2%	18 (64.3)	10 (35.7)	268 (91.2)	26 (8.8)
Ward 7, District 6	361	5.2%	15 (60.0)	10 (40.0)	352 (97.5)	9 (2.5)
Truong Thanh Ward, District 9	490	7.1%	18 (62.1)	11 (37.9)	344 (70.2)	146 (29.8)
Binh Hung Ward, Binh Chanh District	1266	18.2%	14 (51.9)	13 (48.2)	997 (78.8)	269 (21.2)
Ward 4, District 8	1767	25.4%	14 (50.0)	14 (50.0)	1247 (70.6)	520 (29.4)
Linh Xuan Ward, Thu Duc District	2487	35.8%	17 (60.7)	11 (39.3)	2296 (92.3)	191 (7.7)
Total	**6946**	**100%**	**101 (54.9)**	**89 (45.1)**	**5720 (82.4)**	**1226 (17.7)**

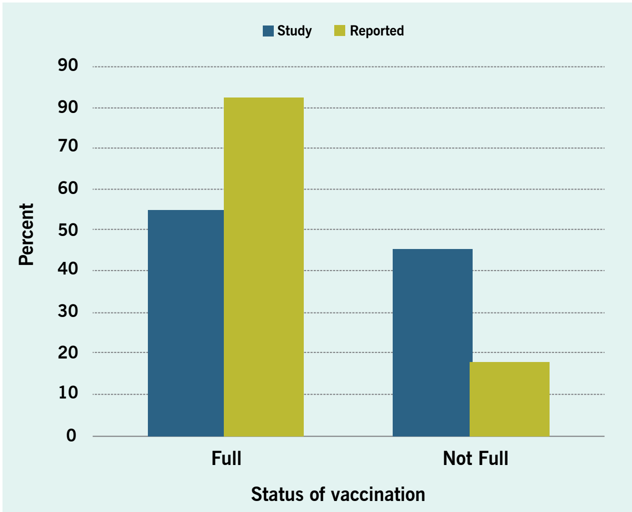
with lower Bayesian information criterion and higher posterior probability are preferred.[17] Odds ratio (OR) and 95% confidence interval (95% CI) were used to identify the relationship between independent and dependent variables. Statistical significance was set at $P = 0.05$ to allow for the incorporation of model uncertainty into inference.

The survey was approved by the Pasteur Institutional Review Board (No: 272/PAS-QĐ on 20 June 2014).

RESULTS

Of the 210 children recruited for enrollment, 207 children (98.5%) were enrolled during the study period in 2014. The youngest child in the study was 9.4 months old and the oldest was 10 years old with a median age of 38 months (interquartile range: 23 to 70 months). The proportion of males in the studied population (54.1%) was higher than females (45.9%). The majority of parents had not finished high school (58.8% for fathers, 55.7% for mothers). Among the 207 children, 179 (86.5%) had lived in HCMC for at least two years. Over half of the parents reported living less than 1 km away from a CHC (56.6%). The proportion of the measles cases that occurred in persons known to have no previous measles vaccines and in those who had only one dose was 3%. The figure for unknown vaccination status was 5.%.

Fig. 1. **Calculated vaccination coverage based on 2014 survey of six districts in Ho Chi Minh City, Viet Nam compared with vaccination coverage previously reported by district preventive medicine centres during 2013**



Measles vaccination coverage

Information on vaccination status was available for 190 of the 207 children (91.8%). The parents of the remaining 17 children were uncertain of their child's vaccination history, and their child's vaccination cards were not avail-

Table 2. **Association between study factors and vaccination status among children aged 9 months to 10 years in six districts in Ho Chi Minh City, Viet Nam, 2014**

Characteristics	*n* (%)	Fully vaccinated *n* (%)	Not fully vaccinated *n* (%)	χ^2	*P*-value*
Age groups (*n* = 190)					
9–18 months	21 (11.0)	13 (61.9)	8 (38.1)	0.7	0.4
≥18 month–10 years	169 (89.0)	88 (52.1)	81 (47.9)		
Gender (*n* = 190)					
Male	103 (54.2)	55 (53.4)	48 (46.6)	0.0	0.9
Female	87 (45.8)	46 (52.9)	41 (47.1)		
Study sites (*n* = 190)					
District 6	25 (13.2)	15 (60.0)	10 (40.0)	9.8	0.1
Binh Chanh District	27 (14.2)	14 (51.9)	13 (48.2)		
Nha Be District	28 (14.7)	18 (64.3)	10 (35.7)		
Thu Duc District	28 (14.7)	17 (60.7)	11 (39.3)		
District 9	29 (15.3)	18 (62.1)	11 (37.9)		
District 8	53 (27.9)	19 (35.9)	34 (64.2)		
Parents' awareness of measles vaccination (*n* = 188)					
Yes	138 (73.4)	72 (52.2)	66 (47.8)	0.1	0.8
No	50 (26.6)	27 (54.0)	23 (46.0)		
Father's education (*n* = 188)					
Under high school	103 (54.8)	63 (61.2)	40 (38.8)	5.1	**0.0**
High school and above	85 (45.2)	38 (44.7)	47 (55.3)		
Mother's education (*n* = 183)					
Under high school	100 (54.6)	56 (56.0)	44 (44.0)	1.1	0.3
High school and above	83 (45.4)	40 (48.2)	43 (51.8)		
Number of children under 10 years old (*n* = 190)					
1–2	173 (91.3)	91 (52.6)	82 (47.4)	0.2	0.6
> 2	17 (8.7)	10 (58.8)	7 (41.2)		
Distance from house to vaccination site (*n* = 188)					
≤ 1 km	102 (54.3)	56 (55.5)	46 (52.9)	0.7	0.7
1–3 km	68 (36.2)	37 (36.4)	31 (35.6)		
> 3 km	18 (9.6)	8 (7.9)	10 (11.5)		
Causes of unvaccinated children investigated through questionnaire (*n* = 190)					
Fear of adverse reactions					
No	187 (98.4)	98 (52.4)	89 (47.6)	-	0.3
Yes	3 (1.6)	3 (100.0)	0 (0.0)		
Not old enough to vaccinate according to immunization schedule					
No	182 (95.8)	95 (52.2)	87 (47.8)	-	0.3
Yes	8 (4.2)	6 (75.0)	2 (25.0)		
Children's illness					
No	182 (95.8)	96 (52.8)	86 (47.3)	-	0.5
Yes	8 (4.2)	5 (62.5)	3 (37.5)		
Busy parents/caregivers					
No	180 (94.7)	94 (52.2)	86 (47.8)	-	0.3
Yes	10 (5.3)	7 (70.0)	3 (30.0)		
Unaware of vaccination need					
No	175 (92.1)	92 (52.6)	83 (47.4)	0.3	0.6
Yes	15 (7.9)	9 (6.0)	6 (40.0)		

* $\chi2$ test, Fisher's Exact test, *p*-value ≤ 0.05 (significance level)

Table 3. **Association between study factors and vaccination status among children aged 9 months to 10 years in six districts in Ho Chi Minh City, Viet Nam, 2014: logistic regression**

Predictors	Adjusted OR	95% CI	*P*-value
Study sites			
District 9, Thu Duc District	Reference	-	-
Districts 6 & 8	0.49	0.24–1.01	**0.05**
Binh Chanh District, Nha Be District	0.78	0.89–3.62	0.54
Father's level of education			
Under high school	Reference	-	-
High school and above	0.53	0.29–0.96	**0.04**

Odds ratio (OR), 95% confidence interval (95% CI)

able. Our survey found that the proportion of children with full vaccination coverage was 54.9% and those not fully vaccinated was 45.06%, weighted by the number of children in each age group. The proportion of children ≥ 18 months that did not have any measles vaccination was 14.8% (25/169). Consequently, there was a large vaccination gap (45.1%), which was three times higher than the vaccination gap (17.7%) reported by DPMCs (**Fig. 1**, **Table 1**).

Epidemiological characteristics

A greater proportion of those who lived less than 1 km away were fully vaccinated, but this was not statistically significant (*p*-value = 0.7) (**Table 2**).

Reasons for non-vaccination

The most common reported reason for not being fully vaccinated was the lack of awareness among parents of the need for a second dose of measles vaccine (7.9%); after their children's first dose, the parents reported thinking that the measles vaccination process was completed. Other reasons cited for not completing the full vaccination course were: parents/caregivers were busy, parental reluctance to vaccinate children during illnesses such as the common cold, parental fear of adverse events after vaccination and children not being old enough to be vaccinated according to the immunization schedule (**Table 2**).

Factors associated with vaccination

Children of fathers with less education (under high school versus high school and above) were more likely to be fully vaccinated ($P < 0.05$) (**Table 2**). The result of unadjusted and multiple logistic regression found that children attending study sites in districts 6 and 8 (OR = 0.49, 95% CI: 0.24–1.01) and those whose fathers had less education (OR = 0.53, 95% CI: 0.29–0.96) were less likely to be fully immunized against measles (**Table 3**).

DISCUSSION

Viet Nam EPI requires the administration of the first dose of measles vaccine at 9 months of age and the second dose at 9 months after the first injection. The goal is to vaccinate at least 95% of eligible children aged 9–24 months across the country.[18] However, an accumulation of susceptible children throughout the years, through failure to complete full vaccine courses and incidents of vaccine failure, contributed to a gap in measles immunity in HCMC. The vaccination coverage reported by the national vaccination system in surveyed wards during the same time as our study was 82.4%. The full vaccination coverage of children in our study was only 54.9%, suggesting that the national surveillance system may be overestimating vaccination coverage. To address this issue, we strongly recommend that all children's vaccinations should be registered in the National Immunization Information System or a digital immunization registry.[19,20] Furthermore, measles vaccination should be provided for all eligible children.

The survey showed that most parents took their children to receive the first dose of measles vaccine at 9 months old but only 52% returned for the second scheduled dose at 18 months, indicating an important but not statistically significant drop off from children receiving their first dose (62%) of measles vaccine to those receiving their second dose (52%). Other studies have found that a lack of awareness of the need for the second vaccination was associated with low coverage in this age group. A cross-sectional study in Mali showed that lack of awareness was the most common reason for non-vaccination against six diseases.[21] A birth cohort of 64 000 children aged 5 years old in Australia also reported that the most important reason for non-uptake of measles vaccination was lack of awareness.[22] However, our study found no difference in vaccination status associated with parental awareness.

We found the father's level of education was significantly associated: children whose father had completed at least high school were less likely to be fully vaccinated compared to those whose fathers had less education. Although education levels were defined differently in our study (high school degree) compared with a study in France (bachelor's degree), the findings were similar.[23] The reason for this finding has not been adequately studied, but it is possible that parents with a higher level of education may be more likely to perceive a risk of adverse side-effects or parents may have been afraid of a complete the vaccinations due to complications and high costs of vaccines.[24]

Children who lived in Districts 6 and 8 were less likely to be fully vaccinated compared to those living in District 9 and Thu Duc District. The difference in vaccination coverage was not significant in Binh Chanh and Nha Be districts compared to District 9 and Thu Duc District. Parents' educational level and population fluctuations possibly account for the difference between sites. The average population change of Districts 6 and 8 was less than District 9 and Thu Duc District from 2012 to 2014.[23]

Limitations of this study included the lack of vaccination histories, especially with regard to the second dose. Vaccination status was based on parental recall in 8.2% of subjects, where the child's vaccination card had been lost or health staff did not record the vaccine when it was administered. We do not have data on immigration, an important risk factor of measles transmission, so we could not take this into account when we compared vaccination coverage among communities. We do not know how many Vietnamese workers, for instance those employed in industrial parks in HCMC who came from the northern regions or the Mekong Delta, did not register their children with the national vaccination system.[26] Furthermore, the study selected only the youngest child instead of all children in each household, which might lead us not to have the most representative data.

CONCLUSIONS

We found that full vaccination coverage was 67% of the vaccination coverage reported by DPMCs of the seven study wards. While 85% percent of children over 18 months had received a first dose of vaccine, the age group from 18 months to 10 years was less likely to be fully vaccinated because parents were unaware of the second measles vaccine dose at 18 months of age. Furthermore, 38% of children aged 9-18 months lacked even a first vaccination dose -- a high rate of under-vaccination for this age range. This highlights the critical importance of increasing first dose coverage in children from 9-18 month, and potentially in children ≥ 18 months of age. Ensuring at least one vaccination dose for children may be as important (or more) as ensuring the second vaccination dose in children over 18 months of age.

Lack of information on measles vaccination and other reasons such as children's illness at immunization time and fear of adverse events contributed to the measles vaccination gap. Health staff should monitor actively for children who received incomplete vaccinations and schedule the second vaccination for children who have had only one dose of measles vaccination. Lack of the second vaccination dose was a key obstacle to eliminating the vaccination gap; therefore, a catch-up mass vaccination campaign should be implemented. Additionally, health promotion of measles vaccination directed towards parents would likely improve vaccination coverage.

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Diphtheria diagnostic capacity in the Western Pacific Region

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Diphtheria is an acute infectious disease affecting the upper respiratory tract and occasionally the skin and is caused by the action of diphtheria toxin produced by *Corynebacterium diphtheriae*, *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis*. Corynebacterium infections are usually difficult to control due to their epidemic patterns, the emergence of new strains, novel reservoirs and their dissemination to susceptible human and animal populations.[1] Although *C. diphtheriae* is largely controlled through mass immunization programmes, diphtheria escalated to epidemic proportions within the Russian Federation and the former Soviet Republics in the 1990s, highlighting the potential for this disease to cause morbidity and mortality when immunization programmes are disrupted.[2] A recent review of global diphtheria epidemiology, which included an analysis of cases and information about age, showed age distribution shifts and found that the majority of cases occur in adolescents and adults.[3] Shifts in age distribution, from children to adolescents and adults, were observed from countries in the Western Pacific Region such as the Lao People's Democratic Republic,[4] the Philippines[3] and Viet Nam.[5]

Early and accurate microbiological diagnosis of each suspected case is essential to inform management and treatment of the case and close contacts. To assess the diphtheria diagnostic capacity across laboratories in the Western Pacific Region, a survey was undertaken as part of a gap analysis (see Appendix 1) by the World Health Organization Collaborating Centre for Diphtheria and Streptococcal Infections with the WHO Regional Office for the Western Pacific. The objectives of the gap analysis were to:

1. assess current microbiological capability for the laboratory diagnosis of diphtheria in the Western Pacific Region;
2. assess public health impact in individual countries where diphtheria diagnostic activities may be limited;
3. assess availability of specialized reagents for diphtheria diagnostics in the Western Pacific Region;
4. assess training needs for scientists/medical/public health staff in this specialized area and identify best practices/gaps in diphtheria diagnostics to establish laboratory training workshops; and
5. assess availability of policies and guidelines related to management and control of diphtheria.

METHODS

A questionnaire used by the European Centre for Disease Prevention and Control (ECDC) to assess diphtheria diagnostic capacity[6] was adapted and sent to laboratories identified as part of the laboratory network for invasive bacterial diseases in the Western Pacific Region. Key topics covered in the survey included:

1. diptheria surveillance;
2. laboratory capacity and diagnostic services;
3. laboratory training, external quality assurance (EQA) and support needs;
4. serology and population immunity screening; and

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5. public health (i.e. use of guidelines/manuals for diagnostics and case management, and availability of antitoxin).

Responses were validated by the Public Health England (PHE) team. This included following up significant omissions or inconsistencies.

A set of criteria was defined against which diagnostic capacity could be evaluated and any gap identified. The criteria were adapted from those used by ECDC, which were originally developed based on the advice of a group of experts from PHE, ECDC and the WHO Regional Office for Europe.[6] The criteria assessed for minimum standards in three areas:

1. Area 1: Microbiological and epidemiological surveillance
2. Area 2: Laboratory diagnostic capacity
3. Area 3: Expertise in laboratory diagnostics.

The survey was sent to 18 laboratory contacts in 15 WHO Western Pacific Region countries, and responses were received from 17 contacts in 14 different countries. The Pacific island countries were assumed to have limited diphtheria diagnostic capacity and the questionnaire was sent to Fiji only; however, there was no response from Fiji. The responses from two countries indicated that there were no laboratories capable of diphtheria diagnostic tests within their country. These same countries, however, did not return full survey responses and we were unable to infer the status of surveillance, policies and guidelines. These countries were excluded from the analysis due to missing/unknown information. They were therefore excluded from the analysis, but this already highlights a gap in diphtheria diagnostics within the Region.

In summary, responses were received from 17 laboratories (94%) in 14 countries (93%); however analysis was done for 15 laboratories (83%) in 12 countries (80%). The denominator for Area 1 was based on 12 countries, because this Area assessed the gap in micro/epi surveillance for which the survey responses were required. The denominator for Area 2 was based on 14 countries because this Area assessed the gap in lab capacity, for which there were limited responses from Cambodia and Papua New Guinea.

RESULTS

Area 1: Microbiology and epidemiological surveillance

Gaps in microbiology and epidemiological surveillance were assessed against the following criteria:

- Diphtheria should be a notifiable disease in every country.
- Every country should have a surveillance system in place for diphtheria.
- Every country should have close collaboration in place between microbiology and epidemiology for diphtheria surveillance.

All 12 countries reported diphtheria was a notifiable disease and had surveillance systems in place. Of these, 87% of laboratories reported a case-based surveillance system in their country ($n = 13$), and 13% reported aggregate surveillance ($n = 2$). One laboratory reported having a combination of case-based and aggregate surveillance. One country did not report a close collaboration between microbiology and epidemiology for surveillance. Overall, Area 1 of the gap analysis was met by 92% ($n = 11$) of countries.

Area 2: Laboratory diagnostic capacity

Gaps in laboratory diagnostic capacity were assessed against the following criterion:

- Each country should ideally have at least one laboratory at the reference laboratory level with additional expertise available through a regional reference laboratory and the WHO reference centre when required.

To reach reference laboratory standards, a laboratory must have at least one method for three analyses: microscopic examination (Gram stain or other), primary culture (blood agar or Tellurite agar) and biochemical identification and toxigenicity by either polymerase chain reaction (PCR) or modified Elek immunoprecipitation test.

Of the 14 surveyed countries, nine countries (64%) reported full reference-level capacity based on culture, biochemical identification and toxigenicity testing methods, and three countries (21%) reported partial diagnostic capacity. Two countries (14%) had no diphtheria laboratory diagnostic capacity at all.

Specific diagnostic issues identified include the following:

- Only six laboratories reported having capacity for molecular typing.
- A range of tests were used for toxigenicity testing; the majority of laboratories use PCR-based methods (73%); six of laboratories (40%) use the Elek test.
- Four out of 15 (27%) laboratories experienced problems in obtaining culture media for diphtheria diagnostics, and four reported issues with supplies of antitoxin for laboratory diagnostics.

Area 3: Expertise in laboratory diagnostics

Gaps in expertise in laboratory diagnostics were assessed against the following criterion:

- At least one current laboratory staff member should have received official training under the auspices of WHO on diphtheria identification and toxigenicity testing in the last five years.

No laboratory staff attended comprehensive external training workshops in the last five years, and 73% of contacts from 15 laboratories felt that a training workshop was needed.

Other findings

- None of the countries stated whether their surveillance encompassed *C. ulcerans* and *C. pseudotuberculosis* as well as *C. diphtheriae*. If surveillance is based on the WHO case definition,[7] then only *C.diphtheriae* is likely to be captured.
- There is a lack of EQA for this specialized area of laboratory diagnostics.
- Only four of 12 countries had the capability to undertake serological tests and had undertaken studies previously.
- Nine laboratories (60%) across nine countries have diphtheria antitoxin procurement in place.

CONCLUSIONS

Key areas for action

The gap analysis demonstrated that there were gaps in diphtheria diagnostics within the WHO Western Pacific Region, with all responding countries fulfilling the minimum criteria for surveillance, specialized laboratory diagnostics and expertise. The areas with the greatest gaps are related to laboratory diagnostics expertise and surveillance of all three potentially toxigenic corynebacteria: *Corynebacterium diphtheriae*, *C.ulcerans* and *C.pseudotuberculosis*. Considering the adequate availability of funds for diphtheria, further studies are necessary. The following areas are highlighted as requiring further action:

- Surveillance systems should ideally be in place for all three pathogens to detect and respond to diptheria; however, this is not mandatory at the moment as the WHO case definition only captures the disease diphtheria as caused by toxigenic strains of *C.diphtheriae*.
- The laboratory diagnostic capability must be enhanced in some countries to isolate the causative pathogen, detect toxigenicity and undertake molecular characterization of the above pathogens; hence, there is an urgent need for some countries' laboratory staff to attend a laboratory training workshop for diphtheria diagnostics.
- An EQA with participation from countries attending the next training workshop needs to be established.
- Adequate availability of specialized media and reagents for diphtheria diagnosis must be assured within the Region.
- Updated guidelines for laboratory diagnosis of diphtheria should be made available.
- Risks related to the lack of availability and procurement of DAT should be addressed.

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