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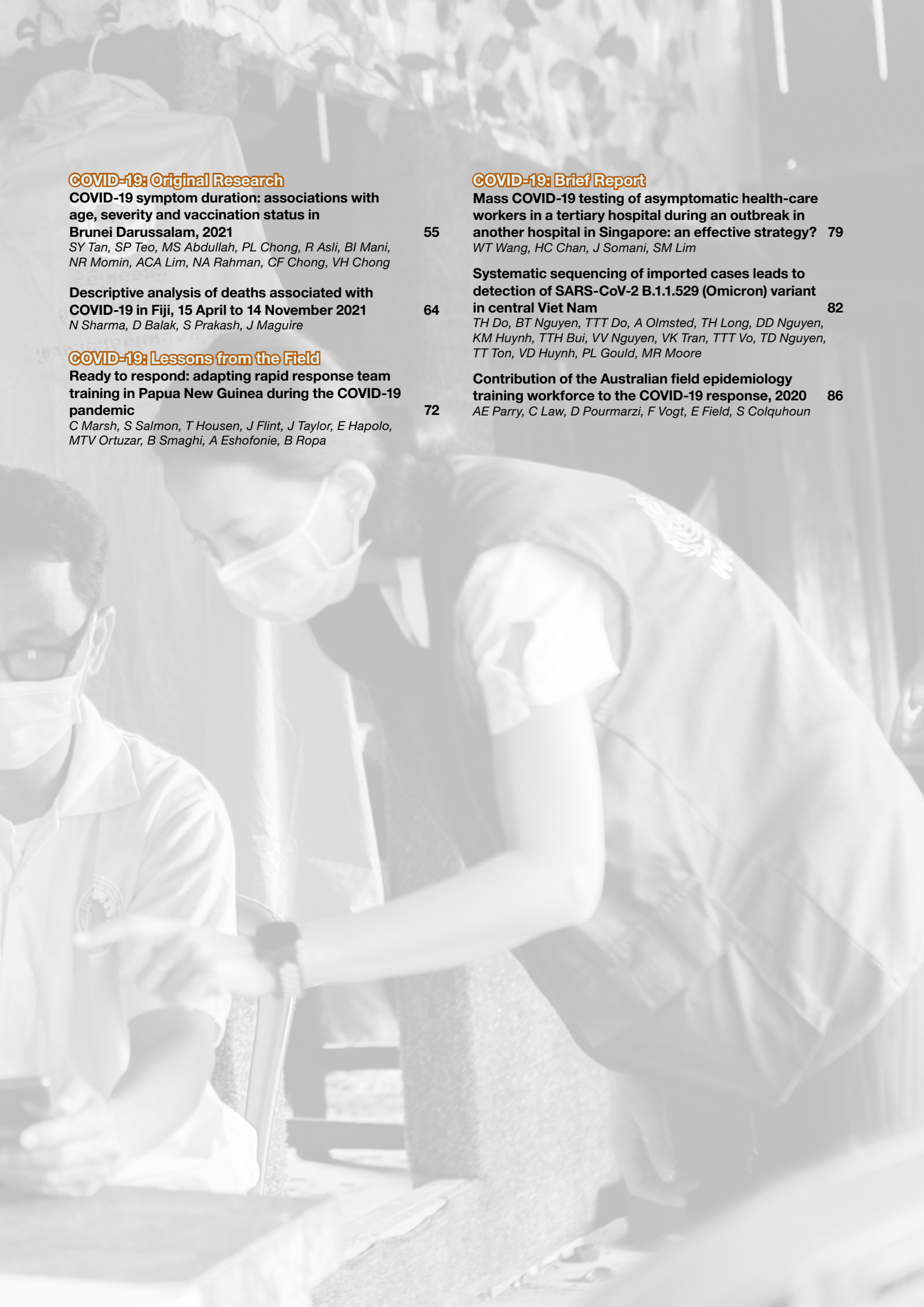

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To contact us:

Western Pacific Surveillance and Response
World Health Organization
Office for the Western Pacific Region
United Nations Avenue
1000 Manila, Philippines
wpsar@who.int
https://ojs.wpro.who.int/

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Prevalence and risk factors for human papillomavirus infection among female sex workers in Hanoi and Ho Chi Minh City, Viet Nam: a cross-sectional study

Quang Duy Pham,[a*] Kiesha Prem,[b*] Tuan Anh Le,[c] Nguyen Van Trang,[c] Mark Jit,[b,d,e] Tuan Anh Nguyen,[c] Van Cao,[a] Tam-Duong Le-Ha,[a] Mai Thi Ngoc Chu,[c] Ly Thi Khanh Le,[c] Zheng Quan Toh,[f,g] Marc Brisson,[h,i] Suzanne Garland,[j,k] Gerald Murray,[i,k] Kathryn Bright,[f] Duc Anh Dang,[c] Hau Phuc Tran[a#] and Edward Kim Mulholland[b,f,g#]

Correspondence to Hau Phuc Tran (email: hautran68@gmail.com) and Kim Mulholland (email: kim.mulholland@lshtm.ac.uk)

Objective: Female sex workers (FSWs) are at high risk of human papillomavirus (HPV) infections and cervical cancer due to their high number of sexual partners. The objectives of this study were to determine the prevalence of HPV and identify risk factors for high-risk HPV infection among FSWs in Hanoi and Ho Chi Minh City (HCMC), Viet Nam.

Methods: A cross-sectional study was conducted in Hanoi and HCMC between December 2017 and May 2018. We surveyed and screened 699 FSWs aged ≥18 years for HPV infection and abnormal cytology. A multivariable modified Cox regression model was used to determine risk factors for high-risk HPV infection.

Results: The overall prevalence of any HPV, high-risk HPV and HPV-16/18 infection in the 699 FSWs was 26.3%, 17.6% and 4.0%, respectively, and were similar in both cities. Multiple infections were identified in 127 participants (69.0%). HPV-52 was the most prevalent (7%), followed by HPV-58 (6%). Abnormal cytology was detected in 91 participants (13.0%). FSWs who are divorced (adjusted prevalence ratio [aPR]: 1.96, 95% confidence interval [CI]: 1.01–3.81), widowed (aPR: 3.26, 95% CI: 1.49–7.12) or living alone (aPR: 1.85, 95% CI: 1.01–3.39) were associated with a higher prevalence of high-risk HPV infection.

Discussion: Almost one in five FSWs in Viet Nam are infected with high-risk HPV. This highlights the importance of prevention strategies such as HPV vaccination and screening in this high-risk group.

Cervical cancer, which is caused by persistent human papillomavirus (HPV) infection usually by oncogenic/high-risk HPV type(s), is the fourth leading cause of cancer mortality among women globally, with an estimated 570 000 new cases and 311 000 deaths in 2018.[1] The majority of these cases occur in low- and middle-income countries (LMICs), primarily due to the low uptake of HPV vaccination, lack of robust HPV screening programmes and limited treatment options.[2] In response to the global public health burden, in 2020, the World Health Organization (WHO) set a threshold of four cervical cancer cases per 100 000 women for the elimination of cervical cancer as a public health problem and launched the 90-70-90 targets, aiming to fully immunize 90% of girls against HPV by 15 years of age, screen 70% of

[a] Pasteur Institute of Ho Chi Minh City, Ho Chi Minh City, Viet Nam.
[b] Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom.
[c] National Institute of Hygiene and Epidemiology, Hanoi, Viet Nam.
[d] School of Public Health, University of Hong Kong, Hong Kong, SAR (China).
[e] Public Health England, Modelling and Economics Unit, London, United Kingdom.
[f] New Vaccines, Murdoch Children's Research Institute, Parkville, Victoria, Australia.
[g] Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia.
[h] Centre de recherche du CHU de Québec-Université Laval, Quebec, Canada.
[i] Department of Social and Preventive Medicine, Université Laval, Quebec, Canada.
[j] Department of Obstetrics and Gynaecology, The University of Melbourne, Parkville, Victoria, Australia.
[k] Centre for Women's Infectious Diseases Research, The Royal Women's Hospital, Parkville, Australia.
[*] These authors are joint first authors.
[#] These authors are joint last authors.
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women for cervical cancer by 35 years of age and treat 90% of those diagnosed.[3] However, the ongoing global pandemic of coronavirus disease of 2019[4] has presented challenges to countries in implementing this strategy.

In Viet Nam, cervical cancer is the second most common cancer in women, affecting more than 9000 women from 2016–2017, of whom more than 40% died.[5] This is most likely an underestimation due to underreporting of cases in rural Viet Nam.[1] In 2016, the Viet Nam Ministry of Health (MOH) and partners launched the National Action Plan on Prevention and Control of Cervical Cancer 2016–2025, which aims to provide HPV vaccination to 25% of all girls and women, to provide cervical cancer screening to 60% of women aged 30–54 years, to increase early diagnosis of cervical cancer by 40% and to reduce premature cervical cancer mortality by 20% by 2025.[6,7] These targets have since been deemed unrealistic due to the limited results of cervical cancer prevention and control programmes since the strategic plan was disseminated.[8]

HPV is one of the most common sexually transmitted infections (STIs) worldwide,[9] with high-risk sexual behaviour being the leading risk factor for infection and subsequent cervical cancer. This includes having multiple sexual partners, early initial sexual intercourse and a compromised immune system.[10,11] Female sex workers (FSWs) are at high risk of HPV infection due to their having multiple sexual partners. It is also common for them to harbour multiple HPV genotypes and cervical cytological abnormalities.[12,13] Previous studies in southern and northern Viet Nam found very high HPV prevalence among FSWs (49.5–85%), with the majority (up to 90%) being high-risk HPV types.[13,14] It was estimated that there are more than 10 000 FSWs in Ho Chi Minh City (HCMC) alone, with the actual numbers to be higher due to challenges in capturing this hard-to-reach population.[15] Targeting this high-risk group will be important in reducing the cervical cancer burden in Viet Nam.

The objective of this study was to determine the prevalence of HPV and identify risk factors for high-risk HPV infection among FSWs in Hanoi and HCMC. The findings from this study are expected to inform the Viet Nam MOH on cervical cancer prevention strategies.

METHODS

Study design

This cross-sectional study was conducted in collaboration with the HIV/AIDS Centres of Hanoi and HCMC and district health facilities. The study population were women aged 18–50 years old of Vietnamese nationality in Hanoi and HCMC who have been engaging in transactional sex (sex in exchange for money, goods or drugs) in the month prior to the study. Sample size calculation based on HPV prevalence of 70%, a desired precision of 5%, and a design effect of 2 to address the increase in the variance derived from the cluster design of this survey, determined that 646 FSWs were required to obtain 80% power with a two-sided 5% significance level. A target of 700 (350 FSWs per site) was recruited to allow for 5–10% participant refusal and invalid sample results.

We used a two-stage recruitment strategy. First, four out of 30 administrative districts in Hanoi and five out of 24 administrative districts in HCMC were purposively selected based on the mapping of FSW venues, the FSW population size overseen by the Provincial AIDS Centres, and the participation in HIV sentinel surveillance among FSWs. Within the selected districts, 212 active venues for transactional sex in Hanoi (estimated range of FSWs: 580–1330) and 516 venues in HCMC (estimated range of FSWs: 2700–4800) were identified. Sex work locations included: (i) street-based venues, for example, streets, parks, and other open public places such as under bridges; and (ii) entertainment-based venues, for example, cafes, restaurants, hotels, motels, nightclubs, karaoke lounges, sauna/massage parlours and billiards clubs.

Second, a sampling framework based on the estimated number of FSWs obtained during the mapping exercise was created for the venue-based FSWs. The target subsample sizes for each selected district were proportional to the estimated population size of FSWs, and venues for recruitment were randomly sampled until the sample size was reached. All street-based or entertainment-based FSWs seen at each venue were invited to participate in the study. Visit timing varied across venue types, from daytime for entertainment-based FSWs to night-time for street-based FSWs. Women who were menstruating at enrolment were advised to return and

resume their participation after their period had ended. A participant information sheet was provided and written informed consent obtained from all participants.

Demographic and behavioural data collection

The survey questionnaire included socio-demographic characteristics, smoking, alcohol and/or drug use, sexual behaviours (such as age of sexual debut, sexual acts and sexual partners), menstrual cycle, presence of vaginal bleeding after sex and history of pregnancy. In order to ensure participants' confidentiality and safety, face-to-face interviews were conducted in a private room at the district health centres. No identifying information (for example, identity card numbers or addresses) was collected. Late in the study period, sex work-related questions, that is the number of years selling sex and the number of clients in the last month, were added to the survey questionnaire. Each interview lasted approximately 30 minutes. The participants received 80 000 Vietnamese Dongs, approximately US$4, for their participation in this study.

Clinical examination, specimen collection and HPV screening

A physical and speculum examination was conducted by trained gynaecologists. Cervical swabs were collected and stored in a vial containing 20 ml PreservCyt® Solution (Hologic Inc., MA, United States of America). At the district health centres, specimens collected from Hanoi and HCMC were stored at room temperature and transferred weekly to the National Institute of Hygiene and Epidemiology in Hanoi and the Pasteur Institute in HCMC, respectively. At these institutes, specimens were tested for HPV DNA and sent to the National Hospital of Obstetrics and Gynecology in Hanoi and the Hung Vuong Hospital in HCMC, respectively, for Papanicolaou (Pap) testing using liquid-based cytology (ThinPrep Pap test, Hologic Inc., ON, Canada). So as to avoid contamination, separate aliquots were used for HPV DNA testing and for cytological examination.

The Bethesda system was used to report Pap smear results, which are categorized as atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, atypical squamous cells, high-grade squamous intraepithelial lesion or squamous cell carcinoma.[16] In each city, one cytological technician and one senior cytologist examined the Pap smears with assistance from the ThinPrep imaging system.

HPV detection and genotyping

HPV detection and genotyping were performed in two steps. First, nucleic acid extraction was performed using the cador Pathogen 96 QIAcube HT Kit (QIAGEN, Hilden, Germany) on an automated platform followed by amplification with PGMY9/11 system by polymerase chain reaction (PCR).[17] Positive PCR samples were genotyped using GenoFlow HPV Array test kit (Diagcor Bioscience, Hong Kong Special Administrative Region [China]), which identified 33 HPV types (17 high-risk types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 82; 16 low-risk types: 6, 11, 40/61, 42, 43/44, 54/55, 70, 57/71, 72, 81, 84/26). Human leukocyte antigen (HLA) and beta-globulin genes were used as internal controls for the PGMY9/11 PCR and Geneflow kit, respectively. Samples negative for the HLA gene were considered invalid and were not included in the analysis. HPV LabNet was used to validate HPV detection and genotyping using 40 study samples from each site: approximately 90% agreement was achieved between the laboratories, as previously reported.[18]

Statistical analysis

We analysed participants' socio-demographic characteristics and compared FSWs in Hanoi and HCMC using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or the Mann-Whitney U test for continuous variables where appropriate. The prevalence of HPV was unweighted due to the lack of reliable data on size estimates and characteristics of the FSW population in both cities. The exact binomial Clopper-Pearson method was used to estimate 95% confidence intervals (CI) of HPV infection.

HPV types were categorized into high-risk and low-risk, and modified Cox regression analysis was performed to determine factors associated with high-risk HPV infection. The multivariable model included known risk factors for high-risk HPV positivity (for example, smoking), variables with $P<0.25$ in the bivariate regression models and variables with the Wald statistic of $P>0.10$ in reduced models. We compared nested models using the likelihood ratio test. We explored co-linearity (for example, between ages at enrolment and sexual debut) and

possible interaction terms (for example, between marital status and parturition, and drug use and type of sex worker). Variables with *P* values ≤0.05 were considered statistically significant. Data analyses were performed using R software.

RESULTS

Participant characteristics

There were 699 FSWs recruited from 67 and 48 active venues for transactional sex in Hanoi and HCMC between December 2017 and May 2018, respectively, with the last 171 participants responding to the additional sex work-related questions.

Participants had a median age of 37 years (range 18–52) and a median age of sexual debut of 19 years (range 11–40). The highest education attained for most participants was secondary school (40.3%). Compared to FSWs in HCMC, a higher number in Hanoi obtained education beyond primary school ($P<0.01$), had heard of HPV prior to this study ($P<0.01$) and lived alone ($P<0.01$) (**Table 1**). Participants had an average of 11 sexual partners, including both clients and personal partners in the month prior to the study (**Table 1**).

HPV prevalence and cytology

The prevalence of HPV among the 349 FSWs screened in Hanoi was 27.7% and among the 350 FSWs screened in HCMC it was 24.9%. The prevalence of high-risk HPV types was similar between the cities (**Fig. 1**). The prevalence of any high-risk HPV infection was 16.4% (95% CI: 12–21.6%) and 18.2% (95% CI: 14.8–22.1%) for FSWs who reported consistent and inconsistent condom use, respectively. Low-risk HPV types were generally more common among FSWs in Hanoi than HCMC, but this was not statistically significant (**Fig. 1**). HPV type 52 was the most common type (7%) among FSWs in both cities, followed by types 58 (6%) and 66 (4%). The prevalence of infection with multiple HPV types was 18.1% (95% CI: 15.4–21.2%) and was similar between both cities (**Fig. 1**).

The bivariate relationship between Pap cytology and HPV prevalence among the FSWs is shown in **Table 2**; 13.0% of the FSWs had abnormal Pap cytology and HPV-16/18 accounted for a third of high-grade squamous intraepithelial lesions. In Hanoi, squamous cell carcinoma was identified in a 33-year-old FSW, with HPV-31 present in samples.

High-risk HPV prevalence among younger FSWs (<25 years old) was higher in Hanoi (27%) than in HCMC (12.5%), while FSWs aged 30–34 years had higher prevalence of high-risk HPV and HPV-16/18 prevalence in HCMC than in Hanoi (**Fig. 2**). Although these analyses were not statistically significant, increasing age was associated with lower risk of both high-risk HPV infection (unadjusted prevalence ratio [PR]: 0.98, 95% CI: 0.96–1, $P=0.035$) and HPV-16/18 infection (unadjusted PR: 0.95, 95% CI: 0.91–1, $P=0.042$) (**Table 3**).

Approximately 25% of FSWs reported their duration of sex work and number of sex clients in the past month. FSWs in Hanoi who had engaged in sex work for ≥20 years had higher prevalence of high-risk HPV than those with <20 years, whereas FSWs in HCMC who had engaged in sex work for <10 years had a higher prevalence of high-risk HPV compared to those with ≥10 years. Additionally, FSWs who had more clients in the past month had higher prevalence of high-risk HPV (**Supplementary Fig. 1**).

Risk factors for high-risk HPV infection

FSWs who were married (adjusted PR [aPR]: 2.94, 95% CI: 1.29–6.68, $P=0.010$), divorced (aPR: 1.96, 95% CI: 1.01–3.81, $P=0.047$) or widowed (aPR: 3.26, 95% CI: 1.49–7.12, $P=0.003$) had higher prevalence of high-risk HPV infection compared to those who were never married. Compared to living with friends, living alone was associated with a higher risk of high-risk HPV infection (aPR: 1.85, 95% CI: 1.01–3.39, $P=0.046$). In our study cohort, FSWs were less likely to be infected with high-risk HPV if they had given birth (aPR: 0.62, 95% CI: 0.38–1.00, $P=0.048$) or reported consumption of drugs (aPR: 0.41, 95% CI: 0.17–0.97, $P=0.042$) (**Table 3**).

The risk factors for FSWs ($n=171$) who responded to the sex work-related questions are presented in **Supplementary Table 1**; there was no evidence of possible interactions or co-linearity (for example, between age at enrolment and sexual debut) and possible interaction terms (for example, between marital status and parturition, and between drug use and type of sex worker).

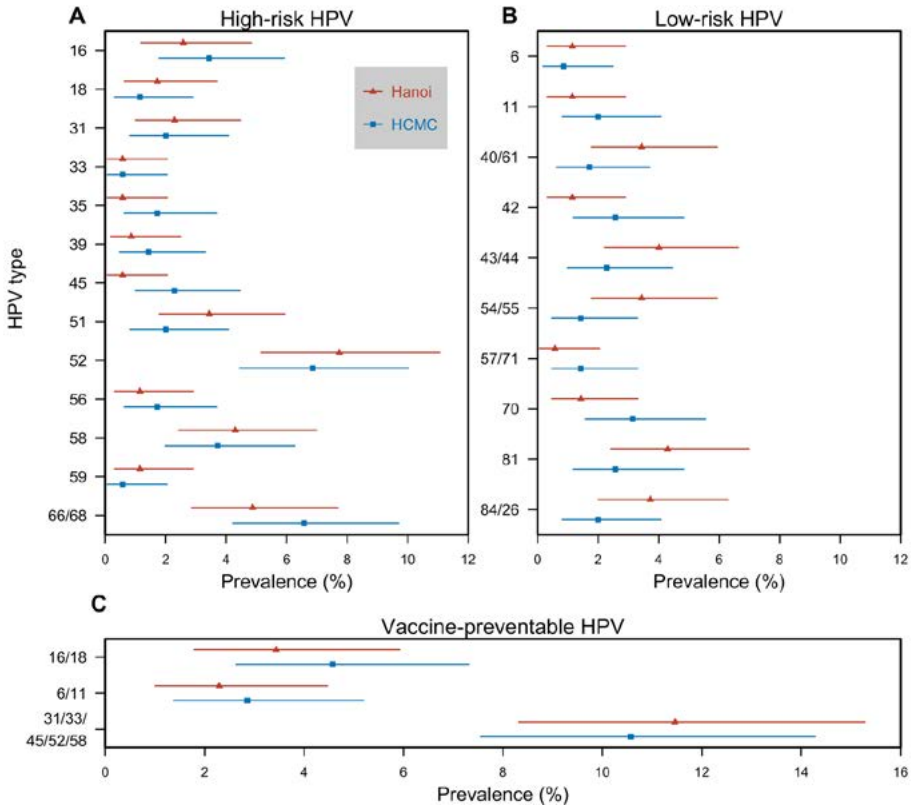
Table 1. **Participants' demographic and behavioural characteristics by city, Hanoi and HCMC, December 2017 to May 2018**

Characteristics of female sex workers	Hanoi (*n*=349)	HCMC (*n*=350)	Total (*n*=699)	*P*
Demographics	***n* (%)**	***n* (%)**	***n* (%)**	
Age, in years, median (range)	35 (18–49)	39 (19–52)	37 (18–52)	<0.001
Age of sexual debut, in years, median (range)	18 (11–27)	19 (14–40)	19 (11–40)	<0.001
Kinh ethnicity	336 (96.3)	347 (99.1)	683 (97.7)	0.012
Highest education attained				<0.001
No formal education	5 (1.4)	22 (6.3)	27 (3.9)	
Primary	51 (14.6)	147 (42)	198 (28.3)	
Secondary	159 (45.6)	123 (35.1)	282 (40.3)	
High school or vocational school	115 (33.0)	54 (15.4)	169 (24.2)	
College or university	19 (5.4)	4 (1.1)	23 (3.3)	
Marital status				<0.001
Never married	80 (22.9)	30 (8.6)	110 (15.7)	
Married	60 (17.2)	106 (30.3)	166 (23.7)	
Separated	83 (23.8)	45 (12.9)	128 (18.3)	
Divorced	88 (25.2)	132 (37.7)	220 (31.5)	
Widowed	38 (10.9)	33 (9.4)	71 (10.2)	
Living arrangements				<0.001
With friends	68 (19.5)	39 (11.1)	107 (15.3)	
With husband, boyfriend, male partner	77 (22.1)	119 (34.0)	196 (28.0)	
Alone	150 (43.0)	81 (23.1)	231 (33.0)	
Temporary housing or with family members	54 (15.4)	111 (31.7)	165 (23.6)	
Behaviour				
Ever smoked	72 (20.6)	101 (28.9)	173 (24.7)	0.015
Ever consumed alcohol	230 (65.9)	234 (66.9)	464 (66.4)	0.85
Ever been pregnant	319 (91.4)	306 (87.4)	625 (89.4)	0.068
Number of times pregnant, median (range)	3 (1–20)	2 (1–8)	3 (1–20)	<0.001
Ever given birth	269 (77.1)	279 (79.7)	548 (78.4)	0.013
Number of times given birth, median (range)	1 (0–5)	1 (0–5)	1 (0–5)	<0.001
Ever had abortion	253 (72.5)	152 (43.4)	405 (57.9)	<0.001
Number of abortions, median (range)	2 (1–20)	1 (1–8)	2 (1–20)	<0.001
Ever used contraception	331 (94.8)	263 (75.1)	594 (85.0)	<0.001
Consistent condom use	131 (37.4)	114 (32.6)	245 (35.1)	<0.001
Age started selling sex, median (range)	25 (17–35)	22 (16–42)	24 (16–42)	<0.001
Number of sexual partners in the last 12 months, median (range)	2 (1–30)	1 (1–65)	1 (1–65)	<0.001
Number of sex clients in the last month, median (range)[a]	15 (3–31)	8 (0–35)	10 (0–35)	0.006
Street-based sex worker	44 (12.6)	46 (13.1)	90 (12.9)	0.92
Ever consumed drugs	32 (9.2)	34 (9.7)	66 (9.4)	0.9

HCMC: Ho Chi Minh City.

[a] The number of female sex workers who answered questions related to sex work was 171.

Fig. 1. **Prevalence of high-risk and low-risk HPV types among female sex workers in Hanoi and HCMC, December 2017 to May 2018**



HCMC: Ho Chi Minh City; HPV: human papillomavirus.

The exact binominal method was used to estimate 95% confidence intervals of HPV infection for Hanoi in northern Viet Nam (in red) and HCMC in southern Viet Nam (in blue). High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73 and 82, and low-risk HPV types include 6, 11, 34, 40/61, 42, 43/44, 54/55, 57/71, 70, 72, 81 and 84/26.

DISCUSSION

In this survey of FSWs in Hanoi and HCMC, the prevalence of HPV was 27.7% and 24.9%, respectively, with almost one in five having high-risk HPV types. HPV types were similar between Hanoi and HCMC with the most common high-risk HPV types being HPV-52, -58 and -66. FSWs who were divorced, widowed or living alone had higher prevalence of high-risk HPV infection. This, as well as being infected with multiple HPV types, has been reported in this group in previous studies,[19–22] and highlights this group as being susceptible to HPV diseases.

The HPV prevalence observed in our study is lower than previous surveys conducted among FSW populations in Viet Nam (49.5–85%)[13,14] and other Western Pacific countries (31.6–57.2%).[23–26] This may be due to a number of reasons. First, the Global Fund-supported free condom distribution programmes have been largely implemented for FSWs in Viet Nam through community-based organizations, and private and public clinics since 2015.[27] Second, our cohort was older and had fewer clients/sexual partners compared to previous studies in southern[14] and northern Viet Nam.[13] Third, we recruited a higher proportion of venue-based FSWs rather than street-based FSWs, who have higher rates of STIs including HIV.[28,29] Fourth, the regions are different than in the other studies.

Our finding that one in 10 FSWs had abnormal cytology supports the need for a national cervical cancer screening programme in Viet Nam. WHO recommends

Table 2. **Prevalence of HPV infection by cytological result among female sex workers in Hanoi and HCMC, December 2017 to May 2018**

			Low-grade lesions		High-grade lesions		Cancer
Cytological results	Total N (%)	Normal	ASCUS	LSIL	ASC-H	HSIL	SCC
Total[a]	699 (100)	607 (86.8)	52 (7.4)	19 (2.7)	4 (0.6)	15 (2.1)	1 (0.1)
HPV type at time of survey							
16	21 (3.0)	12 (2.0)	1 (1.9)	4 (21.1)	0 (0)	4 (26.7)	0 (0)
18	10 (1.4)	7 (1.2)	1 (1.9)	1 (5.3)	0 (0)	1 (6.7)	0 (0)
16 or 18	28 (4.0)	17 (2.8)	2 (3.8)	4 (21.1)	0 (0)	5 (33.3)	0 (0)
16, 18, 31, 33, 45, 52 or 58	92 (13.2)	65 (10.7)	6 (11.5)	8 (42.1)	2 (50.0)	10 (66.7)	1 (100)
6, 11, 16 or 18[b]	43 (6.2)	29 (4.8)	2 (3.8)	6 (31.6)	0 (0)	6 (40.0)	0 (0)
6, 11, 16, 18, 31, 33, 45, 52 or 58[c]	100 (14.3)	71 (11.7)	6 (11.5)	9 (47.4)	2 (50.0)	11 (73.3)	1 (100)
High-risk HPV types[d]	123 (17.6)	85 (14.0)	9 (17.3)	13 (68.4)	2 (50.0)	13 (86.7)	1 (100)
Low-risk HPV types[e]	109 (15.6)	88 (14.5)	10 (19.2)	8 (42.1)	1 (25.0)	2 (13.3)	0 (0)
Undetermined HPV type	15 (2.1)	12 (2.0)	3 (5.8)	NA	NA	NA	NA

All values are presented as n (%). ASC-H: atypical squamous cells cannot exclude HSIL; ASCUS: atypical squamous cells of undetermined significance; HCMC: Ho Chi Minh City; HPV: human papillomavirus; HSIL: high-grade squamous intraepithelial lesion; LSIL: low-grade squamous intraepithelial lesion; NA: not applicable; SCC: squamous cell carcinoma.

The Bethesda system was used to report Pap smear results.

[a] There was one sample insufficient for cytological testing.

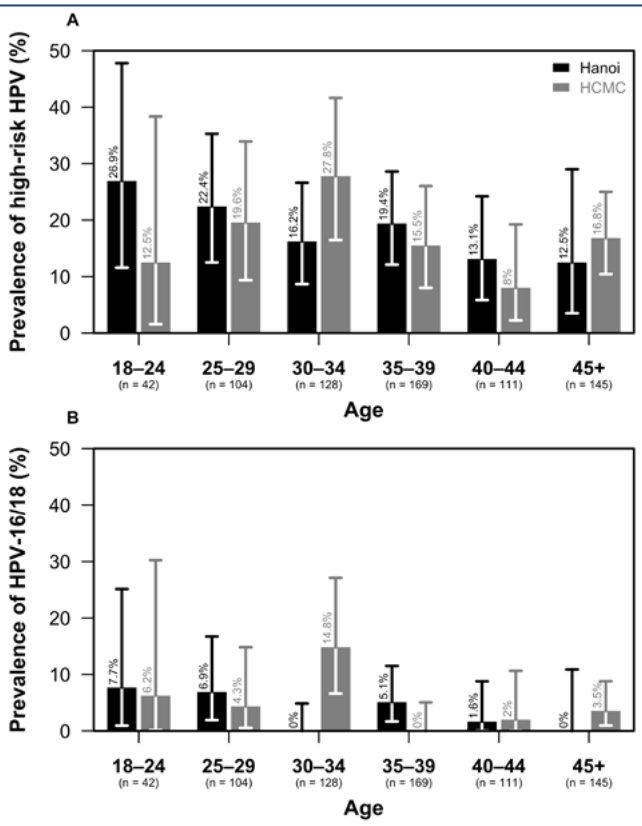
[b] HPV types covered in the licensed 4-valent vaccine.

[c] HPV types covered in the licensed 9-valent vaccine.

[d] High-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73, 82.

[e] Low-risk HPV types: 6, 11, 34, 40/61, 42, 43/44, 54/55, 57/71, 70, 72, 81, 84/26.

Fig. 2. **Prevalence of high-risk HPV and HPV-16/18 by age among female sex workers in Hanoi and HCMC, December 2017 to May 2018**



HCMC: Ho Chi Minh City; HPV: human papillomavirus.

High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66/68, 73 and 82. Error bars represent 95% confidence intervals.

Table 3. **Correlations of factors associated with high-risk HPV infection among female sex workers in Hanoi and HCMC, December 2017 to May 2018**

	Any high-risk HPV[a]				Bivariate analysis		Multivariable analysis	
Variables	**N**	**n**	**%**	***P***	**PR (95% CI)**	***P***	**aPR (95% CI)**	***P***
Age					0.98 (0.96–1)	0.04	0.98 (0.95–1)	0.06
Age of sexual debut					0.94 (0.89–0.99)	0.09	0.95 (0.90–1.01)	0.09
Educational level[b]								
Low	225	44	19.6	0.40	1			
High	474	79	16.7		0.84 (0.58–1.21)	0.35		
Marital status								
Never married	110	16	14.5	0.44	1		1	
Married	166	32	19.3		1.36 (0.75–2.48)	0.31	2.94 (1.29–6.68)	0.01
Separated	128	18	14.1		0.96 (0.49–1.89)	0.92	1.48 (0.72–3.05)	0.29
Divorced	220	39	17.7		1.24 (0.69–2.22)	0.47	1.96 (1.01–3.81)	<0.05
Widowed	71	17	23.9		1.74 (0.88–3.44)	0.11	3.26 (1.49–7.12)	<0.01
Other	4	1	25.0		1.82 (0.24–13.76)	0.56	3.21 (0.40–25.89)	0.27
Living arrangements								
With friends	107	14	13.1	0.14	1		1	
With husband, boyfriend, male partner	196	33	16.8		1.31 (0.70–2.46)	0.39	1.16 (0.54–2.49)	0.70
Alone	231	51	22.1		1.78 (0.98–3.21)	0.06	1.85 (1.01–3.39)	<0.05
Temporary housing or with family members	165	25	15.2		1.17 (0.61–2.25)	0.64	1.37 (0.70–2.70)	0.36
Ever smoked	173	32	18.5	0.81	1.08 (0.72–1.61)	0.72	1.23 (0.80–1.88)	0.36
Ever consumed alcohol	464	77	16.6	0.38	0.83 (0.58–1.2)	0.33		
Ever been pregnant	625	102	16.3	0.02	0.54 (0.34–0.87)	<0.01		
Ever given birth	548	89	16.2	0.09	0.7 (0.47–1.03)	0.07	0.62 (0.38–1.00)	<0.05
Ever had abortion	405	67	16.5	0.46	0.86 (0.60–1.23)	0.39		
Ever used contraception	594	102	17.1	0.57	0.84 (0.53–1.35)	0.48		
Consistent condom use	244	40	16.4	0.61	0.89 (0.61–1.3)	0.54		
Ever consumed drugs	66	6	9.1	0.08	0.47 (0.21–1.06)	0.07	0.41 (0.17–0.97)	0.04
Type of sex work								
Street-based	90	9	10.0	0.06	1		1	
Venue-based	609	114	18.7		1.96 (1–3.87)	0.05	1.85 (0.93–3.67)	0.08
Ever heard of HPV	160	25	15.6	0.54	0.85 (0.55–1.31)	0.46	0.95 (0.90–1.01)	0.09
Ever heard of HPV vaccines	154	29	18.8	0.73	1.1 (0.73–1.67)	0.65		
Ever heard of cervical cancer	325	53	16.3	0.47	0.86 (0.60–1.23)	0.41		
Ever heard of cervical cancer screening	241	36	14.9	0.34	0.72 (0.40–1.28)	0.26		
Study site								
Hanoi, north Viet Nam	349	63	18.1	0.83	1			
HCMC, south Viet Nam	350	60	17.1		0.94 (0.66–1.35)	0.75		

aPR: adjusted prevalence ratio; HCMC: Ho Chi Minh City; HPV: human papillomavirus; PR: prevalence ratio.

[a] High-risk HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66/68.

[b] Low: primary or no formal education; high: secondary and above.

screening and treating from age 30, with regular screening every 5–10 years.[30] For high-risk women, such as FSWs or those infected with HIV, HPV screening may need to start earlier.[31]

HPV-52 was the most prevalent HPV type among FSWs in our cohort, consistent with previous studies of FSWs in Viet Nam.[13,14] HPV-58 and HPV-66 were the second and third most prevalent types in our cohort. Both HPV-52 and -58 are included in the nonavalent HPV vaccine, while limited cross-protection against these types has been shown from both the bivalent and quadrivalent vaccines.[32] This suggests that the nonavalent vaccine may be more appropriate for this high-risk group. HPV vaccination is recommended for individuals before sexual debut, as the vaccines do not clear existing HPV infection,[33] although there may still be benefits to women with existing HPV infection, including FSWs.[34] These benefits include protection against re-infection and infection with other HPV types, reducing their overall risk of HPV-associated diseases such as cervical cancer, as well as preventing transmission within the community.[34]

FSWs who reported consuming drugs or having given birth were less likely to be infected with high-risk HPV; however, these results need to be interpreted with caution. Those who had given birth were almost a decade older than those who had not (median age 38 versus 29 years, respectively), and FSWs who consumed drugs had fewer sexual partners than those who reported no drug use (median 8 versus 10 partners per month, respectively). A review on STIs among FSWs reported an increased risk of infection among drug-using FSWs, possibly due to limited access to health care.[35] Furthermore, strict anti-drug laws in Viet Nam discourage disclosing drug consumption among this already vulnerable population, which may have introduced misclassification which could bias the association.

Our study has several limitations. First, we only recruited FSWs from two main cities in Viet Nam, and the prevalence of high-risk HPV was lower than expected. Therefore, caution must be taken in generalizing these findings to the entire population of FSWs in the country. The non-random selection of survey districts in the two cities may have an unweighted procedure for prevalence and characteristics of the FSW population due to the shortage of data on size estimates, leading to additional biases in estimating HPV prevalence among FSWs. Second, our study cohort was older than previous cohorts and most participants were from venue-based work locations, which may not reflect the true HPV prevalence among the FSW population in Viet Nam. However, our cohort may be more representative of persistent HPV infection and risk of cervical cancer. Third, our cohort was selected as they were willing to speak with non-government organizations (NGOs) and public health officials. Since data were incomplete on the response rate among potential participants, the degree to which they were interested in participating in this study is unknown. Hence, findings from this study should be interpreted with caution. Fourth, self-reporting during face-to-face interviews could limit the reliability of information on sexual risk behaviours and drug use. Fifth, our study did not record the vaccination status of FSWs. Some may have been vaccinated because of other research studies or small pilot vaccination programmes, thus directly or indirectly protecting them from HPV-16 and -18 infection. Lastly, the small number of FSWs with high-grade squamous intraepithelial lesions or cervical cancer limited our ability to identify their association with HPV infection.

CONCLUSIONS

We found high prevalence of high-risk HPV infection among FSWs in Hanoi and HCMC, highlighting the need for a targeted HPV prevention campaign. We recommend HPV prevention strategies such as screening every 5–10 years from age 25 as previously described by WHO30 and HPV vaccination targeting this vulnerable group of women. These strategies will protect FSWs from HPV-associated diseases including cervical cancer, and also help to reduce HPV transmission within the community and the overall cervical cancer burden in Viet Nam and other LMICs with similar settings.

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Conflicts of interest

Suzanne M. Garland has received grants through her institution from Merck and has delivered lectures and received speaking fees from MSD for work performed in her personal time. All other authors report no conflicts of interest.

Ethics approval

The study protocol was reviewed and approved by both local and international review boards of the National Institute of Hygiene and Epidemiology, Viet Nam (reference number: IRB-VN01057-13/2017) and the ethics board of the London School of Hygiene and Tropical Medicine (reference number: 14207).

Data availability statement

The data that support this study will be shared upon reasonable request to the corresponding author.

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Progress on diagnosis and treatment of drug-resistant tuberculosis in line with World Health Organization recommendations in six priority countries in the Western Pacific Region

Kyung Hyun Oh,[a] Maria Imelda Quelapio,[b] Fukushi Morishita,[a] Kalpeshsinh Rahevar,[a] Manami Yanagawa[a] and Tauhid Islam[a]

Correspondence to Kyung Hyun Oh (email: ohk@who.int)

Background: Diagnosis and treatment of drug-resistant tuberculosis (DR-TB) have radically changed in accordance with recommendations from the World Health Organization (WHO) in the past decade, allowing rapid and simple diagnosis and shorter treatment duration with new and repurposed drugs.

Methods: A descriptive analysis of the status and progress of DR-TB diagnosis and treatment in six priority countries in the Western Pacific Region was conducted using information from interviews with countries and the WHO TB database.

Results: Over the past decade, the use of Xpert MTB/RIF has increased in the six priority countries, in parallel with implementation of national policies and algorithms to use Xpert MTB/RIF as an initial diagnostic test for TB and detection of rifampicin resistance. This has resulted in increases in the number of people diagnosed with multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB). Shorter treatment regimens with new and repurposed drugs have also been adopted for MDR/RR-TB cases, alongside a decentralized model of care, leading to improved treatment outcomes.

Discussion: The Western Pacific Region has achieved considerable progress in the diagnosis and treatment of DR-TB, in line with the evolving WHO recommendations in the past decade. The continued commitment of Member States is needed to address remaining challenges, such as the impact of the coronavirus disease pandemic, suboptimal management and health system issues.

Tuberculosis (TB) continues to be a major global health challenge. Despite a concerted global effort to eliminate it, TB remains one of the leading infectious causes of death globally. In 2020, an estimated 10 million incident cases of TB and 1.5 million TB-related deaths occurred worldwide.[1] A major threat to the global effort to end TB is drug-resistant TB (DR-TB), which is caused by organisms that are resistant to any drugs used for TB, including multidrug-resistant TB (MDR-TB), which does not respond to isoniazid and rifampicin, the two most effective first-line anti-TB drugs.[2] DR-TB is a threat because specialized laboratory infrastructure and diagnostics are required for DR-TB, leading to substantial underdiagnosis of DR-TB, especially in low- and middle-income countries (LMICs); also, treatment outcomes are often poor because treatment of DR-TB is of long duration and involves toxic and expensive medicines. In LMICs, DR-TB can be a huge burden on health systems and can contribute to a high proportion of patients and their families experiencing catastrophic health costs. DR-TB diagnosis and treatment have changed radically in the past decade, in accordance with recommendations from the World Health Organization (WHO), including rapid and simple diagnosis and shorter treatment duration with new and repurposed drugs (**Table 1**).[3–11]

The WHO Western Pacific Region is home to 1.9 billion people in 37 countries and areas. The region is diverse, ranging from a large country with a population of more than 1 billion to small Pacific island countries with

[a] End TB and Leprosy Unit, World Health Organization Regional Office for the Western Pacific, Manila, Philippines.
[b] Independent consultant, Cavite, Philippines.
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Table 1. **WHO recommendations on diagnosis and treatment for DR-TB, 2013–2021**

Year	Diagnosis	Treatment
2013	Xpert MTB/RIF to be used as the initial diagnostic test in adults and children suspected of having MDR-TB or HIV-associated TB rather than conventional microscopy, culture and drug susceptibility testing.[3]	
2016	For patients with confirmed RR-TB or MDR-TB, SL-LPA may be used as the initial test to detect resistance to fluoroquinolones, instead of phenotypic culture-based drug susceptibility testing.[4]	In patients with RR-TB or MDR-TB who were not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens.[7]
2017	Xpert MTB/RIF Ultra is non-inferior to the current Xpert MTB/RIF for the diagnosis of MTB and the detection of rifampicin resistance and can be used as an alternative to the latter in all settings.[5]	In patients who require TB retreatment, the category II regimen should no longer be prescribed, and drug susceptibility testing should be conducted to inform the choice of treatment regimen.[11]
2018		In patients with confirmed rifampicin-susceptible and isoniazid-resistant TB, treatment with rifampicin, ethambutol, pyrazinamide and levofloxacin is recommended for a duration of 6 months.[10]
2019		In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included, to ensure that treatment starts with at least four TB agents likely to be effective and that at least three agents are included for the rest of the treatment after bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are to be added.[9]
		Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens.[9]
2020		A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.[8]
		A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in MDR-TB patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks.[8]
2021	In people with bacteriologically confirmed pulmonary TB, low complexity automated NAATs may be used on sputum for the initial detection of resistance to isoniazid and fluoroquinolones, rather than culture-based phenotypic drug susceptibility testing.[6]	

MDR-TB: multidrug-resistant tuberculosis; NAAT: nucleic acid amplification test; RR-TB: rifampicin-resistant tuberculosis; SL-LPA: second-line line probe assay; TB: tuberculosis; Xpert MTB/RIF: an automated NAAT for *Mycobacterium tuberculosis* complex and resistance to the drug rifampicin.

Group A: levofloxacin/moxifloxacin, bedaquiline and linezolid.

Group B: clofazimine and cycloserine/terizidone.

Group C: ethambutol, delamanid, pyrazimide, imipenem-cilastatin, meropenem, amikacin/streptomycin, ethionamide/prothionamide and *p*-aminosalicylic acid.

a few thousand residents, and from countries with a high TB burden to countries in the pre-elimination stage.[12] Five countries (China, Mongolia, Papua New Guinea, the Philippines and Viet Nam) in the region are on the WHO global list of 30 countries with a high burden of TB and multidrug-resistant or rifampicin-resistant TB (MDR/RR-TB) for 2021–2025.[13] Countries and areas of the region have striven to adopt the changing WHO recommendations for the diagnosis and treatment of DR-TB. The regional Green Light Committee (rGLC), established in 2011 as a regional DR-TB advisory committee to WHO, has supported the scale-up of the programmatic management of DR-TB (PMDT) in countries with a high MDR/RR-TB burden in the region.[14] This analysis provides an overview of the status and progress of DR-TB diagnosis and treatment in six priority countries in the Western Pacific Region in line with WHO recommendations.

METHODS

The Western Pacific regional framework to end TB: 2021–2030 indicates 10 priority countries in the region.[15] Six countries that are directly supported by rGLC – Cambodia, the Lao People's Democratic Republic, Mongolia, Papua New Guinea, the Philippines and Viet Nam – were selected for this descriptive analysis of the status and progress of DR-TB diagnosis and treatment using information from interviews with countries and the WHO TB database.

Indicators to assess current diagnosis and treatment processes for DR-TB were based on recommendations in the latest WHO guidelines; they included:

- use of Xpert MTB/RIF, Xpert MTB/RIF Ultra (Xpert Ultra) and Xpert MTB/XDR for diagnostic tests;
- use of shorter all-oral bedaquiline-containing regimens;
- discontinuation of kanamycin and capreomycin for MDR/RR-TB; and
- use of a bedaquiline, pretomanid and linezolid (BPaL) regimen.[6,8]

Indicators to assess the progress of diagnosis and treatment for DR-TB were from the latest WHO global TB reports; they included:

- percentage of TB patients tested for rifampicin resistance;
- proportion of people diagnosed with MDR/RR-TB and enrolled in MDR-TB treatment in the same year (this can be more than 100% owing to cases that are enrolled in the year after they are diagnosed);
- percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones;
- number of MDR/RR-TB cases treated with bedaquiline, shorter regimen and all-oral longer regimen; and
- treatment outcomes for MDR/RR-TB cases started on treatment.[1,16]

Information on the countries' status was obtained through interviews, supported by follow-up communication and rGLC country monitoring missions. Between July and November 2021, interviews with PMDT focal points of the national TB programmes from the six priority countries were conducted virtually using a structured questionnaire. Further information was updated after follow-up communications or subsequent rGLC country monitoring missions in 2021. Information on the countries' progress was collected from the WHO database, to which countries and areas annually report data on TB care and prevention via an electronic platform.[17]

All data analyses and visualizations were conducted using the statistical software package R 4.1.1 (Comprehensive R Archive Network at https://cran.r-project.org/).

RESULTS

Status of DR-TB diagnosis

The six priority countries are at different stages in their uptake of WHO recommendations on diagnostic tools and algorithms for DR-TB (**Table 2**). National policies and algorithms indicate universal access to drug susceptibility testing in all priority countries. Although Xpert MTB/RIF is used as an initial diagnostic test for TB and rifampicin resistance detection in all priority countries, in Cambodia and Viet Nam it does not cover the entire population. In Cambodia, Xpert MTB/RIF was used for all initial diagnostic testing in some areas; in other areas, it was limited to high-risk groups, such as previously treated cases and people living with HIV. The country aims to expand its universal use to all presumptive cases nationwide by 2023. In Viet Nam, Xpert MTB/RIF

Table 2. **Status of DR-TB diagnosis in priority countries in the Western Pacific Region in 2021**

Item	Cambodia	Lao PDR	Mongolia	Papua New Guinea	Philippines	Viet Nam
Xpert MTB/RIF used as an initial diagnostic test for TB and rifampicin resistance detection	In some areas (all areas by 2023)	Yes	Yes	Yes	Yes	Yes (only for high-risk groups and people with abnormal lesion on chest X-ray)
National policy and algorithm indicate universal access to drug susceptibility testing	Yes	Yes	Yes	Yes	Yes	Yes
Number of GeneXpert machines (per 1 million population)	107 (6.4)	57 (7.8)	42 (12.7)	85 (9.6)	587 (5.4)	285 (3.0)
Use of Xpert Ultra	Replacing Xpert MTB/RIF since 2019	Together with Xpert MTB/RIF since 2021	Together with Xpert MTB/RIF since 2021	Together with Xpert MTB/RIF since 2017	Together with Xpert MTB/RIF since 2020	Together with Xpert MTB/RIF since 2018
Use of Xpert MTB/XDR	No	Planned in 2022	No	Planned in 2022	Planned in 2022	Planned in 2022
FL-LPA used to detect isoniazid resistance among rifampicin-susceptible TB	Yes (ad hoc since 2019)	No	No	No	No	No
FL-LPA used to detect isoniazid resistance among rifampicin-resistant TB	Yes (ad hoc since 2018)	No	Yes (routinely since 2016)	Yes (routinely)	Yes (routinely since 2021)	Yes (ad hoc since 2016)
SL-LPA used as an initial test to detect fluoroquinolone resistance among confirmed MDR/RR-TB	Yes (since 2017)	Yes (since 2016)	Yes (since 2016)	Yes	Yes (since 2017)	Yes (since 2016)
Use of Truenat	Planned as a pilot in 2022	No	No	No	Planned as a pilot in 2022	Planned as a pilot in 2022
Phenotypic drug susceptibility testing for new and repurposed drugs	No	Lzd (Bdq, Cfz, Dlm planned)	Bdq, Cfz, Lzd	No	No	Bdq, Cfz, Dlm, Lzd (Pa planned)

Bdq: bedaquiline; Cfz: clofazimine; Dlm: delamanid; FL-LPA: first-line line probe assay; Lzd: linezolid; MDR/RR-TB: multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis; Pa: pretomanid; PDR: People's Democratic Republic; SL-LPA: second-line line probe assay; TB: tuberculosis; Xpert MTB/RIF: an automated nucleic acid amplification test for *Mycobacterium tuberculosis* complex and resistance to the drug rifampicin; Xpert Ultra: Xpert MTB/RIF Ultra.

is limited to high-risk groups such as people living with HIV, children and people with abnormal lesions on chest X-ray. In priority countries, the number of GeneXpert machines per 1 million population ranges from three to 12.7 nationwide.

Xpert MTB/RIF Ultra (Xpert Ultra) has been introduced in all priority countries. In Cambodia, Xpert Ultra had already replaced Xpert MTB/RIF at the time of the interview. In the other priority countries, Xpert Ultra is being used together with Xpert MTB/RIF. There are also plans to introduce Xpert MTB/XDR in 2022 in the Lao People's Democratic Republic, Papua New Guinea, the Philippines and Viet Nam.

In Cambodia, first-line line probe assays (FL-LPAs) are used to detect isoniazid resistance among rifampicin-susceptible TB cases only on an ad hoc basis. However, in Mongolia, Papua New Guinea and the Philippines, FL-LPAs are routinely used to detect isoniazid resistance among rifampicin-resistant TB cases, and in Cambodia and Viet Nam, they are used in such cases but on an ad hoc basis. Second-line line probe assays (SL-LPAs) are used as an initial test to detect fluoroquinolone resistance among confirmed MDR/RR-TB cases in all priority countries. The use of Truenat (a point-of-care rapid molecular test) for detection of TB and rifampicin resistance is planned as a pilot project in 2022 in Cambodia, the Philippines and Viet Nam.

As the use of new and repurposed drugs in shorter and longer regimens is scaled up in priority countries, phenotypic drug susceptibility testing for those drugs is conducted or planned. In the Lao People's Democratic Republic, drug susceptibility testing for linezolid is in place, and drug susceptibility testing for bedaquiline, clofazimine and delamanid is planned. In Mongolia, drug susceptibility testing for bedaquiline, linezolid and clofazimine is conducted. In Viet Nam, drug susceptibility testing for bedaquiline, linezolid, clofazimine and delamanid is conducted and drug susceptibility testing for pretomanid is planned.

Progress of DR-TB diagnosis

The percentage of new and previously treated TB patients tested for rifampicin resistance in four of the priority countries (no reports from Cambodia and Papua New Guinea) increased between 2017 and 2020, with some fluctuations (**Fig. 1**). The number of people diagnosed with MDR/RR-TB and the number starting on treatment per year in all countries has increased since 2010 (**Fig. 2**). However, in the Lao People's Democratic Republic, Mongolia and the Philippines, there was a decrease in the number of MDR/RR-TB cases diagnosed in 2020 compared with 2019. This decrease started in 2014 in Mongolia. The proportion of enrolment in treatment among diagnosed cases exceeded 80% in 2020 in Mongolia (104%) and Viet Nam (89%), whereas it was 80% or below in the Lao People's Democratic Republic (80%), Papua New Guinea (76%) and the Philippines (78%).

The percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones in four priority countries between 2015 and 2020 (no reports from Cambodia and Papua New Guinea) varied with increased coverage in Mongolia and Viet Nam (**Fig. 3**).

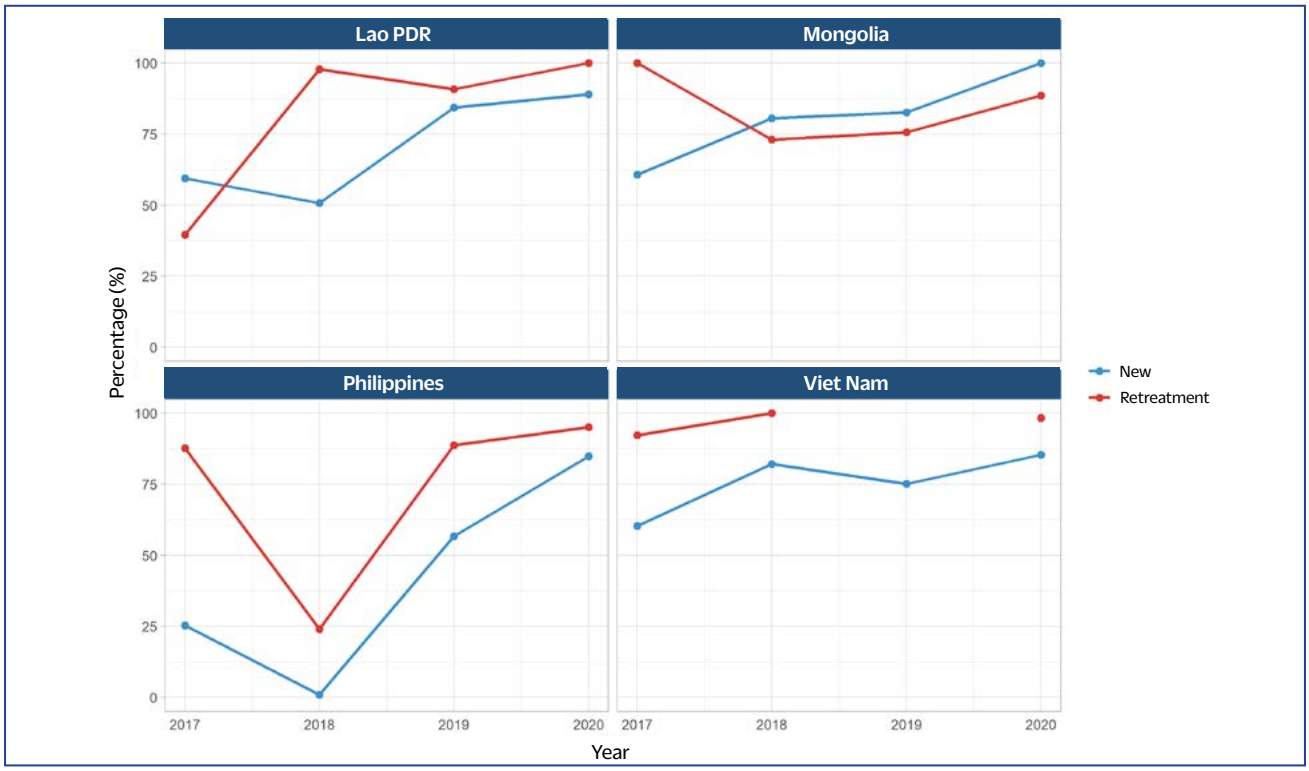
Status of DR-TB treatment

The six priority countries are also at different stages in the uptake of WHO recommendations for DR-TB treatment (**Table 3**). The category II regimen for retreatment cases has been discontinued in all priority countries. However, the WHO-recommended regimen for rifampicin-susceptible and isoniazid-resistant TB (Hr-TB) is used only in Cambodia, Mongolia, Papua New Guinea and Viet Nam.

Shorter injectable-containing regimens started in all priority countries between 2013 and 2017. In accordance with the 2020 update of the WHO guidelines on DR-TB treatment,[8] the shorter all-oral bedaquiline-containing regimen has been used in Cambodia, the Lao People's Democratic Republic, Mongolia, the Philippines and Viet Nam since 2020, with the shorter injectable-containing regimen being phased out accordingly.

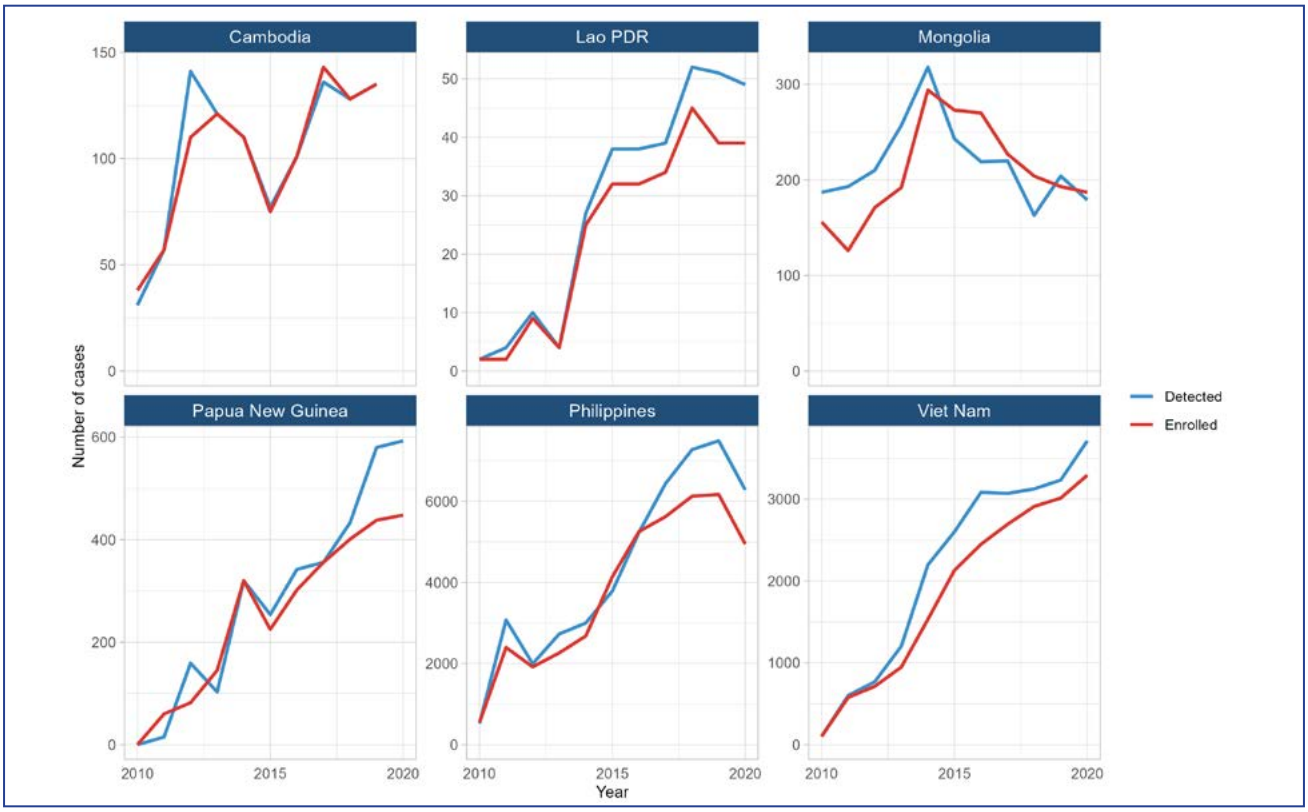
As per the 2019 WHO consolidated guidelines on DR-TB treatment,[9] standardized longer regimens for fluoroquinolone-susceptible or fluoroquinolone-resistant MDR/RR-TB have been revised in Cambodia, Mongolia, Papua New Guinea, the Philippines and Viet Nam, prioritizing Group A drugs including bedaquiline and linezolid. Kanamycin and capreomycin were no longer included in the treatment of MDR/RR-TB patients on longer regimens in all priority countries by 2020. Among the medicines recommended for use in longer regimens,[9] the following drugs are unavailable: imipenem-cilastatin and mero-

Fig. 1. **Percentage of new and previously treated TB patients tested for rifampicin resistance in four priority countries, 2017–2020 (no reports from Cambodia and Papua New Guinea)**



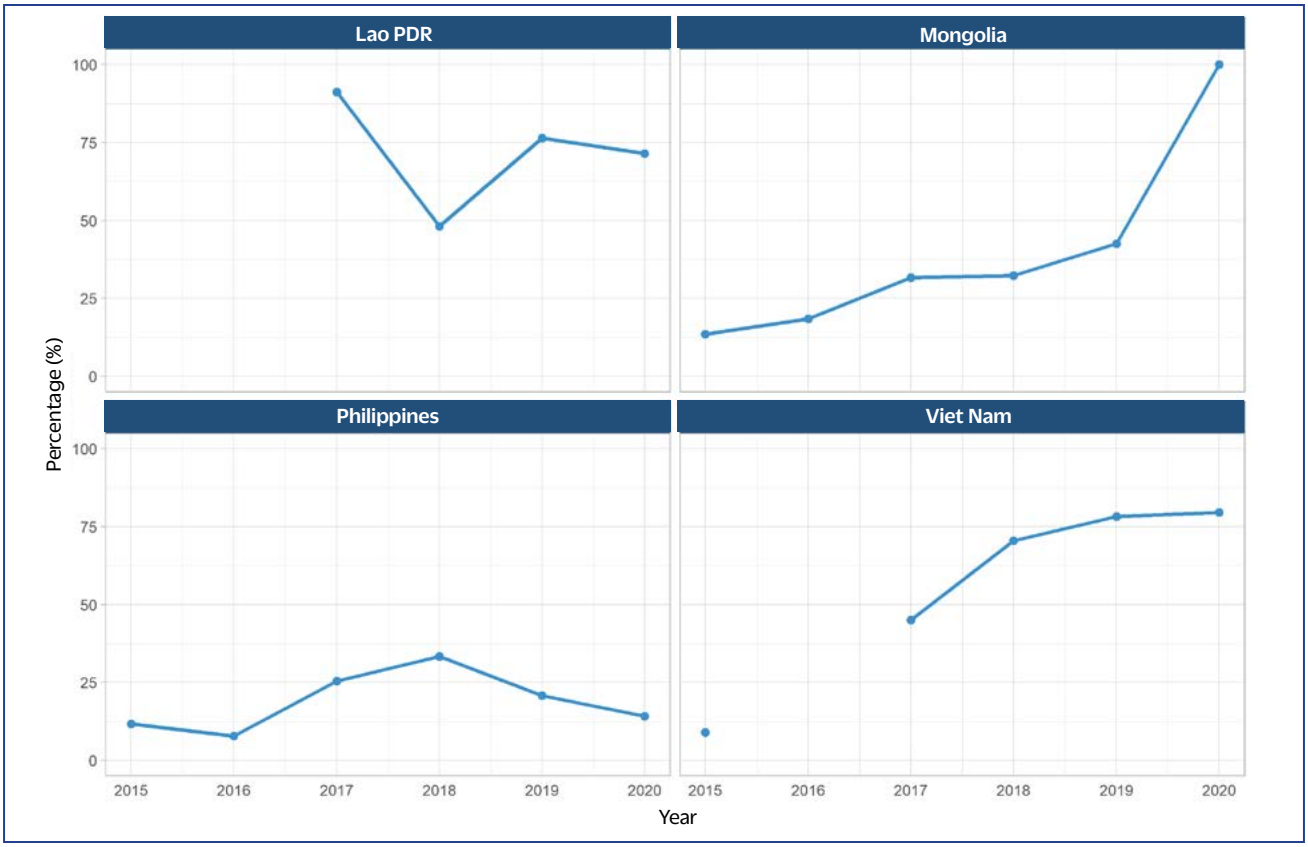
PDR: People's Democratic Republic

Fig. 2. **Number of people diagnosed with MDR/RR-TB and enrolled in MDR-TB treatment in six priority countries, 2010–2020**



PDR: People's Democratic Republic

Fig. 3. **Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones in four priority countries, 2015–2020 (no reports from Cambodia and Papua New Guinea)**



PDR: People's Democratic Republic

penem in Cambodia; cycloserine, imipenem-cilastatin, meropenem, streptomycin and p-aminosalicylic acid in the Lao People's Democratic Republic; none in Mongolia; imipenem-cilastatin and meropenem in Papua New Guinea; meropenem in the Philippines; and meropenem in Viet Nam.

The BPaL regimen recommended in 2019 for operational research has been used in the Lao People's Democratic Republic, the Philippines and Viet Nam since 2020 or 2021. Mongolia commenced the BPaL regimen under programmatic conditions in 2021.

Culture monitoring for MDR/RR-TB patients on treatment is conducted monthly in all priority countries except for Papua New Guinea. Elective partial lung resection (lobectomy or wedge resection) alongside a recommended MDR-TB regimen is being undertaken in Mongolia and the Philippines.

Various treatment adherence interventions for MDR/RR-TB patients are offered in the six priority countries (**Table 2**). Material support (e.g. lunch, transport and cash transfer) is provided in all priority countries. Psychological support is offered in Cambodia, the Lao People's Democratic Republic, Mongolia and Papua New Guinea. Patient and staff education is provided in all priority countries. Digital medication monitoring has been implemented as a pilot project in the Philippines and Viet Nam.

Several treatment administration options for MDR/RR-TB patients are provided in priority countries. In Cambodia and Viet Nam, the main mode of treatment administration is community-based directly observed treatment (DOT) by health-care workers or family members. In Mongolia, Papua New Guinea and the Philippines, both facility-based DOT by health-care workers and community-based DOT by family members are used. In the Lao People's Democratic Republic, the main

Table 3. **Status of DR-TB treatment in priority countries in the Western Pacific Region in 2021**

Item	Cambodia	Lao PDR	Mongolia	Papua New Guinea	Philippines	Viet Nam
Discontinuation of category II regimen	Yes (in 2020)	Yes (in 2018)	Yes (in 2020)	Yes (in 2017)	Yes (in 2017)	Yes (in 2018)
6 REZ-Lfx for Hr-TB	Yes (since 2018)	No	Yes (since 2020)	Yes (since 2020)	No	Yes (since 2018)
Shorter injectable-containing regimen	2017–2021	2013–2020	2016–2020	Yes (since 2016)	2015–2021	2016–2020
Shorter all-oral bedaquiline-containing regimen	Yes (since 2020)	Yes (since 2020)	Yes (since 2020)	No	Yes (since 2020)	Yes (since 2021)
Standardized longer regimen for fluoroquinolone-susceptible MDR/RR-TB	6 months Bdq-Lfx-Lzd-Cfz/12–14 months Lfx-Lzd-Cfz or 12–14 months Lfx-Cfz-Cs	N/A (shorter all-oral Bdq-containing regimen solely used)	6 months of 2–3 in Group A & 1–2 in Group B & 1–2 in Group C/ 12–14 months of 1–2 in Group A & 1–2 in Group B & 1–2 in Group C	6 months Bdq-Lfx-Lzd-Cfz/12 months Lfx-Lzd-Cfz	6 months Lfx-Bdq-Lzd-Cfz/12–14 months Lfx-Lzd-Cfz	Bdq-Lfx-Lzd-Cfz-1 in Group C or Lfx-Lzd-Cfz-Cs-1 in Group C
Standardized longer regimen for fluoroquinolone-resistant MDR/RR-TB	6 months Bdq-Lzd-Cfz-Cs-Dlm/12–14 months Lzd-Cfz-Cs	N/A (BPaL solely used)		N/A (individualized)	6 months Bdq-Lzd-Cfz-Cs/12–14 months Lzd-Cfz-Cs	N/A (individualized)
Discontinuation of kanamycin and capreomycin for MDR/RR-TB	Yes (in 2020)	Yes (in 2019)	Yes (in 2020)	Yes (in 2020)	Yes (in 2019)	Yes (in 2020)
Unavailable drugs in longer regimens	Ipm-Cln, Mpm	Cs, Ipm-Cln, Mpm, S, PAS	None	Ipm-Cln, Mpm	Mpm	Mpm
Use of BPaL regimen	No	Yes (under OR conditions since 2020)	Yes (under programmatic conditions since 2021)	No	Yes (under OR conditions since 2021)	Yes (under OR conditions since 2021)
Culture monitoring for MDR/RR-TB	Monthly	Monthly	Monthly	Irregular due to laboratory instability	Monthly	Monthly
Elective partial lung resection	No	No	Yes	No	Yes	No
Treatment adherence interventions	- Material support (US$ 30 per month) - Psychological support - Patient education - Staff education	- Material support (US$ 5 per day) - Psychological support - Patient education - Staff education	- Material support (lunch & transportation) - Psychological support - Patient education - Staff education	- Material support (US$ 57–100 per month) - Psychological support - Patient education - Staff education	- Material support (US$ 18 per week) - Patient education - Staff education - Digital medication monitor (pilot)	- Material support (US$ 10 per month) - Patient education - Staff education - Digital medication monitor (pilot)
Treatment administration options	- Community-based DOT by health-care workers or family members	- Facility-based DOT by health-care workers	- Facility-based DOT by health-care workers - Community-based DOT by family members - VOT (pilot)	- Facility-based DOT by health-care workers - Community-based DOT by family members	- Facility-based DOT by health-care workers - Community-based DOT by family members - VOT (pilot)	- Community-based DOT by health-care workers or family members - VOT (pilot)
Model of care	Mainly ambulatory care	Mainly hospitalization	Hospitalization until sputum conversion followed by ambulatory care	Mainly ambulatory care	Mainly ambulatory care	Hospitalization up to 1 month followed by ambulatory care

Bdq: bedaquiline; BPaL: bedaquiline, pretomanid and linezolid; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; DOT: directly observed treatment; E: ethambutol; Hr-TB: rifampicin-susceptible, isoniazid-resistant tuberculosis; Ipm-Cln: imipenem-cilastatin; Lfx: levofloxacin; Lzd: linezolid; MDR/RR-TB: multidrug-resistant tuberculosis or rifampicin-resistant tuberculosis; Mpm: meropenem; OR: operational research; PAS: p-aminosalicylic acid; PDR: People's Democratic Republic; R: rifampicin; REZ-Lfx: rifampicin, ethambutol, pyrazinamide and levofloxacin; S: streptomycin; VOT: video-observed treatment; Z: pyrazinamide.

Group A: levofloxacin/moxifloxacin, bedaquiline and linezolid.

Group B: clofazimine and cycloserine/terizidone.

Group C: ethambutol, delamanid, pyrazimide, imipenem-cilastatin, meropenem, amikacin/streptomycin, ethionamide/prothionamide and p-aminosalicylic acid.

modality is facility-based DOT by health-care workers during hospitalization. Video-observed treatment (VOT) has been conducted as a pilot project in Mongolia, the Philippines and Viet Nam.

MDR/RR-TB patients are treated mainly through ambulatory care in Papua New Guinea and the Philippines, whereas most patients are treated during hospitalization in the Lao People's Democratic Republic. In Mongolia, patients are hospitalized until their sputum conversion from positive to negative, and in Viet Nam, patients are hospitalized for up to 1 month. In Cambodia, patients were hospitalized for the first week for a workup and monitoring of a new regimen before the coronavirus disease (COVID-19) pandemic; however, this practice has since been restricted to ambulatory care only.

Progress of DR-TB treatment

Where data were available, the number of MDR/RR-TB cases treated with bedaquiline and the shorter regimen between 2015 and 2019 increased in all six priority countries, although there were decreases observed between 2018 and 2019 in Cambodia, the Lao People's Democratic Republic and the Philippines (**Fig. 4**). The use of the all-oral longer regimen increased between 2019 and 2020 in the Philippines (no report from the other countries).

Treatment outcomes for MDR/RR-TB cases started on treatment in 2014–2018 in the six priority countries differed (**Fig. 5**). The proportion of cases with treatment success increased in the Lao People's Democratic Republic (from 67% in 2014 to 84% in 2018) and the Philippines (from 46% in 2014 to 67% in 2018), mainly due to a reduction in the proportion of treatment failure in the Lao People's Democratic Republic and to patient loss to follow-up in the Philippines. The proportion of cases with treatment success was similar each year in Mongolia and Viet Nam, and fluctuated from year to year in Cambodia and Papua New Guinea.

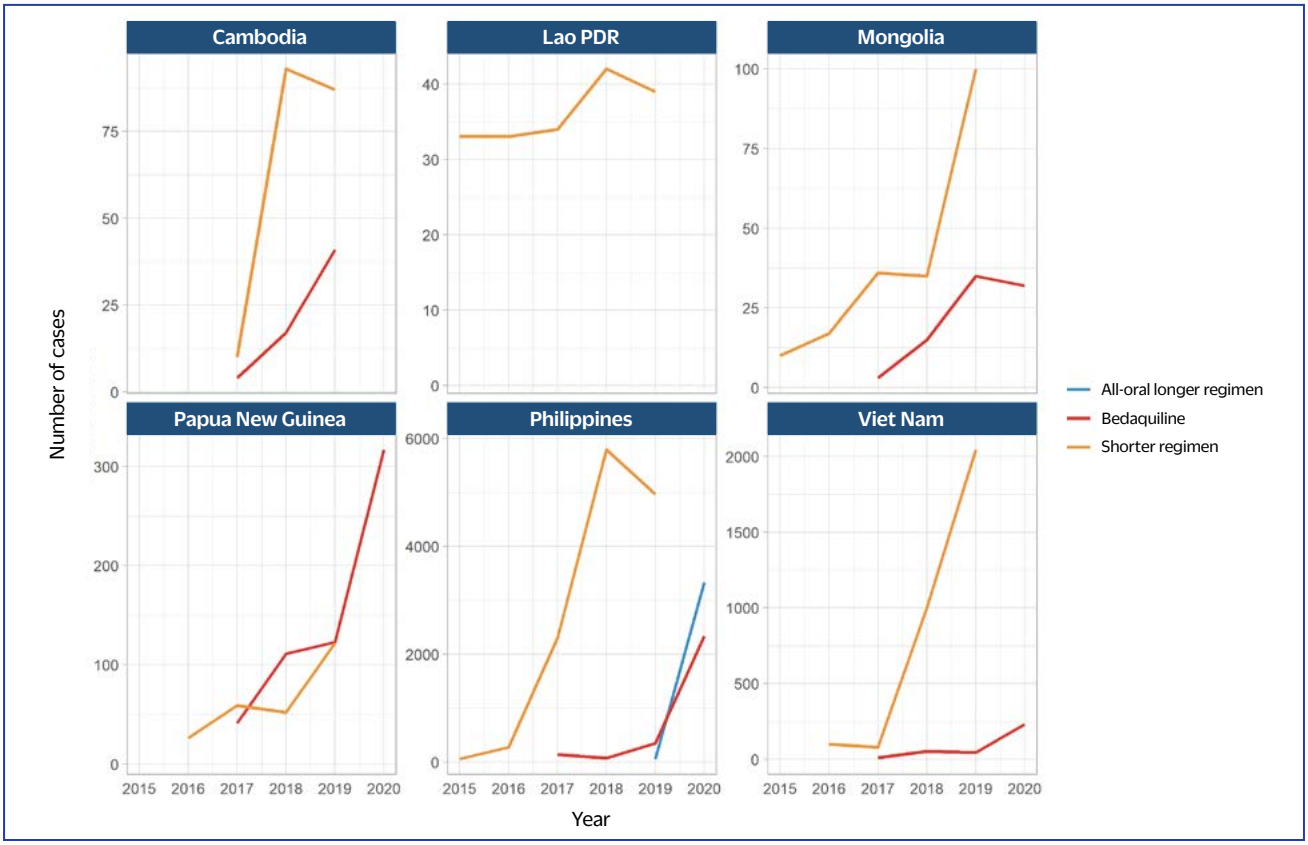
DISCUSSION

DR-TB diagnosis and treatment in the Western Pacific Region have changed drastically over the past decade. As shown by the six priority countries, national policies and algorithms now recommend Xpert MTB/RIF as an initial diagnostic test for TB and rifampicin resistance detection; also, the number of Xpert MTB/RIF sites and GeneXpert machines has increased, with the eligibility criteria extended to all people to be evaluated for TB. As a result, the number of people diagnosed with MDR/RR-TB and the percentage of TB patients tested for rifampicin resistance have also increased. For DR-TB treatment, shorter regimens for MDR/RR-TB treatment are used, with the shorter all-oral bedaquiline-containing regimen replacing the shorter injectable-containing regimen. New and repurposed drugs have been included in shorter or longer regimens, and kanamycin and capreomycin have been withdrawn. The model of care for MDR/RR-TB treatment is transitioning towards decentralization and increased use of ambulatory care. Consequently, the treatment outcomes for MDR/RR-TB cases have improved in these priority countries.

The rGLC has supported the scale-up of programmatic management of DR-TB in priority countries.[14] In accordance with WHO recommendations, the committee has provided technical inputs to national strategies or guidelines related to DR-TB; assisted in national capacity-building activities (e.g. in-person workshops or webinars); and conducted annual rGLC monitoring missions, where members of the committee and WHO staff have provided recommendations and have monitored countries' actions to previous recommendations.[14,18] Therefore, most of the new diagnostics and regimens have been implemented in a timely manner in the priority countries.

COVID-19 has impacted the diagnosis and treatment of TB and DR-TB since 2020.[19] The decrease in the number of MDR/RR-TB cases diagnosed in the Lao People's Democratic Republic, Mongolia and the Philippines in 2020 can be attributed to the decrease in TB notifications due to restricted visits to health facilities and the repurposing of TB staff and facilities for the COVID-19 response. GeneXpert machines have been repurposed for COVID-19 diagnosis; also, stockouts of cartridges and a lack of equipment maintenance may have contributed to the decrease in MDR/RR-TB diagnoses. Despite these difficulties, COVID-19 has facilitated innovations in DR-TB treatment.[20] All priority countries have expedited the transition from injectable-containing shorter or longer regimens to all-oral shorter or longer regimens, to minimize patient visits to health facilities. Hospitalization for treatment and facility-based DOT has been minimized, and community-based DOT has been facilitated in all priority countries. Also, the use of digital technology such as VOT was accelerated in three priority countries during the pandemic.

Fig. 4. **Number of MDR/RR-TB cases treated with all-oral longer regimen, bedaquiline and shorter regimen in six priority countries, 2015–2020**



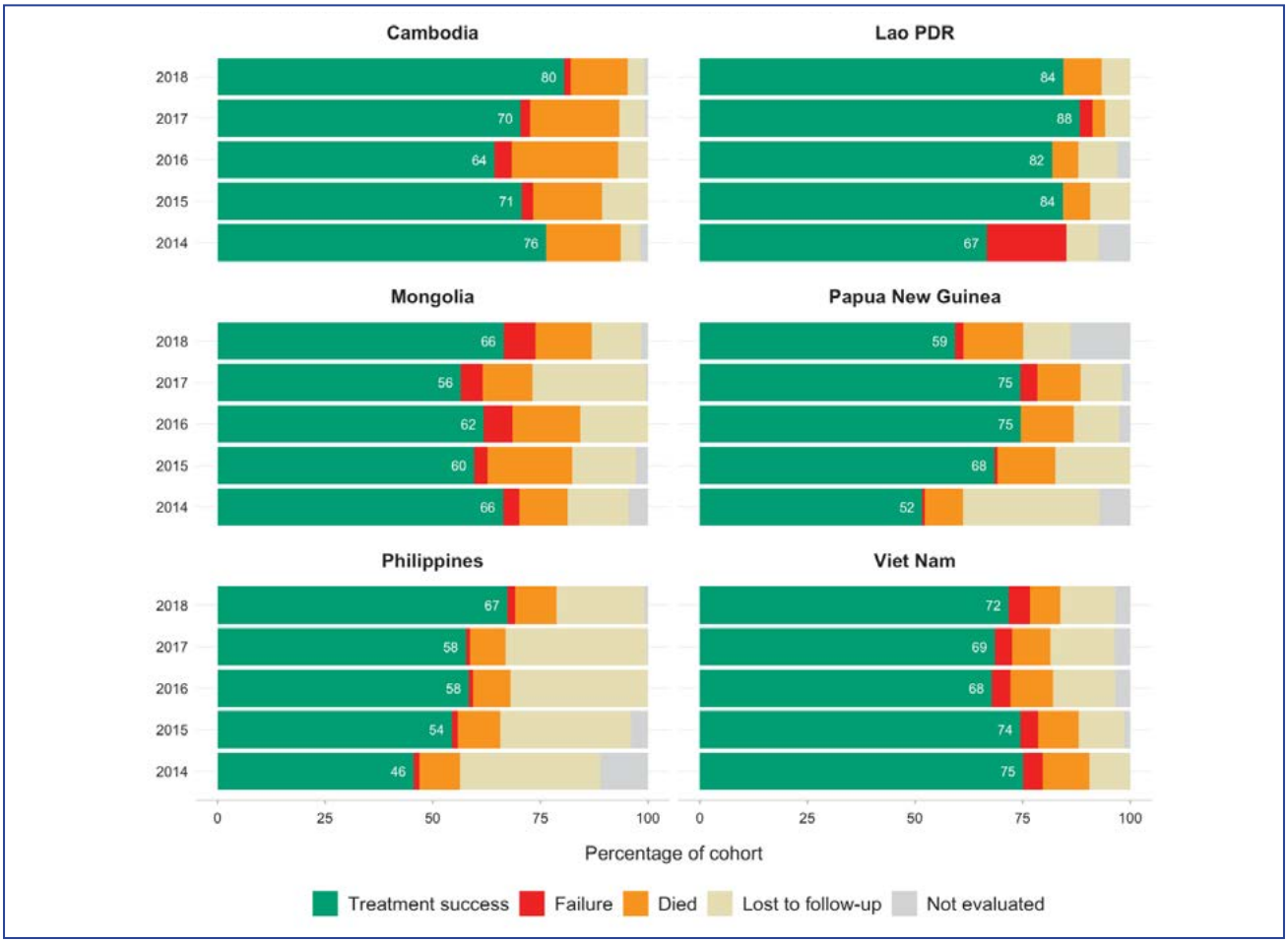
PDR: People's Democratic Republic

This analysis shows that there is still a gap in enrolment in treatment for cases diagnosed with MDR/RR-TB in some priority countries. Programme staff in the field have reported that this might be due to several factors, including death or loss to follow-up of cases before treatment commencement; significant delay in diagnosis due to the long turnaround time of SL-LPA or phenotypic drug susceptibility testing results; and delay in treatment due to health system challenges including drug supply interruption, stockouts or insufficient staff capacities, or inaccuracies in recording and reporting from paper-based systems. There should be a focus on addressing these factors for more timely patient treatment enrolment in those countries.

Although SL-LPA has been successfully promoted as initial drug susceptibility testing for fluoroquinolones in all priority countries, for various reasons, coverage is suboptimal in some of these countries. One issue is that there may be an insufficient number of laboratories for SL-LPA for nationwide coverage. For example, in the Philippines, a large country, there was only one laboratory functional for SL-LPA between 2020 and 2021 from among three designated laboratories, because one facility was repurposed for COVID-19 testing and another had never started SL-LPA testing. It has been reported from the field that SL-LPA may be underused in areas where Xpert MTB/RIF-confirmed RR-TB patients are initiated on MDR-TB treatment without SL-LPA testing against national guidelines. There may also be missing data on SL-LPA results during the recording and reporting process. With the Lao People's Democratic Republic, Papua New Guinea, the Philippines and Viet Nam soon to introduce Xpert MTB/XDR, a new landscape of drug susceptibility testing for fluoroquinolones is expected.

Due to the underuse of FL-LPA and regimens for Hr-TB in most priority countries, diagnosis and treatment of Hr-TB remain limited in the region. FL-LPA or the soon-to-be-introduced Xpert MTB/XDR should be further used to detect isoniazid resistance in cases of rifampicin-susceptible TB (at least among retreatment cases), given the high rate of isoniazid resistance in some countries. Moreover, the regimen for Hr-TB should be implemented in more of the priority countries.

Fig. 5. **Treatment outcomes for MDR/RR-TB cases started on treatment in six priority countries, 2014–2018**



PDR: People's Democratic Republic

There was static and fluctuating MDR/RR-TB treatment success in some priority countries, despite the roll-out of shorter regimens. Although they are shorter, these regimens do not guarantee improved treatment outcomes because they still require clinical management, strong patient support and monitoring systems to ensure patient adherence to treatment. In those countries, expansion of shorter regimens should be reinforced by optimal management and supportive health systems for improved treatment outcomes.

Our analysis has several limitations. First, there were no reported data for some indicators for certain years or from particular countries in the WHO database, impeding a complete analysis. Second, there is a possibility of recall bias from PMDT focal points, despite verification by follow-up communication or subsequent rGLC missions. Although attempts were made to refer to official documents, some answers were provided based on memory. Notwithstanding these limitations, this analysis provides a comprehensive and practical insight into the progress of PMDT in these six priority countries in the region.

In conclusion, these six priority countries in the Western Pacific Region, in collaboration with the rGLC, have achieved considerable progress in the diagnosis and treatment of DR-TB in line with the evolving WHO recommendations over the past decade. Automated nucleic acid amplification tests and shorter all-oral regimens containing new and repurposed drugs are now used for DR-TB diagnosis and treatment in the region, leading to reductions in the case-detection gap and enhanced treatment outcomes. However, several challenges remain, particularly the impact of the COVID-19 pandemic, suboptimal patient management and health system issues. The continued commitment of countries to a speedy recovery from COVID-19, patient-centred care, capacity building and a robust health system is needed to continue progressing towards ending DR-TB in the region.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Ethical clearance was not required because this report was part of a regular evaluation of programme performance.

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An epidemiological overview of human infections with HxNy avian influenza in the Western Pacific Region, 2003–2022

Jozica Skufca,[a] Leila Bell,[a] J C Pal Molino,[a] Dina Saulo,[a] Chin-Kei Lee,[b] Satoko Otsu,[c] Kim Carmela Co,[c] May Chiew,[c] Phetdavanh Leuangvilay,[c] Sarika Patel,[d] Asheena Khalakdina,[d] Vanra Ieng,[d] Tamano Matsui,[a] Babatunde Olowokure[a] and the WPRO Health Emergencies Programme Team[a]

Correspondence to Tamano Matsui (email: matsuit@who.int)

Avian influenza subtype A(HxNy) viruses are zoonotic and may occasionally infect humans through direct or indirect contact, resulting in mild to severe illness and death. Member States in the Western Pacific Region (WPR) communicate and notify the World Health Organization of any human cases of A(HxNy) through the International Health Regulations (IHR 2005) mechanism. This report includes all notifications in the WPR with illness onset dates from 1 November 2003 to 31 July 2022. During this period, there were 1972 human infections with nine different A(HxNy) subtypes notified in the WPR. Since the last report, an additional 134 human avian influenza infections were notified from 1 October 2017 to 31 July 2022. In recent years there has been a change in the primary subtypes and frequency of reports of human A(HxNy) in the region, with a reduction of A(H7N9) and A(H5N1), and conversely an increase of A(H5N6) and A(H9N2). Furthermore, three new subtypes A(H7N4), A(H10N3) and A(H3N8) notified from the People's Republic of China were the first ever recorded globally. The public health risk from known A(HxNy) viruses remains low as there is no evidence of person-to-person transmission. However, the observed changes in A(HxNy) trends reinforce the need for effective and rapid identification to mitigate the threat of a pandemic from avian influenza if person-to-person transmission were to occur.

Avian influenza (AI) viruses are zoonotic but occasionally infect humans through direct or indirect contact with infected animals. In humans, infection ranges from mild to severe illness and death. Wild and domestic birds (poultry and captive birds) and other mammalian species play an important role in the emergence, evolution and transmission of different AI subtypes A(HxNy) to humans. The HxNy subtypes are classified based on the 18 subtypes of haemagglutinin (H1 through H18) and the 11 subtypes of neuraminidase (N1 through N11) on the viral surface.[1,2]

In the Western Pacific Region (WPR) of the World Health Organization (WHO), the strengthening of surveillance systems to identify human infections with AI, along with a coordinated, multisectoral approach under the One Health Initiative, have been priorities for many years. These actions have been guided by the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III).[3] Global reporting mechanisms are well established to share information on A(HxNy) and guide risk assessment. Human A(HxNy) cases are notifiable under the International Health Regulations (IHR 2005)[4] and animal cases are notifiable to the World Organisation for Animal Health under the Terrestrial Animal Health Code.[5]

In 2018, we published a report of notifications of A(HxNy) human cases in the WPR between 1 November 2003 and 30 September 2017.[6] Of the 1838 human infections with A(HxNy) in this report, most were with A(H7N9) (n = 1562, 85%) and A(H5N1) (n = 238, 13%), followed by A(H9N2) (n = 18, 1%) and A(H5N6) (n = 16, 1%).[6] This current report provides an update on human cases of A(HxNy) notified from 1 November 2003 to 31 July 2022.

[a] World Health Organization Regional Office for the Western Pacific, Manila, Philippines.
[b] World Health Organization Representative Office for China, Beijing, People's Republic of China.
[c] World Health Organization Representative Office for Lao PDR, Vientiane, Lao People's Democratic Republic.
[d] World Health Organization Representative Office for Cambodia, Phnom Penh, Cambodia.

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METHODS

Human infections with A(HxNy) are commonly detected via sentinel surveillance systems, such as influenza-like illness, severe acute respiratory infection, and pneumonia with unknown etiology surveillance or through hospital-based surveillance. Member States of the WPR communicate and notify A(HxNy) human cases through the IHR (2005) mechanism to WHO. The WHO Western Pacific Regional Office has maintained a database of all official notifications of A(HxNy) human cases since 2003. This analysis includes all notifications in the WPR with illness onset dates from 1 November 2003 to 31 July 2022. Data on human infections with A(HxNy) subtypes were summarized by person, place and time and compared with results from the previous report. Data were analysed and figures were generated using Microsoft Excel.

RESULTS

From 1 November 2003 to 31 July 2022, there were 1972 human infections with nine different A(HxNy) subtypes notified to WHO from the WPR. Since the last report,[6] 134 additional human AI infections were notified from 1 October 2017 to 31 July 2022, including three new subtypes notified globally for the first time.

In the previous report, human cases with A(H5N1) and A(H7N9) were the predominant subtypes, but the majority of newly notified cases in this report were A(H5N6) (n = 64, 400% increase) and A(H9N2) (n = 59, 328% increase) (**Table 1**, **Fig. 1**).

Human infection with A(H5N6) virus

Since the last report, an additional 64 A(H5N6) cases were reported from the WPR – 63 from the People's Republic of China and one from the Lao People's Democratic Republic. From 2014, when the first A(H5N6) human case was notified, to 31 July 2022, 80 laboratory-confirmed cases were reported from the WPR. In 2021, a small cluster of two cases was reported in a husband and wife.

Of the 80 cases, 44 (55%) were males with ages ranging from 3 to 79 years (median 51 years) and 36 (45%) were females with ages ranging from 1 to 81 years (median 47 years). Overall, 44 (55%) were severe infections and 33 were reported to have died at the time of notification for a case fatality rate (CFR) of 41%. Most (74 cases, 93%) were exposed to wild birds or backyard poultry prior to illness onset (**Table 1**). The number of cases varied from two to nine per year during 2014–2020, but then increased to 37 cases in 2021. Up to the end of July 2022, 14 cases were observed (**Fig. 1**).

All but one of the cases (99%) were notified from China, across 15 different provinces. Cases were reported from Anhui (n = 2), Beijing (n = 1), Chongqing (n = 3), Fujian (n = 2), Guangdong (n = 14), Guangxi (n = 18), Guizhou (n = 1), Henan (n = 1), Hubei (n = 1), Hunan (n = 13), Jiangsu (n = 5), Jiangxi (n = 2), Sichuan (n = 12), Yunnan (n = 2) and Zhejiang (n = 2). In March 2021, the Lao People's Democratic Republic notified the Western Pacific Regional Office of A(H5N6) virus infection in a child identified through sentinel surveillance.

Human infection with A(H9N2) virus

Since the last report, an additional 59 A(H9N2) cases have been notified to WHO from the WPR (57 from China and two from Cambodia). Between 2015, when the first A(H9N2) human case was notified to WHO, and 31 July 2022, 77 laboratory-confirmed cases (including two deaths, CFR: 3%), were notified from the WPR.

There were no family clusters reported, although most cases were children. Of the total cases (n = 77), 27 (35%) were males. Ages ranged from <1 to 39 years (median 3 years) in males and from <1 to 78 years (median 5 years) in females. Overall, 71 (92%) were mild infections and 58 (75%) were exposed to bird markets or backyard poultry prior to illness onset (**Table 1**). The number of cases observed varied from four to seven per year during 2015–2019, and increased to 16 cases in 2020, 25 cases in 2021 and eight cases up to the end of July in 2022 (**Fig. 1**).

Of the total cases, 75 (97%) were notified from China, across 16 different provinces including one from China Hong Kong Special Administrative Region (SAR). Cases were reported from Anhui (n = 9), Beijing (n = 2), Fujian (n = 4), Gansu (n = 1), Guangdong (n = 18), Guangxi (n = 3), Guizhou (n = 5), Henan (n = 2), Hubei (n = 5), Hunan (n = 11), Jiangsu (n = 3), Jiangxi (n = 2), Shandong (n = 1), Shanxi (n = 1), Sichuan (n = 5), Yunnan (n = 2) and Hong Kong SAR (n = 1). Two cases were notified from Cambodia in

Table 1. **Demographic, geographic and temporal characteristics of avian influenza virus subtypes notified from the Western Pacific Region, 1 November 2003–31 July 2022**

Characteristic	Influenza A virus subtype								
	H5N1	H7N9	H5N6	H9N2	H10N8	H6N1	H7N4	H10N3	H3N8
New cases notified since last report[6]: from 1 October 2017 to 31 July 2022									
New cases, *n* (% increase)	1 (<1%)	6 (<1%)	64 (400%)	59 (328%)	0 (0%)	0 (0%)	1 (100%)	1 (100%)	2 (100%)
Total cases notified: from 1 November 2003 to 31 July 2022									
Total cases, *n*	239	1568	80	77	3	1	1	1	2
Sex									
Male	119 (50%)	1096 (70%)	44 (55%)	27 (35%)	1 (33%)	0	0	1 (100%)	2 (100%)
Female	120 (50%)	472 (30%)	36 (45%)	50 (65%)	2 (67%)	1 (100%)	1 (100%)	0	0
Age, median years (range)	20 (<1–81)	57 (0–91)	50 (1–81)	5 (<1–78)	73 (55–75)	20	68	41	4.5 (4–5)
Male	23 (<1–81)	58 (1–91)	51 (3–79)	3 (<1–39)	75	ND	ND	41	4.5 (4–5)
Female	18 (<1–75)	56 (0–85)	47 (1–81)	5 (<1–78)	55, 73	20	68	ND	ND
Severity									
Unknown	ND	142 (9%)	0	1 (1%)	0	0	0	0	0
Mild/stable	ND	89 (6%)	3 (4%)	71 (93%)	0	0	0	0	1 (50%)
Severe	ND	721 (46%)	44 (55%)	3 (4%)	3 (100%)	1 (100%)	1 (100%)	1 (100%)	1 (50%)
Deaths, *n* (CFR %)	134 (56%)	616 (39%)	33 (41%)	2 (3%)	2 (67%)	0	0	0	0
Deaths median age (range), years	19 (<1–69)	60 (3–91)	48 (3–81)	48 (39–57)	74 (73–75)	ND	ND	ND	ND
Exposure to poultry/wild birds									
Yes	146 (61%)	741 (47%)	74 (92%)	58 (75%)	3 (100%)	0	1 (100%)	0	2 (100%)
No	7 (3%)	34 (2%)	3 (4%)	10 (13%)	0	1 (100%)	0	1 (100%)	0
Unknown	86 (36%)	793 (51%)	3 (4%)	9 (12%)	0	0	0	0	0
Countries (% of all cases reported)	Cambodia (*n* = 56, 23%), China (*n* = 53, 22%), Lao PDR (*n* = 3, 1%), Viet Nam (*n* = 127, 53%)	China (*n* = 1565, 99.8%), cases with travel to China from Canada (*n* = 2), Malaysia (*n* = 1)	China (*n* = 79, 99%), Lao PDR (*n* = 1, 1%)	China including China, Hong Kong SAR (*n* = 75, 97%), Cambodia (*n* = 2, 3%)	China (*n* = 3, 100%)	China (*n* = 1, 100%)	China (*n* = 1, 100%)	China (*n* = 1, 100%)	China (*n* = 2, 100%)
Last reported to WHO	31 October 2020	5 April 2019	13 June 2022	24 June 2022	13 February 2014	May 2013	14 February 2018	31 May 2021	17 May 2022

China: People's Republic of China; CFR: case fatality rate; ND: not determined; PDR: People's Democratic Republic; SAR: Special Administrative Region; WHO: World Health Organization.

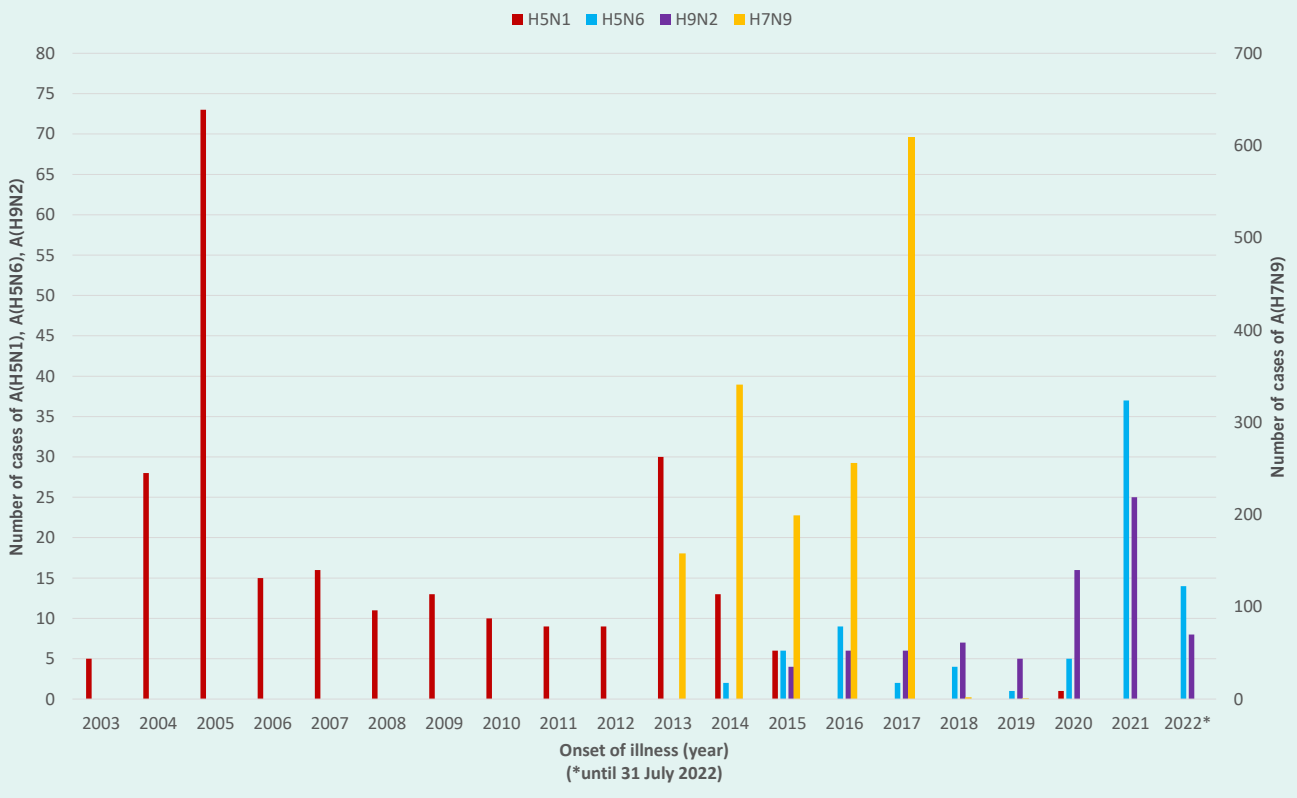
March 2021 and March 2022, both of which were in children (a 13-month-old girl and a 3-year-old boy) from Siem Reap province with mild symptoms.

Human infection with new A(H7N4), A(H10N3) and A(H3N8)

The three different AI subtypes documented for the first time globally were from China in 2018, 2021 and 2022 comprising one case of A(H7N4), one case of A(H10N3) and two cases of A(H3N8), respectively. All cases recovered after being hospitalized and no close contacts of the cases developed illness.

The case of A(H7N4) was a 68-year-old woman with reported comorbidities and a history of exposure to live poultry prior to becoming ill. The case of A(H10N3) was a 41-year-old male with no clear history of exposure to poultry prior to illness onset. A(H10N3) was not detected in environmental samples or poultry within the locality of

Fig. 1. **Cases of human infection with avian influenza subtypes A(H5N1), A(H5N6), A(H9N2) and A(H7N9) notified to WHO from the Western Pacific Region, 1 November 2003–31 July 2022**



the case. One case of A(H3N8) was a 4-year-old boy with exposure to live backyard chickens prior to illness onset and the other case was a 5-year-old boy with exposure to a live poultry market (**Table 1**).

DISCUSSION

In recent years, there has been a change in the primary subtypes and frequency of reports of human A(HxNy) in the WPR, with a reduction of A(H7N9) and A(H5N1), and an increase of A(H5N6) and A(H9N2). Furthermore, new subtypes A(H7N4), A(H10N3) and A(H3N8) were reported from China.

The majority of cases and new A(HxNy) subtypes in the WPR were reported from China. This is likely due to several factors, including the fact that it is the world's largest agricultural country; has an extensive human–animal interface with about 30% of the poultry raised in backyard conditions; and that live poultry markets common in China play a major part in sustaining influenza viruses as well as allowing for new reassortments of A(HxNy).[7–10] However, it could also be an indicator of strong detection, surveillance, case reporting and effective cooperation between different sectors in China. This is exemplified by the decrease in the number of human cases of A(H7N9) since 2018 owing to the united and collaborative response of multiple relevant stakeholders following a One Health approach.[7] Similarly, Cambodia[11] and the Lao People's Democratic Republic[12] demonstrated strong joint One Health investigation and collaboration to control the A(H9N2) and A(H5N6) human cases detected in 2021, respectively.

While human infections with A(H9N2) have mostly caused mild clinical disease and have been mostly among children (median age of 5 years), A(H5N6) can generally be more severe. However, although an increase of A(H5N6) cases was observed in 2021, the disease course and CFRs were comparable to previously detected A(H5N6) cases. In 2021, four newly detected H5N6 genotypes were the major causes of increased A(H5N6) infections.[13] The observed increase may reflect the spread of this virus in poultry, which is enzootic and circulates in poultry and birds in the region.[14] Surveillance of live poultry markets in China from 2014

to 2016 revealed that A(H5N6) replaced A(H5N1) as the dominant subtype in southern China, especially in ducks.[15] Additional mammal-adapted mutations were also detected, indicating the viral adaptation process from birds to humans.[13] However, although human A(H5N6) cases were reported from China from December 2021 to March 2022, no poultry/bird outbreaks of A(H5N6) were notified to the World Organisation for Animal Health, which may suggest an underreporting of poultry outbreaks.[2]

The increase in reported human cases of A(H5N6) may also be due to enhanced diagnostic capacity for respiratory disease surveillance during the COVID-19 pandemic in the context of generally increased awareness of respiratory illness across the public health system.[14,16] While in China the majority of A(H5N6) cases were reported through pneumonia surveillance systems and identified by Chinese National Influenza Surveillance Network laboratories, 15 cases in 2020 and 2021 were first identified through third-party sequencing agencies that then reported to the Chinese National Influenza Surveillance Network laboratories for confirmation. More than one third of cases in 2021 were detected by hospitals that sent samples from patients with pneumonia to these third-party sequencing agencies.[13]

Since our last report, notifications of A(H5N1) infections have remained low despite enhanced surveillance, detection, awareness and reporting following the COVID-19 pandemic. This may indicate a true decline in A(H5N1) not biased by changes in surveillance. The A(H5N1) viruses detected during late 2021 and 2022 are different from earlier H5N1 bird flu viruses. Current viruses are not spreading easily among poultry, are infecting people less easily, and may be less of a risk and cause less severe illness among humans.[17]

In addition to the three new strains reported from China for the first time globally, the first two human cases of A(H5N1) were reported from Europe and the Americas in 2022. In January 2022, the first human A(H5N1) case was reported in the United Kingdom of Great Britain and Northern Ireland in a person who kept birds domestically.[18] At the beginning of May 2022, the first A(H5N1) case in the United States of America was reported in a person involved in bird-culling procedures.[19] These two sporadic cases were not unexpected since the circulation of AI viruses in poultry increases the risk of sporadic human infections, especially for those with occupational exposure. The first human cases of A(H5N8) were documented in seven workers who were involved in culling operations in a poultry outbreak in the Russian Federation in 2020.[20]

There are several limitations in the interpretation of these results as they are based on IHR (2005) notifications. First, the estimated CFRs for A(HxNy) should be interpreted with caution since these are calculated from the last update of notifications without any follow-up of severe cases that may have subsequently died. Given the lack of updated case information, the true number of deaths may also be skewed. Second, the capacity to detect A(HxNy) evolved during the COVID-19 pandemic when influenza surveillance systems were strengthened with changes in the sources of case detection such as through influenza-like illness surveillance. This detection capacity may vary by geographical location due to differences in surveillance systems. In addition, official notification of cases may be underreported, particularly for subclinical infections. A seroprevalence study conducted in Cambodia among poultry workers found an overall prevalence of 4.5% and 1.8% for antibodies against A(H5N1) and A(H9N2), respectively. Hence, the true burden of infection is likely higher than that observed.[21] Despite these limitations, reporting as outlined in the IHR (2005) continues to provide important information about human cases of A(HxNy) in the WPR and globally. It enables Member States to understand the epidemiological situation of human AI cases, assess the risks and take preventive public health actions.

In conclusion, the overall public health risk from known A(HxNy) viruses at the human–animal interface remains low as infections have been almost exclusively associated with contact with infected birds, with no evidence of person-to-person transmission. However, the observed changes in A(HxNy) trends reinforce the need for early detection and strengthening of human and animal surveillance to detect virological, epidemiological and clinical changes associated with circulating A(HxNy). Accordingly, continued multi-sectoral collaboration at the human–animal interface is needed for effective mitigation of the pandemic threat of AI.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Ethical approval was not necessary for this study.

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Epidemiological profile of dengue in Champasak and Savannakhet provinces, Lao People's Democratic Republic, 2003–2020

Sumaira Zafar,[a] Hans J Overgaard,[b,c] Tiengkham Pongvongsa,[d] Nanthasane Vannavong,[e] Sysavanh Phommachanh,[f] Oleg Shipin,[a] Joacim Rocklöv,[g] Richard E Paul,[h] Md Siddikur Rahman[c,i] and Mayfong Mayxay[f,j,k]

Correspondence to Sumaira Zafar (email: sumaira.zafar@ait.asia)

Dengue is a public health issue in tropical south-eastern Asia responsible for significant morbidity and mortality. Information on dengue epidemiology is necessary for developing strategies to control infections effectively. In the Lao People's Democratic Republic (Lao PDR), Champasak and Savannakhet provinces account for around 30% of the national dengue burden. In this study, the dengue epidemiological profile in these two southern provinces of Lao PDR was described by analysing seasonal and spatial dengue notification data from 2003–2020 using the long-term mean (LTM) method. Savannakhet had a higher LTM (132.0 cases/month, 95% confidence interval [CI]: 92.2–171.7) than Champasak (113.3 cases/month, 95% CI: 86.0–140.5), with peaks in dengue notifications following the rainy season in both provinces. The highest notification rates were observed in July to September; these months were also when the LTM was most frequently exceeded. Previously, dengue notifications were largely confined to the western districts of Savannakhet and the northern districts of Champasak, but more recently, notifications have increased in the eastern districts of Savannakhet and southern districts of Champasak. While the notification rate remained high in children and young adults (5–30 years), especially among students and farmers, a shift in the age structure of dengue cases was observed, with a greater proportion of notifications now occurring in those aged over 30 years. Community-based vector control and prevention programmes are needed to restrict the spread of dengue into new geographical areas in the southern provinces of Lao PDR.

Dengue is the most prevalent vector-borne disease in south-east Asia. Caused by the four dengue virus serotypes (DENV-1–4) and transmitted by Aedes mosquitoes, primarily by *Aedes aegypti*, the prime contributors to the emergence and spread of dengue are favourable climatic conditions, urbanization and international trade and travel.[1]

Dengue emerged as a public health concern in Lao People's Democratic Republic (Lao PDR) in 1983, following its first major outbreak in the capital city of Vientiane, during which 1759 cases of dengue haemorrhagic fever (DHF) were recorded.[2] Since then, the country has experienced multiple outbreaks, not just in the capital but also in other parts of the country. About 40% of all dengue cases reported in Lao PDR during 1985–1989 were from Vientiane, with the highest dengue activity occurring during the monsoon season (May to October).

Previous studies of dengue in Lao PDR have focused on a specific province or region and/or have relied on short-term dengue case data. In contrast, this study summarized dengue surveillance data spanning an 18-year period, 2003–2020, from the two most affected southern provinces in Lao PDR. It was designed

[a] Department of Environmental Engineering and Management, Asian Institute of Technology, Bangkok, Thailand.
[b] Faculty of Science and Technology, Norwegian University of Life Sciences, Ås, Norway.
[c] Department of Microbiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.
[d] Savannakhet Provincial Health Department, Phonsavangnuea, Lao PDR.
[e] Champasak Provincial Health Office, Pakse, Lao PDR.
[f] Institute of Research and Education Development, University of Health Sciences, Ministry of Health, Vientiane, Lao PDR.
[g] Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden.
[h] Unité de la Génétique Fonctionnelle des Maladies Infectieuses, Institut Pasteur, Paris, France.
[i] Department of Statistics, Begum Rokeya University, Rangpur, Bangladesh.
[j] Lao-Oxford-Mahosot Hospital-Welcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao PDR.
[k] Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, United Kingdom of Great Britain and Northern Ireland.
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to inform risk assessment of dengue transmission as well as prevention and control strategies.

METHODS

Study area

The current study was conducted within a larger project (DENCLIM project; 2018–2021) which aimed to evaluate the effects of environmental change and climatic variability on community vulnerability and exposure to dengue within four geographically similar, but socioeconomically different, neighbouring provinces in southern Lao PDR and north-eastern Thailand.

Lao PDR has three distinct geographical areas (north, central and south). The two most populated provinces in the south, Champasak and Savannakhet, were selected for this study (**Fig. 1**). Champasak and Savannakhet together account for 24% (1.75 million) of the country's population and both are endemic for dengue with year-round transmission. Peak transmission, however, occurs during the rainy season, from May to October.

Data collection

Daily reports of dengue cases for Champasak and Savannakhet provinces collected by the two provincial health departments between 2003 and 2020, aggregated at the district level, were used in this study. As per the national dengue surveillance system protocols, all public health practitioners and directors of clinical laboratories must report all dengue cases that meet the dengue case definition within 24 hours of case confirmation to their provincial health department.[3] As cases are probably underreported by this surveillance system, data are unlikely to be representative of the true incidence of dengue infection.

Clinically diagnosed dengue cases were initially categorized as either dengue fever (DF), DHF or dengue shock syndrome (DSS). In 2010, Lao PDR adopted the new dengue case classification recommended by the World Health Organization (WHO),[4] which categorizes cases as: dengue without warning signs (DWOS), dengue with warning signs (DWS) or severe dengue (SD).[3] Dengue cases were recorded in the Champasak province according to the new WHO 2009 classification from 2010 onwards, while Savannakhet only adopted the new classification in 2020. Samples of the notified dengue cases were confirmed by laboratory testing using non-structural protein tests. Data on the prevailing serotypes were obtained from the annual reports of the National Center for Laboratory and Epidemiology and from the provincial health department of Savannakhet.

Population data, based on the 2005 and 2015 censuses, were acquired from the official web portal of the national department of statistics.[5] National data on the temporal trends in dengue cases (2003–2020) were also used in the analysis.

Analysis

Dengue notification rate

Available dengue surveillance data included information on the daily number of clinically diagnosed dengue cases and deaths by district, age, sex, occupation, nationality and disease severity. The monthly dengue notification rate was calculated per 100 000 persons (number of cases per month/district population x 100 000). Monthly dengue notification rates were based solely on case data collected by the provincial surveillance system and stored in provincial databases; suspected and unconfirmed cases were not included.

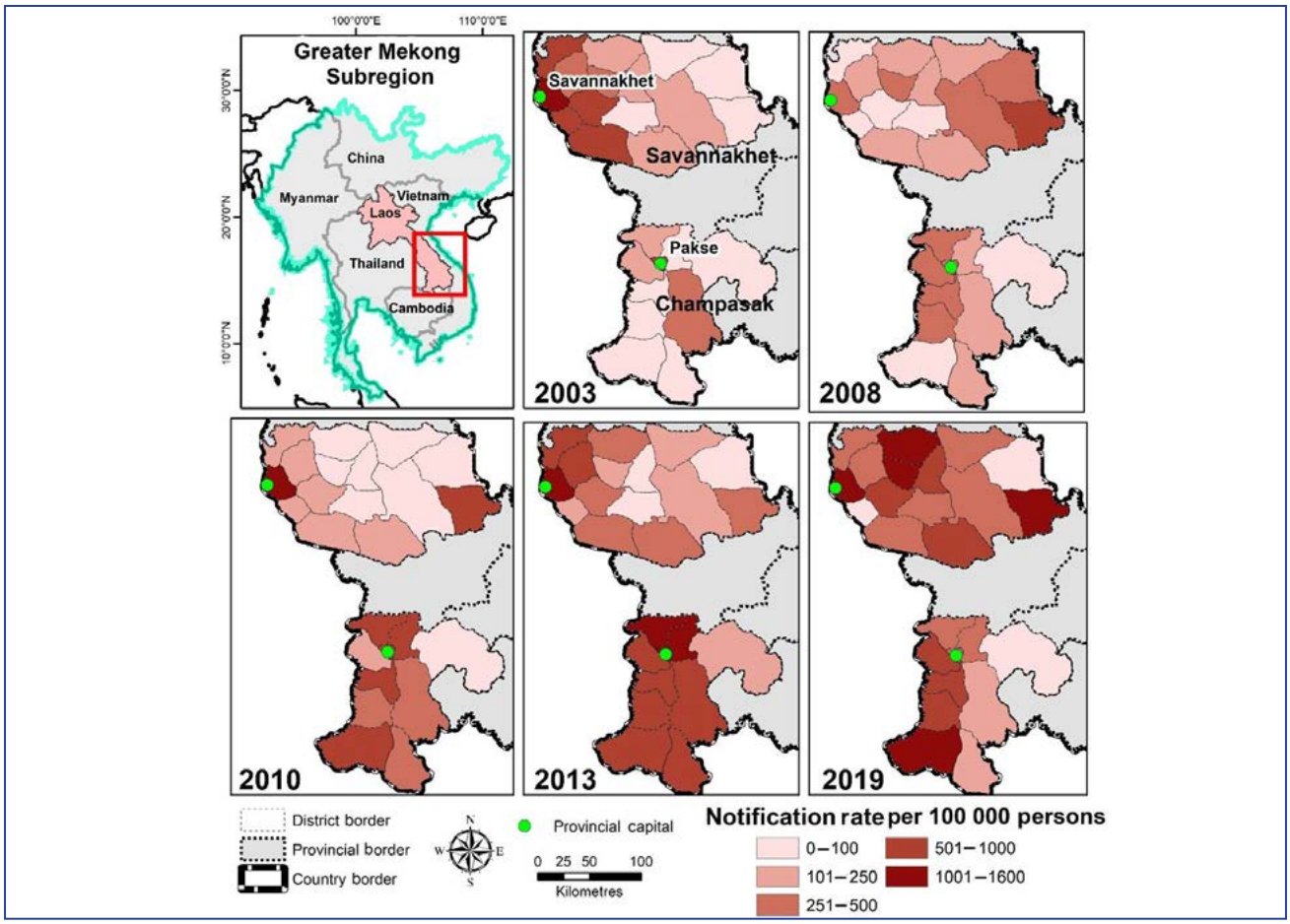
Long-term mean of dengue cases

A long-term mean (LTM) method was used to analyse spatiotemporal variations in dengue cases. The LTM was calculated by dividing the total number of dengue cases observed during a specified time period by the total number of time units (i.e. months) in that time period. The time period used in this study was 216 months (2003–2020).

$$LTM = \frac{\Sigma Dengue\ cases}{\Sigma Months}$$

The LTM was used as a threshold to determine the number of months when the monthly number of cases exceeded or remained below the LTM. When the monthly number of cases exceeded the LTM for 3 or more consecutive months, this period was considered to be a "high transmission season".[6] LTMs and the number of months that exceeded them were calculated and mapped for each district within the two provinces.

Fig. 1. **Annual average dengue notification rates in high transmission years by district, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**



Sociodemographic characteristics of dengue cases

The sociodemographic characteristics of cases including population density, age, sex, occupation and nationality were analysed to identify relative dengue case burdens. The population density of each district in the two provinces was plotted against the dengue notification rate to check for correlation. Dengue cases were also sub-analysed by case definition, age group, occupation and nationality to see which groups were most affected.

RESULTS

Dengue mortality and notification rates

From 2003 to 2020, 24 479 dengue cases in Champasak and 28 509 in Savannakhet were recorded (**Table 1**). On average, these two provinces combined accounted for 32.6% (Champasak for 17.3%, Savannakhet for 15.3%) of the country's total number of notified dengue cases (**Table 2**). High transmission seasons occurred in both provinces in 2013 (5387 and 4959 cases in Champasak and Savannakhet, respectively) and again in 2019 (6320 and 3145 cases in Champasak and Savannakhet, respectively). The highest numbers of deaths due to dengue were recorded in 2003 and 2013, followed by 2019 (**Table 2**).

In both provinces, rates of notified dengue cases were higher in the provincial capital districts than in remote districts away from the provincial capitals (**Fig. 1**). The highest annual dengue notification rate was recorded in the south-western districts of Savannakhet in 2019, when rates reached 1595 cases per 100 000 population. Dengue notification rates in both provinces were highly variable and not limited to densely populated areas.

Table 1. **Characteristics of dengue notifications, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**

Characteristic	Champasak		Savannakhet	
	n	%	*n*	%
Cases	**2003–2020**		**2003–2020**	
Male	12 621	51.6	14 750	51.7
Female	11 858	48.4	13 759	48.3
Total	24 479	100	28 509	100
Deaths				
Male	41	46.6	46	46.4
Female	47	53.4	53	53.6
Total	88	100	99	100
Case definition				
Old classification	**2003–2009**		**2003–2019**	
Dengue fever	7846	97.5	23 716	85.3
Dengue haemorrhagic fever	138	1.7	3406	12.3
Dengue shock syndrome	60	0.7	676	2.4
Total	8044	100	27 798	100
2009 classification	**2010–2020**		**2022**	
Dengue without warning signs	13 590	82.7	508	71.4
Dengue with warning signs	2170	13.2	170	23.9
Severe dengue	675	4.1	33	4.6
Total	16 435	100	711	100

Table 2. **Dengue fever notifications, deaths and notified cases as a proportion of national notifications, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**

Year	No. of cases (% of national total)		No. of deaths (Champasak and Savannakhet)	Total no. of cases (Lao PDR)
	Champasak (*N* = 24 479)	Savannakhet (*N* = 28 509)		
2003	914 (5.2)	6315 (35.7)	42	17 690
2004	700 (20.0)	752 (21.4)	13	3507
2005	1487 (27.2)	795 (14.5)	4	5471
2006	1187 (18.7)	314 (4.9)	1	6356
2007	1284 (26.0)	862 (17.4)	0	4943
2008	1557 (37.5)	1935 (46.6)	12	4149
2009	910 (11.8)	177 (2.3)	5	7706
2010	3029 (13.2)	2512 (11.0)	13	22 929
2011	522 (13.5)	50 (1.3)	4	3871
2012	938 (9.4)	225 (2.2)	3	9952
2013	5387 (12.2)	4959 (11.2)	42	44 171
2014	102 (5.9)	15 (0.9)	0	1716
2015	176 (11.0)	34 (2.1)	0	1600
2016	1343 (23.9)	655 (11.7)	13	5617
2017	732 (13.1)	956 (17.1)	5	11 049
2018	1022 (22.2)	922 (20.0)	11	6446
2019	3145 (8.3)	6320 (16.8)	19	37 700
2020	44 (0.5)	711 (8.6)	0	8305

Years with high transmission seasons are shown in bold.

Spatiotemporal variations in LTMs

The LTMs for Champasak and Savannakhet were 113.3 (24 479/216; 95% confidence interval [CI]: 86.0–140.5) and 132.0 (28 509/216; 95% CI: 92.2–171.7) cases per month, respectively. The number of dengue cases exceeded the LTM for at least 3 consecutive months in 10 of the 18 years of the study period (2003–2020) in Champasak and in 7 of the years in Savannakhet (**Fig. 2A**). Both provinces experienced extended high-transmission periods. In Champasak, the LTM was exceeded for 7 consecutive months in 2013 (March to September) and for 6 consecutive months in 2008, 2010 and 2019 (March to August). Savannakhet experienced five prolonged epidemic periods, three lasting for 7 months (May to October) in 2003, 2008 and 2013, one for 6 months (June to October) in 2010, and one for 9 months (April to November) in 2019. The number of times the LTM was exceeded was greatest during the rainy season (May to September); during the period of our study, the LTM was most often exceeded in June and July (**Fig. 2B**).

In a district-level analysis, the highest LTM values were generally observed in or near the provincial capitals (**Fig. 3A**). In Savannakhet province, three districts exceeded the LTM threshold for 36-45 months and three districts for 46-50 months during the 216-month study period during the 216-month study period. In Champasak province, seven districts exceeded the LTM threshold for 36–45 months and three districts for 56–58 months (**Fig. 3B**).

Dengue serotypes

Occasional dengue serotype identification conducted by the National Center for Laboratory and Epidemiology showed that in Savannakhet, DENV-1 was detected in 9 of the 11 years between 2003 and 2020 for which serotype data were available. DENV-2 and DENV-4 were also relatively common, being present in 6 out of 11 years, whereas DENV-3 was only found in 2012 and 2013 (**Table 3**). However, DENV-3 was responsible for at least 80% of all reported dengue cases in Lao PDR in 2012 and 2013. Data indicate that in more recent years, DENV-1 and DENV-4 have been the more dominant serotypes, followed by DENV-2, both nationally and in the Champasak and Savannakhet provinces (**Table 3**).

Dengue notifications by sociodemographic characteristics

Population density

In both provinces, the highest numbers of dengue notifications were generally observed in the more densely populated provincial capitals and their neighbouring districts (**Fig. 4A**). However, when the capitals were removed, the association between dengue notification rates and population density was not statistically significant (Pearson coefficient = 0.21, $P = 0.013$) (**Fig. 4B**).

Age and sex

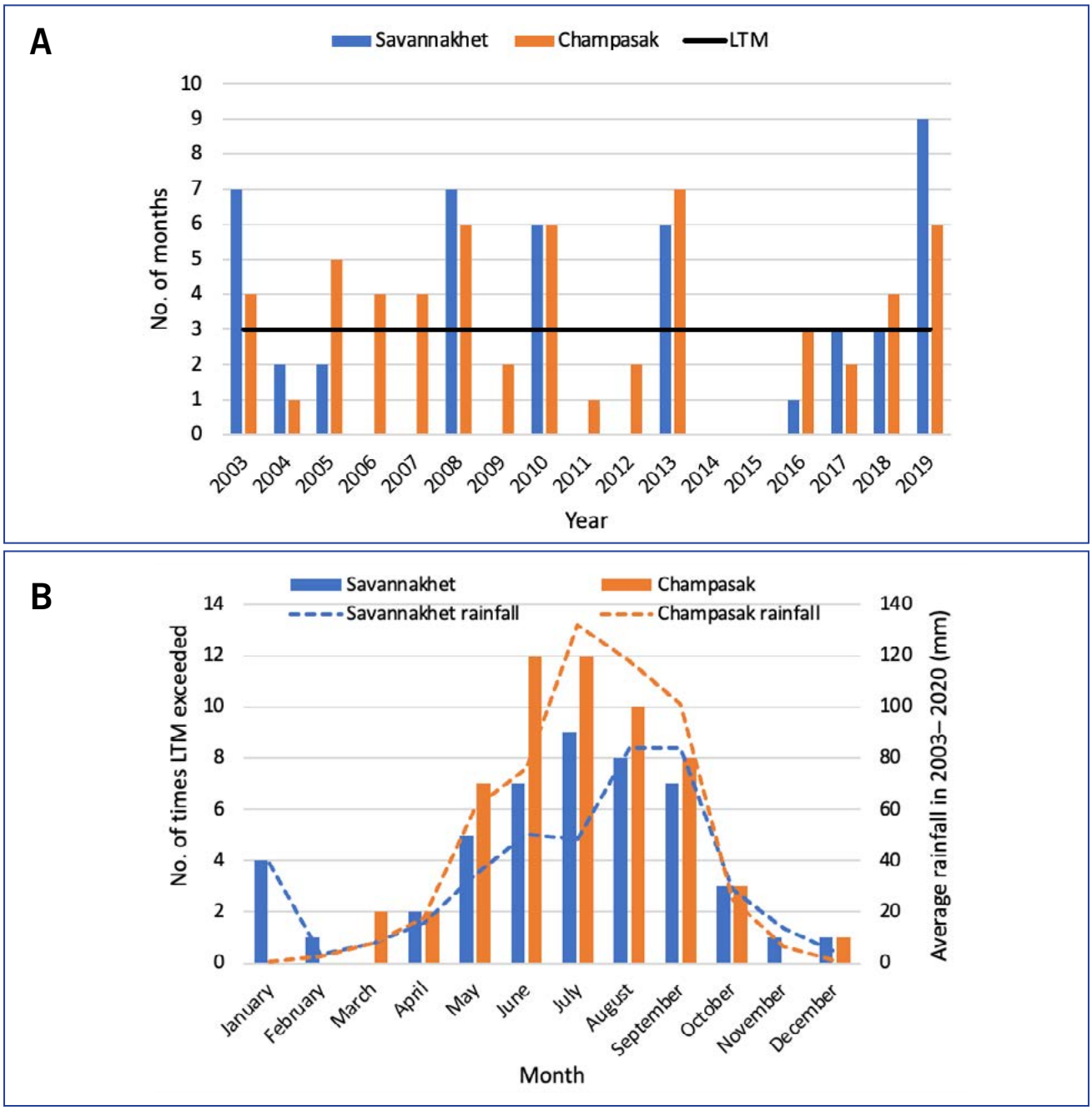
The 5–14-year age group accounted for the highest proportion of cases, followed by the 15–30-year age group. 2007 and 2012 were notable for a higher-than-usual proportion of dengue notifications in those aged <1 year (**Fig. 5A**).

In all age groups, the majority of dengue infections were categorized as DF (or DWOS). The more severe cases, those categorized as DHF/DWS and DSS/SD, occurred most frequently in those aged 5–14 years old (**Table 4**). Overall, cases were more common in males than females (52% vs 48%) (**Table 1** and **Table 5**); this male excess was also apparent in most age groups, in particular, in the 15–30-year age group. However, in absolute terms, the highest number of deaths occurred in females, with high case fatality rates recorded in those aged under 15 years in both sexes (Table 5).

Occupation

Across the study period, young children (<5 years), students (5–18 years) and farmers have consistently experienced the greatest burden of dengue; on average, students accounted for 43% of dengue notifications and farmers for a further 22% (**Fig. 6**). However, there has been a shift in the distribution of cases by occupation; whereas the proportion of cases reported in young children and students has fallen (from 84% in 2003 to 60% in 2019), the proportion of dengue notifications in farmers has increased over the same time period (from 6% to 30%). Dengue cases were especially high among farmers in 2007 and 2011, when this group accounted for 44% and 45% of all cases, respectively (**Fig. 6**).

Fig. 2. **(A) Number of months per year when dengue cases exceeded the long-term mean ; (B) Number of times the long-term mean was exceeded each month compared to average monthly rainfall, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**



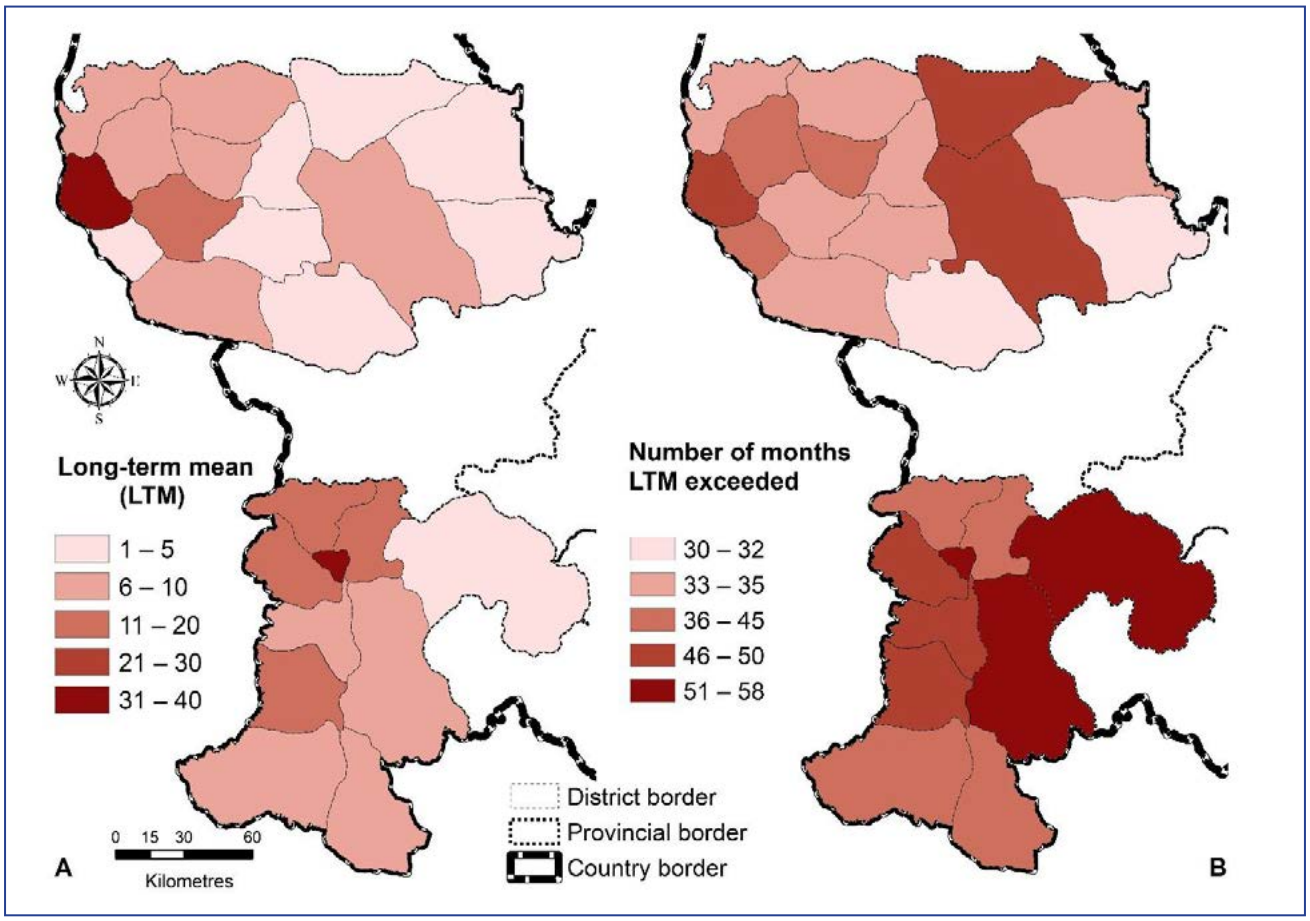
Nationality

A total of 218 cases of dengue were recorded among foreign nationals residing in Lao PDR. Of these, the highest numbers were seen in Chinese and Vietnamese citizens, primarily in those engaged in education, rice farming and trading activities (**Table 6**).

DISCUSSION

This study describes the long-term dengue epidemic profile for Champasak and Savannakhet, two provinces in southern Lao PDR. Surveillance data from the two provinces indicate a high burden of disease. Moreover,

Fig. 3. **(A) Long-term mean of dengue notifications per month, by district; (B) Number of months when the long-term mean was exceeded, by district, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**



especially high transmission seasons were observed in 2003, 2008, 2010, 2013 and 2019 in both of these two southern provinces, and across the country.

Over the study period, there has been a shift in the geographical distribution of cases in these two provinces. Dengue notification rates were higher in more districts during the 2013 and 2019 high transmission seasons compared with 2003, when dengue notifications were largely confined to the more densely populated districts of western Savannakhet and northern Champasak and the provincial capitals. In 2019, four districts in Savannakhet experienced notification rates in excess of 500 cases per 100 000 population, the highest recorded since the start of the study period in 2003. A similar pattern of increased emergence in new localities has also been reported by neighbouring countries.[7] Champasak and Savannakhet provinces are among the four most populated provinces in Lao PDR and have been experiencing extensive development due to agricultural intensification, river dam construction in forests and associated resettlement of workers and inhabitants in remote areas.[8] Previous work has also shown a correlation between high density of built-up areas and high levels of development and dengue vulnerability within Champasak and Savannakhet provinces during 2003–2019.[6]

The LTM method proved useful for identifying not only the length of dengue epidemics in each year, but also the months with the highest dengue activity and the most affected districts. While the LTM remained high in eastern Savannakhet and northern Champasak throughout the study period, districts in central and western Savannakhet exceeded their LTMs for more months of the year than the eastern districts. This signals a change in dengue case distributions that may be linked to climatic and land cover changes, specifically an increase in mean temperature and in the number of new settlements in previously remote, less developed areas.[6]

Table 3. **Prevailing dengue serotypes in Savannakhet and Champasak provinces and Lao PDR, 2003–2020**

Year	Serotype		Lao PDR[a]			
	Savannakhet[b]	Champasak	DENV-1 (%)	DENV-2 (%)	DENV-3 (%)	DENV-4 (%)
2003	DENV-1 DENV-2 DENV-4	–	–	–	–	–
2004	–	–	–	–	–	–
2005	DENV-1	–	–	–	–	–
2006	–	–	–	–	–	–
2007	DENV-1 DENV-4	–	–	–	–	–
2008	–	–	–	–	–	–
2009	DENV-1	–	–	–	–	–
2010	DENV-1 DENV-4	–	**38**	30	22	10
2011	–	–	**75**	12	13	0
2012	DENV-2 DENV-3	–	11	9	**80**	0
2013	DENV-1 DENV-2 DENV-3	DENV-2 DENV-3[9]	3	10	**87**	3
2014	–	–	16	17	17	**50**
2015	–	–	**82**	1	1	16
2016	DENV-4	–	11	2	3	**83**
2017	–	–	21	10	<1	**69**
2018	DENV-1 DENV-2 DENV-4	DENV-1 DENV-2 DENV-4[10]	–	–	–	–
2019	DENV-1 DENV-2	DENV-1[11]	–	–	–	–
2020	DENV-1 DENV-2 DENV-4	–	–	–	–	–

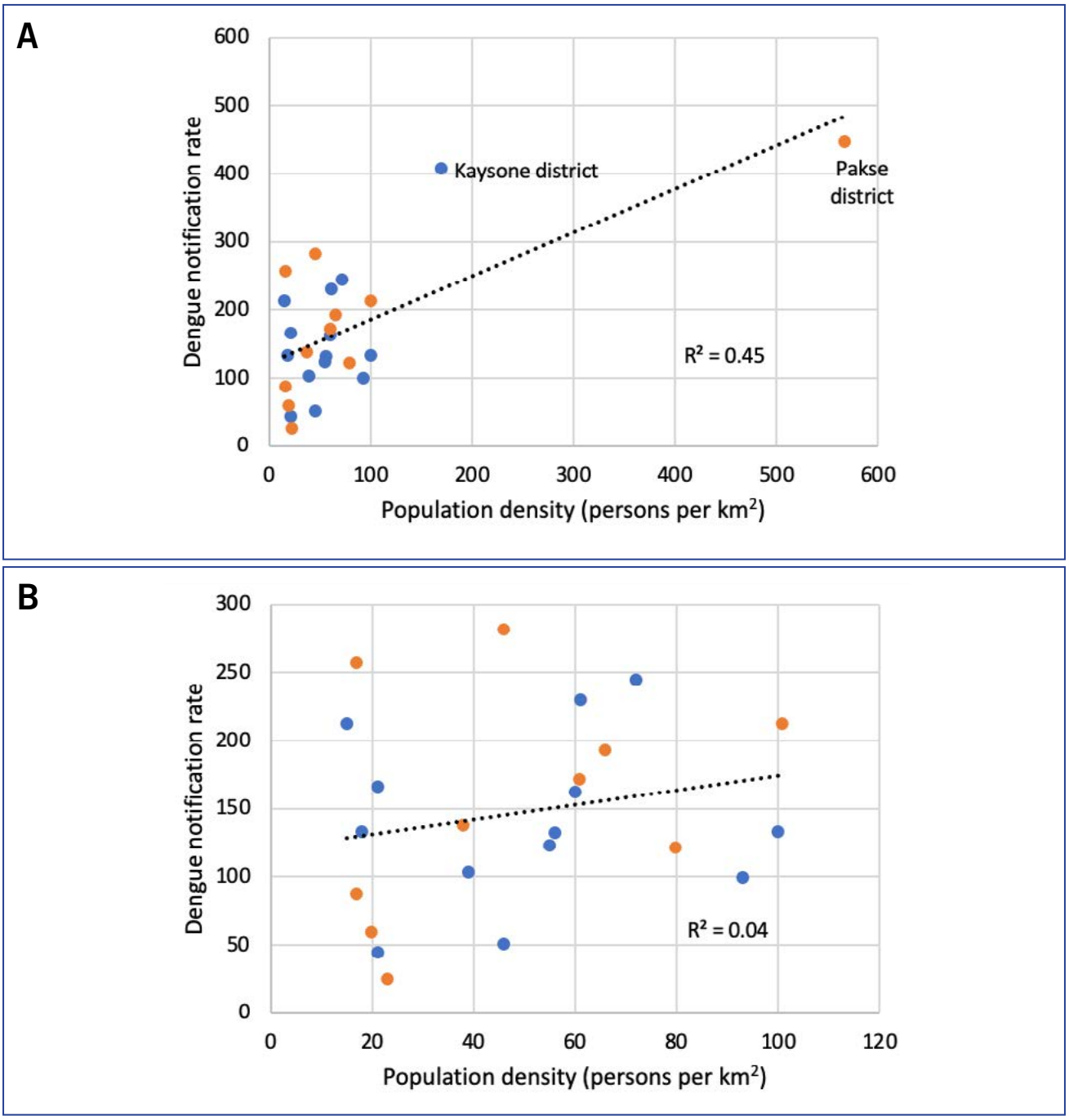
[a] Country-level serotype data are taken from the annual report of the National Center for Laboratory and Epidemiology for 2017 (unpublished). The prevailing serotype is shown in bold.

[b] Data are provided by the Savannakhet Health Department.

Dengue notification rates in both provinces tracked the rainy season, with the highest occurrence in June and July. The LTMs followed a similar pattern – higher monthly LTMs were typically observed for at least 3 consecutive months between May and October of each year. These seasonal and spatial patterns in dengue transmission were consistent with those reported in neighbouring south-east Asian countries.

Lao PDR has been described as a hyperendemic DENV country, and since the first outbreak in the country in 1979 (followed by the first major outbreak in 1983), all four serotypes have been co-circulating.[9–11] However, DENV-1 and DENV-2 have consistently been present throughout much of the study period, both across the country as a whole and in the two southern provinces in this study, while the occurrence of DENV-3 and DENV-4 has been more sporadic. Recent data from the Lao PDR arbovirus surveillance network suggest that since 2016, there has been a steady decrease in the proportion of cases due to DENV-4 (from 70% to 4% in 2020) and an increase in those caused by DENV-2 (from 7% to 74% in 2020).[10]

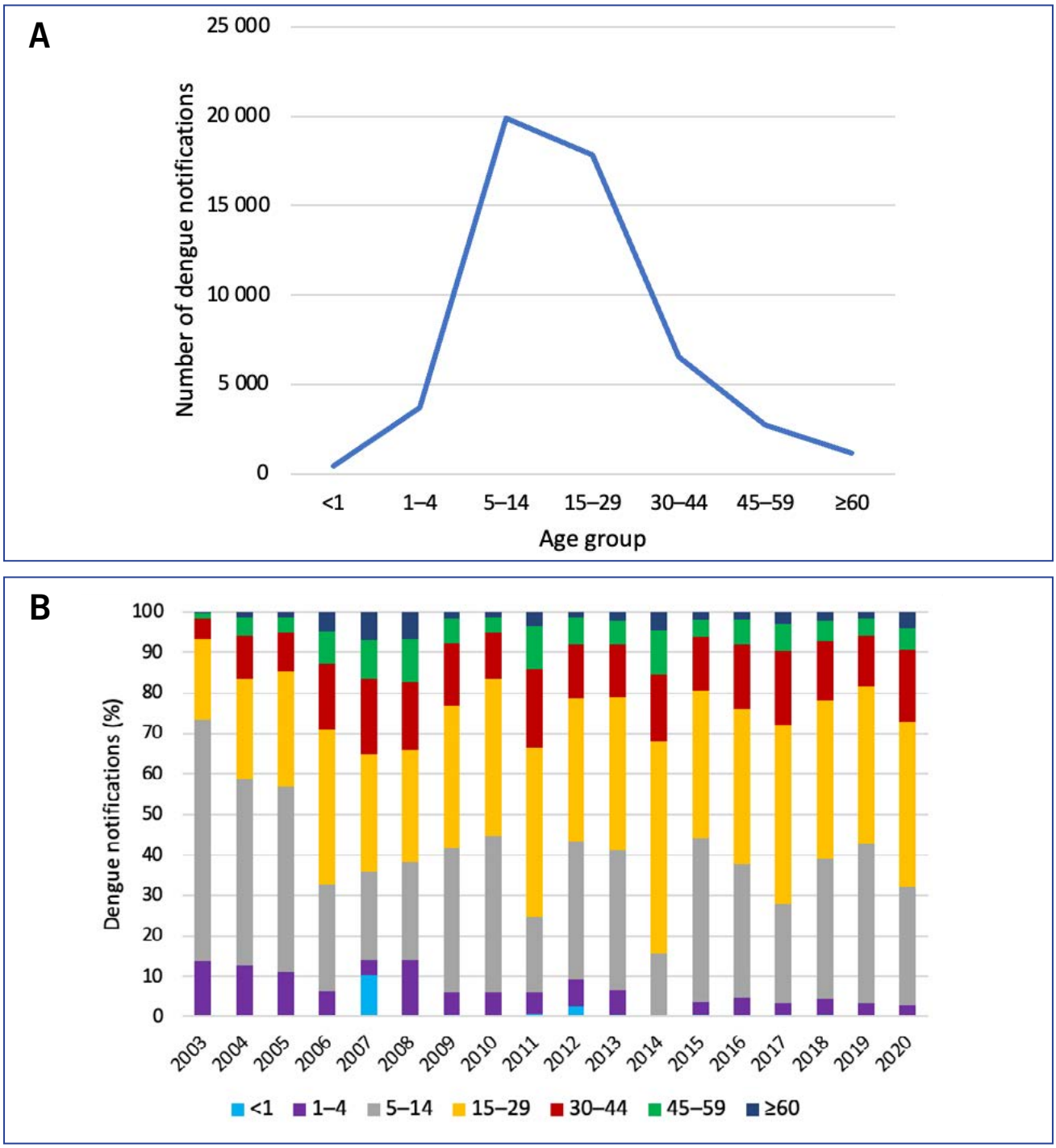
Fig. 4. **Correlation between population density and average annual dengue notification rate (per 100 000 population) in districts of Champasak (orange points) and Savannakhet (blue points) provinces, (A) including and (B) excluding provincial capitals, Lao PDR, 2003–2020**



Population density has been identified as an important driving factor for high dengue transmission. The highest dengue notification rates by far were observed in the densely populated provincial capitals in both southern provinces. Increasing urbanization and high population densities in cities have been associated with an elevated dengue risk with a high vector-to-host ratio.[1]

Dengue infections were disproportionately high among children and adolescents aged <15 years. However, there were signs that age-specific notification rates are beginning to shift to older age groups, as evidenced by the observed 20–30% increase in the number of cases in older adolescents and adults (≥15 years) since 2005 (**Fig. 5A**). Other south-east Asian countries have

Fig. 5. **(A) Total number of dengue notifications by age group; (B) Distribution of dengue notifications by age group and year, Lao PDR, 2003–2020**



reported falls in their dengue notification rates among those aged <15 years. The increase in notification rates in older adults (15–45 years) may be explained by the spread of dengue into areas with lower rates of immunity among the population. Changes in circulating dengue virus serotypes[12] may also have led to a rise in secondary infections that are considered important risk factors for severe clinical presentations.[4]

Dengue case rates among females and males in all age groups remain broadly similar, although we observed a slightly higher case rate in males aged 15–29 years.

Table 4. **Dengue notifications by case definition and age group, Champasak and Savannakhet provinces, Lao PDR, 2003–2020 (percentage of total)**

Dengue case definition (old classification/2009 classification)	Age group (years)						
	<1	1–4	5–14	15–29	30–44	45–59	≥60
Dengue fever/dengue without warning signs	93.6	87.3	79.0	90.1	92.7	94.8	95.5
Dengue haemorrhagic fever/dengue with warning signs	5.7	10.4	15.7	8.7	6.7	5.0	4.0
Dengue shock syndrome /severe dengue	0.6	2.3	5.3	1.1	0.7	0.2	0.5

Table 5. **Dengue cases and deaths by age group and sex, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**

Age group (years)	Dengue cases, n (%)		Dengue deaths, n (%)	
	Female	Male	Female	Male
<1	112 (0.2)	154 (0.3)	1 (0.89)	0 (0)
1–4	1751 (3.4)	1836 (3.6)	17 (0.97)	16 (0.87)
5–14	9726 (18.8)	10 072 (19.5)	67 (0.69)	57 (0.57)
15–29	8120 (15.7)	9528 (18.4)	11 (0.14)	12 (0.13)
30–44	3214 (6.2)	3294 (6.4)	4 (0.12)	2 (0.06)
45–59	1453 (2.8)	1304 (2.5)	1 (0.07)	0 (0)
≥60	632 (1.2)	479 (0.9)	1 (0.16)	0 (0)

Fig. 6. **Proportion of dengue notifications by occupation and year, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**

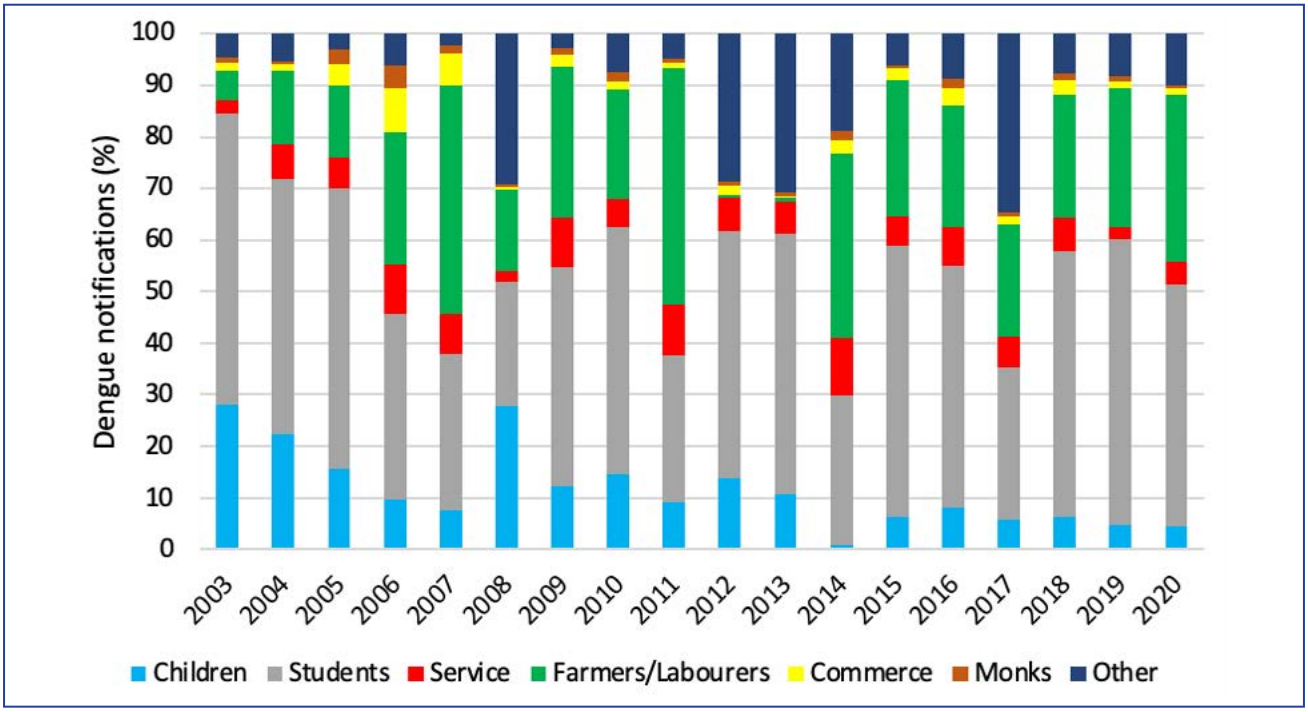


Table 6. **Number of dengue notifications among foreign nationals (N = 218), by nationality and occupation, Champasak and Savannakhet provinces, Lao PDR, 2003–2020**

Nationality	Occupation							
	All	Children	Students	Service	Farmers	Commerce	Monks	Other
All	218	12	21	3	40	110	3	29
Vietnamese	117	8	16	2	28	36	3	24
Chinese	97	3	5	0	10	74	0	5
Other	4	1	0	1	2	0	0	0

Similarly, dengue case data reported through national surveillance systems of other countries in the WHO South-East Asia and Western Pacific regions indicate that adult males aged >15 years are consistently at higher risk of infection than females.[13]

In this study, students and farmers were identified as being at higher risk of dengue infection compared with other occupational subgroups, a finding that is consistent with that of another study from Lao PDR, which also found that farmers were the second most affected occupational group.[14] Dengue vectors are most active during the daytime. The primary dengue vector, *Ae. aegypti*, is predominantly found indoors, which may account for increased exposure of children and students given that this group spends much of their day inside their homes or classrooms. Farmers may have greater exposure to the secondary vector, *Ae. albopictus*, which oviposits in tree holes and leaf axile.[14]

The data collected by provincial health departments inherently come with a few limitations: these include uncertainty in reporting, misdiagnosis and misreporting of symptomatic dengue, and absence of subclinical and asymptomatic infections. For confirmed dengue infections, the serotypes were rarely identified. Travel-related infections are also common in these provinces, but this information was not included in the data and not easy to trace.

In conclusion, this study has characterized the spatiotemporal trends in dengue transmission in southern Lao PDR. Since passive national surveillance data do not always include serotype and entomological information, it is recommended that detailed seroprevalence studies be conducted to further understand dengue epidemiology in Lao PDR. Such studies performed country-wide could help public health authorities develop improved action plans to implement vector control activities each year before the rainy season. As farmers and students under the age of 30 were the most affected groups, combined efforts by the education, agriculture and health ministries to make these groups more aware of the disease risks are recommended. Interventions could include awareness-raising and educational programmes on effective indoor dengue vector control and preventive measures delivered through seminars and medical camps in villages and educational institutions (primary to university level). These could build on the success of the training in epidemic control aimed at village health volunteers, village heads and community schoolteachers currently provided by the International Federation of Red Cross and Red Crescent Societies, which have helped to increase villagers' and communities' health preparedness and response. In addition, community-level initiatives to control the spread of dengue should be encouraged; such initiatives might include reducing use of water storage containers, promoting use of larvicides to prevent mosquito breeding, use of mosquito nets and repellents in homes and in agricultural fields and increasing awareness of the risks posed by the accumulation of waste near households.

Conflicts of interest

Sumaira Zafar is a PhD student at the Asian Institute of Technology under the DENCLIM project funded by the Research Council of Norway (grant number 281077). The other authors declare no conflicts of interest.

Ethics approval

Study protocols were approved by the Khon Kaen University Ethics Committee (reference no. HE611228, 2 August 2018 and HE631077, 24 March 2020) and the Regional Committees for Medical and Health Research Ethics in Norway (2018/1085/REK sør-øst C, 27 June 2018).

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Pulmonary tuberculosis and melioidosis coinfection in Brunei Darussalam: the importance of awareness and screening

Abdur Rahman Rubel,[a] Babu Ivan Mani,[a] Panduru Venkata Kishore[b] and Vui Heng Chong[a,b]

Correspondence to Abdur Rahman Rubel (email: abdur.rubel@gmail.com)

Both tuberculosis (TB) and melioidosis are endemic to certain parts of the world, including Brunei Darussalam, with TB being more widespread. Despite this, coinfection with TB and melioidosis is rarely encountered and reported. Although still uncommon, there has been an increase in the number of cases of this coinfection reported during the past 10 years, all of which have been in India and the World Health Organization's Western Pacific Region. We report a case of coinfection with pulmonary TB and melioidosis in a patient with poorly controlled diabetes mellitus. This 64-year-old man presented with symptoms and radiological features of pulmonary TB, confirmed by sputum smear, but sputum culture also yielded *Burkholderia pseudomallei*, the pathogen that causes melioidosis. Coinfection was detected due to our practice of routinely screening for other infections in patients suspected or confirmed to have pulmonary TB. This highlights the importance of awareness of melioidosis and the need to consider screening for infection, especially in endemic regions.

Tuberculosis (TB) is endemic to many underdeveloped and developing nations, while melioidosis is endemic only to certain tropical regions, in particular Thailand, northern Australia and south-east Asia.[1,2] Of these two infections, TB is by far more common and is encountered almost everywhere in the world. Melioidosis is less common but is now being reported in traditionally non-endemic countries due to increasing population movement.[3] Melioidosis is caused by *Burkholderia pseudomallei*, a Gram-negative, aerobic, saprophytic, non-fermenting bacillus commonly found in the soil in endemic regions, especially in irrigated agricultural fields and in surface water. The incidence of melioidosis increases during the wet season.[2] It is usually transmitted by inhalation; direct contact with infected rodents, food, soil, water or excreta; and inoculation from contaminated soil through abrasions or lesions in the skin.[2] The most common risk factors are occupational exposure, alcoholism and immunosuppressive conditions, such as diabetes mellitus (DM), renal disease and thalassaemia.[2] In Brunei Darussalam, the most commonly associated risk factors are DM, end-stage renal disease and thalassaemia.[4]

Melioidosis has a wide range of manifestations, including asymptomatic infection, but the most common is chronic pneumonia that mimics TB, as well as localized skin ulcers or abscesses, and fulminant septic shock with multiple abscesses in internal organs. Melioidosis has been reported to manifest up to decades after initial exposure.[2] TB and melioidosis share many similarities, from risk factors to varied manifestations that can pose a diagnostic challenge, especially in non-endemic countries where there is less awareness of melioidosis. Despite both TB and melioidosis being endemic in some countries, including Brunei Darussalam and other parts of the World Health Organization's Western Pacific Region, coinfection is uncommon. To date, there have been only 13 cases of coinfection reported in the literature, with most reported during the past 10 years, highlighting a recent increase and the importance

[a] Department of Medicine, Pengiran Muda Mahkota Pengiran Muda Haji Al-Muhtadee Billah Hospital, Tutong, Brunei Darussalam.
[b] Department of Medicine, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam.
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of awareness of these coinfections.[5–14] This report documents a case of coinfection with pulmonary TB (PTB) and melioidosis in a patient with poorly controlled DM in Brunei Darussalam.

CASE REPORT

A 64-year-old man with type II DM, hypertension and dyslipidaemia was admitted with a chronic cough of 3 months' duration that had recently worsened, becoming more productive with sputum. Sputum had been purulent and mixed with fresh blood for 1 week. He also had moderate weight loss of around 5 kg in 3 months. He had been an ex-smoker for more than 10 years and had no history of alcohol consumption. He had a long-standing history of poorly controlled DM (defined as glycated haemoglobin, or HbA1c, >8.5%) and was noncompliant with his medications. He had retired from office work 6 years previously and had never done any farming or agricultural work. He had no history of TB or contact with patients with PTB.

On examination, he was afebrile (temperature, 35.6 °C) and was not in any distress. He had mild pallor but no cyanosis, clubbing or lymphadenopathy. There were coarse crepitations and mild rhonchi heard over the left lung fields. Laboratory investigation showed normal haemoglobin (13.1 g/dL, normal range [NR]: 13.5–17.9), liver function (including serum albumin) and renal function tests, total leukocyte count (67.4% neutrophils, 11.6% monocytes, 17.9% lymphocytes, 2.3% eosinophils), and an elevated erythrocyte sedimentation rate (66 mm/hour, NR: 1–20) and blood glucose (21.2 mmol/L, NR: 4–7.7). Serum HbA1c was very high at 15% (NR: 6.5%, preferred <7.2% for DM). Chest X-ray (CXR) showed extensive interstitial opacities as well as cavities (**Fig. 1**). Ultrasonography of the abdomen and pelvis was normal.

PTB was suspected, and three consecutive morning sputum samples were sent for acid-fast bacilli (AFB) smear and culture, as well as bacterial culture, as part of our routine protocol. All three specimens were positive for AFB on Ziehl–Neelsen staining. A line-probe assay (GenoType MTBDRplus version 2, Hain Lifescience, Nehren, Germany) did not detect resistance to isoniazid or rifampicin. In addition to *Mycobacterium tuberculosis*, sputum microbial culture also isolated *B. pseudomallei*. Identification was done with standard techniques using Gram's staining and biochemical reactions (i.e. auramine stain and antibiotic susceptibility testing). Antibiotic susceptibility testing was performed and interpreted using VITEK 2 and API 20NE (bioMérieux, Marcy-l'Étoile, France), and testing showed universal resistance to aminoglycosides. Blood culture was negative for *B. pseudomallei*. Sputum culture for mycobacteria confirmed pansensitive *M. tuberculosis*. Screening tests for HIV and hepatitis B and C were negative. Computed tomography (CT) imaging of the thorax, abdomen and pelvis, to assess for melioidosis involvement in other organs, showed only consolidation with volume loss in the left upper pulmonary lobe and the tree-in-bud sign (**Fig. 2**). There was no intra-abdominal organ involvement.

The patient was treated for coinfection with melioidosis and PTB. He was started on an intensive phase of intravenous ceftazidime (2 mg three times daily for 3 weeks), followed by maintenance therapy with a double dose of co-trimoxazole (sulfamethoxazole + trimethoprim, 800/160 mg twice daily for 10 weeks). He was also started on standard anti-TB therapy: an intensive phase with rifampicin (600 mg daily), isoniazid (300 mg daily), pyrazinamide (1.5 g daily) and ethambutol (900 mg daily) for 3 months and streptomycin (1 g daily) for 1 month, followed by a continuation phase with rifampicin (600 mg daily), isoniazid (300 mg daily) and ethambutol (900 mg daily) for 6 months. Pyridoxine 25 mg once daily was also given. Weekly liver profile monitoring for 1 month showed no hepatotoxic effects. While the patient was hospitalized, hyperglycaemia was managed with dietary adjustments and insulin therapy, and he was later converted to using oral hypoglycaemic agents. He became symptom-free within 7 days of starting treatment. He was discharged after three consecutive negative sputum AFB tests, and he continued the stipulated period of directly observed therapy for PTB and melioidosis treatment. A repeat CXR 3 months after the first showed marked improvement (**Fig. 3**). He completed 9 months of treatment for PTB and 3 months of melioidosis treatment, and was completely recovered at the end of therapy.

DISCUSSION

Both PTB and melioidosis are common in Brunei Darussalam.[4,15] TB is a notifiable disease in Brunei Darussalam, whereas melioidosis is not. Annually, an average of 227 TB cases were recorded in Brunei Darussalam

Fig. 1. **Initial chest X-ray of a 64-year-old man showing extensive changes in the left lung field, including small cavities**

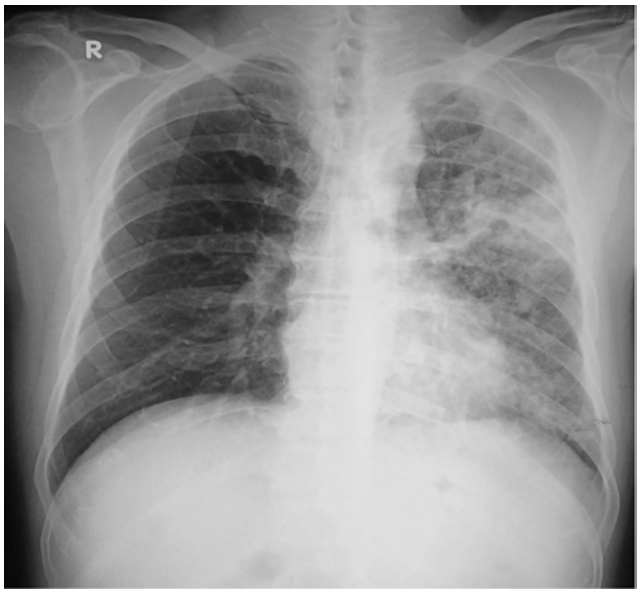
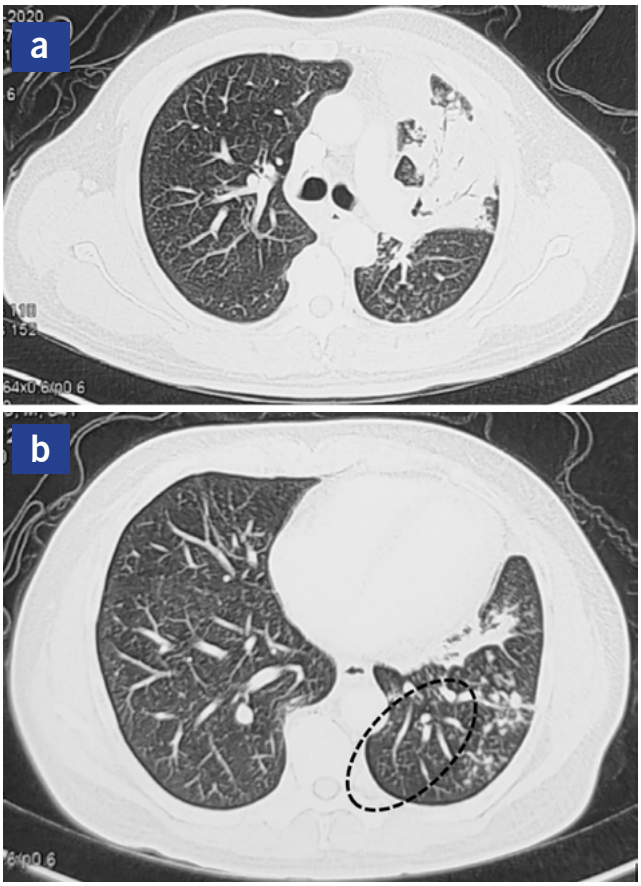


Fig. 2. **Axial computed tomography of a 64-year-old man showing (a) consolidation of the left upper lobe with volume loss and (b) the pulmonary tree-in-bud sign associated with tuberculosis affecting the peripheral pulmonary parenchyma (dotted oval)**

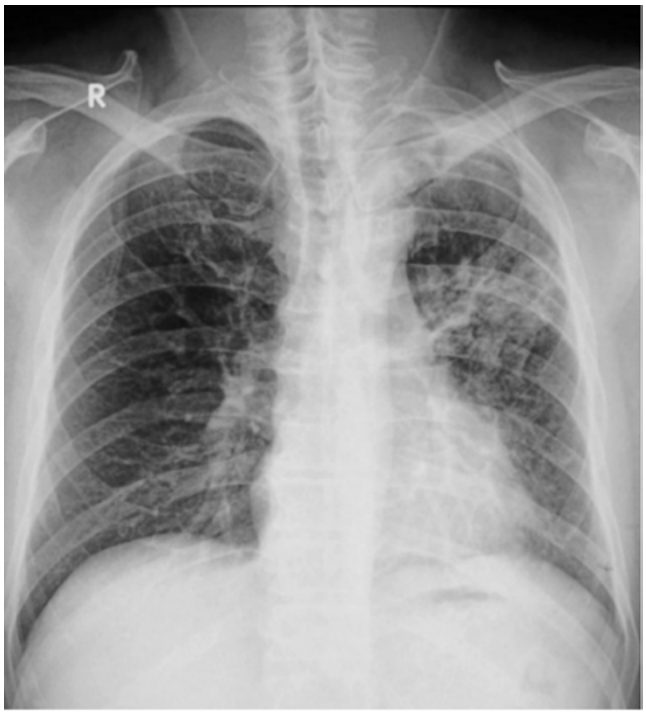


between 2013 and 2018, for a rate of 54/100 000 population per year.[15] The incidence of melioidosis has been increasing in Brunei Darussalam from 2.9/100 000 in 1993 to 16.3/100 000 in 2018.[4] Our case represents the second case of coinfection with TB and melioidosis reported in Brunei Darussalam. The first case, reported in 2020, was in a 39-year-old woman with poorly controlled DM and manifested in a neck abscess.[13] In that case, melioidosis was initially diagnosed and only after surgical drainage and histological examination of the resected tissue was TB diagnosed. As in other countries, poorly controlled DM is the most important risk factor for melioidosis in Brunei Darussalam.[4] Similarly, DM is an important risk factor for TB, and one third of our patients with TB already have DM or are diagnosed within 6 months of their TB diagnosis.[15]

A literature search identified 10 reports of 13 cases of coinfection with TB and melioidosis (**Table 1**).[5–14] All but one occurred in males; their ages ranged from 39 to 64 years, and DM was the most common risk factor. Not all patients reported environmental or occupational exposure. Pulmonary coinfection was the most common manifestation, followed by neck abscess. All patients were successfully treated. The patient in the case reported by Kim et al.[10] was initially treated for PTB, but symptoms and pulmonary changes persisted. Pulmonary melioidosis was diagnosed only after surgical resection. In that case, the interval between the diagnosis of PTB and of melioidosis was 1 year. Whether pulmonary melioidosis was already present at the time of PTB diagnosis is unknown; the patient's only risk factors were working as a welder and travelling to the Philippines, another country endemic for both TB and melioidosis.

One study from India reported on melioidosis during an 8-year period (2007–2015): only two cases of coinfection occurred in 65 cases of pulmonary melioidosis, for a prevalence of 3.1%.[11] Another study from India looked at 301 patients with pyrexia of unknown origin and identified three cases of coinfection, for a prevalence of 1%.[9] A mathematical modelling study from Thailand, where TB and melioidosis are endemic, estimated a very low coinfection rate of 0.0085/100 000 population compared with 4.96/100 000 for melioidosis and 171/100 000 for TB.[16]

Fig. 3. **Repeat chest X-ray of a 64-year-old man done almost 3 months after the first X-ray, showing improvement**



As with any infectious disease, awareness is important. Although melioidosis is increasingly reported in non-endemic regions, awareness is mainly limited to endemic regions.[2] Despite the availability of treatment, the fulminant form of melioidosis is associated with 40% mortality.[2] In contrast, TB is well recognized and awareness is almost universal.[1] Similar to melioidosis, manifestations of TB are varied and any organ can be affected. TB is still associated with significant morbidity and remains an important cause of mortality, especially if left untreated or if treatment is delayed.

Diagnosing PTB is often straightforward, but extrapulmonary TB can be extremely difficult, especially if laboratory confirmation is needed because laboratory investigations may overlap for the two types of TB. Chest imaging such as CXR can aid in diagnosis because for PTB it may show upper lobe changes and manifestations such as fibrosis and bronchiectasis. CT imaging can also provide useful clues: active PTB is often associated with the tree-in-bud sign,[17] as seen in our patient. However, this sign can also be seen in other pulmonary pathologies. Other changes include lobular consolidation, cavitation

Table 1. **Summary of 14 reported cases of coinfection with tuberculosis and melioidosis**

Author	Year	Country	No. of cases	Age/sex	Risk factors	Occupation	Manifestation		Outcome
							TB	Melioidosis	
Azali et al.[5]	2007	Malaysia	1	49/M	NA	NA	Hepatic (histology showing acid-fast bacilli)	Liver abscess (pus)	Survived
Shenoy et al.[6]	2009	India	1	40/M	Diabetes	Agriculture (paddy field)	Neck abscess	Neck abscess	Survived
Shetty et al.[7]	2010	India	1	40/M	Diabetes	Agriculture	Pulmonary (diagnosed by bronchoalveolar lavage)	Pulmonary (sputum)	Survived
Sulaiman et al.[8]	2013	Malaysia	1	54/M	Diabetes	Palm oil plantation worker	Cervical abscess	Cervical abscess	Survived
Sankar et al.[9]	2014	India	3	NA	NA	NA	NA	NA	NA
Kim et al.[10]	2015	Republic of Korea	1	60/M	None	Welder	Pulmonary	Pulmonary	Survived
Patra et al.[11]	2017	India	2	NA	NA	NA	Pulmonary	Pulmonary	NA
San Martin et al.[12]	2018	Philippines	1	59/M	None	NA	Pulmonary	Pulmonary and cutaneous (soft tissue)	Survived
Yap et al.[13]	2020	Brunei Darussalam	1	39/F	Diabetes (newly diagnosed)	Clerk in agriculture department	Neck	Neck	Survived
Tan[14]	2020	Singapore	1	64/M	Alcohol	Cable joiner	Disseminated: gastrointestinal, pulmonary, splenic	Splenic	Survived
Current report	2022	Brunei Darussalam	1	64/M	Diabetes	Retired office worker	Pulmonary	Pulmonary	Survived

F: female; M: male; NA: not available; TB: tuberculosis.

and bronchial wall thickening.[17] Melioidosis, however, is not associated with any typical chest manifestations, and manifestations can range from minimal changes to consolidation of the lung resembling PTB as well as community-acquired pneumonia.[18] The involvement of multiple sites, including the lung, liver and spleen, is common; for example, the honeycomb sign in the liver is typical of melioidosis[18] and can be detected by CT imaging. In cases of coinfection, the typical features of each infection may not be present, and often laboratory confirmation is required.

Given the increasing prevalence of DM, it is likely that TB, melioidosis and coinfection with both may also increase, as is evident by the rising number of reported cases.[4–13] Apart from the cases of coinfection documented in India, the remainder were from the Western Pacific Region. Therefore, in endemic countries, it is important to screen for coinfection with TB and melioidosis in patients with risk factors. In our setting, patients diagnosed with TB are routinely screened for DM or their level of control of DM is assessed. However, we do not routinely screen patients with DM for PTB unless they have symptoms or findings that are suggestive of TB. In non-endemic countries, awareness of melioidosis is important, and screening should be considered, especially for patients with relevant risk factors, such as DM or a history of travel to melioidosis-endemic countries. This is particularly important because both infections are treatable.

In conclusion, coinfection with TB and melioidosis is rarely encountered despite some countries being endemic for both. Most of the reported cases have occurred during the past decade, mostly in India and increasingly in the Western Pacific Region. Coinfection occurs more often in males, and DM is the most common risk factor. TB and melioidosis are treatable but require early diagnosis. To date, the outcomes of patients with this coinfection have been favourable, but these results are based on a small number of cases. As the number of reported cases increases, awareness of melioidosis becomes more important, and screening for coinfection should be considered, especially in patients with risk factors. Further studies exploring the outcomes of patients with coinfection will be needed.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The patient gave his written consent for the publication of this case report. All identifying information has been removed.

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None.

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Outbreak of *Ralstonia* bacteraemia among chronic kidney disease patients in a haemodialysis unit in the Philippines

Denmarc R Aranas,[a] Bernard A Demot[a] and Thea Pamela T Cajulao[a,b]

Correspondence to Denmarc R Aranas (email: aranasdenmarc@gmail.com)

Ralstonia insidiosa is an opportunistic pathogen considered an emerging problem among clinically vulnerable populations such as those with chronic kidney disease. This study presents three cases of *Ralstonia* bacteraemia among chronic kidney disease patients in a haemodialysis unit in Baguio City, the Philippines. Case 1 was an elderly male who experienced chills during two concurrent dialysis sessions. Case 2 was a young female who also experienced chills and dizziness during a dialysis session; as this was thought to be related to hypotension, she was admitted. Case 3 was an elderly female with known hypertension and diabetes who had been newly diagnosed with chronic kidney disease; she was brought to the emergency room hypotensive, dyspnoeic and disoriented with deranged laboratory parameters and was admitted to the intensive care unit. All three cases had blood cultures positive for *R. insidiosa* with an attack rate of 1.67%. Drug and device tracing were conducted and environmental samples collected to identify the source of infection. A sample from the faucet of the reprocessing machine in the haemodialysis unit that was positive for *Ralstonia spp*. was the source of the outbreak. Control measures were implemented and the haemodialysis unit was thoroughly cleaned. No further cases were reported, with active surveillance continuing until January 2022. Taken with previously published outbreaks, these findings suggest that medical products and devices can be contaminated with *Ralstonia spp*. and cause illness. Early identification of cases and the source of infection is required to prevent large outbreaks in this vulnerable population.

Nosocomial infection among immunocompromised patients is an emerging problem commonly encountered with multidrug-resistant Gram-negative bacteria. *Ralstonia spp*. are waterborne Gram-negative bacteria, ubiquitous opportunistic environmental pathogens characterized as strong biofilm producers that are resistant to most antimicrobials. Notable strains are *R. pickettii, R. mannitolilytica* and *R. insidiosa*.[1]

R. insidiosa has recently had increasing clinical relevance,[2] especially in hospitals, because it can survive in different ultra- or high-purification water systems used for industrial and laboratory methods.[3,4] It can contaminate purified or distilled water used for medicinal procedures or products, and can survive in low-nutrient states and be resistant to commonly used antimicrobial agents such as chlorhexidine.[5] The emergence of *R. insidiosa* as a causative agent of nosocomial infections was reported among immunocompromised individuals in the Czech Republic, where it led to bacteraemia among eight haemodialysis patients owing to contaminated haemodialysis solutions.[6,7] A recent report from a Chinese tertiary hospital has noted the emergence of multidrug-resistant *R. insidiosa* in clinical isolates.[8]

In January 2021, the Department of Internal Medicine – Infectious Disease and Infection Prevention and Control Committee (IPCC) in the Philippines declared an outbreak in a haemodialysis unit in Baguio City when three patients were identified with *Ralstonia* bacteraemia. Haemodialysis sessions were suspended until the investigation was completed. The objectives of this study were to describe the three cases of *Ralstonia* bacteraemia and to report the identification process and control measures implemented for this outbreak of *R. insidiosa* in a haemodialysis unit in Baguio City.

CASE SERIES

In this study, a confirmed case was defined as a patient who underwent haemodialysis and experienced a temperature of more than 38.5 °C or chills during or after

[a] Department of Internal Medicine, Baguio General Hospital and Medical Center, Baguio City, Philippines.
[b] Infection Prevention and Control Committee, Baguio General Hospital and Medical Center, Baguio City, Philippines.
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the session with a positive blood culture for *R. insidiosa* from December 2020. Clinical histories and laboratory examinations were reviewed for all reported patients. Active surveillance, whereby symptomatic patients from the haemodialysis unit had specimens collected for blood culture and sensitivity testing, was initiated, and continued until January 2022. All specimens underwent sensitivity testing for a range of antibiotics.

Three patients from the haemodialysis unit fit the case definition (**Table 1**). The haemodialysis centre has 30 units catering to 180 dialysis patients; thus, the attack rate was 1.67%.

Case 1

Case 1 was a 70-year-old male with known stage 5 chronic kidney disease secondary to hypertensive nephrosclerosis. He was on maintenance haemodialysis twice a week at the haemodialysis unit. During a haemodialysis session on 9 December 2020, the patient experienced chills with no associated chest pain or fever. A specimen was collected for blood culture and sensitivity testing before discharge from the haemodialysis unit. Three days later, the patient underwent his next regular haemodialysis with recurrence of chills. After haemodialysis, the patient was sent to the emergency room. He was awake, comfortable, not in distress and had stable vital signs. The patient has an intact right internal jugular catheter. He was sent home and advised to continue maintenance medications and haemodialysis. The blood culture revealed growth of *R. insidiosa*. He was prescribed cotrimoxazole 800/160 one tablet daily for 7 days for the bacteraemia. The patient recovered from the bacteraemia and was discharged.

Case 2

Case 2 was a 32-year-old female with known stage 5 chronic kidney disease secondary to chronic glomerulonephritis. She was on haemodialysis twice a week. A few hours before admission to the haemodialysis unit on 17 December 2020, she experienced chills, dizziness and body weakness, with hypotension at 80/60 mmHg. A 500 mL fast drip of normal saline solution was given and haemodialysis continued. As the chills and body weakness persisted, the haemodialysis was terminated and the patient was transferred to the emergency room. She was diagnosed with sepsis and admitted to the isolation ward. Her chest tube was removed and the tip sent for culture. Blood samples from two sites were submitted for culture and antibody sensitivity testing. The chest tube tip culture was positive for *Enterococcus faecalis* and the blood culture was positive for bacteraemia with *R. insidiosa*. Cefepime 500 mg intravenous once daily for 7 days was given for the *Ralstonia* bacteraemia. The patient recovered from the bacteraemia and was discharged.

Case 3

Case 3 was a 69-year-old female with known hypertension and diabetes mellitus. She had a 1-month history of bipedal oedema with decreasing urine output. She reported shortness of breath and progressive bipedal oedema in November 2020. She attended a different hospital where initial tests detected elevated creatinine, after which she was admitted and managed as a newly diagnosed chronic kidney disease patient secondary to hypertensive nephrosclerosis versus diabetic nephropathy. On 20 December 2020, the patient had bradycardia and hypotension at 80/50 mmHg and was given a dopamine drip. She was referred to our institution for haemodialysis the next day.

The patient arrived at the emergency room with symptoms of drowsiness, disorientation and episodes of desaturation at 79% when on room air, and was afebrile. She had anicteric sclera, slightly pale palpebral conjunctiva and positive neck vein engorgement. Her chest findings had crackles in the middle and basal lobes. The patient had bradycardia with irregular rhythm and no murmurs. Extremities had pitting bipedal oedema, grade 3.

The patient was assessed as having acute respiratory failure secondary to encephalopathy, which had resulted from chronic kidney disease, newly diagnosed, and itself the result of hypertensive nephrosclerosis versus diabetic nephropathy, complicated urinary tract infection, pulmonary congestion, metabolic acidosis, multiple electrolyte imbalance and anaemia; uncontrolled stage 2 hypertension; diabetes mellitus type 2, non-obese, non-insulin requiring; and suspected coronavirus disease (COVID-19). The patient was admitted to the intensive care unit for close monitoring and further management, and was then initiated on haemodialysis. A complete blood count revealed increased white blood cells with neutrophilic predominance. Blood culture detected the

Table 1. **Clinical characteristics of three cases of *Ralstonia* bacteraemia detected among chronic kidney disease patients at a single institution in Baguio City, the Philippines, 2020**

Characteristics	Case 1	Case 2	Case 3
Onset date	9 December	17 December	20 December
Age/Sex	70/Male	32/Female	62/Female
Comorbidities	Chronic kidney disease, hypertension	Chronic kidney disease, hypertension	Chronic kidney disease, hypertension, diabetes mellitus
Haemodialysis access	Right internal jugular catheter	Right internal jugular catheter	Right internal jugular catheter
Time on haemodialysis	1 year	1 year	2 months
Presenting symptoms	Chills	Chills, hypotension	Disoriented, hypotension, fever
Treatment received for bacteraemia	Co-trimoxazole 800/160 1 tablet once daily for 7 days	Cefepime 500 mg intravenous once daily for 7 days	Co-trimoxazole 800/160 1 tablet once daily for 7 days
Outcome	Discharged	Discharged	Discharged

growth of *R. insidiosa*. Co-trimoxazole 800/160 one tablet daily for 7 days was given for the bacteraemia. The patient recovered from the bacteraemia and was discharged.

Antibiotic susceptibility testing

Antibiograms of cases 1 and 2 were both resistant to amikacin and gentamicin with sensitivity to most of the other antibiotics tested. Case 2 was also resistant to piperacillin-tazobactam. Case 3 was sensitive or had intermediate results for all antibiotics (**Table 2**).

INVESTIGATION AND CONTROL MEASURES

A review of all drugs and devices used for each case from 15 days before the onset of symptoms until the confirmation of *Ralstonia* bacteraemia was conducted. On 10–15 January 2021, environmental samples were collected from 44 sites throughout the haemodialysis unit, including reprocessing tubing, faucets, suction tubing, suction containers, water sources, venous or arterial site coupling machines and bleach source machines. Samples were also collected from supplies, disinfectants, working areas and devices. All samples were cultured by the hospital's Department of Pathology for identification to the genus level only. Sensitivity testing was not conducted as per the hospital protocol for environmental samples.

Of the 44 collected samples, 25 were positive for a range of organisms, including: *Ralstonia spp., Aeromonas spp., Pseudomonas aeruginosa, Rhizobium radiobacter, Bacillus spp., Sphingomonas paucimobilis, Pseudomonas putida, Pseudomonas stutzeri, Acinetobacter baumannii, Delftia acidovorans, Serratia plymuthica, Aeromonas hydrophila, Aeromonas punctata, Klebsiella oxytoca*, coagulase-negative *staphylococci, Staphylococcus epidermidis, Staphylococcus haemolyticus* and *Leclercia adecarboxylata* (**Table 3**). The faucet of the reprocessing machine was the only site that was positive for *Ralstonia* species.

Standard and contact infection, prevention and control precautions and disinfection of equipment and the environment were implemented in the haemodialysis unit. The unit was monitored for effectiveness of these preventive measures with follow-up environmental swabs taken to ensure elimination of the source of infection. The wide range of organisms found in the haemodialysis unit indicates the need for maintaining a thorough general cleaning and regular disinfection protocol to prevent opportunistic infections. Upon the results of the environmental testing, thorough disinfection and general cleaning of the haemodialysis unit was conducted.

DISCUSSION

Three cases of *Ralstonia insidiosa* infection were detected within the haemodialysis unit and were linked to a contaminated faucet in the haemodialysis reprocessing machine. Upon detection of these cases, haemodialysis sessions were suspended and an investigation commenced. Environmental evidence determined the source of infection, after which the faucet of the haemodialysis

Table 2. **Antibiogram of *R. insidiosa* isolates in blood cultures in the three clinical cases of *Ralstonia* bacteraemia detected among chronic kidney disease patients at a single institution in Baguio City, the Philippines, 2020**

Antimicrobial	Case 1		Case 2		Case 3	
	MIC (μg/mL)	Interpretation	MIC (μg/mL)	Interpretation	MIC (μg/mL)	Interpretation
Amikacin	≥64	R	≥64	R	8	S
Cefepime	2	S	4	S	≤1	S
Ceftazidime	16	I	16	I	≤1	S
Ciprofloxacin	≤0.25	S	≤0.25	S	≤0.25	S
Gentamicin	≥16	R	≥16	R	8	I
Imipenem	2	S	2	S	2	S
Meropenem	4	S	4	S	2	S
Piperacillin/Tazobactam	64	I	≥128	R	64	I
Trimethoprim/Sulfamethoxazole	≤20	S	≤20	S	≤20	S

I: intermediate; MIC: minimum inhibitory concentration; R: resistant; S: sensitive.

Table 3. **Environmental samples from a haemodialysis unit where *Ralstonia* bacteraemia was detected among chronic kidney disease patients by site and results at a single institution in Baguio City, the Philippines, 10–15 January 2021**

Sites	Growth
1. Faucet, reprocessing machine	*Ralstonia* spp.
2. Reprocessing tubing, station 2	*Aeromonas* spp.
3. Reprocessing tubing, hep c	*Pseudomonas aeruginosa*
4. Reprocessing tubing, hep b	No growth after 48 hours of incubation
5. Water processing machine knobs	*Rhizobium radiobacter*
6. Point of use	No growth after 48 hours of incubation
7. Product tank	No growth after 48 hours of incubation
8. Acid mixer faucet	No growth after 48 hours of incubation
9. Bubbler, station 3	*Bacillus* spp.
10. Oxygen port, station 20	*Sphingomonas paucimobilis*
11. Oxygen port, station 18	No growth after 48 hours of incubation
12. Panasonic refrigerator	*Bacillus* spp.
13. Suction tubing 1	No growth after 48 hours of incubation
14. Suction tubing 2	No growth after 48 hours of incubation
15. Suction container 1	*Pseudomonas putida*
16. Suction container 2	No growth after 48 hours of incubation
17. Suction container 3	No growth after 48 hours of incubation
18. Venous site coupling, machine 30	*Pseudomonas stutzeri*
19. Arterial site coupling, machine 30	*Acinetobacter baumannii*
20. Water source, machine 30	No growth after 48 hours of incubation
21. Citro clean, machine 30	No growth after 48 hours of incubation
22. Bleach source, machine 30	No growth after 48 hours of incubation
23. Chair, machine 30	*Staphylococcus haemolyticus*
24. Venous site coupling, machine 13	No growth after 48 hours of incubation
25. Arterial site coupling, machine 13	No growth after 48 hours of incubation

Sites	Growth
26. Water source, machine 13	*Delftia acidovorans*
27. Bleach source, machine 13	No growth after 48 hours of incubation
28. Citro clean, machine 13	No growth after 48 hours of incubation
29. Oxygen tank, station 4	No growth after 48 hours of incubation
30. E-cart supply box	No growth after 48 hours of incubation
31. Oxygen port, station 20	No growth after 48 hours of incubation
32. Water source, pantry	*Serratia plymuthica*
33. Pantry sink, faucet	*Aeromonas, hydrophila; Aeromonas punctata; Klebsiella oxytoca*
34. Water dispenser	*Bacillus spp.*
35. Locker handles	*Staphylococcus condimenti*
36. Telephone	*Pseudomonas stutzeri*
37. Keyboard and mouse, station 2	Coagulase-negative staphylococci
38. Keyboard and mouse, station 1	Coagulase-negative staphylococci
39. Medicine table drawer handle	*Staphylococcus epidermidis*
40. Medicine preparation table	*Bacillus spp.*
41. Main door handle	*Staphylococcus haemolyticus*
42. Dialysis stretcher	*Pseudomonas stutzeri*
43. Weight log	*Leclercia adecarboxylata*
44. Working area	*Pseudomonas stutzeri*

reprocessing machine was appropriately disinfected and cleaning of the haemodialysis unit was initiated. No further cases have been reported, with active surveillance continuing until January 2022. Several other outbreaks have been reported involving contaminated haemodialysis water as the source of infection.[10,11]

The low attack rate of 1.67% suggests that the three cases were more vulnerable to infection; however, most patients who require dialysis have similar disease profiles with additional comorbidities and are of older age. The finding that cases had the same access site of the internal jugular haemodialysis catheter does not contribute to increased vulnerability. Right-sided catheters do not relate to increased catheter-related dysfunction and infection. It is therefore possible that they had a greater chance of exposure to the source of infection.[12]

Treatment for the three cases in this study was 7 days of cefepime and co-trimoxazole only, given according to the sensitivity of the isolates. In other published outbreaks, most *Ralstonia* infections are treated with ciprofloxacin, amikacin piperacillin-tazobactam, meropenem or a combination of aminoglycosides and cephalosporins with a good response.[8–10] There are no current standard recommendations for drugs or duration of treatment of *Ralstonia* bacteraemia. In a report from the Czech Republic, eight cases of central venous catheter infections by *Ralstonia insidiosa* were observed; all isolates from cases had antibiotic sensitivities to beta-lactams and fluoroquinolones and were resistant to aminoglycosides.[9] Two isolates from this study had similar antibiotic sensitivities to fluoroquinolones, sulfonamide and carbapenems and resistance to aminoglycosides. One case's isolate had antibiotic sensitivity to almost all drug classes with no resistance.

In conclusion, three patients with chronic kidney disease who required haemodialysis developed bacteraemia with *R. insidiosa*. All three cases had good clinical outcomes after identification of the organism and specific antibiotic treatment. The source of the contamination was identified through environmental testing of possible sites within the haemodialysis unit and was determined to be the faucet of the haemodialysis reprocessing machine. Taken with previously published outbreaks of *Ralstonia spp.*, these findings suggest that medical products and devices can be contaminated with these species and should be suspected when cases are detected. Early identification of these cases and the source of infection is required to prevent large outbreaks and to ensure protection of vulnerable populations such as immunosuppressed patients with end-stage renal disease on haemodialysis.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Ethics approval was not required for the study because it was observational and anonymized case data were sourced from hospital medical records.

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COVID-19 symptom duration: associations with age, severity and vaccination status in Brunei Darussalam, 2021

Shi Ying Tan,[a,b] Shyh Poh Teo,[b] Muhd Syafiq Abdullah,[a-c] Pui Lin Chong,[a,b] Rosmonaliza Asli,[a,b] Babu Ivan Mani,[a] Natalie Riamiza Momin,[a,b] Adrian Chin Ann Lim,[a] Noor Affizan Rahman,[a] Chee Fui Chong[a] and Vui Heng Chong[a,b,c]

Correspondence to Shyh Poh Teo (email: shyhpoh.teo@moh.gov.bn)

Objective: This retrospective, cross-sectional, observational study assessed the duration of coronavirus disease 2019 (COVID-19) symptoms during the second wave in Brunei Darussalam.

Methods: Data from COVID-19 cases admitted to the National Isolation Centre during 7–30 August 2021 were included in the study. Symptom onset and daily symptom assessments were entered into a database during hospitalization and disease was categorized by severity. The time between symptom onset and hospital admission, the duration of symptoms and length of hospitalization were assessed separately by age group, disease severity and vaccination status using one-way analysis of variance with Bonferroni post hoc corrections.

Results: Data from 548 cases were included in the study: 55.7% (305) of cases were male, and cases had a mean age of 33.7 years. Overall, 81.3% (446) reported symptoms at admission (mean number of symptoms and standard deviation: 2.8 ± 1.6), with cough (59.1%; 324), fever (38.9%; 213) and sore throat (18.4%; 101) being the most common. Being older, having more severe disease and being unvaccinated were significantly associated with the time between symptom onset and hospital admission, symptom duration and length of hospitalization.

Discussion: Knowing which factors predict the duration of COVID-19 symptoms can help in planning management strategies, such as the duration of isolation, predict the length of hospitalization and treatment, and provide more accurate counselling to patients regarding their illness.

The coronavirus disease 2019 (COVID-19) pandemic, caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues, bringing significant morbidity and mortality. As of 15 September 2022, there were more than 607 million confirmed cases and nearly 6.5 million deaths worldwide.[1] Since the pandemic began, there has been a rapid increase in understanding of the disease and its management, with swift development and approval of vaccines and therapeutics. In Brunei Darussalam, the first wave of the COVID-19 pandemic started on 9 March 2020 with the detection of the first case, a patient who had attended a religious gathering in a neighbouring country. The last community case was detected on 6 May 2020, with a total of 141 cases reported at that point. Only imported cases were detected until the second wave started on 7 August 2021, during which the predominant SARS-CoV-2 strain was confirmed to be Delta (B.1.617.2).[2] The third wave, caused by the more infectious Omicron strain, started on 5 February 2022.[3]

COVID-19 is predominantly a respiratory illness. Common symptoms include fever, cough, fatigue, body aches, sore throat, anosmia and ageusia/dysgeusia.[4] Severe symptoms include shortness of breath and chest pain. Symptoms may appear 2–14 days after exposure and usually last 5–7 days, but they can be prolonged, resulting in more severe illness. Clinically, COVID-19 ranges from an asymptomatic presentation to severe pneumonia requiring ventilatory support and causing death. Nonrespiratory symptoms may also occur, including cardiovascular, gastrointestinal, neurological and cutaneous symptoms.[5] In earlier reports from China, anosmia and ageusia were not recognized as typical COVID-19 symptoms, but they are currently acknowledged as distinctive symptoms.[6–8] Differences in symptoms and

[a] National Isolation Centre, Ministry of Health, Tutong, Brunei Darussalam.
[b] Department of Medicine, Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei Darussalam.
[c] Pengiran Anak Puteri Rashidah Sa'adatul Bolkiah Institute of Health Sciences, Universiti Brunei Darussalam, Bandar Seri Begawan, Brunei Darussalam.
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their duration may be due to viral variants, underlying comorbidities or race, or a combination of these.

While the symptoms of COVID-19 are well known, the duration of symptoms is less well studied. This study aimed to assess the duration of symptoms of COVID-19 by age, disease severity and vaccination status in Brunei Darussalam during the start of the second wave of the pandemic.

METHODS

Study design and population

This was a retrospective, cross-sectional, observational study conducted using data from cases diagnosed with SARS-CoV-2 infection by reverse transcription–polymerase chain reaction (RT-PCR) who were admitted to the National Isolation Centre (NIC) in Brunei Darussalam, between 7 August 2021 (the start of the second wave) and 30 August 2021. Individuals with incomplete records were excluded from the study.

Setting and management

In Brunei Darussalam, all cases diagnosed with COVID-19 were admitted to the NIC for isolation and treatment. This arrangement continued until the second week of the second wave (18 August 2021), when community isolation centres were opened to cope with the increasing number of cases. During admission to the NIC, patients provided a detailed history of symptoms and underwent clinical examination and relevant investigations, such as laboratory testing and chest imaging. During hospitalization, cases had their symptoms assessed and documented daily. Cases underwent an RT-PCR test on day 8 to determine if they could be discharged, and they were considered recovered if this test was negative. If the day 8 test was positive, RT-PCR was repeated at 48-hour intervals. A case was considered recovered if the day 10 or subsequent test was negative or a cycle threshold value >30.0 was obtained.

Disease severity categories

Cases were categorized based on disease severity as follows: category 1 (C1) – asymptomatic; C2 – symptomatic but without pneumonia (clinical or radiological); C3 – pneumonia; C4 – needing oxygen therapy; and C5 – needing intubation and ventilatory support, with or without other organ failure. Category 2 is divided into two subcategories: C2a – milder symptoms (i.e. cough, nausea, vomiting, rhinorrhoea, anosmia or dysosmia, ageusia or dysgeusia, diarrhoea <2 times in 24 hours, myalgia and lethargy); and C2b – worsening C2a symptoms (i.e. new onset fever, fever persistence >2 days, chest pain, dyspnoea, unable to ambulate independently, reduced oral intake and reduced urine output). These categories were introduced and implemented on 13 August 2021.[9]

Symptom categories

Cases were categorized based on their reported symptoms at admission: asymptomatic (no symptoms), presymptomatic (asymptomatic at admission but subsequently developed symptoms during hospitalization; these cases were reassigned at hospital discharge), recovered (symptoms had resolved by admission) and symptomatic (symptomatic at admission).

Data collection

Details of cases and the relevant investigations were collected and prospectively entered into a database. This database was used to track patients' movements between the NIC, community isolation centres and home; track clinical progress; assist in the overall management of COVID-19 cases; and report daily to the Ministry of Health. Data collected included age, sex, vaccination status, symptoms reported, disease severity, and prevalence and duration of oxygen use.

Symptom duration was calculated based on the reported date of symptom onset, with symptom resolution considered to be the first day the case achieved disease category C1.

Vaccination status

The Brunei Darussalam national vaccination programme for COVID-19 was implemented in phases beginning 3 April 2021; the first to be vaccinated were frontline staff and older people, followed by people with comorbidities.[10] The COVID-19 vaccines used were BBIBP-CorV (Sinopharm), Comirnaty (Pfizer–BioNTech), Spikevax (Moderna) and Vaxzevria (Oxford–AstraZeneca). Vaccination status was categorized as complete (received two doses), partial (received one dose), unvaccinated and ineligible (age <18 years or had any contraindication based on recommendations at the time, such as receiving

chemotherapy or on immunosuppressive medications). A vaccine dose was considered complete if the case had received it at least 14 days prior to COVID-19 infection. At the time of the study, COVID-19 vaccine booster doses (third doses) had not yet been introduced.

Statistical analysis

Anonymized data were entered into the database and analysed using IBM SPSS version 26.0 (IBM, New York, United States of America). Descriptive statistics were used to describe case characteristics. Age was divided into several categories: ≤12 years (children), 13–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years and ≥60 years. One-way analysis of variance (ANOVA) testing was used to assess the time between symptom onset and hospital admission, symptom duration and length of hospitalization separately by age group, disease severity and vaccination status. This provided *P* values for trends. Post hoc Bonferroni analysis was used to assess the differences between the age groups, again providing *P* values for each comparison. A scatterplot was used to assess correlations between age and symptom duration. Two-sided tests were used and $P < 0.05$ was considered statistically significant.

RESULTS

Of the 751 COVID-19 cases admitted to the NIC during the study period, 548 (73%) were included in the analysis and 203 cases were excluded. Reasons for exclusion were being admitted prior to use of the disease severity score (163 cases), death (20) and incomplete data (20).

The mean age of COVID-19 cases included in the analysis was 33.7 years; there was a higher proportion of males (55.7%; 305). The most common comorbidities were hypertension (18.1%; 99), dyslipidaemia (10.4%; 57) and diabetes mellitus (9.5%; 52). Most cases were either unvaccinated (59.1%; 324) or ineligible for vaccination because of age (20.8%; 114), with only 13.0% (71) having had at least one dose of vaccine (**Table 1**).

Symptoms were reported at admission by 81.3% (446) of cases, with the most common being cough (59.1%; 324), fever (38.9%; 213) and sore throat (18.4%; 101) (**Table 2**). Among these symptomatic cases, the mean number of symptoms reported on admission was 2.8. There was no significant difference in the number of symptoms reported by disease category (given with the standard deviation [SD]) as classified during hospitalization: C2 = 2.8 ± 1.6; C3 = 2.8 ± 1.6; C4 = 3.1 ± 1.6; and C5 = 3.0 ± 0.9 ($P = 0.065$ by ANOVA).

The mean (SD) number of days between symptom onset and admission was 4.9 (± 3.4). The mean (SD) symptom duration was 10.4 (± 5.1) days. The mean (SD) length of hospitalization was 10.8 (± 4.3) days. There was a positive correlation between age and symptom duration, with a predicted increase in symptom duration of 0.1 day for each additional year increase in age ($y = 6.94 + 0.1x$) (**Fig. 1**). Each of these categories was also significantly different by age group ($P = 0.034$ for symptom onset to admission, $P < 0.001$ for symptom duration, $P = 0.004$ for length of hospitalization; **Table 3**).

When comparing each of these by age group, for time of symptom onset to admission, the youngest age group (≤12 years) had a significantly shorter interval compared with those in the 50–59 year group. There were no differences in this category between any of the other age groups. Symptom duration was significantly shorter for each of the three youngest age groups (≤12, 13–19 and 20–29 years) when compared with each of the two oldest age groups (50–59 and ≥60 years). Length of hospitalization was significantly shorter in adolescents (13–19 years) compared with those in the 40–49 year group, with all other comparisons being non-significant (**Table 3**).

There was a statistically significant difference between each of these categories and the disease category ($P < 0.001$ each for time from symptom onset to admission, symptom duration and length of hospitalization). When comparing each of these categories with the disease category groups, C2 cases had a significantly shorter interval from symptom onset to admission when compared with C3 cases; symptom duration was significantly shorter in C2 cases when compared with C3 and C4 cases; and length of hospitalization was significantly shorter for the less severe category for most comparisons between C1, C2, C3 and C4 cases (**Table 3**).

Altogether, 6.0% (33) of cases were categorized as C4 at admission and 11.5% (63) were assessed as C4 at any time during their hospitalization. For the 63 cases assessed as C4 at any time during their illness, the mean

Table 1. **Characteristics of 548 COVID-19 cases admitted to the National Isolation Centre, 7–30 August 2021, Brunei Darussalam**

Characteristic	No. (%)
Age group (years)	
≤12	64 (11.7)
13–19	55 (10.0)
20–29	118 (21.5)
30–39	101 (18.4)
40–49	111 (20.3)
50–59	59 (10.8)
≥60	40 (7.3)
Sex	
Male	305 (55.7)
Female	243 (44.3)
Comorbidities	
Diabetes mellitus	52 (9.5)
Dyslipidaemia	57 (10.4)
Hypertension	99 (18.1)
Vaccination status	
Ineligible	114 (20.8)
Unvaccinated	324 (59.1)
Partial (1 dose)	71 (13.0)
Complete (2 doses)	39 (7.1)

Table 2. **Reported symptoms in 548 COVID-19 cases admitted to the National Isolation Centre, 7–30 August 2021, Brunei Darussalam**

Symptom	No. (%)
Symptoms reported at admission	446 (81.3)
Cough	324 (59.1)
Fever	213 (38.9)
Sore throat	101 (18.4)
Rhinorrhoea	97 (17.7)
Anosmia	86 (15.7)
Dyspnoea	74 (13.5)
Ageusia or dysgeusia	70 (12.8)
Loose stool or diarrhoea	54 (9.9)
Myalgia	48 (8.8)
Headache	41 (7.5)
Nausea or vomiting	19 (3.5)
Symptom category	
Asymptomatic	73 (13.3)
Recovered	40 (7.3)
Presymptomatic	29 (5.3)
Symptomatic	406 (74.1)
Disease category at admission	
C1	187 (34.1)
C2	315 (57.5)
C3	13 (2.4)
C4	33 (6.0)
C5	0
Most severe disease category during hospitalization	
C1	113 (20.6)
C2	267 (48.7)
C3	95 (17.3)
C4	63 (11.5)
C5	10 (1.8)

C1: asymptomatic; C2: symptomatic but without pneumonia (clinical or radiological); C3: pneumonia; C4: needing oxygen therapy; C5: needing intubation and ventilatory support with or without other organ failure.

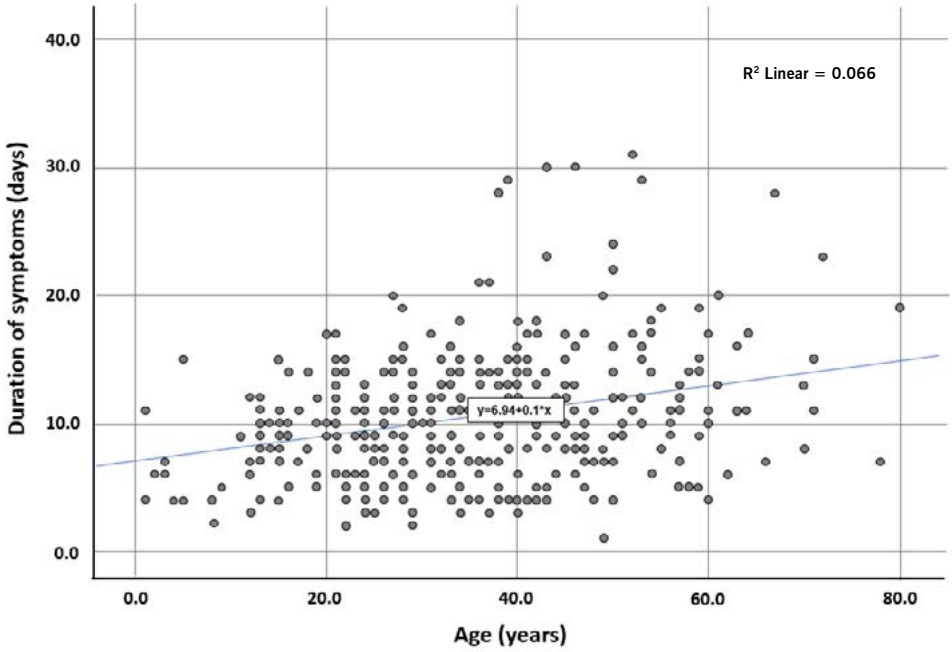
(SD) interval from symptom onset to admission was 4.6 (± 3.9) days, and the mean (SD) interval from admission to needing oxygen therapy was 2.1 (± 2.5) days. For all cases, the mean (SD) interval from symptom onset to needing oxygen was 6.8 (± 3.9) days. For all cases, the mean (SD) duration of oxygen therapy was 6.4 (± 5.4) days.

Cases who had received two doses of COVID-19 vaccine had a significantly shorter symptom duration than cases who had received one dose of vaccine or were unvaccinated. Those ineligible for vaccination had a significantly shorter symptom duration compared with unvaccinated cases (**Table 4**).

DISCUSSION

This study showed that the duration of COVID-19 symptoms was associated in separate analyses with being older, having more severe disease and being unvaccinated. Younger cases had a shorter duration of symptoms compared with older cases; cases with less severe disease (C1 and C2) had a shorter duration of symptoms than those with more severe disease (C3 and C4); and those who were fully vaccinated had a shorter duration of symptoms than those who were unvaccinated. Knowing about symptoms, including their likely duration, can help in planning management strategies, such as the duration of isolation or quarantine, predicting the length of hospitalization and treatment, as well as providing better and more accurate counselling to

Fig. 1. **Scatterplot of age and duration of COVID-19 symptoms for 548 cases admitted to the National Isolation Centre, 7–30 August 2021, Brunei Darussalam**



patients regarding COVID-19, depending on the severity of their disease at the time of presentation. This information may also encourage cases to present in a timely manner if their illness does not improve as expected, particularly those who have not been admitted or are isolating at home.

The mean (SD) duration of symptoms of COVID-19 in this study was 10.4 (± 5.1) days, with the duration of symptoms increasing approximately linearly with age. Symptom duration was associated with age group, with younger cases having shorter duration. Generally, symptomatic children have mild disease and a short duration of illness,[11,12] with one study from the United Kingdom of Great Britain and Northern Ireland reporting that the median duration of illness was shorter for younger children (duration: 5 days, interquartile range [IQR] = 2–9) compared with older children (duration: 7 days, IQR = 3–12).[12] A study from Italy reported that 4.4% of children had prolonged illness lasting up to 28 days, and this was more common in older children (5.1%) than in younger children (3.1%) (P = 0.046).[13] A study from the United States of America reported that at least one in five young, healthy adults aged 18–34 years had unresolved symptoms up to 3 weeks after diagnosis.[14]

Symptom duration has also been correlated with the duration of viral shedding and infectivity, especially during the first 2 weeks of symptoms.[15,16] Knowledge of symptom duration may be useful as a proxy measure for infectivity in patients, removing the need for laboratory testing. This is important for advising patients about the required period of isolation or quarantine, and it also applies to asymptomatic cases, as studies have shown no differences in clinical features and virological course in cases with asymptomatic or symptomatic non-severe COVID-19.[17]

Apart from the correlation with age, this study also showed that symptom duration was associated with disease severity. Cases in the C2 symptomatic category had a mean (SD) duration of symptoms of 8.7 (± 3.9) days. This was significantly shorter than in those who had pneumonia on imaging (C3: 11.4 ± 4.8 days) and those needing oxygen therapy (C4: 16.1 ± 5.1 days). This is expected: the more severe the illness, the longer it would take to recover. To date, no studies have assessed symptom duration based on the severity of disease. Viral shedding has been shown to correlate with symptom duration and severity of illness.[18]

This study also showed that vaccination status was associated with symptom duration: fully vaccinated cases had a significantly shorter duration of symptoms than unvaccinated and partially vaccinated cases. Vaccination reduces the risk of COVID-19,[19–22] as well as the dura-

Table 3. **Time from symptom onset to admission, and duration of symptoms and hospitalization, by age group and disease category for 548 COVID-19 cases admitted to the National Isolation Centre, 7–30 August 2021, Brunei Darussalam**

Characteristic	Time from symptom onset to admission (days)	*P*	Duration of symptoms (days)	*P*	Duration of hospitalization (days)	*P*
Age group (years)						
≤12	3.5 ± 2.5[a]	0.034	6.9 ± 3.3[b]	<0.001	10.9 ± 3.3	0.004
13–19	4.1 ± 2.3		8.8 ± 2.8[c]		9.1 ± 3.3[e]	
20–29	4.8 ± 3.3		9.2 ± 4.2[d]		10.4 ± 3.6	
30–39	5.0 ± 3.3		10.7 ± 4.9		10.5 ± 4.0	
40–49	4.9 ± 3.1		10.9 ± 5.6		11.5 ± 5.3	
50–59	6.2 ± 4.7		12.6 ± 6.3		11.5 ± 4.4	
≥60	4.4 ± 2.9		13.3 ± 5.9		12.5 ± 5.6	
Disease category						
C1	NA	0.018	NA	<0.001	9.2 ± 4.2[j]	<0.001
C2	4.4 ± 3.0[f]		8.7 ± 3.9[g]		10.1 ± 3.5[k]	
C3	5.7 ± 3.5		11.4 ± 4.8[h]		11.7 ± 4.1[l]	
C4	4.6 ± 3.9		16.1 ± 6.0[i]		14.9 ± 4.9[m]	
C5	5.8 ± 3.3		NA		NA	
Overall	4.8 ± 3.3		10.4 ± 5.1		10.8 ± 4.3	

Values are mean ± SD.

C1: asymptomatic; C2: symptomatic but without pneumonia (clinical or radiological); C3: pneumonia; C4: needing oxygen therapy; C5: needing intubation and ventilatory support with or without other organ failure; NA: not applicable; SD: standard deviation.

[a] Significant compared with 50–59 year age group ($P = 0.045$).

[b] Significant compared with 50–59 year age group ($P = 0.002$) and ≥60 year age group ($P = 0.002$).

[c] Significant compared with 50–59 year age group ($P = 0.019$) and ≥60 year age group ($P = 0.022$).

[d] Significant compared with 50–59 year age group ($P = 0.004$) and ≥60 year age group ($P = 0.012$).

[e] Significant compared with 40–49 year age group ($P = 0.019$) and ≥60 year age group ($P = 0.006$).

[f] Comparison between C2 and C3 categories ($P = 0.017$).

[g] Significant compared with C3 and C4 categories (both $P < 0.001$).

[h] Significant compared with C2 and C4 categories (both $P < 0.001$).

[i] Significant compared with C2 and C3 categories (both $P < 0.001$).

[j] Significant compared with C3 and C4 categories (both $P < 0.001$).

[k] Significant compared with C3 category ($P = 0.005$) and C4 ($P < 0.001$).

[l] Significant compared with C1 category ($P < 0.001$), C2 ($P = 0.005$) and C4 ($P < 0.001$).

[m] Significant compared with C1, C2 and C3 categories (all $P < 0.001$).

tion and severity of illness.[23] In the United Kingdom, vaccinated cases were more likely to be asymptomatic, had fewer symptomatic days and less severe illness, and had lower hospitalization rates, with the analysis including patients aged ≥60 years.[24] The impact of vaccination on symptom duration should reinforce the drive to vaccinate as many people as possible during the current pandemic. While the first vaccine dose provides some protection, completing the two-dose primary vaccination series provides better protection against infection.[25] This study showed that cases who had received a two-dose vaccination regimen had shorter duration of symptoms compared with unvaccinated and partially vaccinated cases.

Among cases who required oxygen therapy (C4), the requirement for oxygen occurred a mean (SD) of 6.8 (± 3.9) days after symptom onset. The mean (SD) duration of oxygen therapy was 6.4 (± 5.4) days, similar to cases in Ethiopia (6.0 days),[26] but shorter than patients in Germany (8.0 days).[27] This may be due to the relatively

Table 4. **Duration of COVID-19 symptoms by vaccination status for 548 cases admitted to the National Isolation Centre, 7–30 August 2021, Brunei Darussalam**

Vaccination status	Duration of symptoms (days, mean ± SD)	*P*
Overall	10.4 ± 5.1	
Complete	6.8 ± 3.5[a]	
Partial	10.1 ± 5.2	<0.001
Unvaccinated	11.3 ± 5.3	
Ineligible	8.2 ± 3.1[b]	

SD: standard deviation.

[a] Significant compared with partial ($P = 0.024$) and unvaccinated ($P < 0.001$).

[b] Significant compared with unvaccinated ($P < 0.001$).

high proportion of young cases in this study. Older cases required a longer time to be weaned off oxygen therapy due to their comorbidities and reduced immunity.[26] With the Delta variant of COVID-19, there is a rapid transition from becoming symptomatic to having dyspnoea and needing oxygen therapy, perhaps exacerbated by the phenomenon of happy (or silent) hypoxia.[28,29] For cases admitted to hospital, pneumonia can be identified early by the deterioration in their condition and with chest imaging so that the need for oxygen therapy can be anticipated. However, knowing the average time from symptom onset to oxygen requirement can be useful to gauge when to closely monitor cases at risk of further deterioration.

There are several limitations to this study. First, while it was a retrospective study, it used prospectively collected data from a real-time database used for patient management. Retrospective studies are associated with missing or incomplete data. Even though the data used in this study were captured prospectively, some data were missing due to the number of cases; thus, a small number had to be excluded. Second, this study included cases from the first few weeks of the second wave of the pandemic, when all cases were admitted to the NIC. This enabled the whole spectrum of COVID-19 disease severity to be studied, but it meant that cases occurring after this time were excluded. In addition, cases admitted during the first 6 days of the second wave were excluded from the study, as disease was categorized differently.[9] Third, symptoms were closely followed only during hospitalization; thus, cases with mild to moderate disease (C1 or C2) or symptoms persisting after discharge were not evaluated. However, using the length of hospitalization was deemed to be adequate to cover the duration of illness, taking into account the interval from symptom onset to admission. Additionally, management protocols permit patients to be discharged only after clinical improvement, with most being fully recovered on discharge.

The main strength of this study is its link to the patient management system that required all cases to be assessed daily and included information about their symptoms, and this daily assessment was continued for the duration of hospitalization. This allowed accurate data to be collected systematically, which was possible due to the local management protocol requiring cases to be asymptomatic or minimally symptomatic before repeating SARS-CoV-2 testing to document recovery. Furthermore, this study also assessed the association between symptom duration and vaccination status, information that has not been published previously.

In conclusion, this study showed that symptom duration was associated separately with age, disease severity and vaccination status, with longer duration of symptoms associated with being older and having more severe disease. Receiving two doses of COVID-19 vaccine was significantly associated with a shorter duration of symptoms, highlighting the importance of vaccination. These findings are relevant as they illustrate that the duration of symptoms varied and was affected by several factors. Recommendations about the duration of isolation for patients who do not require hospitalization, discharge planning and counselling of patients diagnosed with COVID-19 can be guided by this information. This is mostly relevant for cases infected with the Delta strain of SARS-CoV-2, but it may also provide a reference for other variants that may emerge during the pandemic.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The study was performed in accordance with the principles of the Declaration of Helsinki.

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Descriptive analysis of deaths associated with COVID-19 in Fiji, 15 April to 14 November 2021

Nashika Sharma,[a] Dashika Balak,[a] Shaneel Prakash[b] and Julia Maguire[c]

Correspondence to Nashika Sharma (email: nashika92@gmail.com)

Objective: There is limited published information about deaths due to coronavirus disease 2019 (COVID-19) in Fiji, the World Health Organization's Western Pacific Region and low- and middle-income countries. This report descriptively analyses deaths directly associated with COVID-19 in Fiji by age group, sex, ethnicity, geographical location, vaccination status and place of death for the first 7 months of the 2021 community outbreak.

Methods: A retrospective analysis was conducted of deaths directly associated with COVID-19 that occurred from 15 April to 14 November 2021 in Fiji. Death rates per 100 000 population were calculated by utilizing divisional population estimates obtained from medical zone nurses in 2021.

Results: A total of 1298 deaths relating to COVID-19 were reported, with 696 directly associated with COVID-19 and therefore included in the analysis. Of these, 71.1% (495) were reported from the Central Division, 54.6% (380) occurred among males, 75.6% (526) occurred among people of indigenous (iTaukei) ethnicity and 79.5% (553) occurred among people who were unvaccinated. Four deaths were classified as maternal deaths. The highest percentage of deaths occurred in those aged ≥70 years (44.3%, 308), and the majority of deaths (56.6%, 394) occurred at home.

Discussion: At-risk populations for COVID-19 mortality in Fiji include males, iTaukei peoples, and older (≥70 years) and unvaccinated individuals. A high proportion of deaths occurred either at home or during the first 2 days of hospital admission, potentially indicating both a reluctance to seek medical care and a health-care system that was stressed during the peak of the outbreak.

Coronavirus disease 2019 (COVID-19) was first reported as clusters of unexplained pneumonia in late December 2019 in Wuhan, China, and was found to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization (WHO) declared COVID-19 a public health emergency of international concern on 30 January 2020.[1]

Fiji's first COVID-19 case was imported on 15 March 2020 and resulted in a small local outbreak of 18 cases. Over the next year, 50 additional imported cases were reported without any community transmission. By 14 November 2020, 70 cases of confirmed COVID-19 had been reported, including two deaths.[2] There were no other cases until 15 April 2021, 364 days after the last reported, locally acquired case, when travellers tested positive for COVID-19 in government quarantine in a hotel. A subsequent locally acquired case of COVID-19 occurred when a hotel worker at the quarantine facility inadvertently had close contact with the infected travellers, and this marked the start of the second wave of the COVID-19 outbreak in Fiji. The sequencing of the local case's specimen confirmed a SARS-CoV-2 Pango lineage B.1.617.2 variant – that is, the Delta variant – which at that time was classified as a variant of concern by WHO.[1]

During the same period in WHO's Western Pacific Region, 10 of the 21 Pacific Island countries and territories reported cases of COVID-19: some had only imported cases contained in quarantine facilities (i.e. the Republic of the Marshall Islands, Samoa, the Solomon Islands and Vanuatu) and others had large-scale outbreaks (i.e. French Polynesia, Guam, New Caledonia, the Common-

[a] Ministry of Health and Medical Services, Suva, Fiji.
[b] Ministry of Lands and Mineral Resources, Suva, Fiji.
[c] World Health Organization Representative Office for the South Pacific, Suva, Fiji.

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wealth of the Northern Mariana Islands, and Wallis and Futuna). The remaining 11 Pacific Island countries and territories remained COVID-free by closing their international borders and accepting only citizens and emergency support workers into their country or territory.[1]

There is limited published information regarding deaths due to COVID-19 in Fiji, the Western Pacific Region and low- and middle-income countries.[3–5] This report provides a descriptive analysis of the first 7 months of the 2021 outbreak for deaths directly associated with COVID-19 in Fiji by age group, sex, ethnicity, geographical location, vaccination status and place of death.

METHODS

We conducted a retrospective study of deaths directly associated with COVID-19 that occurred during the second wave of community transmission in Fiji between 15 April and 14 November 2021.

SARS-CoV-2 infection was identified using reverse transcription polymerase chain reaction (RT-PCR) testing. During this period, all RT-PCR samples were sent to the Fiji Centre for Communicable Disease Control, also known as Mataika House, which is Fiji's national public health laboratory for analysis and reporting. Deaths were classified as either directly associated with COVID-19 (i.e. due to COVID-19) or indirectly associated with COVID-19 (i.e. people with COVID-19 infection at the time of death).[6] Classification was determined by the attending physician at the medical facility or by a mortality review panel, with COVID-19 categorized as a primary or secondary cause of death based on the case definition used by the Fiji Ministry of Health and Medical Services,[7] clinical records, medical history from relatives and results of COVID-19 investigations.

For each death directly associated with COVID-19, the Ministry of Health and Medical Services obtained the following information: age, sex, ethnicity, residential address, place of death, COVID-19 test type, date the specimen was collected for laboratory testing, date the specimen was tested, date of death, hospitalization status, date of hospital admission, COVID-19 vaccination status and dates of vaccination doses. In the analyses, deaths were classified as occurring at home or at a health facility (i.e. a health centre or hospital). Postmortem testing for COVID-19 was implemented for all deaths occurring during the study period.

A descriptive analysis was conducted for deaths directly associated with COVID-19. Death rates per 100 000 population were calculated by age group, sex, ethnicity and geographical location using division population estimates obtained from medical zone nurses in 2021. Note that the administrative boundaries (e.g. provincial boundaries) differ slightly from the medical division boundaries, hence medical zone demographic data were used.

RESULTS

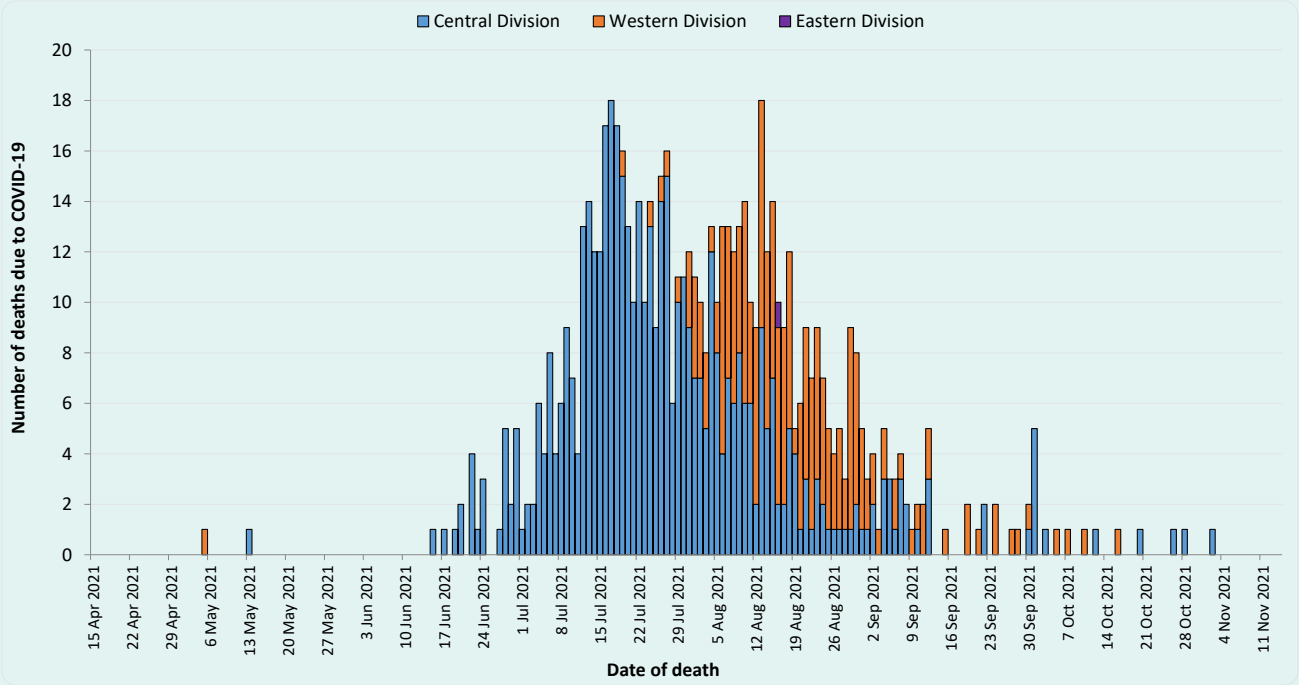
A total of 1298 deaths relating to COVID-19 were reported during the study period. Of these, 696 were categorized as being due to COVID-19 and were included in the analysis. For the first 4 months of the outbreak, deaths directly associated with COVID-19 primarily occurred in the Central Division; they later spread to the Western Division and then to the Eastern Division (**Fig. 1**).

Most deaths (71.1%, 495/696) were reported from the Central Division, and 54.6% (380/696) occurred among males, 75.6% (526/696) occurred among people of iTaukei ethnicity and 79.5% (553/696) occurred among unvaccinated people (**Table 1**). Although deaths were reported across all age groups, the median age of deaths due to COVID-19 was 67 years, and the highest percentage of deaths occurred in those aged ≥70 years (44.3%, 308/696). The death rate per age group–specific population increased with age (**Table 1**).

Four deaths were classified as maternal deaths, all of which occurred during the postpartum period at divisional hospitals between 4 and 6 days from the date of admission (data not shown). Three maternal deaths occurred in the Central Division, while one death occurred in the Western Division. The mean age of those categorized as a maternal death was 36.5 years (median, 35 years), and all women in this group were reported to be unvaccinated.

The majority of deaths directly associated with COVID-19 occurred at home (56.6%, 394/696), and of these 53.8% (212/394) were among males, 86.3% (340/394) were among iTaukei people and 50%

Fig. 1. **Deaths directly associated with COVID-19 by geographical division, Fiji, 15 April to 14 November 2021 (*N* = 696)**



(197/394) were among people aged ≥70 years. Of the 43.4% (302/696) of deaths that occurred in a hospital or health-care setting, 56.3% (170/302) were among males, 61.6% (186/302) were among iTaukei people and 36.8% (111/302) were among people aged ≥70 years (**Table 2**). Of the deaths that occurred in the hospital or health-care setting, 44.0% (133/302) occurred within 1 day of admission, 9.3% (28/302) occurred 2 days after admission and 46.7% (141/302) occurred ≥3 days after admission. Early in the outbreak when there were fewer cases, less than half of deaths occurred at home; however, during the peak of the outbreak (15 July–12 August) more than 60% of deaths occured at home rather than in a health facility (**Fig. 2**). From September onwards, this proportion decreased as the number of cases and deaths decreased.

The place of deaths directly associated with COVID-19 (i.e. at home or at a health centre or hospital) varied by division. In the Central Division, most deaths occurred at home (60.2%, 298/495), with the remaining occurring in hospitals (35.2%, 174/495) and at health centres (4.6%, 23/495). Conversely, in the Western Division, most deaths occurred in hospitals (52.0%, 104/200), with slightly fewer occurring at home (47.5%, 95/200) and 0.5% (1/200) occurring at a health centre. In the Eastern Division, one death occurred at home; no deaths were reported in the Northern Division during the study period.

DISCUSSION

Our study describes deaths directly associated with COVID-19 occurring in Fiji during its second wave of community transmission in 2021. Most of these deaths occurred among males, people aged ≥70 years and those living in the Central Division (the most populous division in Fiji).

Geographically, the deaths directly associated with COVID-19 followed a similar pattern to that of the cases, occurring first in the Central Division, then the Western Division and later in the Eastern Division.[8] The delayed spread of cases through the country can be attributed to the restriction of movement across the major divisional borders and from areas with localized outbreaks. With cases initially concentrated in the Central Division, the remaining divisions had the opportunity to prepare their health systems for an influx of cases and also rapidly increase vaccination coverage to prevent widespread disease transmission.

Table 1. **Characteristics of 696 people whose death was directly associated with COVID-19, Fiji, 15 April to 14 November 2021**

Characteristic	Deaths directly associated with COVID-19 (N = 696)	
	No. (%)	Rate/100 000 population
Sex		
Male	380 (54.6)	42.9
Female	316 (45.4)	35.7
Age (years)		
Median (IQR)	67.0 (21.0)	NA
Mean (SD)	65.6 (15.9)	NA
Age group		
<20	9 (1.3)	2.7
20–29	9 (1.3)	6.3
30–39	22 (3.2)	16.4
40–49	58 (8.3)	56.3
50–59	120 (17.2)	132.4
60–69	170 (24.4)	327.3
≥70	308 (44.3)	1079.2
Ethnicity		
iTaukei	526 (75.6)	NA
Fijian of Indian descent	139 (20.0)	NA
Other	31 (4.5)	NA
Place of death		
Hospital or health-care setting	302 (43.4)	NA
Home	394 (56.6)	NA
Vaccination status		
Unvaccinated	553 (79.5)	NA
One dose	130 (18.7)	NA
Two doses	13 (1.9)	NA
Geographical division		
Central	495 (71.1)	123.4
Western	200 (28.7)	56.3
Eastern	1 (0.1)	2.6
Northern	0 (0.0)	0

IQR: interquartile range; NA: not applicable; SD: standard deviation.

Table 2. **Characteristics of 696 people whose death was directly associated with COVID-19 by place of death, Fiji, 15 April to 14 November 2021**

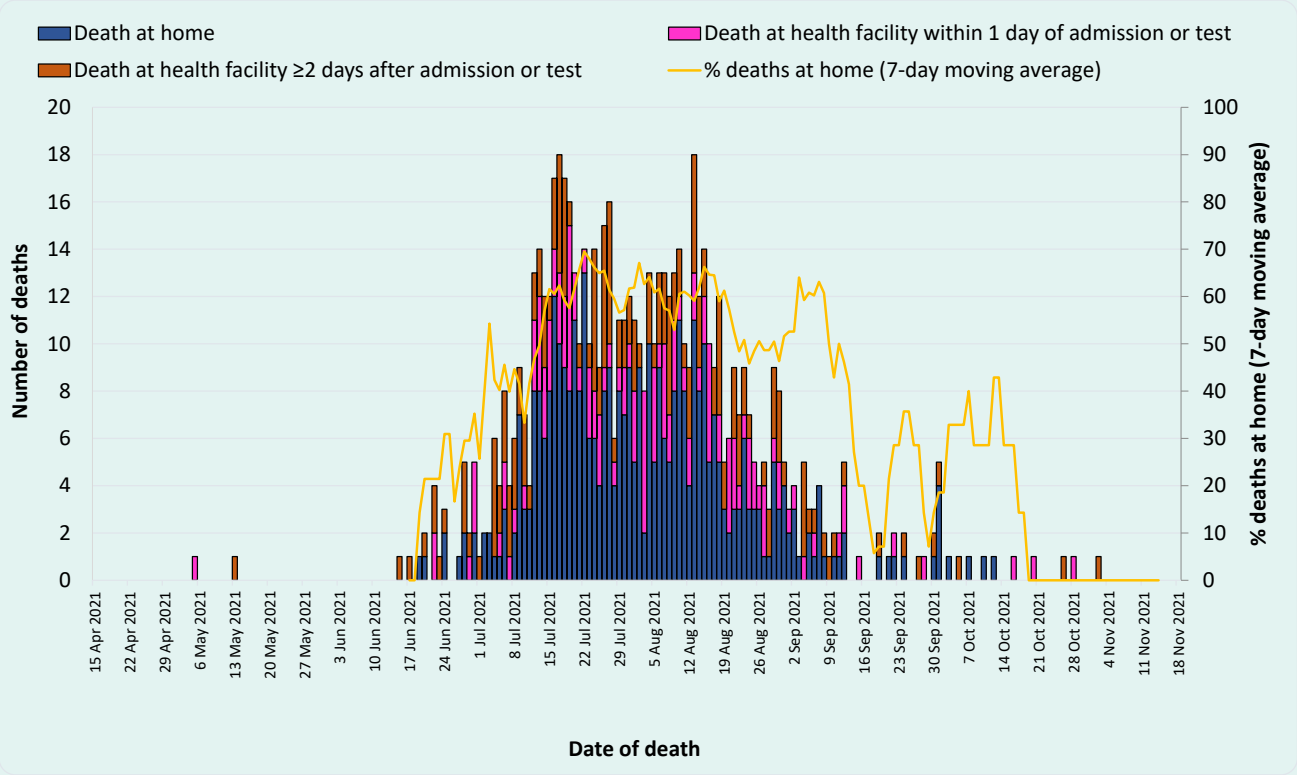
Characteristic	No. (%) of deaths	
	At home (n = 394)	In hospital or health-care setting (n = 302)
Sex		
Male	212 (53.8)	170 (56.3)
Female	182 (46.2)	132 (43.7)
Age group (years)		
<20	3 (0.8)	6 (2.0)
20–29	3 (0.8)	6 (2.0)
30–39	10 (2.5)	12 (4.0)
40–49	22 (5.6)	36 (11.9)
50–59	61 (15.4)	59 (19.5)
60–69	98 (24.9)	72 (23.8)
≥70	197 (50.0)	111 (36.8)
Ethnicity		
iTaukei	340 (86.3)	186 (61.6)
Fijian of Indian descent	39 (9.9)	100 (33.1)
Other	15 (3.8)	16 (5.3)

In this study, more than half of the deaths directly associated with COVID-19 were among males, which is consistent with other studies, demonstrating that male sex is associated with higher mortality.[9,10] A paper by Nguyen et al. additionally reported that male sex is not only associated with a higher rate of mortality but also with a higher rate of respiratory intubation and a longer length of hospital stay.[9] Although there is limited information about the relationship between sex and COVID-19, the literature has highlighted the importance of understanding the role of comorbidities, immune system responses and sex hormones as drivers of COVID-19 mortality.[9,10]

During our study period, deaths directly associated with COVID-19 were reported in all age groups. However, the number and rate of COVID-19 deaths were highest in those aged ≥70 years, highlighting that COVID-19 mortality increases with age.[11–13] A paper by Jergović et al. emphasized that the loss of immune function and reduced protection from infectious agents that occur with age are factors associated with increased disease severity and mortality from COVID-19.[12]

The deaths directly associated with COVID-19 in our study population occurred predominantly among unvaccinated people, who accounted for 79.5% of deaths, whereas 18.7% of those who died had received one dose of vaccine and 1.9% had received two doses. This is similar to other studies, highlighting that mortality from

Fig. 2. **Deaths directly associated with COVID-19 by place and date of death, Fiji, 15 April to 14 November 2021 (*N* = 696)**



COVID-19 is higher in the unvaccinated population than the vaccinated population.[14–17] COVID-19 vaccinations have successfully reduced the incidence and severity of, and hospitalization and deaths from, COVID-19.[14–17] Although many countries are utilizing different vaccines and booster regimens, it is evident that COVID-19 vaccinations have the potential to reduce morbidity and mortality.[15–17] The Fiji national COVID-19 vaccination programme commenced on 6 April 2021, with 61 667 individuals aged >18 (approximately 10% of the eligible population) receiving their first dose of vaccine by the end of April 2021; by 14 November 2021, 599 423 (97% of the eligible population) had received their first dose and 553 943 (89.6%) had received their second dose.

During the study period, four maternal deaths were reported. We have limited antenatal, intrapartum and postpartum information about these maternal deaths, so it is difficult to draw meaningful associations with other studies conducted around the world; however, a review of the literature highlights that pregnant women are at higher risk of severe COVID-19 infection; of needing caesarean delivery, intensive care admission and invasive ventilation; and of having adverse maternal and neonatal outcomes.[18–22] Three separate studies conducted in the United States of America and Scotland found that severe complications known to be associated with COVID-19 in pregnancy (such as admission to a critical care unit, perinatal mortality and developing severe or critical COVID-19 infection) were more common in pregnant women who were unvaccinated at the time they were diagnosed with COVID-19 than in vaccinated pregnant women.[23–25] Therefore, this highlights the importance of vaccinating pregnant women to reduce the severe maternal and neonatal health outcomes associated with COVID-19.

We found that although all ethnicities in Fiji were at risk of contracting and dying from COVID-19, indigenous populations (i.e. iTaukei) had a disproportionately higher rate of death from the disease. A review of the literature shows that globally indigenous populations seem to have higher rates of infection, more severe disease, higher rates of hospitalization, and poorer health and health outcomes from COVID-19.[26–28] Although there is limited knowledge about the relationship between ethnicity and COVID-19 morbidity and mortality, research suggests that pre-existing social, economic, political and cultural

determinants of health are important factors in the health and health outcomes of indigenous populations.[26] Therefore, it is important to collect timely, relevant, high-quality and disaggregated data to better understand the needs of vulnerable and at-risk populations and to ensure that COVID-19 response and mitigation measures are delivered in a way that ensures health equity and health equality.[29]

We found that the majority of deaths directly associated with COVID-19 occurred at home (56.6%). While the reason for this is not clear, it is important to understand a population's health-seeking behaviours and the factors that drive these behaviours. Two studies conducted in Pakistan and Viet Nam examined health-seeking behaviours and factors that altered these during the COVID-19 pandemic.[30,31] They found that individuals increased self-medication with unprescribed drugs, decreased their hospital visits and had an increased preference for visiting private general practitioners, traditional healers and unregistered clinics rather than visiting government facilities. The main factors that limited or altered health-seeking behaviours, or both, during the pandemic included fears of being stigmatized, of whole families being transferred to quarantine facilities and of disclosing past activities to contact tracing teams, and these fears were enhanced by misinformation, panic and uncertainties that spread over social media platforms.[30,31] The two countries in these studies are developing countries, and these findings may be applicable to the context in Fiji. It is also important to consider the immense and unprecedented stress placed on the health-care system in Fiji during the peak of the outbreak, and its impact on the system's ability to provide adequate and timely services to people with COVID-19. Indeed, we found that a high proportion of deaths occurred at home or soon after hospital admission, but this may be due to multiple factors, such as a limited ability to identify people with deteriorating health, limited availability of transportation to hospital and limited bed capacity to treat patients within the hospital, rather than a lack of health-seeking behaviour. As the outbreak progressed, strategies were implemented to increase the ability of the health system to identify those most at risk of severe disease and place them into an appropriate care pathway. More research on health-seeking behaviours and the factors that drive these behaviours within the context of Pacific Island countries and territories is pivotal for informing future pandemic response and mitigation measures.[30,31]

There were some limitations to this study. The classification of deaths depended on the assessment of the attending physician and, therefore, there was potential for misclassification. If the death occurred outside a health-care facility (e.g. at home), there may have been a delay in receiving the death certificate; therefore, there is potential for delayed reporting or underreporting of deaths during our study period. We were also unable to calculate mortality rates by ethnicity due to a lack of recent population data. In this study, deaths directly associated with COVID-19 were reported by geographical divisions; however, it would be valuable to analyse deaths by urban, periurban and rural settings because some communities have poorer access to health-care services, water, hygiene and sanitation and, as a result, are reported to have poorer health and health outcomes. It would also be interesting to assess the common signs and symptoms, and severity of COVID-19 disease, as well as underlying comorbidities, especially since about 80% of all deaths that occur in Fiji are due to noncommunicable diseases.[32] However, this information is not reported in the Medical Cause of Death Certificates, and a detailed review of inpatient data and clinical notes would be required. Occasionally, the clinical severity of disease was classified on the death certificate, but the investigative team was unsure how physicians classified the severity and whether all physicians in Fiji utilized standard definitions. Therefore, this information was not analysed. Understanding the common comorbidities among those who died from COVID-19 would help to highlight populations that are at risk for severe outcomes in Fiji, and understanding the severity of disease would provide a way to assess the required levels of health-care preparedness, health-care delivery and future clinical and public health forecasting in a developing country like Fiji. Information on the common signs and symptoms of COVID-19 experienced within our population can be utilized to increase knowledge and awareness among our frontline and allied health-care workers and can also be used to develop risk communication material to increase knowledge of and awareness about COVID-19 among our population.

In addition, understanding the patterns of disease among other at-risk populations would be useful, such as individuals with underlying mental health disorders or illnesses, those who are immunocompromised, those who have a disability, and residents of aged-care facilities, as well as low-income or unemployed individuals, unhoused

individuals, and members of the lesbian, gay, bisexual, transgender and queer communities; however, this information was not available. Having these data would allow health promotion activities to be targeted to reduce morbidity and mortality in these groups.

This retrospective analysis of deaths directly associated with COVID-19 that occurred in Fiji during the second wave of the pandemic (15 April to 14 November 2021) found that at-risk groups included male, indigenous (iTaukei), older (≥70 years) and unvaccinated individuals. Therefore, we conclude that individuals belonging to these risk groups in Fiji should adhere to the recommended COVID-19 precautions and preventive measures to avoid becoming infected with SARS-CoV-2, and we recommend that future public health prevention strategies, health promotion activities, risk communication materials and public health policies for COVID-19 in Fiji are tailored to these at-risk populations. Strategies should include providing education about the signs and symptoms of severe and progressing COVID-19, and increasing the capacity of health systems to identify and respond to a rapid influx of deteriorating patients.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This study was approved by the Human Health Research Ethics Review Committee of the Ministry of Health and Medical Services, Fiji (FNHRERC: 59/2021).

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Ready to respond: adapting rapid response team training in Papua New Guinea during the COVID-19 pandemic

Celeste Marsh,[a,b] Sharon Salmon,[b,c] Tambri Housen,[a,b,d] James Flint,[a,b,e] Joanne Taylor,[a,e] Emmanuel Hapolo,[f] Maria Trinidad Velasco Ortuzar,[a] Bernnedine Sissai Smaghi,[f] Anthony Eshofonie[c,g] and Berry Ropa[f]

Correspondence to Sharon Salmon (email: salmons@who.int)

Problem: Rapid response teams (RRTs) are critical for effective responses to acute public health events. While validated training packages and guidance on rolling out training for RRTs are available, they lack country-specific adaptations. Documentation is limited on RRT programming experiences in various contexts.

Context: In Papua New Guinea, there remain gaps in implementing standardized, rapid mobilization of multidisciplinary RRTs at the national, provincial and district levels to investigate public health alerts.

Action: The human resources needed to respond to the coronavirus disease (COVID-19) pandemic forced a review of the RRT training programme and its delivery. The training model was contextualized and adapted for implementation using a staged approach, with the initiation training phase designed to ensure RRT readiness to deploy immediately in response to COVID-19 and other public health events.

Lessons learned: Selecting appropriate trainees and using a phased training approach, incorporating after-training reviews, and between-phase support from the national programme team were found to be important for programme design in Papua New Guinea. Using participatory training methods based on principles of adult learning, in which trainees draw on their own experiences, was integral to building confidence among team members in conducting outbreak investigations.

Discussion: The RRT training experience in Papua New Guinea has highlighted the importance of codeveloping and delivering a context-specific training programme to meet a country's unique needs. A staged training approach that builds on knowledge and skills over time, used together with ongoing follow-up and support in the provinces, has been critical in operationalizing ready-to-respond RRTs.

PROBLEM

The International Health Regulations (2005) require Member States to be prepared to detect and respond to public health threats and emergencies.[1] Core to fulfilling this requirement are public health rapid response teams (RRTs), groups of trained professionals from different disciplines with the capacity to rapidly deploy to such events.[2] According to the World Health Organization's (WHO's) *Asia Pacific strategy for emerging diseases and public health emergencies (APSED III): advancing implementation of the International Health Regulations (2005)*,[3] RRTs are integral to systems designed to rapidly detect and contain public health threats. Under APSED III, the key focus areas of surveillance, risk assessment and response, and therefore public health systems overall, are strengthened through the establishment of RRTs and field epidemiology training programmes (FETPs).[4]

There is limited published evidence on the effectiveness of well-functioning RRTs during the early investigation and containment of infectious disease outbreaks and clusters. RRTs established at the local, national and international levels for West Africa during the Ebola virus

[a] University of Newcastle, Newcastle, New South Wales, Australia.
[b] Global Outbreak Alert and Response Network, World Health Organization, Geneva, Switzerland.
[c] World Health Organization Regional Office for the Western Pacific, Manila, Philippines.
[d] Australian National University, Acton, Australian Capital Territory, Australia.
[e] Hunter New England Health, New Lambton, New South Wales, Australia.
[f] Surveillance and Emergency Response Unit, National Department of Health, Port Moresby, Papua New Guinea.
[g] World Health Organization Bangladesh Country Office, Dhaka, Bangladesh.
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disease epidemic in 2014–2016 have been credited with containing an outbreak of *Neisseria meningitidis* in Liberia in 2017[5] and another Ebola virus disease outbreak in the Democratic Republic of the Congo in 2017.[6,7]

Across the WHO Western Pacific Region – where infectious disease outbreaks, emerging infectious disease threats and environmental challenges such as unsafe water and natural disasters frequently occur[3] – national RRTs exist in various forms and at different stages of development. A 2015 evaluation of progress towards goals under APSED III reported that substantial gains had been made in the effectiveness of the Region's RRTs. However, countries also ranked RRTs high on their priority lists for improvement.[8]

To assist countries in building a trained RRT workforce, WHO's Health Emergencies Programme produced a validated and standardized all-hazards approach training package in 2015.[9] In 2021, a condensed version, aimed at those working on the coronavirus disease (COVID-19) response, was developed in conjunction with the Government of India and the U.S. Centers for Disease Control and Prevention.[10] Although these are valuable resources, it is essential that such packages, including their mode of delivery, are adapted to local contexts within the Region. To support the establishment and capability of RRTs, experiences with training and the lessons identified should be documented. We present a model of RRT training and capacity strengthening being piloted in provinces across Papua New Guinea.

CONTEXT

In Papua New Guinea, public health threats are compounded by a population of 8.8 million that is widely spread across extremely diverse terrain, with 80–85% of people living in rural or geographically isolated settings.[11] In recent years, Papua New Guinea has faced many major public health events, including outbreaks of measles (2017) and cholera (2019), the re-emergence of vaccine-derived poliovirus (2018) and the current COVID-19 pandemic. These outbreaks occur in addition to a high baseline burden of endemic diseases and natural disasters that have public health impacts.

Papua New Guinea has an established FETP that has trained 96 field epidemiologists between 2013 and June 2022. The programme has strengthened prevention, detection and response capabilities throughout the country.[12] FETP Papua New Guinea (FETPNG) graduates often take lead roles in outbreak responses and surveillance initiatives. However, there remain gaps at the national, provincial and district levels in the standardized, rapid mobilization of multidisciplinary teams to investigate public health alerts. In recognition of these gaps, the RRT training programme for multidisciplinary RRTs within Provincial Health Authorities was conceived and initiated by national leaders in field epidemiology. The vision was for RRTs to be operationalized through national and provincial emergency operation centres (EOCs) under the leadership of an appointed incident manager (**Fig. 1**). EOCs were first established to support the response to the polio outbreak in three provinces (the Eastern Highlands, Madang and Morobe), and they were subsequently set up in other provinces.

ACTION

In November 2019, on request from the National Department of Health, the WHO Regional Office for the Western Pacific led an RRT training for the National Capital District Provincial Health Authority using the WHO all-hazards approach package.[9] With the arrival of the COVID-19 pandemic in March 2020, the need to establish functional RRTs in other provinces became urgent. An RRT programme team – composed of representatives from the National Department of Health; FETPNG; Field Epidemiology in Action, from the University of Newcastle, Australia, and Hunter New England Health, Australia; and the WHO Representative Office for Papua New Guinea – collaborated to accelerate the roll out of training across the country. This began with an after-training review with the National Capital District RRT in May 2020 that highlighted key limitations of the initial training and the need to codevelop a training package tailored to the Papua New Guinea context.

Human resources limitations in the context of the pandemic meant that it was not feasible to remove teams from ongoing response operations for 5 days of training. Therefore, the training was converted to a 2-day initiation training that covered the basic principles and structure of an RRT to assist provinces in quickly mobilizing teams to respond to both COVID-19 and other public health events. Initiation training was aimed at incident managers, disease control officers, clinicians, surveillance officers, laboratory scientists, environmental health officers, logisticians, finance administrators, risk communication specialists and health promotion officers. Graduates of

Fig. 1. **Infographic of the Rapid Response Team training process distributed to Provincial Health Authorities across Papua New Guinea, February 202**

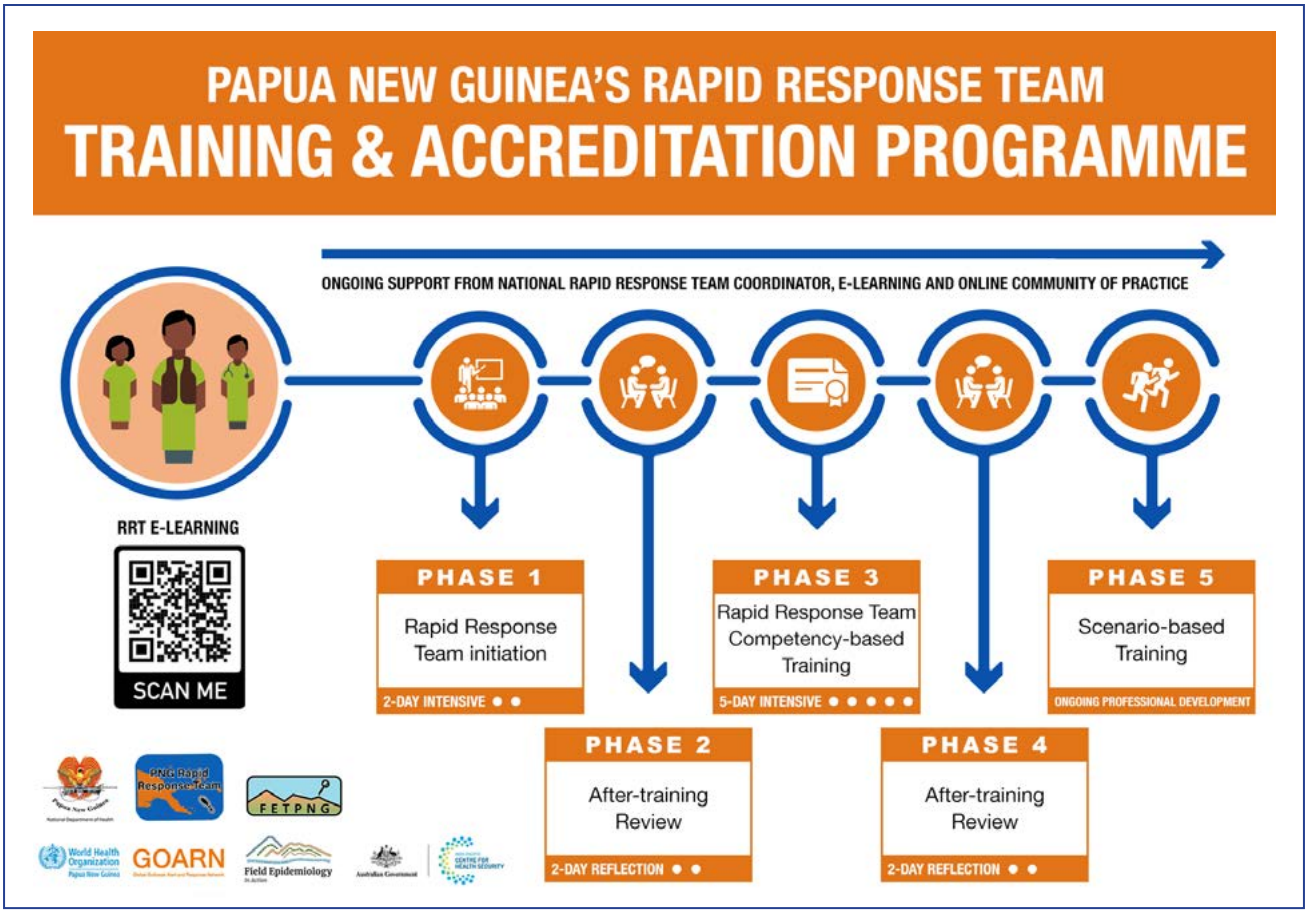
FETPNG filled one or more of these roles and were the primary provincial contact points for coordinating the training. Graduates working at the National Department of Health served as trainers.

Building on the initiation training, the RRT programme team codeveloped a phased delivery approach that provided an iterative and sequential pathway to establishing and strengthening RRTs over five phases (**Fig. 2**). Initiation training (Phase 1) facilitates the establishment of an RRT and is the first phase towards RRT accreditation. After-training reviews (Phases 2 and 4) support reflections by RRTs on their prior training and post-training implementation, and the development of action plans for improving operationalization of the teams. Competency-based training (Phase 3) focuses on extending multidisciplinary skills and knowledge. Ongoing scenario-based training (Phase 5) provides the opportunities for RRTs to keep current their early detection and response skills, continue to practice after-action reviews and refine RRT operationalization in different emergency contexts. Additionally, during Phase 5, neighbouring provincial teams come together to strengthen people-to-people links, collaboration and the regional community of practice.

In April 2021, to facilitate the development of a national RRT community of practice, the National Department of Health's RRT coordinator set up a group channel on the encrypted messaging service WhatsApp. This platform has enabled members to seek out information and share ideas about potential clusters or outbreaks. In June 2022, the platform was used to discuss a possible multiprovincial pertussis outbreak.

RRT e-learning modules are being designed to complement the various phases of the training programme. These provide an introduction for RRT members who are unable to attend in-person trainings and act as refreshers for those who have attended. Although these e-learning

Fig. 2. **Infographic of the Rapid Response Team training process distributed to Provincial Health Authorities across Papua New Guinea, February 2022**



modules reflect the context in Papua New Guinea, the training has been made available globally to support RRTs in similar contexts (e.g. on the Field Epidemiology in Action website at https://www.fieldepiinaction.com and the Global Outbreak Alert and Response Network training site at https://extranet.who.int/goarn).

RRT programme activities are led and coordinated by national FETPNG faculty with the support of Field Epidemiology in Action, the WHO Global Outbreak Alert and Response Network and the WHO Representative Office for Papua New Guinea. The programme is funded by the Indo-Pacific Centre for Health Security, Department of Foreign Affairs and Trade, Australia, and WHO.

LESSONS LEARNED

As of June 2022, RRT initiation training (Phase 1) had been conducted in 11 provinces, training 190 RRT members. The programme aims to complete initiation training in all 22 provinces by the end of 2022, with content and delivery continuing to be adapted based on ongoing monitoring and evaluation activities. Where initiation training conducted in 2020–2021 took a just-in-time training approach in response to the pandemic and included specific material related to COVID-19, training in 2022 has pivoted to focus on roles and responsibilities within RRTs.

Initiation training has been well received. Evaluations from training in the first six provinces showed most participants agreed that the RRT outbreak manual was useful (94%, 49/52), the content was relevant to their work (84%, 59/70) and the training was interactive (81%, 55/68). The most common reaction to training by participants – particularly the provincial surveillance and disease control officers, who often felt they carried the rapid response burden alone – was relief that a multidisciplinary team was being formalized and trained.

Five after-training reviews were conducted prior to June 2022. Factors that had reportedly worked well since initiation training included applying knowledge in the field: the steps of an outbreak investigation, pre-deployment preparation, the use of checklists and, in one province, the use of psychological first aid in a response to a landslide. Reported challenges included developing the RRT manual for the province, ensuring the most appropriate people were selected for training, assigning RRT roles and responsibilities, and accessing timely financial and logistical support for deployment. Through root cause analysis, RRTs found that progress had been hindered by factors such as team diversion to the COVID-19 response, lack of engagement by management, and human resources constraints, which led to many members straddling multiple roles. After-training reviews have identified critical challenges and best practices to help RRTs develop their own action plans.

The commitment of senior leadership to the operationalization of provincial RRTs was found to be essential to establish functional teams. Senior provincial leaders were invited to the trainings, but their presence varied across provinces. Greater effort is needed to communicate early with provincial leaders about the purpose and significance of their presence at the training.

The importance of equipping RRT trainers with skills and knowledge about teaching adults was recognized early in the roll out of initiation training. In May 2022, RRT trainers and FETPNG faculty attended a train-the-trainers workshop focused on revising training materials and methods of delivery to facilitate adult learning based on Kolb's learning theory.[13] Lessons learned from this training have been applied to amend the 2-day initiation training and will be applied to the development of Phases 3–5.

In May 2022, a new position within FETPNG was created for a national RRT coordinator, and this has been of significant value to the programme. The role includes conducting ongoing post-training follow-up with provincial RRTs; coordinating training activities, monitoring and evaluation; and following up on alerts received through RRT social networks.

DISCUSSION

Provincial public health RRTs are a critical component of Papua New Guinea's public health emergency response architecture and are key to strengthening health security in a context where epidemic and endemic diseases continually challenge the country's fragile public health system. While validated training packages[9] and guidance on rolling out training and managing RRTs[2] are available, experiences in RRT programming in various contexts should be documented. The experience in Papua New Guinea has highlighted the importance of developing a training programme that meets the needs of a country and its provinces and shifts away from a tick-the-box training model towards a comprehensive, staged training approach that builds knowledge and skills over time.

The staged training approach, which includes multiple after-training reviews and ongoing scenario-based training, reflects the U.S. Centers for Disease Control and Prevention's recommendation that individuals involved in RRT undergo "regular, continual training throughout their membership on the RRT".[14] The planned, intermittent, scenario-based training aligns with one of the priorities set for the Western Pacific Region in APSED III that advises Member States to "conduct after-action reviews or simulation exercises that test the readiness of the national surveillance and response system as a whole to respond to outbreaks and other acute public health events".[3]

The application of adult learning principles to the design and delivery of training allows RRT members to share their lived experience of the principles being taught and ensures the training is relevant to the local context in which it is delivered. In Papua New Guinea, the training programme continues to evolve based on findings from the after-training reviews, which have been essential to understanding the contextual challenges in establishing and implementing functional RRTs.

An evaluation of RRTs conducted across 21 countries between 2016 and 2018 found that they faced common challenges in establishing and managing the teams, including developing rosters for RRTs, ensuring that RRT members are trained, and that adequate standard operating procedures are lacking.[14] That these factors were

also common challenges in the provinces of Papua New Guinea, where after-training reviews were conducted, emphasizes the importance of ensuring ongoing support from the national programme team throughout the programme cycle and beyond.

CONCLUSIONS

Papua New Guinea has one of the world's most rural and remote populations, so it is challenging to rapidly mobilize response teams. The development of a highly contextualized training programme built on adult learning theory and delivered in a phased approach is an important part of strengthening Papua New Guinea's health security. Important lessons have been and will continue to be learned as the roll out of the RRT programme progresses. We hope the approach taken in Papua New Guinea and the lessons learned will be of benefit to RRT training programmes in similar contexts.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Formal ethical approval was not sought as research was not undertaken. Approval and permission to publish was received through the Papua New Guinea National Department of Health before the paper was submitted for publication.

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Mass COVID-19 testing of asymptomatic health-care workers in a tertiary hospital during an outbreak in another hospital in Singapore: an effective strategy?

William T Wang,[a] Hwang Ching Chan,[a] Jyoti Somani[a] and See Ming Lim[a]

Correspondence to William T Wang (email: william.wang@mohh.com.sg)

In response to Singapore's first coronavirus disease (COVID-19) hospital outbreak from late April to early May 2021, we conducted a mass testing exercise on 3–7 May 2021. This cluster in a single hospital marked the arrival of the Delta (B.1.617.2) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Singapore, and was characterized by breakthrough infections in vaccinated health-care workers (HCWs) and some patients.[1] By late May, 47 cases of COVID-19 had been linked to this hospital cluster.

At the time of the hospital outbreak, close contacts of positive cases were identified and quarantined at government isolation facilities for 14 days. However, in light of concerns that contact tracing of positive cases alone may not prevent further transmission of SARS-CoV-2, especially by asymptomatic or very mildly symptomatic HCWs, all public hospitals were encouraged to conduct mass testing exercises as part of a strategy to minimise the risk of further spread to other hospitals.

This report describes the results of the national mass testing exercise in one public hospital, in an effort to assess the effectiveness of the mass testing of asymptomatic HCWs as a strategy to track and prevent viral spread through casual exposure to the Delta variant of SARS-CoV-2.

METHODS

Staff at our tertiary care hospital who had any contact with the source hospital at which the Delta variant outbreak occurred within 14 days of the mass testing exercise (3–7 May 2021) were invited to take a COVID-19 test and to complete a short online questionnaire. Participation was voluntary; staff who had already been identified as direct contacts through the Ministry of Health's and the source hospital's own extensive contact tracing programme were exempted. Staff were informed about the testing exercise by department heads and reporting officers, and invitations to participate were sent out via email. Out of a total of approximately 7000 hospital staff, 427 indicated that they had had recent contact with the source hospital and attended for testing. Of the 427 tested, 165 presented to the staff clinic, while the remaining 262 attended the testing stations that were set up specifically for the purposes of the exercise. Nasopharyngeal swab samples were collected for polymerase chain reaction (PCR) testing for SARS-CoV-2.

The online questionnaire was designed to capture basic demographic data for each participant. Participants were also asked to provide information relating to their recent exposure history by selecting from a list of five possible exposure routes (multiple selections were allowed):

- "I live in the same household as someone who works at the source hospital"
- "I met with someone working on the source hospital campus for more than 30 minutes"
- "I attended a meeting or training at the source hospital"
- "I visited someone in the source hospital's inpatient wards"

[a] Department of Medicine, National University Hospital, Singapore.
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- "I attended to patients or worked on the source hospital campus"

The data were anonymized by an independent third party and were retrospectively aggregated by the study team.

RESULTS

None of the 427 asymptomatic HCWs who participated in the testing exercise conducted at the tertiary hospital during 3–7 May 2021 tested positive for COVID-19. Of those tested, 163 (38.2%) reported living in the same household as a member of staff from the source hospital, 108 (25.3%) met with someone working on the source hospital campus for >30 minutes, 59 (13.8%) attended a meeting or training at the source hospital, 18 (4.2%) visited someone in the source hospital's inpatient wards and 16 (3.7%) attended to patients or worked on the source hospital campus during the time period of interest (**Table 1**). Twenty-two (5.2%) reported more than one reason for exposure at the source hospital, while 41 (9.6%) went for testing without indication of any exposure.

DISCUSSION

Previous studies have suggested that mass testing of asymptomatic HCWs may help to reduce nosocomial transmission of COVID-19 by allowing early identification and isolation of positive cases, and contact tracing and quarantining of close contacts.[2] Additionally, the pre-symptomatic and early symptomatic periods have been identified as times of considerable transmission risk, with one study suggesting that more than 40% of cases may be infectious in the pre-symptomatic period.[3] The increased transmissibility of emerging variant strains of SARS-CoV-2 with shorter incubation periods adds further weight to the arguments in favour of employing HCW screening as a strategy to limit hospital transmission of COVID-19.[4]

In this relatively small, single-centre study, we did not detect a single case of COVID-19 in a group of 427 HCWs who submitted for PCR testing, despite the fact that 90.4% of participants reported possible exposure to someone from the source hospital. Our study sample excluded those HCWs who had a known exposure to a confirmed case at the source hospital and for this reason might be considered to be at greater risk of infection; however, all known contacts of positive cases at the source hospital also tested negative for COVID-19 on PCR swab tests.

Our testing exercise suggests that mass screening of asymptomatic HCWs is an ineffective strategy for preventing the spread of the Delta variant of SARS-CoV-2 in a hospital setting when there is a rapid and thorough contact tracing programme already in place. Any potential benefits would need to be weighed against any potential harms; for instance, a high proportion of negative tests may inadvertently result in complacency among hospital staff, leading to reduced compliance with infection control measures. Furthermore, implementing a mass testing exercise at any scale can be costly and may further exacerbate strained staffing and laboratory resources.[5] In many countries, increased infection rates among HCWs are typically proportional to increased infection rates within the community, suggesting that tracking community incidence to focus efforts on targeted screening may be more effective than conducting mass testing exercises.[6]

Limitations of this study include the possibility of incomplete capture of demographic and exposure history information; we mitigated against this by requiring staff to register and complete the online questionnaire before attending for their PCR test. In relying on self-reports to determine exposure through casual contact, our study will inevitably be subject to a degree of recall bias, especially in terms of the duration and level of exposure. Additionally, we acknowledge that some staff may have avoided the mass testing exercise despite known possible exposure. This was addressed by disseminating reminders through various communication channels to all staff about their obligation to public health safety and responsibility to participate in the mass testing if they had had any contact with the source hospital. Moreover, given the status of the pandemic at the time of our exercise (May 2021), motivation to be tested among staff was fairly high, prompted mainly by a desire to protect household members.

CONCLUSION

Our mass testing exercise failed to uncover any instances of asymptomatic inter-hospital transmission. Within the limitations of this study, the results suggest that mass

Table 1. **Self-reported sources of possible exposure to COVID-19 cases among staff at a tertiary care hospital who participated in a voluntary mass testing exercise (3–7 May 2021), as part of the response to an outbreak at another hospital, Singapore (*N* = 427)**

Sources of possible exposure	"Yes" answers, n (%)
Lives in the same household as someone who works at the source hospital	163 (38.2)
Met with someone working on the source hospital campus for more than 30 minutes	108 (25.3)
Attended a meeting or training at the source hospital	59 (13.8)
Visited someone in the source hospital's inpatient wards	18 (4.2)
Attended to patients or worked on the source hospital campus	16 (3.7)
More than one of the above	22 (5.2)
None of the above	41 (9.6)

testing of asymptomatic HCWs may be an impractical infection control strategy to track and prevent COVID-19 transmission from one hospital to another. We suggest that an institutional testing strategy which mirrors local community incidence rates – whereby hospitals increase the frequency of asymptomatic testing when there is a surge in community cases but relax testing during periods of lower case rates – would be a more effective option, especially when combined with continued strict adherence to infection control measures and internal contact tracing and a recommendation that staff stay home when they feel unwell and report any cold/flu-like symptoms or close household exposures.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval

This study was conducted retrospectively using existing anonymized data, and was exempted from ethics review by the National Healthcare Group Domain Specific Review Board.

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Systematic sequencing of imported cases leads to detection of SARS-CoV-2 B.1.1.529 (Omicron) variant in central Viet Nam

Do Thai Hung,[a] Nguyen Bao Trieu,[a] Do Thi Thu Thuy,[b] Allison Olmsted,[b] Trinh Hoang Long,[a] Nguyen Duc Duy,[a] Huynh Kim Mai,[a] Bui Thi Thu Hien,[b] Nguyen Van Van,[c] Tran Van Kiem,[d] Vo Thi Thuy Trang,[d] Nguyen Truong Duy,[d] Ton That Thanh,[e] Huynh Van Dong,[f] Philip Gould[b] and Matthew Moore[b]

Correspondence to Allison Olmsted (email: rzu9@cdc.gov)

As authorities braced for the arrival of the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infrastructure investments and government directives prompted action in central Viet Nam to establish capacity for genomic surveillance sequencing. From 17 November 2021 to 7 January 2022, the Pasteur Institute in Nha Trang sequenced 162 specimens from 98 150 confirmed SARS-CoV-2 cases in the region collected from 8 November to 31 December 2021. Of these, all 127 domestic cases were identified as the B.1.617.2 (Delta) variant, whereas 92% (32/35) of imported cases were identified as the B.1.1.529 (Omicron) variant, all among international flight passengers. Patients were successfully isolated, enabling health-care workers to prepare for additional cases. Most (78%) of the 32 Omicron cases were fully vaccinated, suggesting continued importance of public health and social measures to control the spread of new variants.

Genomic surveillance has become a critical tool for monitoring variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease (COVID-19).[1] Recognizing this, capacity building for genomic surveillance towards a National Sequencing Network has become a principal goal in Viet Nam. The aim of the network is to standardize sequencing to empower the Ministry of Health (MoH) to detect and respond to emerging public health threats, determine outbreak etiologies and enhance overall surveillance capacities in the country. The Pasteur Institute of Nha Trang (PI Nha Trang) is the agency within the MoH responsible for public health surveillance and response in 11 central coastal provinces in Viet Nam, including key population centres such as Da Nang as well as major tourist destinations such as Hoi An and Nha Trang. In May 2021, motivated by the desire to participate in the development of the National Sequencing Network, PI Nha Trang acquired its first next-generation sequencer and developed a protocol to identify and monitor the relative prevalence of SARS-CoV-2 variants among COVID-19 cases identified in the central region.

In early 2020, all passengers arriving on inbound flights to Viet Nam underwent testing using real-time reverse transcription polymerase chain reaction (RT-PCR) (requirement expired 15 May 2022) and mandatory 14-day quarantine in centralized facilities (requirement expired 1 January 2022).[2] These provisions allowed for quick detection and isolation of cases, as well as targeted genomic surveillance for imported cases.

The B.1.1.529 (Omicron) variant of SARS-CoV-2 was first reported to the World Health Organization by South Africa and was designated a variant of concern on 26 November 2021.[3] It has since been closely monitored by countries worldwide. Through heightened genomic surveillance measures, the first imported case of the Omicron variant in Viet Nam was detected on 19 December 2021 in a traveller entering the northern part of the country. This brief report characterizes 32 of

[a] Pasteur Institute in Nha Trang, Nha Trang, Viet Nam.
[b] U.S. Centers for Disease Control and Prevention, Hanoi, Viet Nam.
[c] Quang Nam Department of Health, Quang Nam, Viet Nam.
[d] Quang Nam Center for Disease Control, Quang Nam, Viet Nam.
[e] Da Nang Center for Disease Control, Da Nang, Viet Nam.
[f] Khanh Hoa Center for Disease Control, Viet Nam.
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Viet Nam's first imported Omicron cases in the central region and highlights the importance of public health and social measures to detect and contain the spread of new variants.

METHODS

Specimens were collected from domestic and imported laboratory-confirmed cases of COVID-19 from 8 November to 31 December 2021. Not all COVID-19 cases were sequenced; each province was required to submit 2–3 specimens per week, while areas with international airports (Khanh Hoa and Da Nang provinces), border controls (Quang Binh and Quang Tri provinces) or a high case burden submitted 4–6 specimens per week. The selection of samples for sequencing was prioritized to imported cases or special cases (e.g. index cases of large clusters, patients infected after two vaccine doses, reinfected, or with severe symptoms or death).

Sequencing was performed on specimens with a cycle threshold value of ≤28 and volume of at least 800 μL, and with accompanying epidemiological data such as patient characteristics and clinical presentation. Specimens were stored at 2–8°C for ≤72 hours from the time of collection. PI Nha Trang has the capacity to sequence 24–46 specimens per week using a MiSeq platform (Illumina, San Diego, CA, United States of America). The Dragen Covid Lineage software (Illumina) was used for genomic analysis and phylogenetic trees were generated using Nextclade (https://clades.nextstrain.org/). Outputs included quality metrics, lineage determination, amino acid substitutions for novel strain detection, and Fasta format files for epidemiological analysis using accompanying epidemiological data.

Sequences were posted to the GISAID Initiative database as per the protocol developed jointly by PI Nha Trang and the U.S. Centers for Disease Control and Prevention in Viet Nam (unpublished). To improve understanding of the effects of systematic testing and quarantine, sequence data for community cases were reported from November 2021 to February 2022.

RESULTS

There were 98 150 confirmed cases of COVID-19 detected in central Viet Nam (97 985 domestic and 165 imported) from 1 November to 31 December 2021. Among all cases, 162 patient specimens collected between 8 November and 31 December 2021 were sequenced. The majority (78%; 127/162) were domestic cases while 22% (35/162) were imported cases. All domestic cases were identified as the B.1.617.2 (Delta) variant while 92% (32/35) of imported cases were the Omicron variant. Phylogenetic relationships among sequenced cases demonstrate close relationships with sequences from multiple continents (**Supplementary Fig. 1**). No community cases of Omicron were detected in the 11 provinces in central Viet Nam from November 2021 to early February 2022.

Descriptive epidemiology revealed that 66% (21/32) of Omicron cases were under 40 years old, 53% (25/32) were fully vaccinated and 25% (8/32) had received booster doses (**Table 1**). Most of the cases (24/32; 75%) were asymptomatic at detection. None were hospitalized or died. A total of 13 individuals arrived on direct flights from the United States of America to Viet Nam and 13 additional passengers departed from various countries with stopover points in the Republic of Korea, where layover time ranged from 4 to 30 hours.

Sequencing results were reported promptly to the originating province and the MoH, which shared them publicly via Internet news outlets. All sequences were also uploaded to GISAID within 2 weeks; GISAID accession numbers are listed in **Supplementary Fig. 2**.

DISCUSSION

Viet Nam's practice of universal testing and mandatory quarantine for international visitors, combined with preferential selection of imported cases for whole genome sequencing, enabled the early detection of imported Omicron cases. Prompt identification and isolation of these cases gave the government additional time to communicate with the public and prepare for eventual community transmission. This supports previous studies demonstrating that public health and social measures such as systematic targeted testing programmes remain important, even among highly vaccinated populations such as travellers.[5] Multiple flight origins further highlight the need for cooperation between countries to detect and respond to emerging variants. Testing and sequencing strategies should be revisited and updated as outbreak situations continue to evolve.

Table 1. **Characteristics of confirmed B.1.1.529 (Omicron) SARS-CoV-2 cases (*N* = 32), central Viet Nam, 8 November–31 December 2021**

Characteristic	No.	%
Age group (years)		
0–19	3	9
20–29	12	38
30–39	6	19
40–64	11	34
≥65	0	0
Sex		
Male	12	38
Female	20	63
COVID-19 vaccination status[a]		
Fully vaccinated	17	53
Fully vaccinated plus booster dose	8	25
Unvaccinated (ineligible)	1	3
Unknown	6	19
Symptom profile[b]		
Asymptomatic	16	50
Symptomatic	8	25
Unknown	8	25
Initial signs or symptoms[c]		
Cough	4	13
Sore throat	3	9
Fever	2	6
Congestion or runny nose	1	3
Headache	1	3
Nausea or vomiting	1	3
Outcome		
Hospitalization	0	0
Death	0	0
Flight origin		
Republic of Korea[d]	16	50
United States of America	13	41
Malaysia	3	9

[a] Fully vaccinated is defined as having received the complete immunization series according to the vaccine manufacturer.

[b] Self-reported symptoms.

[c] Cases may exhibit multiple symptoms.

[d] Includes passengers with flights originating in the Republic of Korea (*n* = 3) as well as passengers with layovers in the Republic of Korea (*n* = 13) whose flights originated in the United States of America (*n* = 9), Canada (*n* = 3) or the Netherlands (*n* = 1).

Government policies prioritizing whole-genome sequencing may improve the speed of variant detection, and collecting epidemiological data provides important context for sequenced cases. For example, the observation that most cases in this series were fully vaccinated supports previous data demonstrating that vaccination does not prevent transmission of the Omicron variant.[6] Similarly, the lack of hospitalization or death supports data that Omicron causes severe illness less frequently than Delta.[7] The integration of laboratory and epidemiological data is critical in ensuring the most useful information is available as quickly as possible, although the low proportion of specimens sequenced compared to total cases limits interpretation.

As of 14 August 2022, Viet Nam reached 84.1% population coverage with two vaccine doses, allowing the country to slowly re-open to international travel and commerce.[8] Genomic surveillance for SARS-CoV-2 has become the international standard of surveillance.[9] In addition to contributing to the understanding of clinical and epidemiological trends of COVID-19, genomic surveillance provides critical data necessary for rapidly developing newer, more effective vaccines against SARS-CoV-2.

Early investment in infrastructure for genomic sequencing made it possible for authorities in central Viet Nam to respond quickly to the detection of a newly imported SARS-CoV-2 variant of concern. However, implementing new programmes always comes with challenges. For example, current limitations include overrepresentation of specimens from certain provinces and underrepresentation from others, as well as resource constraints at the local level for specimen collection and transfer. Despite these issues, the data described here provide valuable evidence for further investment to overcome current limitations and scale up towards the greater goal of developing a National Sequencing Network in Viet Nam.

Disclaimer

The findings and conclusions are those of the authors and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention, Department of Health and Human Services.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This work was carried out as a part of routine surveillance activities of the Pasteur Institute in Nha Trang and no ethics review was required.

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Contribution of the Australian field epidemiology training workforce to the COVID-19 response, 2020

Amy Elizabeth Parry,[a] Charlee Law,[a] Davoud Pourmarzi,[a] Florian Vogt,[a,b] Emma Field[a] and Samantha Colquhoun[a]

Correspondence to Amy Elizabeth Parry (email: amy.parry@anu.edu.au)

The range of public health emergencies that occurred in Australia during 2020 illustrates the complexity of contemporary acute public health issues. In 2020 alone, Australia mounted responses to bush-fires, storms, drought, floods and rodent plagues, as well as the coronavirus disease (COVID-19) pandemic. Such events have highlighted not just the vital role played by the field epidemiology workforce in rapidly and effectively managing a wide range of public health emergencies but also the need to continually train and invest in this workforce to ensure high levels of public health emergency preparedness.[1–5]

Health workforce strengthening is essential to achieving the International Health Regulations (IHR 2005) core capacities.[6] The Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III) also makes specific reference to the need for a skilled and experienced local public health workforce for preventing the escalation of public health emergencies.[7]

The Australian Field Epidemiology Training Programme (FETP), commonly known as the Master of Philosophy in Applied Epidemiology (MAE), is one of several public health training programmes in Australia. Established in 1991 to address a recognized gap in the public health workforce, the programme is Australia's accredited FETP.[8,9] Utilizing the approach of "learning through doing", students spend most of the 22-month-long programme working within a field placement. This approach ensures alumni are appropriately trained to contribute to the detection, investigation, response and control of acute public health events.[8] As of June 2021, there were 58 students and 255 alumni in the network.

Australian FETP alumni work in senior roles in health departments at local, state, national and international levels, in Aboriginal and Torres Strait Islander health services and organizations, in United Nations agencies, as well as in research institutions and academia. Alumni and students have been consistently involved in national and international epidemic responses, including severe acute respiratory syndrome (SARS) (2002–2003), H1N1 influenza (2009), Middle East respiratory syndrome coronavirus (MERS-CoV) (2012–) and Ebola virus disease in West Africa (2014–2016). The experiences of alumni and students have been used to modify the programme to make it more relevant, adaptive and "pandemic ready".

The aim of this study was to describe the level and scope of Australian FETP alumni and student contributions to the COVID-19 response during the first 10 months of the pandemic so that these experiences could inform programme learning priorities going forward.

METHODS

In 2020, the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET) developed a survey to document the contribution of FETP trainees and alumni to COVID-19 preparedness and response internationally.[10] We adapted this instrument to conduct a cross-sectional survey of Australian FETP network members (survey available upon request to the corresponding author). Our survey collected participants' demographic data and information about their employment and role in the COVID-19 response. Invitations to participate, with a link to the survey, were emailed to alumni and students in July 2020. Participants were

[a] National Centre for Epidemiology and Population Health, College of Health and Medicine, Australian National University, Canberra, Australian Capital Territory, Australia.
[b] The Kirby Institute, University of New South Wales, Sydney, New South Wales, Australia.
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also recruited using convenience and snowball sampling methods, with recipients asked to share the invitation with other Australian FETP alumni.

Roles were categorized into 10 main areas; each main area was assigned a list of associated activities. Multiple answers within each category were allowed. Open-ended questions were included to obtain additional details about participants' roles and responsibilities. Data were stratified and descriptively analysed by category using Stata 15 (StataCorp LLC, College Station, TX, United States of America).

RESULTS

We received 66 responses, 57 from alumni (86%) and nine (14%) from current students. The majority (89%, 59/66) were involved in COVID-19 response activities in Australia; within this group, 61% (36/59) reported working for state or territory government departments, 10% (6/59) for a federal government department and 3% (2/59) for a local government department. Other workplaces included nongovernmental agencies (5%, 3/66), universities (21%, 14/66) and Aboriginal and Torres Strait Islander health services and organizations (3%, 2/66), with some respondents reporting multiple workplaces. Seven respondents reported working internationally (11%, 7/66).

Information on participant involvement in 43 COVID-19-related response activities is summarized in Table 1. Of the 66 respondents, 65 (98%) were involved in at least one listed activity and 36 (55%) in more than five activities. Over two fifths of respondents reported being involved in "surveillance" (82%, 54/66); 80% (53/66) were engaged in "reporting of data" and 71% (47/66) in activities related to "'incident command".

Within the "surveillance" category, the most frequently reported activities included active disease surveillance (50%, 33/66), case-based reporting (44%, 29/66) and contact tracing (39%, 26/66) (**Table 1**). Other activities mentioned by participants included establishing customized COVID-19 surveillance systems, developing dashboards, responding to outbreaks on cruise ships and providing expert advice within a variety of settings.

Commonly reported activities in the "reporting of data" category included developing internal situation reports (62%, 41/66), preparing articles for publication in peer-reviewed journals (26/66, 39%) and sharing information on dashboards (27%, 18/66). Within the "incident command" category, the most frequently reported activity was involvement in emergency operations centres (33%, 22/66), followed by involvement in incident command systems (24%, 16/66). Six (9%) respondents were engaged in incident command activities within Aboriginal and Torres Strait Islander health services and organizations (**Table 1**).

Sixty-eight per cent (45/66) of participants reported involvement in "operational research" and 56% (37/66) participated in one or more activities related to "risk communication and community engagement". Over a quarter (29%, 19/66) were involved in the preparation of communication for health-care providers; an equal number (29%, 19/66) interacted with or provided information to media (**Table 1**). All seven (11%) respondents working in international COVID-19 response reported participating in activities related to the development of risk communication briefings and messages.

Around a third of participants reported involvement in "infection prevention and control" (36%, 24/66), "operational support" (32%, 21/66) and "laboratory" (30%, 20/66) activities. Fewer respondents reported being involved in activities relating to "point of entry" (27%, 18/66) and "case management" (21%, 14/66) (**Table 1**).

DISCUSSION

Our survey revealed that Australian FETP alumni and students were involved in a wide range of pandemic response activities during the early months of the COVID-19 pandemic, suggesting that the programme provides a relevant and important contribution to the health response workforce in Australia and internationally. Alumni and students have been providing support during the COVID-19 pandemic in a variety of settings, including the public sector, academia and nongovernmental agencies, with many seconded into surge capacity roles.

Table 1. **Australian FETP survey respondents' involvement in COVID-19 response activities, July–December 2020 (*N* = 66)**

Category	Associated activities	n (% of total)
Surveillance	NOT involved in surveillance activities	12 (18%)
	Active disease surveillance	33 (50%)
	Case-based reporting	29 (44%)
	Contact tracing	26 (39%)
	Dissemination of case definitions	16 (24%)
	Other	33 (50%)
Reporting of data	NOT involved in reporting of data	13 (20%)
	Development of internal situation reports	41 (62%)
	Writing short reports or papers for publication in peer-reviewed journals	26 (39%)
	Sharing information on dashboards	18 (27%)
	Other	6 (9%)
Incident command	NOT involved in incident command activities	19 (29%)
	Emergency operations centre	22 (33%)
	Incident command system	16 (24%)
	Emergency management	9 (14%)
	Aboriginal and Torres Strait Islander health services and organizations	6 (9%)
	Other	12 (18%)
Operational research	NOT involved in operational research	21 (32%)
	Surveillance research	19 (29%)
	State, province, country-level coordination, regional or national planning and monitoring research	8 (12%)
	Risk assessment research	6 (9%)
	Community engagement research	2 (3%)
	Other	20 (30%)
Risk communication & community engagement	NOT involved in risk communication and community engagement activities	29 (44%)
	Development of communication for health-care providers	19 (29%)
	Media briefs and/or interviews	19 (29%)
	Construction of information sheets for the public	15 (23%)
	Construction of material for open access web pages for communication to the public	14 (22%)
	Communication for Aboriginal and Torres Strait Islander health workers or communities	11 (17%)
	On call for community queries	13 (20%)
	Hotline	5 (8%)
	Other	3 (5%)
Infection prevention and control (IPC)	NOT involved in IPC activities	42 (64%)
	Reporting and investigating cases of health-care-associated infections	11 (17%)
	Training staff in IPC	6 (9%)
	IPC risk assessment in facilities	6 (9%)
	Development of guidelines for IPC in facilities	5 (8%)
	Implementation of triage and control measures	2 (3%)
	Other IPC activities	5 (8%)

Category	Associated activities	n (% of total)
Operational support	NOT involved in operational support or logistics activities	45 (68%)
	Preparation of staff surge capacity and deployment mechanisms	15 (23%)
	Review of supply chain control and management system for medical and other essential supplies	2 (3%)
	Other	8 (12%)
Laboratory	NOT involved in laboratory activities	46 (70%)
	Standard operating procedures adopted for specimen collection and transportation for diagnostics	3 (5%)
	Access to designated COVID-19 reference laboratories	3 (5%)
	Development of surge plans to manage increased demand for testing	3 (5%)
	Conducting whole genome sequencing	2 (3%)
	Vaccine development for COVID-19	0 (0%)
	Development of rapid tests	0 (0%)
	Development or trial of point-of-care tests	0 (0%)
	Clinical trials for medications or vaccines	0 (0%)
	Other	11 (17%)
Point of entry	NOT involved in point-of-entry activities	48 (73%)
	Preparation of isolation facilities or quarantine measures	4 (6%)
	Communication of information about COVID-19 to travellers	2 (3%)
	Establishing standard operating procedures equipping staff to manage ill passengers	2 (3%)
	Other	12 (18%)
Case management	NOT involved in case management activities	52 (79%)
	Guidance made available for self-care of patients with mild symptoms	4 (6%)
	Health-care facilities prepared for high volume of cases	3 (5%)
	Dedicated teams to transport and treat suspected and confirmed cases	3 (5%)
	Other	6 (9%)

Respondents were allowed to give multiple answers within each main topic area. Percentages do not therefore sum to 100%.

The ability to redeploy the skilled field epidemiology workforce has been essential to the COVID-19 response at state, national and international levels.[2] Public health training programmes, such as the Australian FETP, need to remain responsive to workforce needs and continue to align with national, regional and international IHR workforce priorities.[4] That the programme is practical has been advantageous to the overarching Australian response by building a skilled and adaptive epidemiological workforce that is able to rapidly respond to acute public health emergencies.

Due to the sampling method used, it was not possible to accurately estimate the number of alumni the survey reached, with reasons for non-response remaining unknown. Therefore, the results presented are not generalizable to the Australian FETP population, though they do provide insight into some of the roles alumni and students played in the early phases of the response.

The Australian FETP has trained public health professionals who have contributed to different aspects of the COVID-19 response. The programme needs to continually adapt to ensure the training it provides remains relevant and addresses the breadth of skills required of field epidemiologists. It is important that support for the programme is maintained so that it can continue to play its critical role in building Australia's public health capacity.

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Conflicts of interest

AP and EF are associate editors of the Western Pacific Surveillance and Response journal. They were not involved in the editorial decision to publish this manuscript.

Ethics approval

The protocol for this study was approved by the Australian National University Human Research Ethics Committee (approval no. 2020/201).

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