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Tuberculosis outbreaks in schools: Experiences from the Western Pacific Region

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Reports of tuberculosis (TB) outbreaks among schoolchildren have increased in recent years in countries across the Western Pacific Region. Cases from China, Japan, Mongolia and the Republic of Korea were studied to derive lessons from the challenges and responses to TB outbreaks in schools. Despite differences in the TB burden and outbreak preparedness, the four countries reported similar challenges. These included delayed diagnosis of index cases, lack of experienced health professionals and sustained financial support, and difficulty in responding to intensified media and community attention. Early detection of outbreaks, established resource mobilization networks, coordination among stakeholders and proactive communication were highlights of successful outbreak responses. These principles could be adapted to each context for responses to future TB outbreaks in schools.

Despite continued progress in reducing the burden of tuberculosis (TB) in the World Health Organization (WHO) Western Pacific Region, TB remains a leading cause of death from infectious diseases in the Region.[1] The TB burden ranges widely across the Region, from countries in which TB has been eliminated as a public health concern to countries with some of the highest burdens of TB globally.

Reports of TB outbreaks among schoolchildren have been increasing recently. Congregated settings, overcrowded classrooms and various risk profiles among students may contribute to rapid transmission of TB in school settings. Moreover, TB outbreaks in schools and among children attract intense media and community attention and increase scrutiny of TB programmes. To date, there are limited international guidelines on responses to TB outbreaks in schools.

We report a range of experiences in responding to TB outbreaks in schools in the Western Pacific Region in four case studies compiled by WHO collaborating centres (in China, Japan and the Republic of Korea) and by the Ministry of Health, Mongolia. These case studies could inform the responses of countries that have minimal experience in responding to and preventing TB outbreaks in schools.

Case study: China

TB burden

In 2019, the incidence rate among children aged 0–14 years was 58 per 100 000 population, representing 1% of all notified cases.[2]

Outbreak definition

Ten or more cases or any TB-related deaths associated epidemiologically with a school during one semester.

Laws, regulations and TB control and management in schools

Standards for TB prevention and control in schools are detailed in the National TB Plan within the Thirteenth Five-year Plan and in Implementing Standards for Tuberculosis Prevention and Control in Schools and the TB Control Action Plan 2019–2022. The last was issued jointly by nine ministries, including the National Health Commission, to increase the capacity of schools

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to detect TB cases early and to prevent public health emergencies. TB outbreak investigations are guided by the Expert Consensus on Epidemiological Investigation and Onsite Disposition of TB Outbreaks in Schools. TB case reporting is mandated by the Interim Regulation on Public Health Emergencies.

Contacts are screened for TB by chest X-ray and symptoms and for latent TB infection (LTBI) with the tuberculin skin test (TST; recommended) or an interferon-gamma release assay (IGRA).

Example outbreak

An outbreak was announced in August 2017 after the identification of cases of active TB at a middle school. During the initial investigation, all students and staff were screened four times, and asymptomatic close contacts and classes in which a high TB incidence was detected were screened at regular intervals. The response was guided by a committee of experts, chaired by the county's top officials. The school infrastructure was disinfected daily. Counselling (at home visits or by phone) and online study schemes were offered to students. The medical costs incurred by students were fully covered by the county government or by medical insurance. Of 72 students treated (29 for pulmonary TB, 5 for presumptive pulmonary TB and 38 for LTBI), 50 satisfied the criteria for successful treatment and resumed school in November 2017.

Case study: Japan

TB burden

In 2019, the incidence rate among children aged 0–14 years was 13 per 100 000 population, representing <1% of all notified cases.[2]

Definition of outbreak

A single-source case infects >20 persons in more than two families.

Laws, regulations and TB control and management in schools

Epidemiological surveys and contact investigations for TB are described in the Infectious Diseases Control Law, which prohibits people with smear-positive results from working until their sputum is negative. The country's contact investigation guide gives the criteria for extending contact investigation. An outbreak identified by a public health centre must be reported to the Ministry of Health, Labour and Welfare.

Public health centres are primarily responsible for contact investigation. The Infectious Diseases Control Law recommends the establishment of an ad-hoc outbreak investigation committee that includes officials from schools, local education committees and public health centres, local laboratory staff, TB experts and representatives of local medical associations. Representatives of parents' associations are usually not invited to preserve the confidentiality of the index case.

Contacts are screened for TB with a chest X-ray and for LTBI with IGRA.

Example outbreak

An outbreak investigation was initiated after the diagnosis of TB in a junior high-school student in April 2009. The student experienced intermittent fever, cough and sputum for 6 months and visited several clinics 2 months before diagnosis, but did not receive a chest X-ray. Initial investigation of close contacts resulted in the identification of one case of active TB and two cases of LTBI among family members and a high rate of IGRA positivity among classmates. TB preventive treatment was given to 50% of classmates. Another case of pulmonary TB (with the same variable number of tandem repeat patterns as the index case) was identified in July 2009. The second stage of the investigation was campus-wide, and 15 cases of active TB and 45 cases of LTBI were identified overall.

Case study: Mongolia

TB burden

In 2019, the incidence rate among children aged 0–14 years was 428 per 100 000 population, representing 10% of all notified cases.[2]

Definition of outbreak

CDC definition of a higher occurrence of cases than expected in a specific area and/or time.[3]

Laws, regulations and TB control and management in schools

As of 2019, there were no regulations or standards for TB management in schools. A meeting of the Ministry of Health, the Ministry of Education, Culture and Sports, the Ulaanbaatar Governor's office and occupational inspection agency and others was convened to develop plans for the management of TB in schools after reports of TB outbreaks. A draft guideline on TB outbreak management was planned for approval by the Minister of Health.

In contact investigations, younger students are screened for TB with TST and teachers and older students with a chest X-ray.

Example outbreak

An outbreak was notified after 60 cases of active TB (3% of 1732 students and staff) were reported at a secondary school between 2015 and 2017. In the initial investigation in April 2017, a high proportion (49% of 889 students) of students had a positive TST. Isoniazid preventive therapy could not be offered because of insufficient stock. The second stage of the school-wide investigation was conducted between May and June by chest X-ray for all staff and students in grades 8–12 and/or TST for those in grades 1–7. Two cases of active TB were detected among 1618 students tested. Three subsequent field investigations were conducted 6 months apart on selected students. The response was coordinated jointly by the Khan-Uul District Health Care Centre, the Tuberculosis Surveillance and Research Department and the Diagnostics Division of the National Centre for Communicable Disease. Follow-up investigations were originally planned every 6 months for 2 years or until no new cases were detected. This was not, however, implemented due to limited financial and human resources.

Case study: Republic of Korea

TB burden

In 2019, the incidence rate among children aged 0–14 years was 59 per 100 000 population, representing 1% of notified cases.[2]

Definition of outbreak

More TB cases are detected during contact investigations in congregated settings.

Laws, regulations and TB control and management in schools

The Infectious Diseases Prevention and Control Act states the legal responsibility of the central and local governments for epidemiological investigation. The Tuberculosis Prevention Act details measures to be taken during outbreaks and for the management of contacts of patients with infectious TB.

Once a school reports a TB case to a health centre, the head of the health centre notifies the provincial TB officials, the Korea Disease Control and Prevention Agency (KCDA) and the electronic TB surveillance system. The health centre organizes an investigation team of a physician and a TB nurse from the health centre, a medical officer from the provincial health department, a member of the Tuberculosis Epidemic Investigation Service at the KCDA, the principal and a health teacher from the school and a focal person from the provincial department of education. The health centre is responsible for conducting field investigations, with administrative support from the provincial health department. The health centre also treats patients, reports the results of contact investigations through the TB surveillance system and briefs parents and students when necessary.

Contact investigations are conducted by screening for TB with a chest X-rays and LTBI with IGRA.

Example outbreak

An outbreak investigation was initiated after a high-school student with active TB was notified in June 2018, 2 weeks after symptom onset. The initial investigation was conducted among 250 individuals by chest X-ray, and another student was diagnosed with active TB. Of the 63 individuals tested for LTBI, 14 (seven close contacts, seven teachers) tested positive.

Ethics statements

As routinely available data were used and no personal identifying information was collected, ethical clearance was not required.

DISCUSSION

The four country case studies show the range of experiences in the Western Pacific Region. The lessons and challenges experienced are summarized in **Table 1**. While the countries faced similar challenges, the causes differed according to the TB burden and the resources available. Some elements of the responses differed from WHO guidance on TB management (e.g. environmental sanitation). A systematic review was therefore conducted to guide interpretation of the case studies to understand evidence on TB outbreaks in schools globally (Supplementary material).

In most outbreaks, the index case was a secondary school or university student. As young adults and older children are likely to have more casual contacts than younger students, the size and complexity of field investigations may depend on the age of the affected students. Some guidelines recommend a "stone-in-the-pond" approach to contact investigation, whereby contacts are prioritized according to their risk of exposure and susceptibility to TB;[4–7] however, the approach is difficult to implement when the index case is a child.

Delayed diagnosis of TB was reported repeatedly. In countries with a low TB incidence, clinicians may be less aware of the symptoms and misdiagnose cases. Delayed diagnosis may also be due to poor knowledge about TB among students, parents and teachers and to poor health-seeking behaviour by students. In some outbreaks, health promotion material has been distributed to increase awareness of TB and reduce stigmatization. China has developed online modules for students with TB to reduce interruption of schooling, which may reduce their hesitancy to seek care.

As field investigations should begin soon after an outbreak is identified, there is a surge in demand for human resources (e.g. clinicians, nurses) and medical supplies (e.g. test kits, drugs). Mongolia was unable to treat patients with LTBI because of a drug shortage and had to limit the number of follow-up investigations because of financial constraints. Japan reported a lack of paediatricians with experience in TB for screening. In some outbreaks, assistance was obtained by recruiting resources from neighbouring districts or by screening over a longer period (Supplementary material). Guidelines suggest that the resources that will be required should be assessed at the beginning of an investigation, so that staff could be recruited from outside TB teams.[4,7] Sustained financial and human resources are crucial, as investigations may be prolonged. The Republic of Korea reported that a high turnover of nurses disrupts patient monitoring, and school breaks may interrupt field investigations.

The importance of communication was evident, as TB outbreaks in schools often result in intensified attention from the media and communities. Designating communications personnel to coordinate media requests and to brief the public and the media regularly was reported to be valuable. Certain guidelines[4–7] state that proactive communication with parents, the school administration, students, health practitioners and the general public is essential. The WHO Outbreak Communications Guidelines detail best practices for effective communication with the public during an outbreak.[8]

In terms of cooperation in outbreak response, local public health centres were those primarily responsible, sometimes sharing the burden with school officials and external experts. This is consistent with the guideline of the European Centre for Disease Control and Prevention, which recommends that the core TB management team consult when necessary.[7] In the four case studies, policies for managing TB outbreaks in schools were usually covered by the national TB strategy, with no specified contribution from other government bodies. A universal coordination mechanism might be difficult to define, as ministry jurisdictions and public health administrative structures differ among countries.

In resource-limited settings, health care programmes may be supplemented with external resources (e.g. from nongovernmental or faith-based organizations). Therefore, the most effective way of coordinating stakeholders is unclear. As large-scale outbreaks could deplete the available resources, guidelines for outbreak prevention and control are critical in resource-limited settings. There is also limited guidance on integrating outbreak response into the national TB programme. There are therefore gaps in the current knowledge base, particularly in settings most impacted by TB outbreaks in schools.

CONCLUSION

The case studies illustrate the challenges and lessons learnt from TB outbreaks in schools across the Western Pacific

Table 1. **Key challenges and lessons learnt**

Challenge	Lessons and solutions
Delayed TB diagnosis	• Empower students to identify and manage their health issues proactively by TB-related health promotion in schools and by reducing stigmatization. • Outbreaks could be an opportunity to educate health care professionals and the general public about the persistence of TB in their community. • Improve schools' capacity to detect potential TB cases.
Low LTBI treatment uptake	• Educate students, teachers and parents about the importance of LTBI treatment. • Offer LTBI treatment at the site of the outbreak. • Create a treatment monitoring system to ensure that patients initiate and complete the full course of treatment.
Lack of financial support and human resource capacity	• Recruit staff (e.g. nurses, laboratory staff) and resources from neighbouring cities or from outside TB teams. • The available resources should be assessed at the start of a field investigation to ensure continuity of services.
Poor coordination among stakeholders	• Establish national policies and local plans to coordinate outbreak response. • Health and education authorities, at all levels, should support schools in prevention and control activities. • Clarify the role of each organization to ensure harmony and complementarity.
Media and community attention interference with outbreak response	• Outbreak communications should ensure 1) a clear, early announcement, 2) building and maintaining trust, 3) transparency and 4) understanding by the public. • Designate a communications staff to coordinate media requests and to provide regular public briefings. • Provide TB information and counselling to parents and students from the beginning of the outbreak.

LTBI, latent tuberculosis infection; TB, tuberculosis

Region. Despite differences in the TB burden and in outbreak preparedness, the countries faced similar challenges. The key lessons include the importance of early outbreak detection to prevent delayed TB diagnosis, establishment of resource mobilization networks to meet the demands for specialized clinicians and supplies for TB screening and treatment, coordination of stakeholders in non-health sectors (e.g. education) and proactive communications. Countries could adapt the principals to their context when developing a protocol for the prevention and control of TB outbreaks in schools.

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Conflicts of interest

The authors have no conflict of interests.

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Genomic surveillance of methicillin-resistant *Staphylococcus aureus* in the Philippines, 2013–2014

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Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the leading causes of both nosocomial and community infections worldwide. In the Philippines, MRSA rates have remained above 50% since 2010, but resistance to other antibiotics, including vancomycin, is low. The MRSA burden can be partially attributed to pathogen-specific characteristics of the circulating clones, but little was known about the *S. aureus* clones circulating in the Philippines.

We sequenced the whole genomes of 116 *S. aureus* isolates collected in 2013–2014 within the Antimicrobial Resistance Surveillance Program. The multilocus sequence type, *spa* type, SCC*mec* type, presence of antimicrobial resistance (AMR) determinants and virulence genes and relatedness between the isolates were all derived from the sequence data. The concordance between phenotypic and genotypic resistance was also determined.

The MRSA population in the Philippines comprised a limited number of genetic clones, including several international epidemic clones, such as CC30-*spa*-t019-SCC*mec*-IV-PVL+, CC5-SCC*mec*-typeIV and ST239-*spa*-t030-SCC*mec*-typeIII. The CC30 genomes were related to the South-West Pacific clone but formed a distinct, diverse lineage, with evidence of global dissemination. We showed independent acquisition of resistance to sulfamethoxazole/trimethoprim in various locations and genetic clones but mostly in paediatric patients with invasive infections. The concordance between phenotypic and genotypic resistance was 99.68% overall for eight antibiotics in seven classes.

We have made the first comprehensive genomic survey of *S. aureus* in the Philippines, which bridges the gap in genomic data from the Western Pacific Region and will constitute the genetic background for contextualizing prospective surveillance.

Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the leading causes of both nosocomial and community infections worldwide.[1] Asian countries such as China, Japan, the Republic of Korea and Taiwan (China) have reported high prevalence rates of 70–80% for nosocomial MRSA.[2,3] In the Philippines, the MRSA rates have increased steadily since 2004 and remained above 50% since 2010, while resistance rates to antibiotics other than β-lactams are low[4,5] (**Fig. 1A-B**).

Several notable epidemic clones have spread across Asia, their multilocus sequence types (MLSTs) being ST30 (China, Hong Kong SAR [China], Japan, Kuwait, Malaysia, the Philippines, Singapore and Taiwan [China]), ST239 (China, India, the Philippines, the Republic of Korea, Taiwan [China], Thailand and Viet Nam), ST5 (China, Hong Kong SAR [China], Japan, the Philippines, the Republic of Korea, Sri Lanka and Taiwan [China]), ST59 (China, Hong Kong SAR [China], Sri Lanka, Taiwan [China] and Viet Nam) and ST72 (Republic of Korea).[3,6,7] MRSA strains have emerged independently in the context of different epidemic clones[8] by acquiring the staphylococcal cassette chromosome *mec* (SCC*mec*) that carries the *mec*A or *mec*C gene, which confers resistance to methicillin and most β-lactam antibiotics. Importantly,

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Fig. 1. **Annual resistance rates of *S. aureus* isolates to nine antibiotics, 2005–2014**

Fig. 1A. PEN: penicillin; OXA: oxacillin; VAN: vancomycin.

Fig. 1B. GEN: gentamicin; ERY: erythromycin; CLI: clindamycin.

Fig. 1C. TCY: tetracycline; CIP: ciprofloxacin; SXT: sulfamethoxazole/trimethoprim.

some MRSA clones have also acquired resistance to vancomycin, the first-line antibiotic treatment for severe MRSA infections in hospitals,[9] although vancomycin resistance has remained very low in the Philippines.[5]

Current infection control in the Philippines includes following patients with MRSA infection and laboratory-based surveillance to determine the antimicrobial susceptibility pattern. The MRSA burden can, however, be attributed partially to pathogen-specific characteristics of the circulating clones, such as antibiotic resistance and virulence genes.[1] Hence, good understanding of the genomic epidemiology of MRSA in the Philippines will aid in the control and management of MRSA infections.

METHODS

Bacterial isolates

Data on a total of 6211 *S. aureus* isolates were collected by the Antimicrobial Resistance Surveillance Program (ARSP) of the Philippines Department of Health during the period January 2013 to December 2014. Isolates found to be resistant to oxacillin (i.e. MRSA) were subsequently referred to the ARSP reference laboratory for confirmation. Of the 412 and 384 isolates referred in 2013 and 2014, respectively, a total of 118 MRSA isolates from 17 sentinel sites were selected for whole-genome sequencing (WGS) on the basis of their resistance profile (**Table 1**), with the following criteria: i) referred to the ARSP reference laboratory in 2013–2014; ii) complete resistance profile (i.e. no missing susceptibility data); iii) overall prevalence of the resistance profile in the ARSP data (both referred and non-referred isolates); iv) geographical representation of different sentinel sites, with the number of isolates included from each site proportional to their relative abundance and estimated from (n/N)*100 (rounded up), where n is the total number of isolates from one site and N is the grand total of isolates; and v) when both invasive and non-invasive isolates representing a combination of resistance profile, sentinel site and year of collection were available, invasive isolates (i.e. from blood, or cerebrospinal, joint, pleural and pericardial fluids) were given priority. We used a proxy definition for "infection origin", whereby the first isolates collected from patients in the community or on either of the first two days of hospitalization were categorized as isolates from community-acquired infections, while isolates collected on day three in hospital or later were categorized as isolates from hospital-acquired infections.[10]

Antimicrobial susceptibility testing

All *S. aureus* isolates in this study were tested for susceptibility to 14 antibiotics in eight classes: penicillin, oxacillin, cefoxitin, chloramphenicol, sulfamethoxazole/trimethoprim, gentamicin, erythromycin, clindamycin, tetracycline, ciprofloxacin, levofloxacin, rifampicin, linezolid and vancomycin. The susceptibility of the isolates was determined at the ARSP reference laboratory with

Table 1. **Numbers of *S. aureus* and MRSA isolates analysed by the ARSP and referred to the reference laboratory during 2013 and 2014, isolates submitted for WGS and high-quality MRSA genomes obtained, discriminated by sentinel site and AMR profile**

	Number of isolates		
	2013	2014	Total
Total ARSP			
S. aureus	2682	3529	6211
MRSA	1421 (53%)	2128 (60%)	3549 (57%)
Referred to reference laboratory			
S. aureus	412	384	796
MRSA	381 (92%)	354 (92%)	735 (92%)
MRSA submitted for WGS	57	61	118
MRSA high-quality genomes	55	61	116
By sentinel site[a]			
BGH	6	3	9
BRH	0	1	1
CMC	2	2	4
CVM	6	4	10
DMC	4	3	7
EVR	2	3	5
FEU	3	3	6
GMH	2	3	5
JLM	2	4	6
MAR	4	5	9
MMH	1	2	3
NKI	3	4	7
NMC	3	3	6
SLH	0	1	1
STU	5	5	10
VSM	12	13	25
ZMC	0	2	2
By AMR profile			
PEN OXA	45	59	104
PEN OXA SXT	7	2	9
PEN OXA GEN ERY CLI TCY CIP	2	0	2
PEN OXA ERY	1	0	1

[a]: BGH: Baguio General Hospital and Medical Center; BRH: Batangas Medical Center; CMC: Cotabato Regional and Medical Center; CVM: Cagayan Valley Medical Center; DMC: Southern Philippines Medical Center; EVR: Eastern Visayas Regional Medical Center; FEU: Far Eastern University - Nicanor Reyes Medical Foundation; GMH: Governor Celestino Gallares Memorial Hospital; JLM: Jose B. Lingad Memorial Regional Hospital; MAR: Mariano Marcos Memorial Hospital & Medical Center; MMH: Corazon Locsin Montelibano Memorial Regional Hospital; NKI: National Kidney and Transplant Institute; NMC: Northern Mindanao Medical Center; SLH: San Lazaro Hospital; STU: University of Santo Tomas Hospital; VSM: Vicente Sotto Memorial Medical Center; ZMC: Zamboanga City Medical Center.

b CIP: ciprofloxacin; CLI: clindamycin; ERY: erythromycin; GEN: gentamycin; PEN: penicillin; OXA: oxacillin; SXT: sulfamethoxazole/trimethoprim; TCY: tetracycline.

the Kirby-Bauer disc diffusion method and/or a Vitek 2 Compact automated system (bioMérieux, Marcy-l'Étoile, France). The zone of inhibition and the minimum inhibitory concentration of antibiotics were interpreted according to the 26th edition of the Clinical and Laboratory Standard Institute guidelines.[11]

DNA extraction and whole-genome sequencing

A total of 118 MRSA isolates were shipped to the Wellcome Trust Sanger Institute for WGS. DNA was extracted from a single colony of each isolate with a QIAamp 96 DNA QIAcube HT kit and QIAcube HT (Qiagen, Hilden, Germany). DNA extracts were multiplexed and sequenced on the Illumina HiSeq platform (Illumina, CA, USA) with 100-bp paired-end reads. Raw sequence data were deposited in the European Nucleotide Archive under study accession No. PRJEB17615. Run accessions are provided on the Microreact projects.

Bioinformatics analysis

Genome quality was evaluated with metrics generated from raw read files, assembly files, annotation files and alignment of the isolates to the reference genome of *S. aureus* subsp. *aureus* strain TW20 (accession FN433596), as previously described.[12] Annotated assemblies were produced as previously described.[13] Briefly, sequence reads were assembled with VelvetOptimiser v2.2.5 and Velvet v1.2. Automated annotation was performed with PROKKA v1.5 and a genus-specific database from RefSeq. A total of 116 high-quality *S. aureus* genomes were included in the study, characterized by assemblies of < 60 contigs and N50 $> 144\,000$.

We derived the MLST, the *spa* type and SCC*mec* type of the isolates in silico from the whole-genome sequences. The sequence types (STs) were determined from assemblies with Pathogenwatch (https://pathogen.watch/) or from sequence reads with ARIBA[14] and the *S. aureus* database hosted at PubMLST.[15] The *spa* type was inferred with *spa*Typer v1.0.[16] The SCC*mec* type was derived from sequence reads with SRST2[17] and the database available at http://www.sccmec.org/joomla3/index.php/en/.

Evolutionary relations among isolates were inferred from single nucleotide polymorphisms (SNPs) by mapping the paired-end reads to the reference genomes of *S. aureus* strain TW20 (FN433596) or ILRI_Eymole1/1

(NZ_LN626917) with the Burrows Wheeler aligner (BWA) v0.7.12, as described in detail previously.[12] Mobile genetic elements were masked in the alignment of pseudogenomes with a script available at https://github.com/sanger-pathogens/remove_blocks_from_aln. For clonal complex (CC) 30 phylogeny, recombination regions detected with Gubbins[18] were also removed. SNPs were extracted with snp_sites,[19] and maximum likelihood phylogenetic trees were generated with RAxML[20] and the generalized time-reversible model with the GAMMA method of correction for among-site rate variation and 100 bootstrap replications. The tree of 7821 global *S. aureus* genomes available at the European Nucleotide Archive with geolocation and isolation date was inferred by an approximately maximum likelihood phylogenetic method with FastTree.[21] The CC30 genomes were contextualized with global genomes by using Pathogenwatch (https://pathogen.watch/), which infers trees based on genetic similarity and predicts genotypic AMR. Genome assemblies were generated from read files as described above or downloaded from the National Center for Biotechnology Information if raw Illumina data were not made available. The project and sample accessions are listed on the Pathogenwatch table (https://pathogen.watch/collection/vi3stmhtqnbs-arsp-sau-cc30-2013-2014-global).

Known AMR determinants and the Panton-Valentine leukocidin (PVL) *lukF-PV* and *lukS-PV* genes were identified from raw sequence reads with ARIBA[14] and a curated database of known resistance genes and mutations.[22] Resistance was predicted from the presence of known AMR genes and mutations identified in the genome sequences. The genomic predictions of AMR (test) were compared with the phenotypic results (reference), and the concordance between the two methods was computed for each of eight antibiotics (928 total comparisons). Isolates with either a resistant or an intermediate phenotype were considered non-susceptible for comparison purposes. An isolate with the same outcome for both the test and reference (i.e. both susceptible or both non-susceptible) was counted as a concordant isolate. The concordance was the number of concordant isolates over the total number of isolates assessed (expressed as per cent).

All project data, including inferred phylogeny, AMR predictions and metadata, were made available through the web application Microreact (http://microreact.org).

Ethics statement

Ethical approval is not applicable. This study is based on archived bacterial samples processed by ARSP. No identifiable data were used in this study.

RESULTS

Demographics and characteristics of MRSA isolates

Of the 118 MRSA isolates submitted for WGS, 116 were confirmed as *S. aureus* in silico, while two isolates were identified as *Staphylococcus argenteus* and were not included in the downstream analyses. The age range of the patients was <1 to 90 years; 20% (n = 23) of the isolates were from patients aged <1 year (**Table 2**). Of the 116 isolates, 56% were recovered from male patients (n = 66) and 44% from females (n = 50). As invasive isolates were prioritized, the most common specimen source was blood (62%, n = 72), followed by wounds (19%, n = 22). The majority of the infections (68%, n = 79) were classified as community-associated MRSA.

Concordance between phenotypic and genotypic AMR

Isolates were tested for susceptibility to 14 antibiotics in eight classes. All the isolates were susceptible to vancomycin and linezolid and resistant to penicillin, oxacillin and cefoxitin, consistent with the presence of the *blaZ* and *mecA* genes (**Table 3**). Nine isolates were resistant to cotrimoxazole, which was associated with the presence of the *dfrG* gene. Two isolates were multidrug-resistant and carried genes and mutations for resistance to penicillin (*blaZ, mecA*), oxacillin (*mecA*), cefoxitin (*mecA*), gentamicin (*aacA-aphD*), erythromycin (*ermC, msrA*), clindamycin (*ermC*), tetracycline (*tetM, tetK*), ciprofloxacin and levofloxacin (GyrA_S84L, GyrA_G106D, and GrlA_S80F mutations), chloramphenicol (*catA1*) and rifampicin (*rpoB*_H481N). The *IleS* gene

Table 2. **Demographics and clinical characteristics of 116 MRSA isolates**

Characteristic	No. of isolates
Sex	
Male	66
Female	50
Age (years)	
<1	23
1–4	9
5–14	16
15–24	14
25–34	8
35–44	17
45–54	14
55–64	9
65–80	1
≥81	5
Patient type	
Inpatient	104
Outpatient	12
Specimen origin	
Community-acquired	79
Hospital-acquired	37
Specimen type	
Abdominal fluid*	1
Abscess	4
Aspirate	2
Blood*	72
Bone	1
Cerebrospinal fluid*	2
Pericardial fluid*	1
Tracheal aspirate	5
Urine	2
Wound	22
Others	1

Isolates considered to be invasive are those obtained from specimen types marked with an asterisk (*).

that confers resistance to mupirocin and the *sdrM* gene conferring resistance to norfloxacin were identified in three and 23 isolates, respectively; however, mupirocin was not tested in the laboratory, and norfloxacin was tested only against isolates from urine specimens. Hence, these two antibiotics were not included in the concordance analysis.

Comparisons between phenotypic and genotypic data are presented for eight key antibiotics in seven classes (**Table 3**). The overall concordance for the 928 comparisons was 99.68%, and the concordance for individual antibiotics was >98% in all cases (**Table 3**). The notable exceptions were two false-negative results for oxacillin resistance, i.e. isolates confirmed to be phenotypically resistant but without the *mec*A resistance gene. Conversely, one isolate was falsely predicted to be resistant to sulfamethoxazole/trimethoprim on the basis of the presence of the *dfrG* gene.

Genotypic findings

In silico genotyping

MLST, *spa* type and SCC*mec* type were predicted in silico from the WGS data for the 116 MRSA isolates. A total of 18 STs were identified; 74.1% (n = 86) of the isolates belonged to clonal complex (CC) 30, distributed between ST30 (n = 81), its single-locus variant ST1456 (n = 2) and three ST30 genomes showing novel *aroE* (n = 2) and *yqiL* (n = 1) alleles. CC5 was represented by nine genomes and ST834 by six. The most prevalent of the 29 different *spa* types identified was t019 (62%), which coincided with genomes assigned to CC30. The *spa* types identified for the CC5 genomes were t002 (n = 5), t105 (n = 3) and t067 (n = 1). Most of the

Table 3. **Comparison of genomic predictions of antibiotic resistance with laboratory susceptibility testing at the ARSP reference laboratory**

Antibiotic class	Antibiotic	Resistant isolates	False-positive	False-negative	Concordance (%)	Resistance genes/SNPs
Penicillin	Penicillin	116	0	0	100	*blaZ, mecA*
Penicillin	Oxacillin	116	0	2	98.28	*mecA*
Folate pathway antagonist	Sulfamethoxazole/ Trimethoprim	9	1	0	99.14	*dfrG*
Aminoglycoside	Gentamicin	2	0	0	100.00	*aacA_aphD*
Lincosamide	Clindamycin	2	0	0	100	*ermC*
Macrolide	Erythromycin	3	0	0	100	*ermC, msrA*
Tetracycline	Tetracycline	2	0	0	100	*tetM, tetK*
Fluoroquinolone	Ciprofloxacin	2	0	0	100	GyrA_S84L, GyrA_G106D, GrlA_S80F

SCC*mec* cassettes identified in the genomes belonged to type IV (n = 108, 93.1%), followed by type III (*n* = 2, 1.7%). The SCC*mec* type could not be determined for four genomes. The numbers and most common ST and *spa* types found in each of the sentinel sites are shown in **Table 4**. Overall, the typing results for the genome sequences showed that CC30-*spa*-t019-SCC*mec*-IV was the most prevalent MRSA clone in this retrospective collection (*n* = 67, 57.8%).

Population structure of MRSA in the Philippines

The phylogenetic tree shows that the population was composed of discrete clades that matched the ST distribution and were separated by long branches (**Fig. 2A**), in agreement with the clonal population previously described for *S. aureus*.[23] The largest clade represented by CC30-*spa*-t019-SCC*mec*-IV was characterized by broad geographical distribution across the 17 sentinel sites in this data set (**Table 4**), as it was found in both community- and health-care-associated isolates obtained from at least 11 different specimen types. WGS revealed distinct major sublineages within the CC30 clade (**Fig. 2B**), none of which displayed a strong phylogeographical signal. Both genes *lukS-PV* and *lukF-PV* that encode the PVL were found in 75 of the 86 CC30 genomes (**Fig. 2B**), indicating that the majority (87.2%) are PVL-positive (**Fig. 2B**).

Two additional epidemic clones were identified, CC5 and ST239 (CC8). Six of the nine CC5-SCC*mec*-typeIV (71%) were from paediatric patients (compared with 20% of the entire data set) and were generally clustered according to their *spa* type; however, they displayed no clear phylogeographical distribution. Two isolates from different, distant locations carried both *lukS-PV* and *lukF-PV* genes (PVL-positive). The two ST239 isolates were from the same patient, *spa* type t030, SCC*mec*-typeIII, PVL-negative and multidrug-resistant.

The nine isolates with resistance to sulfamethoxazole/trimethoprim were from four locations (Cagayan Valley Medical Center [CVM], Southern Philippines Medical Center [DMC], Vicente Sotto Memorial Medical Center [VSM] and Zamboanga City Medical Center [ZMC]) and belonged to four different clones (CC30, CC5, ST1649 and ST834), which suggests that resistance to this antibiotic has emerged independently (**Table 4**). The isolates were obtained from blood (*n* = 8) and an abscess (*n* = 1) and, interestingly, mainly from paediatric patients (6 of 7, 85.7% of pediatric patients, in comparison with 46.6% of paediatric patients in the total data set).

MRSA in the Philippines in the global context

We placed the genomes from our retrospective collection in the global context of 7821 contemporary *S. aureus* public genomes available from sequence data archives with linked geographical and temporal information, collected between 2010 and 2017. This public collection of genomes represents 57 countries and 379 STs, but it is heavily biased towards genomes from Europe (*n* = 3556) and the United States of America (*n* = 3241) and the epidemic clones ST8 (*n* = 2343), ST22 (*n* = 1526) and ST5 (*n* = 720) prevalent in those regions (**Fig. 3A**). Health-care-associated EMRSA-15 (ST22) was notably absent from our collection, as was livestock-associated CC398 (**Fig. 3A**). The Philippine ST5 genomes did not form a monophyletic group within the CC5 clade, suggesting more than one origin. CC30-*spa*-t019-SCC*mec*-IV-PVL+ MRSA genomes from the Philippines formed a discrete cluster within ST30 with small numbers of genomes from the United States of America (*n* = 5), the United Kingdom of Great Britain and Northern Ireland (*n* = 3) and Germany (*n* = 1, **Fig. 3B**).

Several successful pandemic clones have emerged within CC30, such as the methicillin-sensitive phage type 80/81,[24] the MRSA South-West Pacific clone,[25] the hospital-endemic epidemic MRSA-16 (ST36[26]) and epidemic MSSA-ST30.[27] We investigated the relations between the Philippine MRSA genomes in this study and these clones with Pathogenwatch. The Philippine genomes were clustered into several clades related to but distinct from the South-West Pacific clone, representing a new diversification from this clone (**Fig. 3B**). In addition, the genomes from the Philippines clustered with genomes from Argentina, Germany, the United Kingdom and the USA (**Fig. 3C**), indicating that the epidemic diversification from the South-West Pacific clone was accompanied by global dissemination.

DISCUSSION

In this study, we combined WGS and laboratory-based surveillance to characterize MRSA circulating in the Philippines in 2013 and 2014. High levels of concord-

Table 4. **Distribution of isolates, STs, *spa* types, resistance profiles and AMR genes and mutations at the 17 sentinel sites**

Laboratory[b]	No. of isolates	No. of STs	Prevalent ST (no. of isolates)	No. of *spa* types	Prevalent *spa* type (no. of isolates)	Resistance profiles[a]	Resistance genes
BGH	9	4	30 (6)	5	t019 (5)	PEN OXA (9)	*blaZ, mecA* (6) *blaZ, mecA, sdrM* (2) *blaZ, sdrM* (1)
BRH	1	1	30 (1)	1	t019 (1)	PEN OXA (1)	*blaZ, mecA* (1)
CMC	4	1	30 (4)	2	t019 (3)	PEN OXA (4)	*blaZ, mecA* (4)
CVM	10	6	30 (4)	6	t019 (4)	PEN OXA (9) PEN OXA SXT (1)	*blaZ, mecA* (5) *blaZ, mecA, sdrM* (3) *mecA* (1) *blaZ, mecA, dfrG, sdrM* (1)
DMC	7	4	30 (4)	3	t019 (5)	PEN OXA (3) PEN OXA SXT (4)	*blaZ, mecA* (3) *blaZ, mecA, dfrG* (3) *blaZ, mecA, dfrG, sdrM* (1)
EVR	5	3	30 (3)	3	t019 (3)	PEN OXA (5)	*blaZ, mecA* (4) *blaZ, mecA, dfrG, sdrM* (1)
FEU	6	1	30 (6)	3	t019 (3)	PEN OXA (6)	*blaZ, mecA* (6)
GMH	5	1	30 (5)	1	t019 (5)	PEN OXA (5)	*blaZ, mecA* (5)
JLM	6	3	5 (3)	3	t002 (3)	PEN OXA (6)	*blaZ, mecA* (5) *blaZ, mecA, sdrM* (1)
MAR	9	3	30 (6)	2	t019 (7)	PEN OXA (7) PEN OXA GEN ERY CLI TCY CIP (2)	*blaZ, mecA* (7) *blaZ, mecA, aacA_aphD, ermC, tetM, tetK*, GyrA_S84L, GyrA_G106D, GrlA_S80F, *catA1, sdrM, ileS_2* (2)
MMH	3	1	30 (3)	3	t019 (1), t3800 (1), t975 (1)	PEN OXA (3)	*blaZ, mecA* (3)
NKI	7	4	30 (4)	4	t019 (4)	PEN OXA (7)	*blaZ, mecA* (6) *blaZ, sdrM* (1)
NMC	6	1	30 (6)	1	t019 (6)	PEN OXA (6)	*blaZ, mecA* (6)
SLH	1	1	30 (1)	1	t019 (1)	PEN OXA (1)	*blaZ, mecA* (1)
STU	10	3	30 (8)	2	t019 (9)	PEN OXA (10)	*blaZ, mecA* (9) *blaZ, mecA, sdrM* (1)
VSM	25	6	30 (17)	14	t019 (12)	PEN OXA (21) PEN OXA SXT (3) PEN OXA ERY (1)	*blaZ, mecA* (16) *mecA, sdrM* (1) *blaZ, mecA, sdrM* (3) *blaZ, mecA, sdrM, ileS_2* (1) *blaZ, mecA, dfrG* (1) *blaZ, mecA, dfrG, sdrM* (2) *blaZ, mecA, msrA, sdrM* (1)
ZMC	2	2	30 (1), 5 (1)	2	t019 (1), t105 (1)	PEN OXA (1) PEN OXA SXT (1)	*blaZ, mecA* (1) *blaZ, mecA, dfrG, sdrM* (1)

[a] PEN: penicillin; OXA: oxacillin; GEN: gentamicin; ERY: erythromycin; CLI: clindamycin; TCY: tetracycline; CIP: ciprofloxacin; SXT: sulfamethoxazole/trimethoprim.

[b] BGH: Baguio General Hospital and Medical Center; BRH: Batangas Medical Center; CMC: Cotabato Regional and Medical Center; CVM: Cagayan Valley Medical Center; DMC: Southern Philippines Medical Center; EVR: Eastern Visayas Regional Medical Center; FEU: Far Eastern University - Nicanor Reyes Medical Foundation; GMH: Governor Celestino Gallares Memorial Hospital; JLM: Jose B. Lingad Memorial Regional Hospital; MAR: Mariano Marcos Memorial Hospital & Medical Center; MMH: Corazon Locsin Montelibano Memorial Regional Hospital; NKI: National Kidney and Transplant Institute; NMC: Northern Mindanao Medical Center; SLH: San Lazaro Hospital, STU: University of Santo Tomas Hospital; VSM: Vicente Sotto Memorial Medical Center; ZMC: Zamboanga City Medical Center.

ance between phenotypic and genotypic resistance were observed for all the antibiotics tested. This was previously reported for *S. aureus* collections in Europe and the United Kingdom,[27,28] but our results, the first from the Philippines, show no significant gaps in the epidemiology of known resistance mechanisms in this country. The integration of laboratory and WGS data showed independent acquisition of resistance to sufamethoxazole/trimethoprim mainly in paediatric patients with invasive infections. This is probably due to the selective pressure of antibiotic use, as co-trimoxazole was recommended by the Department of Health in the Philippines as one of the first-line antibiotics for paediatric patients with pneumonia in the 1990s and is currently the first-line antibiotic for skin and soft tissue MRSA infections in paediatric patients recommended in the Philippines National Antibiotic

Fig. 2. **Genomic surveillance of *S. aureus* from the Philippines, 2013–2014**

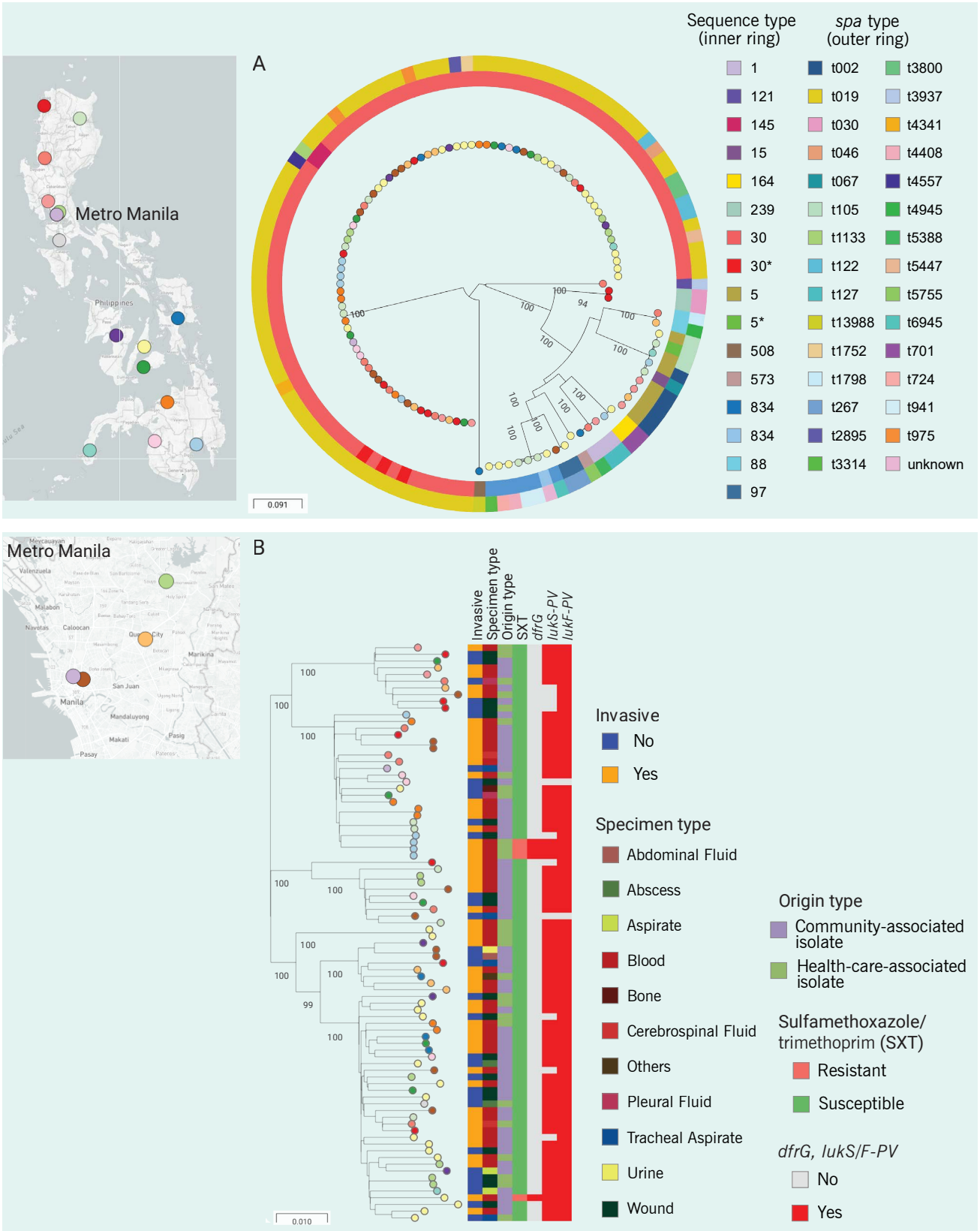

Fig. 2A. Phylogenetic tree of 116 MRSA isolates from the Philippines, inferred with RAxML from 96 514 single nucleotide polymorphism (SNP) sites. Inner ring: Sequence type. Outer ring: *spa* type. The data are available at https://microreact.org/project/ARSP_SAU_2013-2014.

Fig. 2B. Phylogenetic tree of 86 CC30 isolates inferred with RAxML from 4780 core SNPs obtained after mapping the genomes to the complete genome of strain Eymole1 (ST30) and masking mobile genetic elements and recombination regions from the alignment. The data are available at https://microreact.org/project/ARSP_SAU_CC30_2013-2014.

The tree leaves are coloured by sentinel site. The scale bars represent the number of SNPs per variable site. The major tree branches are annotated with bootstrap values.

Fig. 3. ***S. aureus* from the Philippines in the global context**

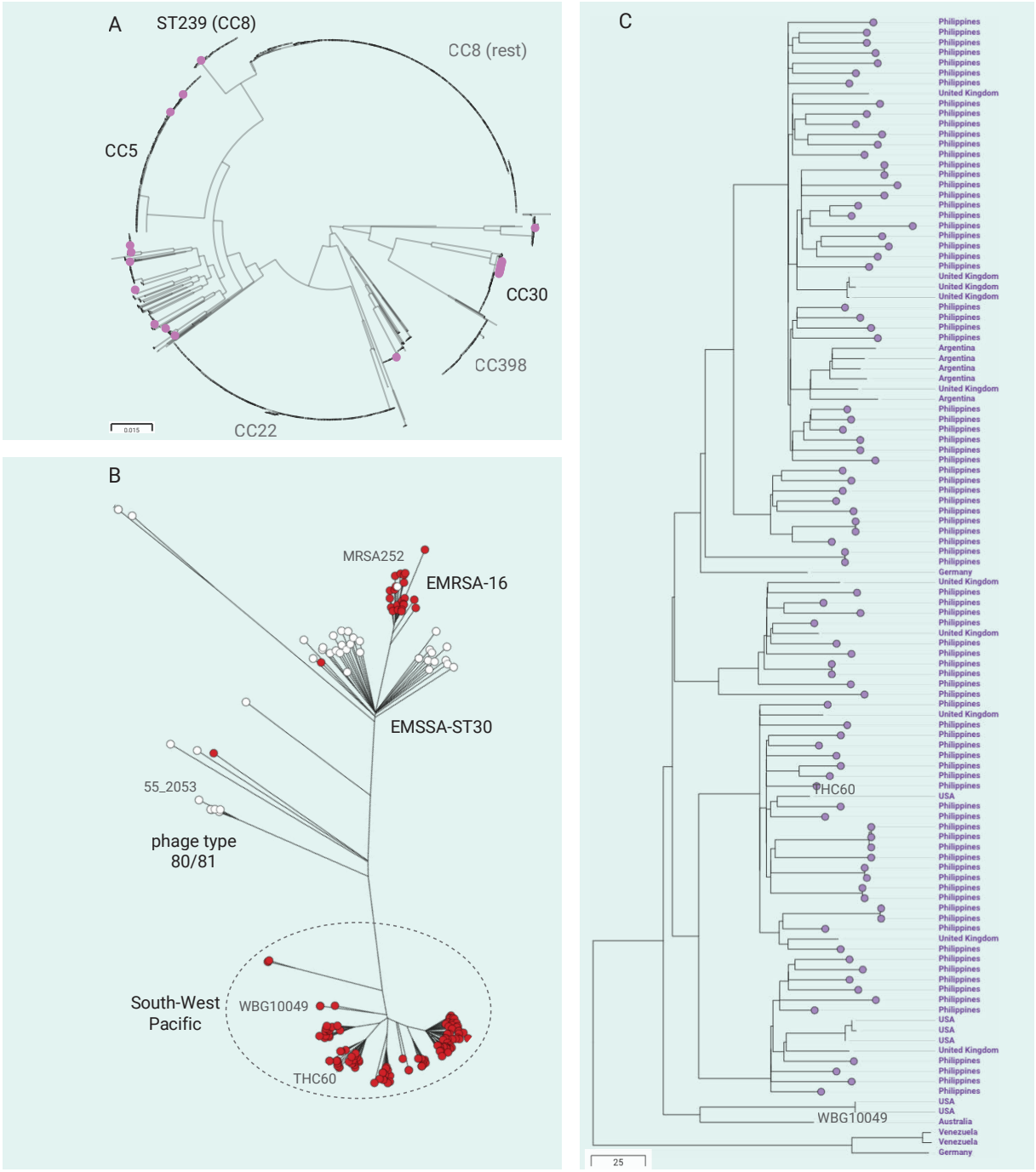

Fig. 3A. Phylogenetic tree of 7821 *S. aureus* isolates from the Philippines (n = 116, this study) and from 57 other countries inferred with FastTree from 485 031 SNP positions. The magenta tree nodes indicate the genomes from this study. The major lineages (CCs and STs) are labelled in black if represented by genomes of this study or in grey if they are not. The scale bar represents the number of SNPs per variable site. The data are available at https://microreact.org/project/Global_SAU.

Fig. 3B. Pathogenwatch tree of 176 CC30 genomes comprising 86 genomes from this study and 90 global genomes. Red nodes denote MRSA genomes and white nodes methicillin-sensitive genomes. The tree is annotated with previously described CC30 clones (black) and their representative reference genomes (grey). The genomes from this study are found within the group of genomes encircled with a dotted line, which is displayed in detail with geographical locations in panel C. The collection is available at https://pathogen.watch/collection/qtfy5h5q34a7-arsp-sau-cc30-2013-2014-global.

CC: clonal context; MRSA: methicillin-resistant *Staphylococcus aureus*; SNP: single nucleotide polymorphism; ST: sequence type.

Guideline for 2017. While none of the isolates referred to the Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL) were confirmed to display intermediate resistance or to be resistant to vancomycin by broth microdilution as per Clinical & Laboratory Standards Institute (CLSI) guidelines, susceptibility testing at ARSRL does not currently include protocols for the detection of vancomycin heteroresistance (hVISA).

Few studies of the molecular epidemiology of MRSA in the Philippines have been published. We found that the MRSA population in 2013 and 2014 comprised a limited number of genetic lineages, dominated by CC30-*spa*-t019-SCC*mec*-IV-PVL+. Community-acquired CC30-*spa*-t019-PVL+ MRSA was previously reported in one hospital in the Philippines between 2004 and 2006 and from other countries in South-East Asia, with potential clonal expansion.[3,6] This suggests that the increase in the burden of MRSA observed in the Philippines since 2004 is linked to extension of this clone. A longer retrospective sequencing survey would provide more detailed insight into the dynamics of this clone. The lack of a clear phylogeographical structure in this established clone may be related to its ability to disseminate both within hospitals and in the community and within the community, followed by nosocomial transmission,[29] in the dense population of the Philippines. However, specimens were collected from patients for clinical purposes, not screening, and only a subset of isolates were sequenced. Thus, we cannot rule out the possibility that the lack of phylogeographic structure is the result of incomplete coverage. In addition, the ARSP hospital-based surveillance would have to be complemented by community surveillance to determine the dynamics of MRSA in the population at large. Only a few publicly available global genomes were found to be closely related to the CC30 genomes in this study, highlighting the paucity of WGS data from continents other than Europe and North America. The availability of other genomes would enhance our understanding of the global epidemiology of this clone.

Genotypic characterization of circulating MRSA strains, with phenotypic and epidemiological data, led to the identification of several global epidemic clones and revealed the lack of a strong phylogeographic structure in the population from patients admitted to health-care facilities in a country with a high burden of MRSA. This supports interventions to reduce the burden of disease in the general population.[6] Targeted eradication interventions may be useful in individual hospitals, where high-risk epidemic clones such as ST239 may cause local outbreaks. Our results represent the first comprehensive genomic survey of *S. aureus* in the Philippines, bridging the gap in genomic data from the Western Pacific Region, and provides the genetic background for contextualizing prospective surveillance for infection control.

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Conflicts of interest

The authors declare no conflicts of interest.

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Genomic surveillance of *Neisseria gonorrhoeae* in the Philippines, 2013–2014

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Antimicrobial-resistant *Neisseria gonorrhoeae* is a major threat to public health and is of particular concern in the Western Pacific Region, where the incidence of gonorrhoea is high. The Antimicrobial Resistance Surveillance Program (ARSP) has been capturing information on resistant gonorrhoea since 1996, but genomic epidemiology studies on this pathogen are lacking in the Philippines.

We sequenced the whole genomes of 21 *N. gonorrhoeae* isolates collected in 2013–2014 by ARSP. The multilocus sequence type, multiantigen sequence type, presence of determinants of antimicrobial resistance and relatedness among the isolates were all derived from the sequence data. The concordance between phenotypic and genotypic resistance was also determined.

Ten of 21 isolates were resistant to penicillin, ciprofloxacin and tetracycline, due mainly to the presence of the bla_{TEM} gene, the S91F mutation in the *gyrA* gene and the *tetM* gene, respectively. None of the isolates was resistant to ceftriaxone or cefixime. The concordance between phenotypic and genotypic resistance was 92.38% overall for five antibiotics in four classes. Despite the small number of isolates studied, they were genetically diverse, as shown by the sequence types, the *N. gonorrhoeae* multiantigen sequence typing types and the tree. Comparison with global genomes placed the Philippine genomes within global lineage A and led to the identification of an international transmission route.

This first genomic survey of *N. gonorrhoeae* isolates collected by ARSP will be used to contextualize prospective surveillance. It highlights the importance of genomic surveillance in the Western Pacific and other endemic regions for understanding the spread of drug-resistant gonorrhoea worldwide.

Neisseria gonorrhoeae is a leading cause of sexually transmitted infections, with an estimated 78 million cases of gonorrhoea each year worldwide, including 35.2 million in the WHO Western Pacific Region.[1] In the Philippines, the prevalence of gonorrhoea in 2002 was reported to be <2% for both men and women,[2] with higher rates of 7.7% and 10.8% among men who have sex with men at two different sites in 2005.[3]

N. gonorrhoeae has developed resistance to first-line antibiotics such as sulfonamides, penicillins, tetracyclines, macrolides, fluoroquinolones and early cephalosporins. Currently recommended monotherapy for gonorrhoea is limited to one last effective class of antimicrobials, the extended-spectrum cephalosporins (e.g. cefixime and ceftriaxone); however, because of the recent emergence of resistance to these drugs, dual therapy with the injectable ceftriaxone plus oral azithromycin is the recommended treatment in many countries.[4] While resistance to azithromycin has also increased globally,[1] resistance to the dual therapy remains low.[5]

The increase in *N. gonorrhoeae* infections resistant to front-line antibiotics triggered a global action plan from WHO to control the spread and impact of gonococcal resistance and a call for international collaborative action, especially in the Western Pacific Region.[1] The WHO

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Gonococcal Antimicrobial Surveillance Programme has operated in the Western Pacific and South-East Asian regions since 1992, but surveillance of gonococcal antimicrobial resistance (AMR) remains limited in the Asia–Pacific region.[6] In a recent report, 18 of 21 countries in the Asia and the Pacific reported isolates with decreased susceptibility to ceftriaxone and/or isolates resistant to azithromycin between 2011 and 2016.[6] The Antimicrobial Resistance Surveillance Program (ARSP) of the Philippines Department of Health has been contributing AMR surveillance data to the Western Pacific Gonococcal Antimicrobial Surveillance Programme since 1996 and did not confirm isolates with decreased susceptibility or resistance to these antibiotics during 2011–2016,[6] while high gonococcal resistance rates against other first-line antibiotics have long been reported (**Fig. 1**). Continuous surveillance is thus key to detecting potential emergence or introduction of resistance to current treatment options.

Molecular methods for defining the epidemiology of gonococci include both *N. gonorrhoeae* multiantigen sequence typing (NG-MAST)[7] and multilocus sequence typing (MLST),[8] although NG-MAST is more widely used to investigate specific gonococcal AMR phenotypes.[8] Whole-genome sequencing (WGS) was recently shown to provide better resolution and accuracy than NG-MAST or MLST.[9] Good understanding of the population structure and the mechanisms of resistance of *N. gonorrhoeae* in the Philippines would allow detection of high-risk clones associated with high-risk groups and contribute to the clinical management of gonococcal-related diseases and the creation of policies to prevent the spread of drug resistance.[10,11] Here, we describe the results of the first genomic survey of gonococcal isolates in the Philippines.

METHODS

Bacterial isolates

A total of 51 *N. gonorrhoeae* isolates were collected at ARSP sentinel sites in 2013 and 2014 (**Table 1**). Of the 36 isolates referred to the ARSP reference laboratory for confirmation, 22 isolates from seven sentinel sites were resuscitated and submitted for WGS.

Antimicrobial susceptibility testing

All *N. gonorrhoeae* isolates in this study were tested at the ARS reference laboratory for susceptibility to five antimicrobials representing four different classes, namely penicillin (PEN), ciprofloxacin (CIP), tetracycline (TCY), ceftriaxone (CRO) and cefixime (CFX), by disc diffusion and gradient diffusion (Etest, BioMerieux). The minimum inhibitory concentrations were interpreted as resistant, intermediate or susceptible according to the interpretative criteria in the Performance Standards for Antimicrobial Susceptibility Testing (26th edition) of the Clinical and Laboratory Standards Institute (CLSI).[12] All isolates were screened for β-lactamase production on cefinase paper discs (BD BBL). Azithromycin was not included in the panel of antibiotics, because, at the time isolates were collected, it was not in the treatment guidelines of the Philippines and no CLSI breakpoint was available.

DNA extraction and whole-genome sequencing

DNA was extracted from a single colony of each isolate with a Wizard® Genomic DNA Purification Kit (Promega), and the quantity and quality were determined with a Quantus Fluorometer (Promega) with picogreen and a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific). The DNA extracts were then shipped to Wellcome Trust Sanger Institute for sequencing on the Illumina HiSeq platform with 100-bp paired-end reads. Raw sequence data were deposited in the European Nucleotide Archive under the study accession number PRJEB17615. Run accessions are provided on the Microreact projects.

Bioinformatics analysis

Genome quality was evaluated according to metrics generated from assemblies, annotation files and the alignment of the isolates to the reference genome of *N. gonorrhoeae* strain TCDC-NG08107 (accession CP002441.1), as previously described.[13] Annotated assemblies were produced with the pipeline previously described.[14] We included 21 high-quality *N. gonorrhoeae* genomes in this study.

The MLST sequence types (STs) and NG-MAST types, as well as the presence of AMR determinants (known genes or mutations) and clustering of the isolates according to genetic similarity (tree), were predicted in *silico* from genome assemblies with Pathogenwatch (https://www.sanger.ac.uk/tool/pathogenwatch/).[15] In parallel, the evolutionary relations among the isolates were inferred from single nucleotide polymorphisms

Fig. 1. **Annual resistance rates of *N. gonorrhoeae* between 2000 and 2014 for penicillin (PEN), ciprofloxacin (CIP) and tetracycline (TCY)**

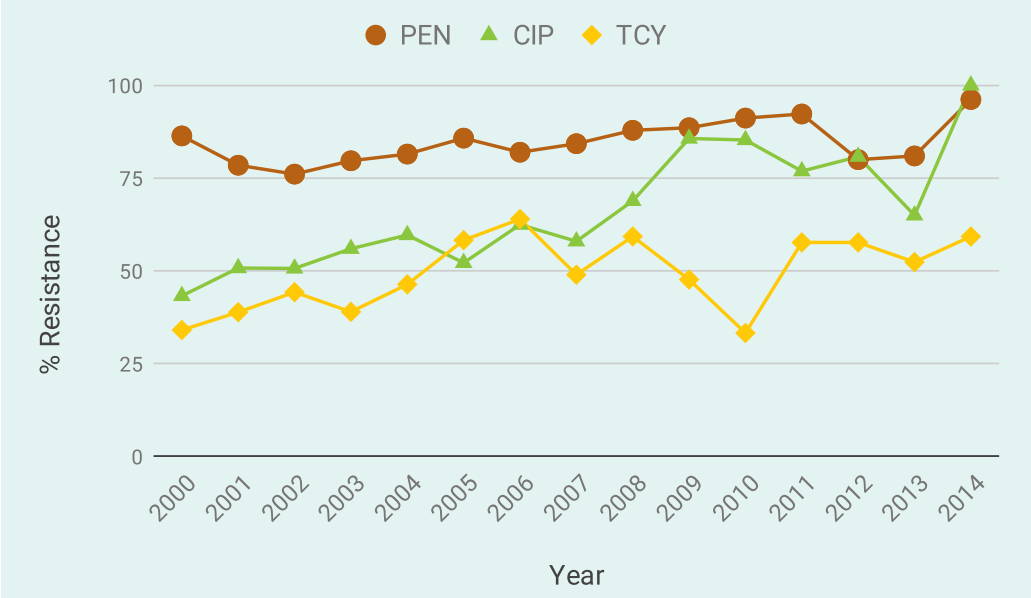


Table 1. **Number of *N. gonorrhoeae* isolates analysed by ARSP and referred to the reference laboratory during 2013 and 2014, isolates submitted for WGS and high-quality *N. gonorrhoeae* genomes obtained, by sentinel site and AMR profile**

	Number of isolates		
	2013	2014	Total
Total ARSP	24	27	51
Referred to reference laboratory	16	20	36
Submitted for WGS	8	14	22
High-quality genomes	8	13	21
By sentinel site			
CVM	0	1	1
DMC	1	0	1
EVR	1	0	1
MMH	1	1	2
NMC	0	1	1
VSM	5	6	11
ZPH	0	4	4
By AMR profile			
PEN CIP TCY	2	8	10
PEN CIP	4	4	8
PEN	2	0	2
CIP TCY	0	1	1

CVM: Cagayan Valley Medical Center, DMC: Southern Philippines Medical Center, EVR: Eastern Visayas Regional Medical Center, MMH: Corazon Locsin Montelibano Memorial Regional Hospital, NMC: Northern Mindanao Medical Center, VSM: Vicente Sotto Memorial Medical Center, ZPH: Zamboanga Del Norte Medical Center

PEN: penicillin, CIP: ciprofloxacin, TCY: tetracycline

(SNPs) by mapping the paired-end reads to the reference genome of *N. gonorrhoeae* strain FA 1090 (accession AE004969.1), as described in detail previously.[13] Mobile genetic elements described in the FA 1090 genome[16] were masked in the alignment of pseudogenomes with a script available at https://github.com/sanger-pathogens/remove_blocks_from_aln. SNPs were extracted with snp-sites,[17] and a maximum likelihood phylogenetic tree was generated from 7518 SNP positions with RAxML,[18] the generalized time-reversible model and the GAMMA method of correction for among-site rate variation, with 500 bootstrap replicates.

To complement the Pathogenwatch AMR results, known AMR determinants were identified from raw sequence reads with ARIBA[19] and a curated database of known resistance genes and mutations available at https://github.com/martinghunt/ariba-publication/tree/master/N_gonorrhoeae/Ref. The combined genotypic predictions of AMR (test) were compared with the phenotypic results (reference), and the concordance between the two methods was computed for each of five antibiotics (105 total comparisons). Isolates found to be resistant or to have reduced susceptibility (intermediate) were pooled as non-susceptible for comparison purposes. An isolate with the same outcome for both the test and reference (i.e. both susceptible or both non-susceptible) was counted as a concordant isolate. Concordance was the number of concordant isolates

over the total number of isolates assessed (expressed as a percentage).

The maximum likelihood tree, genotyping results and AMR predictions and the metadata collected from the sentinel sites were visualized with Microreact.[20]

To contextualize the genomes from this study with publicly available global genomes, we combined them with two surveys available on Pathogenwatch, a European survey of 1054 genomes[10] and a global survey of 395 genomes.[21]

Ethics statement

Ethical approval is not applicable, as we used archived bacterial samples processed by ARSP. No identifiable data were used in this study.

RESULTS

Demographic and clinical characteristics of the *N. gonorrhoeae* isolates

The 21 genomes included in this study represented seven sentinel sites, with Vicente Sotto Memorial Medical Center (VSM) contributing the most isolates (n = 11). The highest incidence was in the age group 15–24 years (47.6%, n = 10), followed by the age groups 5–14 years (28.6%, n = 6), 25–34 years (14.3%, n = 3) and 1–4 years (9.5%, n = 2, **Table 2**). The numbers of isolates from females and males were almost equal (n = 11 and n = 10, respectively). The most frequent specimen source was the vagina (n = 8) for female patients and penile discharge (n = 5) for males. All the patients were outpatients (n = 21).

Table 2. **Demographic and clinical characteristics of 21 *N. gonorrhoeae* isolates**

Characteristic	No. of isolates
Sex	
Male	10
Female	11
Age (years)	
1–4	2
5–14	6
15–24	10
25–34	3
Patient type	
Inpatient	0
Outpatient	21
Specimen origin	
Community	21
Hospital	0
Specimen origin	
Vagina	8
Penile discharge	5
Cervix	3
Genital discharge, male	2
Decubitus ulcer	1
Urine	1
Other	1

Concordance between phenotypic and genotypic AMR

Isolates were tested for susceptibility to five antibiotics representing four classes. In line with the resistance trends shown in **Fig. 1**, the most prevalent resistance profile was PEN CIP TCY, identified in 10 isolates from five sentinel sites and linked mainly to the presence of the bla_{TEM} gene, the S91F mutation in GyrA and the *tetM* gene, respectively (**Table 3**). One penicillin-resistant isolate (13ARS_DMC0024) harboured three mutations, the –57delA mutation in the *mtrR* promoter and the non-synonymous substitutions in *ponA* (L421P) and porB (A121D), which may contribute to high-level penicillin resistance.[22] The partially assembled bla_{TEM} gene was also detected in this genome but was not considered in the concordance analysis. We also identified the non-synonymous mutation in the *folP* gene (R228S), which confers resistance to sulfonamides in 20 of 21 genomes; however, isolates are not routinely tested for resistance to this antibiotic class.

The concordance between antimicrobial susceptibility testing results and genotypic predictions (**Table 3**) was >95% for all antibiotics except tetracycline (66.67%), resulting in an overall concordance of 92.38% (**Table 3**). The discrepancies were attributed to seven false-positive results (isolates with a susceptible phenotype but with known AMR determinants in their genomes), all of which contained the mutation V57M in the rpsJ gene; two isolates also carried the *tetM* gene.[23]

Table 3. **Comparison of genomic predictions of antibiotic resistance with susceptibility testing at the ARS reference laboratory**

Antibiotic class	Antibiotic	Resistant isolates	False positive	False negative	Concordance (%)	Resistance genes/ SNPs
Cephalosporin	Cefixime	0	0	0	100	
Cephalosporin	Ceftriaxone	0	0	0	100	
Penicillin	Penicillin	18	0	1	95.24	bla_{TEM}, *mtrR*_promoter_–57delA, *mtrR*_A39T, *mtrR*_disrupted, *penA*_ins346D, *ponA1*_L421P, *porB1b*_A121D, *porB1b*_G120K
Tetracycline	Tetracycline	14	7	0	66.67	*tetM, rpsJ*-V57M, *mtrR*_promoter_–57delA, *mtrR*_A39T, *mtrR*_disrupted
Fluoroquinolone	Ciprofloxacin	19	0	0	100	*gyrA*_D95G, *gyrA*_D95A, *gyrA*_S91F, *parC*_D86N, *parC*_S87N, *parC*_E91K

Genotypic findings

In silico genotyping

A total of 15 different STs were identified, with only four (9364, 10316, 1582 and 8133) represented by more than one isolate. Nine genomes were assigned to eight known NG-MAST types and 12 genomes to nine novel types. Only three sentinel sites, namely Corazon Locsin Montelibano Memorial Regional Hospital (MMH), VSM and Zamboanga Del Norte Medical Center (ZPH), submitted more than one isolate, and all were represented by almost as many STs as isolates submitted. Details of the numbers and the most common STs and NG-MAST types found at each sentinel site are shown in **Table 4**.

Population structure of N. gonorrhoeae in the Philippines

The diverse gonococcal population was represented by a tree with three deep-branching clades and no clear geographical signal (**Fig. 2**). Clades II and III were characterized by a different repertoire of AMR genes and mutations. Clade II contained mostly isolates susceptible to or with reduced susceptibility to tetracycline and with the V57M mutation in the *rpsJ* gene alone, while clade III was composed of isolates resistant to tetracycline and also containing the *tetM* gene. Similarly, while both clades contained isolates resistant to ciprofloxacin harbouring the *gyrA*_S91F mutation, clade II was characterized by the presence of gyrA_D95G alone or in combination with the one mutation in *parC*, while clade III was characterized by the presence of *gyrA*_D95A with one or two mutations in *parC* in all but one isolates. Clades II and III showed different geographical distributions, although both were present at the VSM and ZPH sentinel sites, which submitted the most isolates. The genome from sentinel site Southern Philippines Medical Center (DMC) with a deletion in the *mtrR* promoter (–57delA) was found on a separate branch (I) in the tree and also carried a different complement of AMR determinants, indicating that it is genetically distinct from the others (**Fig. 2**).

N. gonorrhoeae from the Philippines in the global context

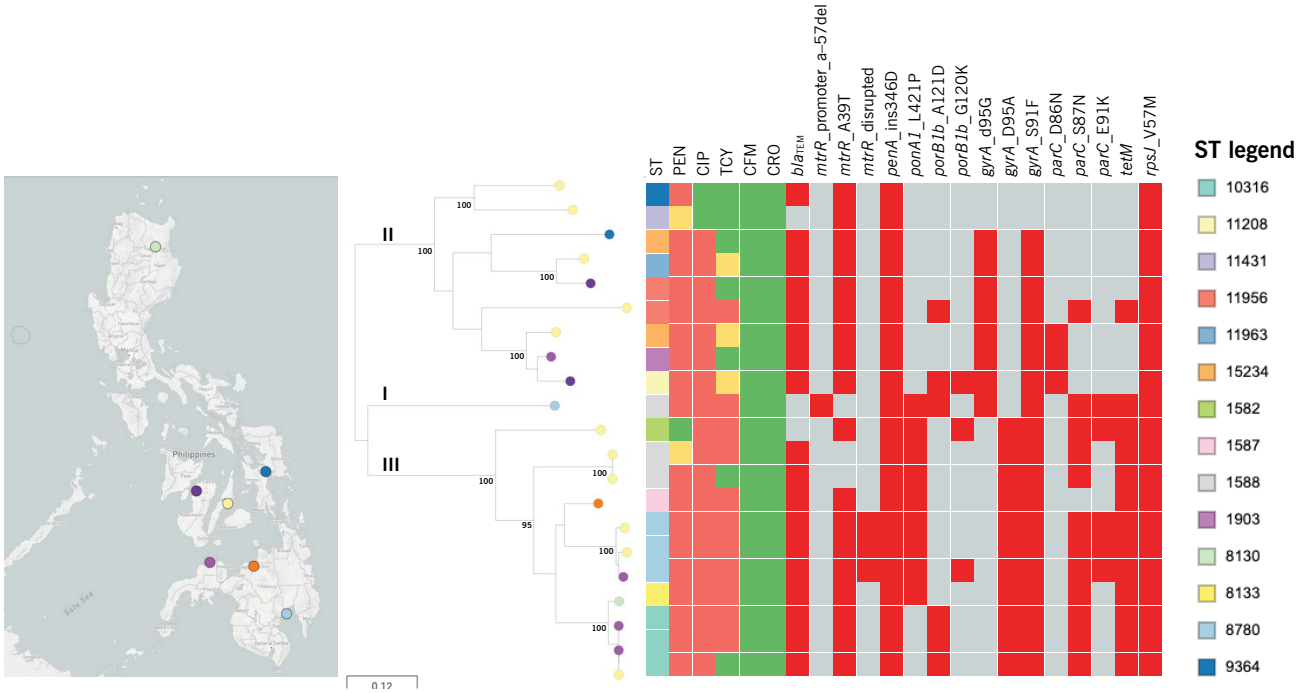
The Philippine genomes were contextualized with two recently published collections[10,21] available in Pathogenwatch. A recent global collection of 395 genomes from 58 countries (including the Philippines) showed two major lineages with different evolutionary strategies. Most of the genomes in this study were found within a subclade of lineage A, a multidrug-resistant lineage associated with infection in high-risk sexual networks (**Fig. 3A**), and mixed with genomes from Europe, Pakistan and South-East Asia, including genomes previously isolated in the Philippines

Table 4. **Distribution of isolates, STs, NG-MAST types, resistance profiles and resistance genes and mutations at the seven sentinel sites. The genetic resistance mechanisms for all the isolates from each site are listed.**

Laboratory	No. of isolates	STs (no. of isolates)	NG-MAST types (no. of isolates)	Resistance profile± (no. of isolates)	Resistance genes and SNPs
CVM	1	8780	Novel	PEN CIP TCY	bla_{TEM}, *penA*_ins346D, *ponA1*_L421P, *mtrR*_A39T, *gyrA*_S91F, *gyrA*_D95A, *parC*_S87N, *tetM*, *rpsJ*-V57M
DMC	1	1903	Novel	PEN CIP TCY	*penA*_ins346D, *ponA1*_L421P, *porB1b*_A121D, *mtrR*_promoter_–57delA, *gyrA*_D95G, *gyrA*_S91F, *parC*_S87N, *parC*_E91K, *tetM*, *rpsJ*-V57M
EVR	1	1582	13 796	PEN CIP	bla_{TEM}, *penA*_ins346D, *mtrR*_A39T, *gyrA*_D95G, *gyrA*_S91F, *rpsJ*-V57M
MMH	2	11 956, 11 208	1631, novel	PEN CIP	bla_{TEM}, *penA*_ins346D, *mtrR*_A39T, *porB1b*_A121D, *porB1b*_G120K, *gyrA*_D95G, *gyrA*_S91F, *parC*_D86N, *rpsJ*_V57M
NMC	1	1588	Novel	PEN CIP TCY	bla_{TEM}, *penA*_ins346D, *mtrR*_A39T, *ponA1*_L421P, *gyrA*_S91F, *gyrA*_D95A *tetM*, *rpsJ*-V57M
VSM	11	8133 (2), 9364 (2), 10 316 (1), 1587 (1), 11 431 (1), 11 963 (1), 1582 (1), 11 956 (1), 15 234 (1)	2187(2), 1691 (1), 1498 (1),1797 (1), novel (6)	PEN CIP (4) PEN CIP TCY (4) CIP TCY (1) PEN (2)	bla_{TEM}, *penA*_ins346D, *mtrR*_disrupted, *mtrR*_A39T, *ponA1*_L421P, *porB1b*_A121D, *porB1b*_G120K, *gyrA*_D95G, *gyrA*_D95A, *gyrA*_S91F, *parC*_D86N, *parC*_S87N, *parC*_E91K, *tetM*, *rpsJ*-V57M
ZPH	4	10 316 (2), 9364 (1), 8130 (1)	2080 (1), 11 821 (1), novel (2)	PEN CIP TCY (3) PEN CIP (1)	bla_{TEM}, *mtrR*_disrupted, *mtrR*_A39T, *porB1b*_A121D, *gyrA*_D95G, *gyrA*_D95A, *gyrA*_S91F, *parC*_D86N, *parC*_S87N, *parC*_E91K, *tetM*, *rpsJ*-V57M

CVM: Cagayan Valley Medical Center; DMC: Southern Philippines Medical Center; EVR: Eastern Visayas Regional Medical Center; MMH: Corazon Locsin Montelibano Memorial Regional Hospital; NMC: Northern Mindanao Medical Center; VSM: Vicente Sotto Memorial Medical Center; ZPH: Zamboanga Del Norte Medical Center
PEN: penicillin, CIP: ciprofloxacin, TCY: tetracycline

Fig. 2. **Genomic surveillance of *N. gonorrhoeae* from the Philippines, 2013–2014**



Maximum likelihood phylogenetic tree of 21 isolates from the Philippines, inferred from 7518 SNP sites. The tree leaves are coloured by sentinel site (map). The tree is annotated with the MLST ST as per the legend, the resistance phenotype for five antibiotics (red: resistant, yellow: intermediate, green: susceptible), and the distribution of known AMR mechanisms (red: present, grey: not found). The tree branches are annotated with the bootstrap values and clade designations (I, II and III). The scale bar represents the number of SNPs per variable site. The data are available at https://microreact.org/project/ARSP_NGO_2013-14 and https://pathogen.watch/collection/flnkisnu6giu-arspngo2013-2014 .

Fig. 3. **Global context of *N. gonorrhoeae* from the Philippines**

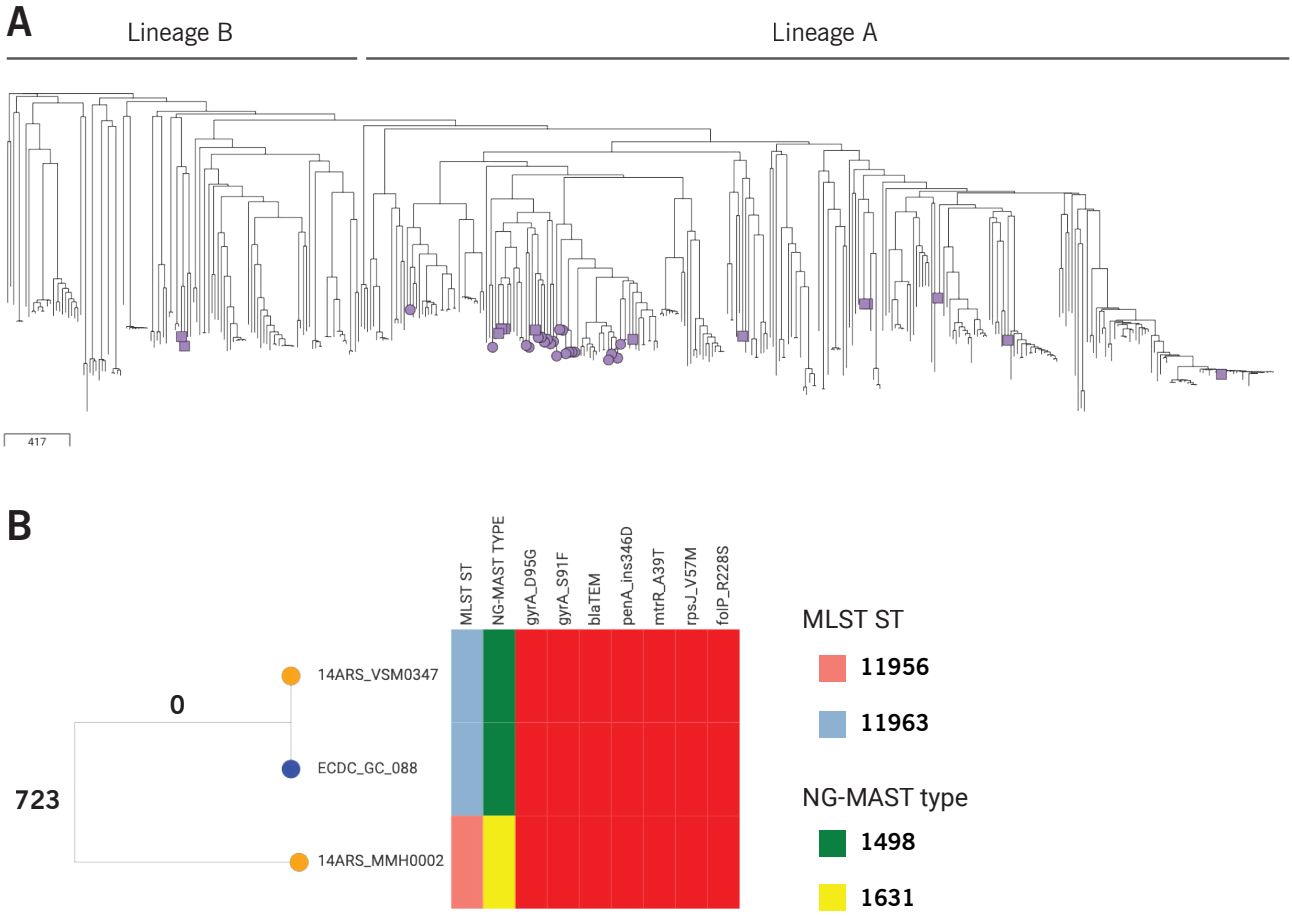


Fig. 3A. Tree of 416 genomes from this study (n = 21) and a recent global collection (n = 395), inferred with Pathogenwatch from 22 558 variant sites in 1542 core genes. Purple nodes indicate genomes from the Philippines from this study (circles) or the global collection (squares). The scale bar represents the number of SNPs. The data are available at https://pathogen.watch/collection/wrdonfwhju6f-arsp-ngo-2013-2014-global-context.

Fig. 3B. Detail of the subtree of closely related genomes from the Philippines (orange nodes) and Norway (blue node), inferred with Pathogenwatch. The tree branches are annotated with the number of pairwise SNP differences between isolates. The metadata blocks indicate the ST, NG-MAST type and the presence (red blocks) of seven AMR determinants. The full collection is available at https://pathogen.watch/collection/xtusqgwqhxcy-arsp-ngo-2013-2014-european-context.

(1998 and 2008[21]). The genome from DMC was found within a separate subclade with genomes from Europe, India and Pakistan, which also carried the *mtrR*_–57delA promoter deletion.

We further contextualized our isolates with 1054 genomes from 20 countries collected in 2013 in a European survey.[10] Notably, the genome of strain 14ARS_VSM0347 isolated from a female on 25/04/2014 in the Philippines was highly similar to that of ECDC_GC_088 isolated from a male on 31/12/2013 in Norway (**Fig. 3B**), with no SNP differences found in the Pathogenwatch core genome (1542 genes). One SNP was identified in the reference-based alignment of the two pseudogenomes, confirming that these two genomes are highly similar. The two strains also shared the same complement of AMR genes and mutations (**Fig. 3B**). The genetic distance between the two genomes is consistent with isolates from the same location,[10] suggesting an epidemiological link and a route of international transmission. The gonococcal reference laboratory at the Norwegian Institute of Public Health confirmed that the isolate was also resistant to penicillin and ciprofloxacin and susceptible to extended-spectrum cephalosporins (tetracycline not tested) and that the Norwegian male had visited the Philippines and claimed to have contracted gonorrhoea during his stay (personal communication).

DISCUSSION

WGS showed that the *N. gonorrhoeae* genomes from the Philippines are genetically diverse and carry a variety of AMR determinants, such as chromosomal mutations and acquired genes. The concordance between phenotypic

and genotypic resistance was high (>95%) for most antibiotics but only 66% for tetracycline. Susceptible isolates carrying only the *rpsJ*_V57M mutation, which confers low-level tetracycline resistance, have been reported previously.[24] The two susceptible isolates with a full-length *tetM* gene reported by Pathogenwatch were re-tested by disc diffusion and their susceptibility confirmed. The discrepancy, which could be explained for example by the lack of expression of the gene, errors in susceptibility testing or low-level DNA contamination, will be further investigated. Although *N. gonorrhoeae* remains largely susceptible to extended-spectrum cephalosporins and azithromycin in the Philippines, we identified one isolate (13ARS_DMC0024) with a –57delA mutation in the *mtrR* promoter, which results in overexpression of the MtrCDE efflux pump and, in combination with other mutations, can increase the minimum inhibitory concentrations of azithromycin (as well as penicillin and tetracycline).[4,22] Prospective surveillance with WGS can detect in real-time the acquisition of additional mutations that could result in decreased susceptibility.

A recent report suggested rapid recent intercontinental transmission of gonorrhoea, with common introductions from Asia to the rest of the world.[21] In support of this finding, the Philippine genomes, most of which were within a subclade of global lineage A, were interspersed with those from other countries (**Fig. 3A**). In addition, we found evidence of an introduction event from the Philippines to Norway associated with travel of a Norwegian male to the Philippines (**Fig. 3B**).

Global lineage A is associated with infection in high-risk sexual networks.[21] The combination of WGS with epidemiological information can reveal transmission routes and risk factors, which can be used to design better control measures.[25] The small size of our retrospective data set ($n = 21$) and the linked epidemiological data did not permit any inferences about sexual networks or risk factors, which is a limitation of this study. The number of reported isolates by ARSP has, however, since increased to more than 100 per year, and data on risk factors are also collected, which will allow a more comprehensive analysis of the population diversity and of risk factors in future reports.

Our results represent the first genomic survey of *N. gonorrhoeae* isolates collected by ARSP and will constitute the background for contextualizing continuous prospective surveillance. In addition, it highlights the importance of genomic surveillance in the Western Pacific and other endemic regions to understand the spread of drug-resistant gonorrhoea worldwide.

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Conflicts of interest

The authors declare no conflicts of interest.

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Lessons from a community vaccination programme to control a meningococcal disease serogroup W outbreak in remote South Australia, 2017

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Problem: From December 2016 to February 2017, two cases of invasive meningococcal disease and one case of meningococcal conjunctivitis, all serogroup W, occurred in Aboriginal children in the Ceduna region of South Australia. The clustering of cases in time and place met the threshold for a community outbreak.

Context: The Ceduna region is a remote part of South Australia, with more than 25% of the population identifying as Aboriginal or Torres Strait Islander.

Action: As part of the outbreak response, a community-wide meningococcal vaccination programme against serogroups A, C, W and Y was implemented in a collaboration among different agencies of the South Australia Department for Health and Wellbeing, Aboriginal health and community services providers, and other local service providers and government agencies. The programme comprised an outbreak vaccination schedule, targeting all people aged ≥ 2 months residing in the cases' places of residence or in towns with close links.

Outcome: Between March and June 2017, 3383 persons were vaccinated, achieving an estimated coverage of 71–85% of the target population, with 31% (n = 1034) of those vaccinated identifying as Aboriginal or Torres Strait Islander. No local cases of serogroup W occurred during the vaccination programme, but two further cases were notified by the end of 2018.

Discussion: The participation of a large number of local and non-health-sector stakeholders in programme planning and implementation, a clear response management structure and high community acceptability were identified as key factors that contributed to the programme achieving high vaccination coverage. The need to develop standard operating procedures for community-based outbreak response interventions to ease logistical challenges was considered an important lesson learnt.

Neisseria meningitidis is a Gram-negative diplococcus and the causative agent of invasive meningococcal disease (IMD). IMD commonly presents with meningitis and septicaemia.[1,2] Long-term sequelae may include limb amputation, hearing loss and neurological impairment.[2] Six serogroups account for nearly all human cases globally;[1] in some reports, serogroup W is associated with higher case fatality rates and more frequent atypical presentations.[3,4] Worldwide, an estimated 10–20% of people asymptomatically carry *N. meningitidis* in their upper respiratory tract,[1] with the highest carriage rates found in adolescents and young adults.[5]

IMD is a notifiable disease in all Australian jurisdictions. Meningococcal conjunctivitis may precede IMD in cases or contacts and is usually notified.[6] Nationally, the epidemiology of IMD has changed markedly in the past several years, with serogroup W replacing serogroup B as the most common serogroup since 2016.[7] By contrast, in South Australia (SA), serogroup B was responsible for 81% (22/27) of notifications in 2016 and serogroup W

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for the remainder. Compared with non-Indigenous Australians, Aboriginal and Torres Strait Islander people have higher rates of IMD, particularly serogroup W.[8]

Several meningococcal vaccines against serogroups A, C, W and Y are available for private purchase in Australia and have been funded under the National Immunisation Program from July 2018 for infants and April 2019 for adolescents.

PROBLEM

From December 2016 to February 2017, the Communicable Disease Control Branch at the SA Department for Health and Wellbeing (SA Health) was notified of two cases of IMD serogroup W and one case of meningococcal conjunctivitis serogroup W in the Ceduna Local Government Area. Serogroup W had not been notified in this region since records started in 1990. All three cases occurred in Aboriginal children aged 2 to 12 years, with no additional epidemiological links between the cases. Fine typing was available for two of the three cases: both were P1.5,2:F1–1. As part of routine public health follow-up of sporadic cases, the Communicable Disease Control Branch directed that close contacts should receive clearance antibiotics, and approximately 300 contacts, including close contacts, were vaccinated in January and February 2017.

The Ceduna Local Government Area is a remote part of Australia, with an estimated resident population of 3716 persons as of 30 June 2016. Approximately 25% of residents identify as Aboriginal or Torres Strait Islander. The estimated attack rate of 81 cases (or 54 invasive cases) per 100 000 population during the three months from December 2016 through February 2017 exceeded not only the threshold for defining a community outbreak of 10 cases per 100 000 population as defined by the National Guidelines of the Communicable Diseases Network Australia, but also the lower thresholds for implementing population-wide disease control measures in remote Aboriginal or Torres Strait Islander communities.[6] An outbreak response was commenced, and a community-wide vaccination programme was implemented to prevent the occurrence of further cases of IMD serogroup W in the Ceduna region.

ACTION

Programme design and setting

At the time of programme inception and implementation, publicly funded health services in regional and remote SA were provided by the Country Health SA Local Health Network (CHSALHN), which was part of SA Health. In addition, Aboriginal Community Controlled Health Services operate across SA. Multiple national, state and local organizations were involved in planning and implementing the vaccination programme (**Box 1**).

Box 1. **Organizations involved in planning and implementing the Ceduna community vaccination programme, South Australia, 2017**

Commonwealth (national), state and local government entities

- Commonwealth Department of the Prime Minister and Cabinet, Ceduna Office
- SA Health, including:
  - Country Health SA Local Health Network, Eyre and Far North Region and Corporate Office
  - Communicable Disease Control Branch
  - Media and Communications Branch
  - SA Ambulance Service
- SA Department for Child Protection, Ceduna Office
- SA Department for Communities and Social Inclusion, Housing SA and Ceduna Street Beat
- District Council of Ceduna

Aboriginal health and community services

- Ceduna Koonibba Aboriginal Health Service
- Tullawon Health Services, Yalata
- Oak Valley Health Services, Maralinga Tjarutja lands
- Aboriginal Health Council of South Australia
- Pangula Mannamurna Aboriginal Corporation
- Nunkuwarrin Yunti of South Australia Inc.

Other community services

- Centacare Catholic Family Services, Ceduna Office

A steering committee was convened to coordinate the outbreak response and was composed of representatives from the Communicable Disease Control Branch, CHSALHN and the Media and Communications Branch of SA Health; the Aboriginal Health Council of South Australia; and Ceduna Koonibba Aboriginal Health Service.

Target population

Based on cases' residence and known links between towns, the programme area (**Fig. 1**) encompassed Ceduna, Thevenard, Denial Bay, Koonibba, Yalata, Penong, Oak Valley in the Maralinga Tjarutja lands (lands owned by the Aboriginal traditional owners and administered as an Aboriginal Council, or AC), the homeland property Scotdesco (all of these are in postcode area 5690) and Smoky Bay (part of postcode area 5680). Given a lack of knowledge of meningococcal W carriage rates and the likely extent of population mixing, all Aboriginal and non-Aboriginal persons aged ≥ 2 months were targeted for vaccination (meningococcal ACWY vaccines are not licensed for individuals aged < 2 months). Based on numbers from the Australian Bureau of Statistics and local records, eligibility for vaccination was estimated at 4000–4500 individuals.

Vaccination schedule

The dosing schedule recommended in the *Australian Immunisation Handbook* for persons travelling to epidemic-prone areas or mass gatherings[9] was used, that is, a primary vaccination course consisting of one to three doses, depending on the vaccine, age of the individual and their medical risk factors. At the time, Menveo® (GlaxoSmithKline) was the only vaccine registered for use in infants younger than 12 months and was used to vaccinate children aged 2 months to < 12 months. Nimenrix® (Pfizer) was originally intended to be used in all persons aged ≥ 12 months because only one dose is required for all age groups in the absence of medical risk factors. However, due to limited vaccine supply following the concomitant introduction of adolescent meningococcal ACWY vaccination programmes in other Australian states, the vaccination schedule was altered to allow either Nimenrix or Menveo to be used in persons aged ≥ 2 years. Because two doses of Menveo are required in children aged 12–23 months, Nimenrix was used exclusively in this age group.

Resources

In order to staff vaccination clinics, additional clinical staff were made available from Aboriginal Health Services, other CHSALHN sites and regions, and from metropolitan areas. Other government and nongovernmental organizations contributed non-clinical staff. Standing medication orders for administering Menveo and Nimenrix had to be signed by each participating service.

A communication campaign was developed and implemented within two weeks and delivered for less than 2000 Australian dollars. Paid communications included a Facebook post, a local newspaper advertisement and a radio advertisement in English and Pitjantjatjara (the local Aboriginal language). Posters and fact sheets were created for both the public and health-care workers, and three press releases featuring local spokespersons targeted local and state newspapers. All information was made available centrally on the SA Health website.

In addition to developing the schedule and standing medication orders for both vaccines, an immunization screening and consent form and a separate consent resource were developed for use on immunization day. Programme data were entered into a database, and the vaccines administered were retrospectively entered onto the Australian Immunisation Register for patients whose Medicare numbers had been collected.

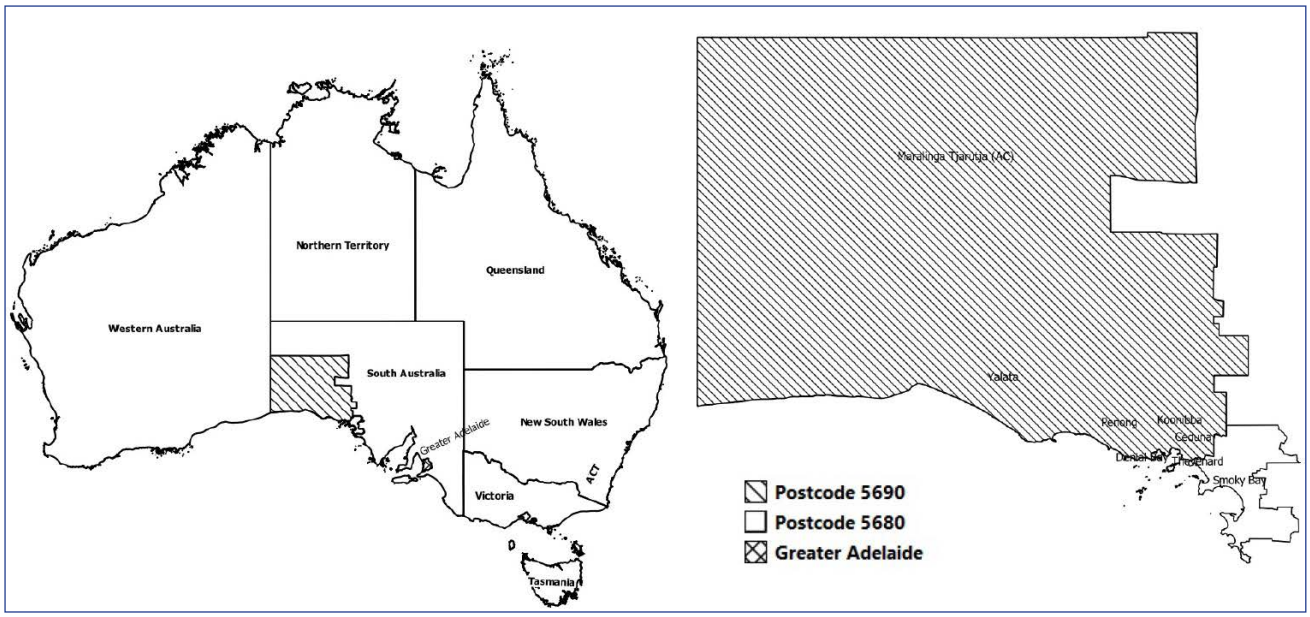
Ethics statement

This article describes public health actions undertaken as part of an outbreak response under the South Australian Public Health Act 2011 that did not require ethics approval.

OUTCOMES

The community vaccination programme commenced on 6 March 2017 and ran for two weeks at the Ceduna Town Hall. It continued until 30 June 2017 at Penong Town Hall (and included residents of Scotdesco), the Koonibba clinic, the Smoky Bay and Districts Community Club, the Tullawon Health Services Clinic at Yalata, the Oak Valley Health Clinic, the Ceduna Koonibba Aboriginal Health Service and the Ceduna Family Medical Practice. A total of 3383 individuals received a meningococcal

Fig. 1. **Map of the programme target area for vaccination with meningococcal ACWY vaccine including Australian Bureau of Statistics postal areas, state suburbs and the Maralinga Tjarutja Aboriginal Council (AC) Local Government Area, South Australia, 2017**



ACWY vaccination, with 87 individuals recorded as requiring follow-up vaccination due to their age or medical risk status. No serious side-effects were reported. Data completeness exceeded 98% for the categories of Indigenous status, gender and age. Of those vaccinated, 52% (n = 1757) were female; 31% (n = 1034) identified as Aboriginal or Torres Strait Islander; and 91% (n = 3082) lived in a target suburb or one of the two postcodes containing those suburbs. The median age was 37 years (interquartile range: 17–55 years). Inclusive of the contacts of the first two cases, the programme reached almost 3700 people, estimated to represent 71–85% of the target population (**Table 1**).

No cases of IMD or meningococcal conjunctivitis caused by the quadrivalent vaccine serogroups were notified in either of the postcodes targeted by the programme during the duration of the vaccination campaign. Overall, there have been 11 cases of serogroup W meningococcal disease in SA since the end of the programme in June 2017 until the end of 2018, including two cases in the Ceduna area targeted by the vaccination programme: in July 2017, a case was notified in an adult male of non-Aboriginal background who had declined vaccination in Ceduna and whose three household contacts were also unvaccinated. In August 2018, another case was notified in an Aboriginal child who had not been born at the time of the vaccination programme and was a household contact of a previous Ceduna-area case. Fine typing for the first case in the post-vaccination period showed the strain to be of the same type as two of the pre-vaccination cases.

DISCUSSION AND LESSONS LEARNT

The Ceduna community vaccination programme did not prevent the occurrence of further cases of IMD serogroup W in the area. Nevertheless, it demonstrated that community-wide vaccination is a useful public health response to a geographically limited outbreak of meningococcal disease. Despite the considerable logistical effort required, the programme reached up to 85% of the target population. Ongoing transmission was interrupted in the short term, and given the high vaccination coverage, the large majority of residents can be assumed to have achieved immunity even if the programme may have failed to sufficiently reduce carriage rates and provide herd immunity in the medium term to long term. Given the large knowledge gaps in the community,[10] the vaccination programme provided the additional benefit of educating the community about the signs and symptoms of IMD. As meningococcal ACWY vaccination has been funded under the National Immunisation Program from July 2018 for infants and April 2019 for adolescents, there may not be a need for ad hoc community vaccina-

Table 1. **Number and overall coverage estimates of meningococcal ACWY vaccination by suburb and postcode, South Australia, 2017**

Location	Vaccination events (*n*)	Population denominator[a]	Estimated coverage
Total No. in target suburbs and case contacts[b]	**3180**	**4000–4500**	**71–80%**
Ceduna	1584		
Thevenard	352		
Denial Bay	89		
Koonibba	129		
Smoky Bay	182		
Yalata	315		
Oak Valley	69		
Scotdesco	24		
Penong	135		
Case contacts	301		
No. in postcode 5690 (other than target suburbs above)	145	No denominator available	No separate estimate feasible
No. in postcode 5680 (other than target suburbs above)	58		
Total No. in wider target area (target suburbs and wider postcodes containing target suburbs)	**3383**	**4000–4500**	**75–85%**
Total No. with suburb or postcode not stated or from another area	306	No denominator available	No separate estimate feasible

[a] Population estimates used as the denominator for both suburb total and the total for suburb and wider postcodes containing target suburbs are those used in programme planning (4000–4500 persons). The lower bounds of the coverage estimates are based on the higher population estimate, and the higher bounds are based on the lower population estimate.

[b] These are the household or household-like contacts vaccinated as part of immediate case follow-up.

tion programmes in Ceduna and elsewhere in Australia unless an outbreak specifically affects cohorts who were not eligible for vaccination.

A post-response evaluation meeting identified three elements as critical to the successful implementation of the community vaccination programme. First, the response was locally driven, with a large number of health- and non-health-sector stakeholders involved in planning and implementing the programme. In particular, local community engagement ensured that clinics were appropriately staffed and vaccinations could be delivered in readily accessible community locations, such as the Ceduna Town Hall, which had the most regularly visited clinic. Second, the inclusion of a wide variety of stakeholders was supplemented with a clear response management structure, involving leads from all key agencies. The steering committee responded flexibly to external challenges, including the shortage of Nimenrix and initial confusion about the relation of the meningococcal W vaccination programme to a concomitant state-wide adolescent meningococcal B vaccination study.[11] Third, the community was generally receptive to the meningococcal W vaccination programme, which may have been helped by the involvement of local staff familiar with the programme and attuned to identifying local solutions. For instance, local Aboriginal health workers and Aboriginal health practitioners were able to assist Aboriginal participants in providing informed consent.

While more than 90% of vaccinations were administered to persons known to reside in the target postcodes, no proof of address was required. As a result, data completeness and quality for addresses was poor for a subset of records, and the majority of the remaining 10% for whom their postcode could not be determined are likely to also reside in the target area. Addresses given in surrounding areas, Greater Adelaide and other Australian jurisdictions suggest that a small number of persons vaccinated were not considered residents from an administrative point of view. As this may reflect travel patterns and community ties in a mobile, remote population, the vaccination of additional persons

who may be de facto members of the target community is likely to have aided the response.

The programme encountered several logistical challenges. Estimating the quantity of vaccine required at different sites was challenging due to a lack of current population data at the town level and considerable fluctuation of population numbers in Aboriginal communities. Nevertheless, there was minimal wastage of vaccines: 79 vaccine doses needed to be discarded due to cold chain breaches at two separate sites, and there was no surplus vaccine because several other ACWY vaccination programmes were commenced simultaneously due to ongoing cases in other remote areas of SA. The vaccination programme at only one clinic had to be repeated due to an underestimation of population numbers at the site. Areas for improvement were identified with regard to several operational aspects of the response. These are related to the overarching recommendation to develop standard operating procedures for community-based interventions for outbreak response that can be adapted for state-wide use. They include:

1. standardizing provisions to allow staff to move between different regions of the CHSALHN and different departments of SA Health and avoiding the use of separate standing medication orders;
2. designating a single point of contact for clinical enquiries and decision support during the entire vaccination period;
3. streamlining media communications to reduce delays and lead-in time, including critical assessment of the value added by translations;
4. maximizing the use of community venues and offering extended and weekend opening times, resources permitting; and
5. improving data collection during the outbreak response, including recording Medicare numbers for the Australian Immunisation Register and integrating clinical management software to enable follow-up of vaccinations.

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Conflicts of interest

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Coronavirus disease 2019 (COVID-19) outbreak during a Chinese New Year dinner in a restaurant, Hong Kong SAR (China), 2020

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Coronavirus disease 2019 (COVID-19) was first detected in Wuhan, China, on 31 December 2019.[1] The first confirmed case of COVID-19 imported from Wuhan to Hong Kong SAR (China) was recorded on 23 January 2020,[2] and on 30 January 2020 the World Health Organization (WHO) declared the COVID-19 outbreak a public health emergency of international concern.[3] Between January and May 2020, 1084 confirmed cases of COVID-19 were reported in Hong Kong SAR (China). The local epidemic progressed through four phases: (1) preparedness and imported infection from mainland China, (2) local transmission, (3) imported infection from overseas countries associated with local transmission, and (4) controlled imported infection with limited local transmission.[4] During the second phase – local transmission (4 February to 3 March) – we reported a local family cluster of six confirmed COVID-19 cases among 29 people who attended a Chinese New Year family dinner gathering in a restaurant on 26 January 2020 (the second day of Chinese New Year).

METHODS

We conducted an epidemiological investigation of a confirmed case of COVID-19. On 10 February 2020, we received notification of a confirmed case of COVID-19 involving a 37-year-old female (patient 1) who had developed fever, cough and sore throat from 2 February 2020. She was admitted to a public hospital on 10 February 2020 and her nasopharyngeal aspirate tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid (RNA) using real-time reverse transcription polymerase chain reaction. Symptomatic contacts were isolated in public hospitals for SARS-CoV-2 testing and management. Asymptomatic close contacts were quarantined in quarantine centres, while other contacts who were asymptomatic were put under medical surveillance.

RESULTS

Patient 1 was home based, had no recent travel history outside Hong Kong SAR (China) and denied having any contact with confirmed COVID-19 cases. Contact tracing revealed that her husband (patient 2), who resided with her, developed fever and cough on 30 January 2020. In addition, her father (patient 3), who did not reside with her, developed fever and cough from 3 February 2020. Patients 2 and 3 were admitted for isolation on 10 February 2020 and tested positive for SARS-CoV-2.

Patients 1–3 shared a Chinese New Year dinner with 26 other relatives on 26 January 2020. Between 31 January and 8 February 2020, three more relatives were found to be symptomatic and tested positive for SARS-CoV-2 (patients 4–6).

The 29 attendees at the dinner lived in various separate residences, and the family dinner was the only common exposure among all six confirmed cases during the incubation period. The dinner, which was held in a restaurant, lasted for about 7 hours and included mahjong playing. Three of the six confirmed cases had played mahjong. The 29 diners were seated at two tables in the same room, in a partitioned area within the restaurant. None of the attendees were symptomatic during the gathering. The restaurant where the outbreak occurred was closed permanently because of business considerations before the notification of a COVID-19 case

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on 10 February 2020. Hence, it was not possible to undertake contact tracing of the wait staff or environmental investigations.

Contact tracing identified one domestic helper (patient 7) who did not join the family dinner but shared a bedroom with patient 4 (symptom onset on 31 January); patient 7 developed a fever and cough from 2 February and tested positive for SARS-CoV-2 (**Fig. 1**) (four other members of that household were sent to a quarantine centre and were not infected).

In summary, the cluster was six (from the family cluster) plus one (the domestic helper) confirmed cases, comprising three males and four females aged between 32 and 75 years (median: 37 years). None of the seven patients had a travel history outside Hong Kong SAR (China) and they all denied having any contact with confirmed COVID-19 cases during the incubation period; all seven were discharged home uneventfully.

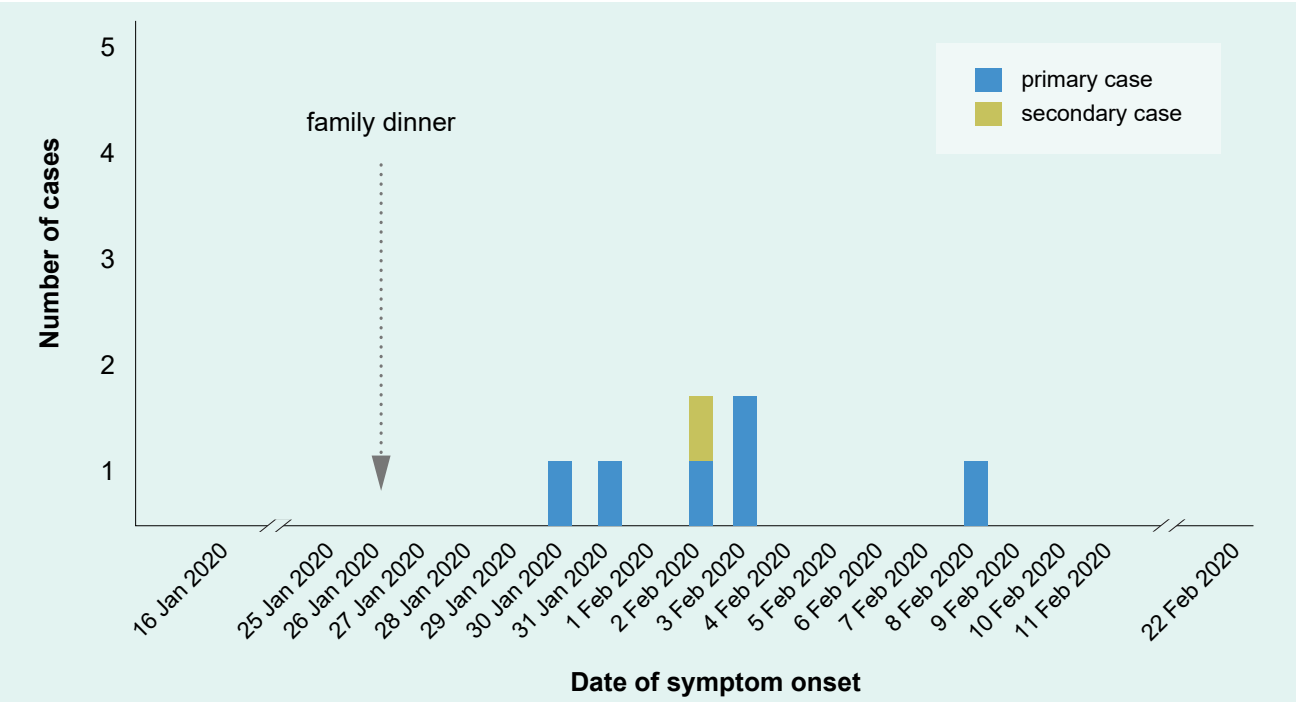
DISCUSSION

WHO advises maintaining social distancing of at least 1 m (3 feet) as a basic protective measure against COVID-19.[5] Mahjong is generally played by four people sitting around a square table in close proximity for hours, with the distance between players usually being less than 1 m (a distance at which transmission of respiratory droplets is possible). A Chinese dinner is commonly shared by 12 diners sitting close together at a round table, but in this particular instance, 29 diners were seated at two tables that usually accommodated 24 people, further reducing the distance between people.

This investigation had limitations. Information on viral load might have indicated who was more likely to be the heavier spreader, but no laboratory investigation of viral load was conducted. Also, it was not possible to undertake contact tracing of the wait staff or conduct environmental investigations.

It appears that some people can be positive for COVID-19 for 1 to 3 days before they develop symptoms.[6] Although the source of the family cluster could not be identified, our findings support pre-symptomatic transmission and effective human-to-human transmission of COVID-19 through social activities. Non-pharmaceutical interventions (e.g. social distancing) have been associated with reduced transmission of COVID-19 in

Fig. 1. **Epidemic curve of Chinese New Year restaurant dinner COVID-19 outbreak**



Hong Kong SAR (China).[7] The Centre for Health Protection appeals to the public to properly maintain social distancing at all times during the COVID-19 pandemic.

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Conflicts of interest

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Dengue–COVID-19 coinfection: the first reported case in the Philippines

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The rainy season in the Philippines is from June to October; this is when the number of dengue cases typically increases. In 2020 during this time, the world was facing the threat of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Coronavirus disease 2019 (COVID-19) and dengue viral infections have similar presentations and laboratory findings, including fever and thrombocytopenia, and there have been reports of coinfection with SARS-CoV-2 and arthropod-borne virus. Here, we report a case of SARS-CoV-2–dengue virus coinfection in the Philippines in a female aged 62 years, whose early symptom was fever and who was positive for SARS-CoV-2 and positive for dengue. Early recognition of such coinfection is important so that proper measures can be taken in the management of the patient.

Dengue fever is a mosquito-borne viral infection found mostly in tropical climates, including the Philippines. The clinical manifestations of dengue may include high-grade fever, headache, retro-orbital pain, muscle and joint pains, and rashes. In 2019, the Philippines had one of the highest numbers of reported dengue cases among countries in Asia and South-East Asia.[1] According to the World Health Organization (WHO), there were 55 160 cases of dengue in the Philippines from 1 January to 18 July 2020, a 66% reduction compared with the same period in 2019.[2] The endemic occurrence of dengue in 2020 coincided with the outbreak of COVID-19 infection. As of 11 August 2020, the Philippines has recorded 139 538 confirmed cases of COVID-19, making it the country with the highest number of cases in the WHO Western Pacific Region.[3] Here, we present the case of a female aged 62 years who presented at the emergency department with suspected COVID-19 and a suspicion of dengue fever; diagnostic tests were positive for both infections.

Case identification

A female aged 62 years with hypertension who resided in the northern part of the Philippines presented at the emergency department on the evening of 4 August 2020 with body malaise and fever. Two days before her admission, the patient started to experience high-grade fever (highest recorded at 39.5 °C), with associated headache (frontoparietal in location, rated 5/10 and bandlike in character) and retro-orbital pain, generalized body ache, myalgia and arthralgia. There was no associated nausea, vomiting or blurring of vision. The patient had pain over the ankle joints, with no associated warmth or limitation of movement, and no rashes, cough or dyspnoea. The patient had self-medicated with paracetamol, which afforded temporary relief; however, her condition was persistent, with body malaise and weakness, prompting consultation at Baguio General Hospital and Medical Center Emergency Department.

The patient was admitted to the COVID-19 ward under the Internal Medicine Service, as a suspected case of COVID-19. The patient denied any history of travel outside the town or direct contact with anyone positive for COVID-19. She reported attending the public market three days before onset of her symptoms. At the emergency department, the initial physical examination of the patient was unremarkable except for decreased breath sound on the right basal lung field. Given the history of fever, the patient was managed as a suspected case of COVID-19.

Laboratory tests included reverse transcriptase polymerase chain reaction (RT-PCR) for COVID-19 (Sansure Biotech®), chest X-ray, complete blood count, blood culture, and inflammatory markers such as lactate

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dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), ferritin, C-reactive protein (CRP), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The complete blood count initially revealed leukopenia at 3.16 × 109/L (neutrophils 75%, lymphocytes 18%), with haemoglobin and platelet counts being normal (140 g/L and 156 × 109/L, respectively). Chest X-ray revealed pneumonia on the right lower lobe of the lung (**Fig. 1**). There was no growth on blood culture. Markers of inflammation were elevated, including ferritin at 2156 ng/mL, ESR at 35 mm/hour, CRP at 18.73 mg/L and LDH at 317.92 U/L. Liver enzymes were elevated, with AST at 100.24 U/L (× 2.86) and ALT at 65.11 U/L (×1.86).

Course in the ward

In the COVID-19 ward, the patient's social and environmental history was further investigated. A suspicion of dengue fever was considered after a comprehensive history had been taken from the patient, as she stated that dengue cases were present in her neighbourhood, with the latest case occurring one week before her symptoms commenced. The patient could not recall having any previous dengue infection. Rapid diagnostic tests (RDTs) for dengue non-structural protein 1 (NS1) antigen and Dengue Duo (WONDFO®) for immunoglobulins (IgM/IgG) were requested. The patient was positive for NS1 but negative for both IgM and IgG. The patient was then managed for suspected coinfection with dengue fever and COVID-19.

On the second day in hospital, the patient received a positive result from the COVID-19 RT-PCR (FAM/ORF1AB 36.46). A repeat of the complete blood count showed a sudden drop in the platelet count, from the initial 156 × 109/L to 85 × 109/L. There was persistent leukopenia at 2.85 × 109/L, with a notable increase in the lymphocyte count (from 18% to 37%). The patient consented to receiving favipiravir, started at 1800 mg (9 tablets twice a day) as a loading dose then reduced to four tablets twice a day for 13 days. Later tests showed further decreases in platelet counts, falling to 37 × 109/L on the fourth day of hospitalization (**Table 1**). A differential count of white blood cells (WBC) showed a further increase in lymphocytes to 49%.

A chest computed tomography (CT) scan showed posterior-basal pneumonia with features atypical of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia and minimal pleural effusion on the right. On the fifth day of hospitalization (day 7 of illness) maculopapular rashes appeared over the patient's lower extremity, with some areas of erythematous petechial confluence and islands of normal skin (**Fig. 2**). A repeat test for dengue IgM/IgG on day 8 of illness was positive for IgG but negative for IgM. A repeat chest X-ray on day 9 of illness showed regression of previously noted densities in both lobes (**Fig. 1**). On the succeeding days, increasing trends in the number of platelets and leukocytes were noted. A further dengue IgM/IgG test on day 10 of illness yielded the same result as the previous test. After 10 days in hospital, the patient was discharged with her symptoms improved.

DISCUSSION

Fever is the most common symptom of COVID-19 infection.[4] In the case presented here, the patient had experienced two days of febrile episodes. Given her recent frequent travels to the public market, she was managed as a suspected case of COVID-19 and was isolated pending the result of a swab. However, the patient also manifested with typical symptoms of dengue, such as fever, generalized body ache, myalgia, arthralgia, retro-orbital pain and headache.[5] Because the patient could not remember any history of mosquito bite, we hypothesize that she was exposed to the dengue virus one week before her symptoms, at which time there were cases of dengue in her neighbourhood. The appearance of her symptoms coincided with the incubation period of the dengue virus – usually 4–10 days after the mosquito bite[5] – suggesting a high probability of dengue infection in this patient.

The decreasing numbers of WBCs and platelets also made the diagnosis of dengue likely.[5] However, thrombocytopenia and leukopenia are also common in COVID-19 patients.[6] The patient's complete blood count result was consistent with both viral infections (i.e. leukopenia, with progressive thrombocytopenia occurring on succeeding days). The positive result from the dengue NS1 antigen test from the sample taken on the first day of hospitalization confirmed the dengue infection, although the IgG/IgM test at that time was negative.

Dengue RT-PCR, enzyme-linked immunoassay (ELISA) and viral culture are the ideal laboratory tests

Table 1. **Summary of laboratory tests during the hospital stay (day 3 to day 11 of illness)**

Laboratory tests		Day of illness[a]								
		Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
CBC	Hgb	140		147	152	136	140	137		
	HCT	0.40		0.43	0.45	0.39	0.40	0.40		
	WBC	3.16		2.85	6.43	9.41	9.62	8		
	Neu	75		55	39	34	35	49		
	Lym	18		37	43	49	48	42		
	PLT	156		85	49	37	100	197		
LDH		317.92								
CRP		18.73								
ESR		35								
AST		100.24								
ALT		65.11								
Ferritin		2156								
Blood A and B		(–)								
COVID-19 RT-PCR		(+)								(–)
Dengue NS1			(+)				(–)		(–)	
Dengue IgM/IgG			(–)				IgG (+)		IgG (+)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CBC: complete blood count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HCT: haematocrit; Hgb: haemoglobin; Ig: immunoglobulin; LDH: lactate dehydrogenase; Lym: lymphocytes; Neu: neutrophils; PLT: platelets; RT-PCR: reverse transcriptase polymerase chain reaction; WBC: white blood cells.

[a] The patient developed clinical illness on 2 August 2020 and was admitted to hospital on 4 August 2020 (day 3 of illness).

Fig. 1. **Chest radiographic image**

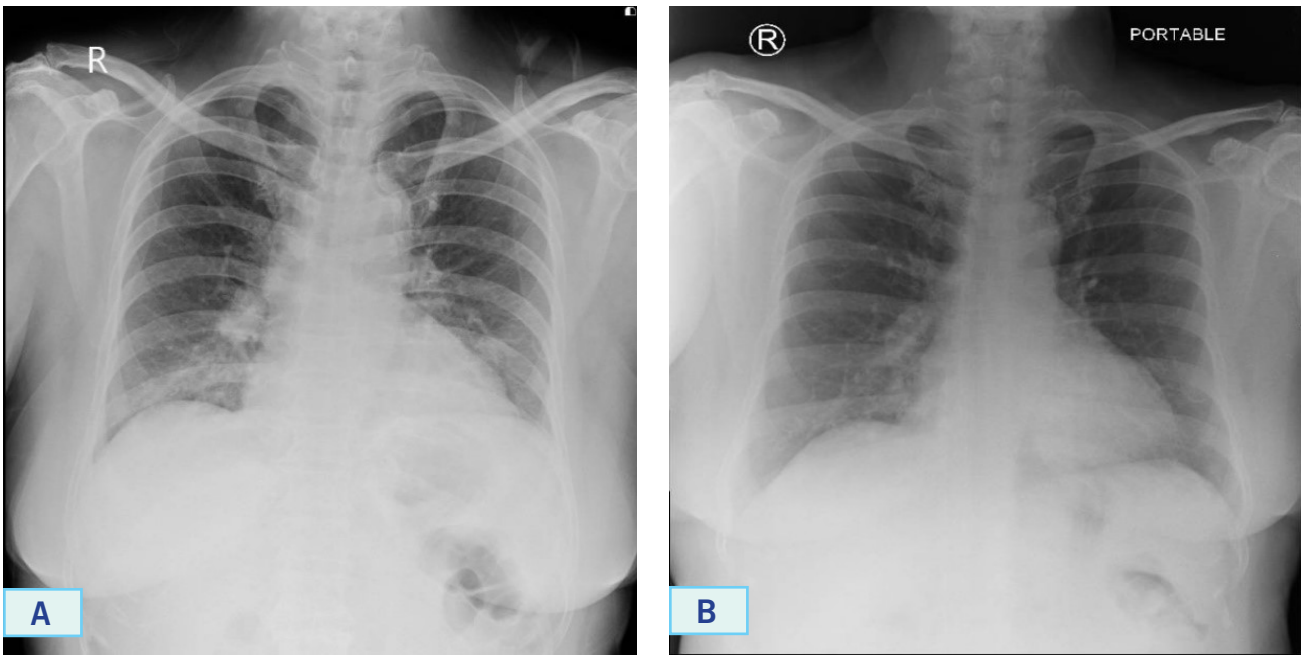
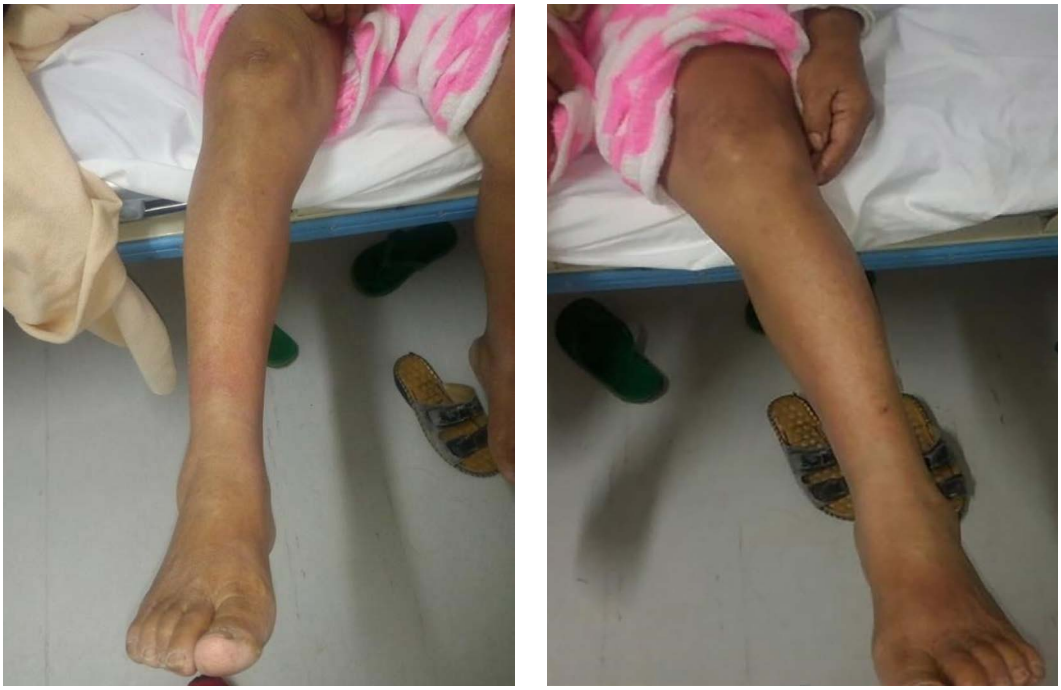


Fig. 1A. Initial X-ray: pneumonia, both lower lobes.

Fig. 1B. Repeat image: regression of pneumonia.

Fig. 2. **Erythematous petechial rashes on the lower extremities on day 7 of illness**



for the diagnosis of dengue. However, the only diagnostic tests available to the institution were the RDTs for dengue IgM/IgG and the NS1 antigen. The Handbook for clinical management of dengue notes that diagnosis of dengue infection is confirmed by the detection of the virus, the viral genome or NS1 antigen, or by seroconversion of IgM or IgG (i.e. from negative to positive).[5] Thus, the positive NS1 antigen test in this patient supported the diagnosis of dengue. The negative IgG and IgM may have been due to the timing of the collection of serum, given that dengue IgM serology has been shown to have low sensitivity during the early phase of dengue fever.[7] However, a negative antibody serology does not rule out dengue fever, especially when the dengue NS1 antigen test is positive. Samples taken from the patient on days 5 and 8 of hospitalization showed seroconversion of IgG but not of IgM. Given that the patient resided in a locality where dengue is endemic and cases have been reported, and had symptomatology and physical examination results suggestive of dengue fever, the combined positive NS1 test and the seroconversion of IgG improved the accuracy of the dengue fever diagnosis in this case.

In the natural course of dengue, IgM appears a few days following the onset of fever, followed by detectable IgG from day 5 onwards. The patient in this case study had a persistent negative IgM assay despite seroconversion of IgG, suggesting probable secondary dengue infection. Although the patient could not recall a previous dengue infection, she resides in a locality where dengue cases occur year-round; thus, it is possible that she had an undetected primary dengue infection. Primary dengue virus infections are often asymptomatic, and 90% of cases of dengue fever with symptoms occur following a second exposure.[8] Also, a low to negative IgM and a positive IgG for dengue may relate to recent secondary infection rather than being a marker of past infection.[9]

In the setting of a positive COVID-19 RT-PCR result, persistence of a positive IgM or IgG result on follow-up studies supports coinfection with dengue and COVID-19.[10] There have been few reported cases of such coinfections globally. Two cases reported were patients with a history of travel presenting with respiratory symptoms or rashes (or both).[11,12] However, there have also been false positive results of dengue tests concurrent with SARS-CoV-2 infection.[13,14] In March 2020, two patients in Singapore were reported as having false positive results from a dengue RDT but were later found to have confirmed SARS-CoV-2 infection.[13] Dengue IgM and IgG were noted to have cross-reactions with other flaviviruses such as malaria and leptospirosis. NS1 antigen testing is useful for differentiating between true dengue infections and false positives or coinfections, especially in resource-limited institutions, because the

NS1 antigen is highly specific for dengue fever and has no cross-reactions, even with other flaviviruses.[10]

Studies on coinfections with SARS-CoV-2 and arboviruses are lacking, which is not surprising given that SARS-CoV-2 is a new disease. An extensive literature search on dengue and COVID-19 in the Philippines suggested that no previous case of dengue and COVID-19 coinfection has been reported in the country. The medical challenge of such coinfection lies in the similarity of the clinical and laboratory features of the two infections;[13] that is, fever, myalgia and headache, associated with leukopenia, thrombocytopenia and abnormal liver function.[14] Hence, it is important to consider the possibility of COVID-19 in patients positive for dengue and vice versa, since the result will affect management and prognosis. To avoid missing the diagnosis, we recommend testing for dengue infection once there is a high level of suspicion of dengue fever. At the same time, we recommend that testing for COVID-19 infection be considered in patients who present with history of fever or whose symptomatology is suggestive of infection by an agent other than SARS-CoV-2.

ETHICS

Informed verbal and written consent was given by the patient.

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Conflict of interest

None declared.

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Using open-source intelligence to identify early signals of COVID-19 in Indonesia

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Objective: Open-source data from online news reports and informal sources may provide information about outbreaks before official notification. This study aims to evaluate the use of open-source data from the epidemic observatory, *EpiWATCH*, to identify the early signals of pneumonia of unknown cause as a proxy for COVID-19 in Indonesia.

Methods: Using open-source data on pneumonia of unknown cause in Indonesia between 1 November 2019 and 31 March 2020 (extracted from *EpiWATCH*, an open-source epidemic observatory), a descriptive analysis was performed to identify the trend of pneumonia of unknown cause in Indonesia before official notification of COVID-19 cases.

Results: A rise in reports of pneumonia of unknown cause was identified in Indonesia, starting from late January 2020. There were 304 reported cases of pneumonia of unknown cause, 30 of which occurred before the identification of the first COVID-19 cases on 2 March 2020. The early signals of pneumonia of unknown cause in Indonesia may indicate possible unrecognized circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) before official detection.

Discussion: Open-source data may provide rapid, unvalidated information for early detection of outbreaks. Although unvalidated, such information may be used to supplement or trigger investigation and testing. As *EpiWATCH* sources global information, this methodology can be repeated for other countries within the Western Pacific Region, and for other diseases.

On 31 December 2019, China reported an increased occurrence of pneumonia of unknown cause in Wuhan,[1] which was later confirmed as coronavirus disease 2019 (COVID-19), a respiratory illness caused by the newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 13 January 2020, Thailand became the first country to identify imported cases of COVID-19. Other countries in South-East Asia, including Singapore and Malaysia, also reported their first imported cases in January 2020.[2,3] On 31 January 2020, the World Health Organization (WHO) declared COVID-19 a public health emergency of international concern,[4] and on 11 March 2020, it declared the outbreak a pandemic.[5] Indonesia reported its first two confirmed positive cases of COVID-19 on 2 March 2020.[6]

Early identification of an infectious disease outbreak is essential, to allow for immediate initiation of public health interventions and to mitigate global impacts of transnational spread of the disease. Traditional public health surveillance, especially where there is low testing capability, is often not timely due to delays in reporting and validation by local health authorities.[4]

Open-source intelligence may serve as a valuable tool for rapid epidemic surveillance.[5] WHO reports that more than half of early epidemic information can be obtained through unofficial sources, including online news outlets and social media.[6] This study aims to evaluate the use of open-source data from the epidemic observatory, *EpiWATCH*, to identify the early signals of pneumonia of unknown cause as a proxy for SARS-CoV-2 circulation in Indonesia.

METHODS

EpiWATCH is a semi-automated open-source epidemic observatory that collects and analyses outbreak data from publicly available sources, such as online news outlets and social media.[7] *EpiWATCH* has been used to collect outbreak data since 2016. The observatory col-

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lects information on outbreaks of diseases and emerging infections, globally, to detect early signals and trends, which can then be used by researchers. The system was established and is managed by the Australian National Health and Medical Research Council (NHMRC) Centre for Research Excellence, Integrated Systems for Epidemic Response (ISER).[7]

EpiWATCH gathers open-source data from online news outlets and social media through an intelligent and modular system. To enable enhanced surveillance, searches are modified for specific languages and for specific infectious disease syndromes. Modifications include changing and adding keywords and languages for searching. The observatory system supports various intelligent data-gathering algorithms, including natural language processing algorithms, regular expression matching and supervised machine-learning algorithms. The data are stored in a PostgreSQL database.[8] Within *EpiWATCH*, reports are reviewed and entered manually by the team, to ensure collection of key data points identified by the automated data-gathering system and prevent duplication of reports.

In this study, enhanced surveillance was performed through *EpiWATCH* using keywords reflecting SARS or pneumonia, such as "pneumonia, lung infection, lung inflammation, severe acute respiratory infection (SARI), cough, fever, cough AND fever", with Indonesia as a location, in Bahasa Indonesia (the country's official language). The obtained reports were manually reviewed, and any reported cases of pneumonia of unknown cause in Indonesia dated between 1 November 2019 and 31 March 2020 were included in the *EpiWATCH* database. Reports matching the keywords were analysed and were excluded if they were not reporting cases from Indonesia or cases of pneumonia of unknown cause, or if they were reporting duplicate news or pneumonia cases with a known cause. Indonesia was chosen for this study as its first official COVID-19 notification was made later than that of other South-East Asian countries.

A descriptive epidemiological analysis was performed using Microsoft Excel 2016 to group cases by geolocation and by the date on which they were reported. Data reported from Indonesia's Ministry of Health were also reviewed and compared with the news reports.

Ethics and permissions

No ethics approval was required for this study because it uses publicly available open-source data from online media.

RESULTS

Between November 2019 and March 2020, *EpiWATCH* documented 217 entries or reports related to pneumonia of unknown cause in Indonesia. Six duplicates were removed, leaving a total of 211 included reports. The highest number of reports (184 entries) were from March 2020, after the official identification of the first cases of COVID-19 in Indonesia. However, a steady increase in the reports of pneumonia of unknown cause was seen from late January 2020 (five entries) to the end of February 2020 (17 entries).

These 211 entries correspond to 304 reported cases of pneumonia of unknown cause in Indonesia, 30 (9.9%) of which occurred before the identification of the first COVID-19 cases on 2 March 2020. Among those 30 cases, 17 were suspected for COVID-19, including the case of a toddler from China, aged 18 months, who was treated for pneumonia in Lombok, West Nusa Tenggara, on 27 January 2020.[9] COVID-19 diagnosis was ruled out based on a blood laboratory count that was suggestive of bacterial infection; however, no further results of polymerase chain reaction (PCR) or bacterial culture were reported.[9]

Fig. 1 shows the count of pneumonia of unknown cause from 1 November 2019 to 31 March 2020 as obtained from *EpiWATCH* reports. In November and December 2019, there were five *EpiWATCH*-reported cases of pneumonia of unknown cause. The number of reports increased slightly from late January (six identified cases) to February 2020 (19 identified cases), six weeks before the official identification of the first two COVID-19 cases in Indonesia. In March 2020, the count of *EpiWATCH*-reported cases of pneumonia of unknown cause increased significantly to 274 cases, which may represent an increase in COVID-19 cases or growing media attention and reporting following the official notification of COVID-19 in Indonesia on 2 March 2020. In the same period in the previous year, there were far fewer reports of pneumonia of unknown cause, with only

five *EpiWATCH*-reported cases of pneumonia of unknown cause from January to March 2019.

Almost half of all *EpiWATCH*-reported cases of pneumonia of unknown cause were from provinces in Java. East Java (39 cases; 12.8%) and Jakarta (37 cases; 12.1%) were the provinces with the highest number of *EpiWATCH*-reported cases, followed by Central Java (26 cases; 8.5%), West Java (17 cases; 5.6%), Yogyakarta (15 cases; 4.9%) and Banten (seven cases; 2.3%). Outside Java, Bali had the highest number of *EpiWATCH*-reported cases (28 cases; 9.2%) (**Fig. 2** and **Fig. 3**).

Gender information was given for 157 of the 304 *EpiWATCH*-reported cases. Among those 157 cases, there was a higher proportion of males (96 cases; 61.1%) than females (61 cases; 38.9%), with a 1.5:1 ratio of males to females. Information on age was given for 138 of the 304 *EpiWATCH*-reported cases, with the highest proportion of cases being those aged 50–60 years.

DISCUSSION

This study provides a descriptive analysis of cases of pneumonia of unknown cause that occurred in Indonesia from November 2019 to March 2020 as detected by the *EpiWATCH* observatory. These *EpiWATCH*-reported cases of pneumonia of unknown cause in Indonesia increased from late January 2020, which may reflect the presence of COVID-19 cases in the country before official identification of two cases at the start of March 2020.

Data from the Ministry of Health[10] show that, by 31 March 2020, Indonesia had 1528 laboratory-confirmed cases of COVID-19, with 136 documented deaths. Among these cases, almost half (48.9%) were identified in Jakarta, followed by other provinces in Java: West Java (11.9%), Banten (9.2%), East Java (5.9%), Central Java (5.2%) and Yogyakarta (1.2%).[10] At that time, Bali had reported only 19 confirmed cases of COVID-19 (1.2% of total cases).[10]

The spatial distribution of notified COVID-19 cases in Indonesia is similar to that of pneumonia of unknown cause from *EpiWATCH*, suggesting the potential use of pneumonia of unknown cause as a proxy for COVID-19 cases in Indonesia. However, there were proportionately more notified cases from Jakarta compared with the spatial distribution of pneumonia of unknown cause from *EpiWATCH* in our study. This might suggest geographical differences in the ability to identify and report COVID-19 cases. Health infrastructure gaps have been cited as one of the most critical issues in the Indonesian health system.[11] Health facilities, including hospital and laboratory services, are more readily available in the urban Java region, where Jakarta, the capital city, is located.[12]

Provinces in Java, especially Jakarta, might have better capability for identifying cases of COVID-19. Meanwhile, other provinces may have underdetection of COVID-19 cases; for example, Bali notified a low number of confirmed COVID-19 cases compared with the *EpiWATCH*-reported cases of pneumonia of unknown cause. Of the 12 COVID-19 national reference laboratories in Indonesia, only three are located outside Java, which may hinder the ability of provinces outside Java to rapidly identify and respond to the presence of COVID-19.[13]

This study is the first of its kind to describe the epidemiological pattern of pneumonia of unknown cause reported from open-source intelligence before and after the official notification of COVID-19 cases in Indonesia. It shows that monitoring trends of pneumonia of unknown cause in open-source data could provide rapid, unvalidated information for early detection of COVID-19 outbreaks. Although the information is unvalidated, once a signal is detected, it could prompt further investigation and validation. Consequently, such information may supplement traditional surveillance, which is frequently subject to delays in reporting and validation by local health authorities.[4]

This study has several limitations. First, there is a possibility of reporting bias because we may have captured increasing media awareness rather than an actual increase in disease occurrence. The early signal was detected in late January 2020, when COVID-19 had been detected in many countries worldwide. Second, this study relies on an online news-based surveillance system, which is unvalidated and may include other etiologies of pneumonia that were not COVID-19.[14] Third, we only included pneumonia in our study; however, COVID-19 has a wide range of symptoms, with most of those infected having a mild illness.[15] Nevertheless, this study has highlighted the ability of open-source data to identify

Fig. 1. **Number of *EpiWATCH* reported cases of pneumonia of unknown cause in Indonesia between 1 November 2019 and 31 March 2020**

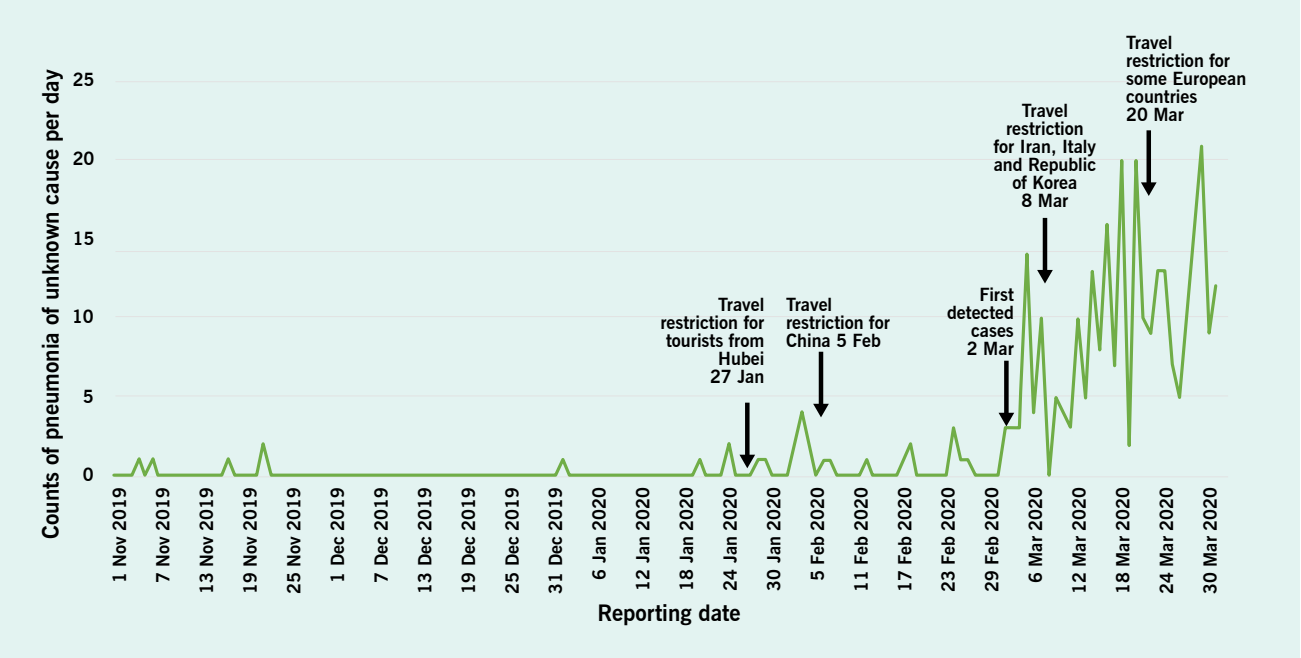
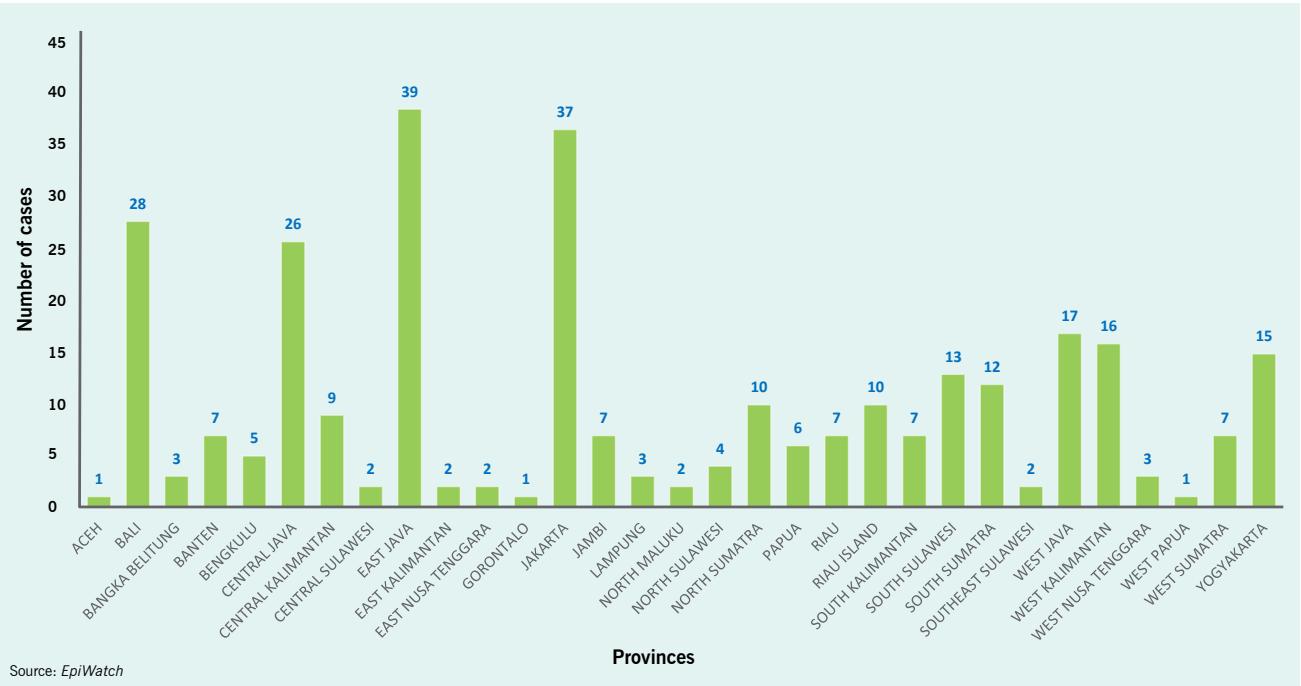
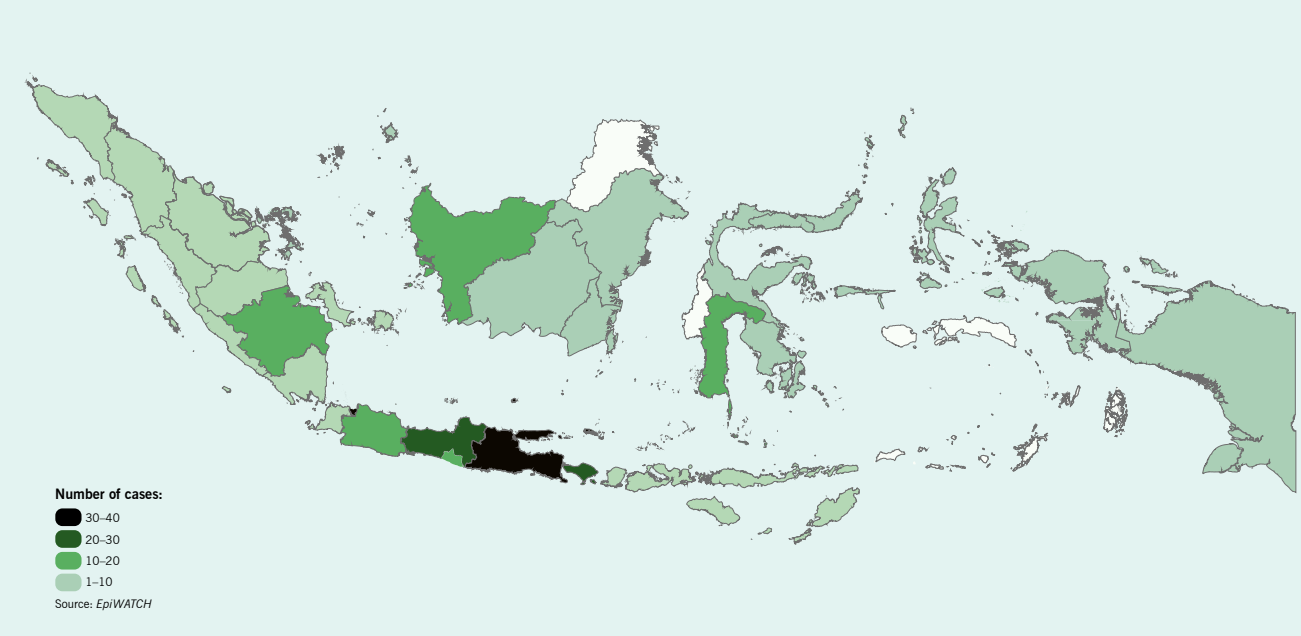


Fig. 2. **Number of *EpiWATCH* reported cases of pneumonia of unknown cause in Indonesia, by province (November 2019 to March 2020)**



Source: *EpiWatch*

Fig. 3. **Geographical distribution of *EpiWATCH* reported cases of pneumonia of unknown cause in Indonesia (November 2019 to March 2020)**



early alerts of pneumonia before the initial confirmation of COVID-19 cases in Indonesia, making such data a promising option to enhance epidemic surveillance.

CONCLUSION

In this study, we detected possible early signals of the COVID-19 outbreak in Indonesia using an online news-based surveillance system that used Bahasa Indonesia through *EpiWATCH*. The earliest signals from the *EpiWATCH* observatory of pneumonia of unknown cause in Indonesia were in late January 2020, indicating possible unrecognized circulation of COVID-19 cases in Indonesia before the country's official notification of cases. The observed spatial pattern of cases between *EpiWATCH*-reported pneumonia of unknown cause and officially confirmed COVID-19 cases in Indonesia was similar.

Monitoring trends in open-source data can provide rapid, unvalidated information for the early detection of outbreaks. Although unvalidated, such information may be used to supplement or trigger investigation and testing. As *EpiWATCH* sources global information, this methodology can be repeated for other diseases and other countries within the Western Pacific Region.

Conflicts of interests

The content of this manuscript is solely the responsibility of the authors, and we have no conflicts of interest to declare. We verify that all authors have seen and approved the final manuscript and declare the manuscript content herein has not been submitted for consideration or published elsewhere.

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Comorbidities and clinical features related to severe outcomes among COVID-19 cases in Selangor, Malaysia

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Background: Pre-existing comorbidities can predict severe disease requiring intensive care unit (ICU) admission among COVID-19 cases. We compared comorbidities, clinical features and other predictive factors between COVID-19 patients requiring ICU admission for intubation/mechanical ventilation and all other COVID-19 cases in Selangor, Malaysia.

Method: Field data collected during the COVID-19 outbreak in Selangor, Malaysia, up to 13 April 2020 were used, comprising socio-demographic characteristics, comorbidities and presenting symptoms of COVID-19 cases. ICU admission was determined from medical records. Multiple logistic regression analysis was performed to identify factors associated with ICU admission requiring intubation/mechanical ventilation among COVID-19 cases.

Results: A total of 1287 COVID-19-positive cases were included for analysis. The most common comorbidities were hypertension (15.5%) and diabetes (11.0%). More than one third of cases presented with fever (43.8%) or cough (37.1%). Of the 25 cases that required intubation/mechanical ventilation, 68.0% had hypertension, 88.0% had fever, 40.0% had dyspnoea and 44.0% were lethargic. Multivariate regression showed that cases that required intubation/mechanical ventilation had significantly higher odds of being older (aged ≥60 years) [adjusted odds ratio (aOR) = 3.9] and having hypertension (aOR = 5.7), fever (aOR = 9.8), dyspnoea (aOR = 9.6) or lethargy (aOR = 7.9) than cases that did not require intubation/mechanical ventilation.

Conclusion: The COVID-19 cases in Selangor, Malaysia requiring intubation/mechanical ventilation were significantly older, with a higher proportion of hypertension and symptoms of fever, dyspnoea and lethargy. These risk factors have been reported previously for severe COVID-19 cases, and highlight the role that ageing and underlying comorbidities play in severe outcomes to respiratory disease.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The infection was first detected in Wuhan, China, and has since spread across mainland China[1] and all over the world. COVID-19 is the third coronavirus infection that has spread widely, after SARS and Middle East respiratory syndrome (MERS).[2] On 11 March 2020, WHO declared COVID-19 a pandemic.[3] As of 14 April 2020, COVID-19 had led to 1 848 439 diagnosed cases and 117 217 deaths worldwide.[4] Up to 14 April 2020, Malaysia has had a total of 4987 infected people and 82 deaths.[5]

With the increasing numbers of confirmed cases and fatalities due to COVID-19, underlying comorbidities such as cardiovascular diseases and immune deficiency, especially among elderly patients, have been shown to be predictors of severe disease outcomes and poor prognoses in COVID-19 patients.[6–8] Severe cases of

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COVID-19 often require admission to an intensive care unit (ICU). In China, about 15% of patients developed severe pneumonia, and about 6% required non-invasive or invasive ventilatory support.[9]

Early identification of the risk factors of severe COVID-19 disease requiring intensive care in hospital would be helpful for managing hospital admissions. Studies in China and Italy suggest that the risk factors for severe COVID-19 include underlying comorbidities.[10,11] Therefore, we compared the comorbidities, clinical features and other predictive factors of COVID-19 patients requiring admission to ICU for intubation/mechanical ventilation with all other COVID-19 cases in Selangor, Malaysia.

METHODS

In this retrospective study, data were collected during a COVID-19 outbreak in Selangor, Malaysia, a state on the west coast of peninsular Malaysia. At the time of the study, Selangor had recorded the highest number of COVID-19 cases in the country, with the first case reported on 4 February 2020. The analysis included all laboratory-confirmed cases in the state up to 13 April 2020. Cases were confirmed by reverse transcriptase polymerase chain reaction (RT–PCR) testing.[12]

Descriptive methods were used to analyse sociodemographic characteristics, comorbidities, clinical presentation and the proportion of ICU admissions requiring intubation/mechanical ventilation. Clinical and sociodemographic characteristics were derived from case investigation reports obtained from district health offices in charge of each patient. The symptoms were self-reported during telephone interviews of cases by district health officers upon notification of a positive COVID-19 case. Admission to ICU for intubation/mechanical ventilation was verified from hospital records.

Multiple logistic regression analysis was performed to identify factors associated with intubation/mechanical ventilation among COVID-19 cases. The outcome variable was ICU admission requiring intubation/mechanical ventilation. The predictor variables included a history of hypertension, diabetes, heart disease, chronic respiratory disease (including asthma, chronic obstructive pulmonary disease and emphysema), cancer and kidney disease and the main symptoms of COVID-19, such as fever, cough, dyspnoea, lethargy, arthralgia, myalgia, headache and diarrhoea. Variables with P values < 0.25, based on Wald $\chi 2$ statistics in univariate analysis,[13] as well as those variables considered to be biologically plausible, were selected for the multivariate analysis.

The final model included sex, age, hypertension, diabetes, heart disease, fever, cough, dyspnoea and lethargy. The univariate test P value cut-off was set at 0.25 because the usual level of 0.05 may fail to identify variables known to be important.[14] A backwards selection method was used to select variables. Starting with all candidate variables, the least significant effect for the model was removed, and the process was repeated until no further variables could be deleted without a statistically significant loss of fit. After this process, only age, hypertension, fever, dyspnoea and lethargy were significant in the multivariate model. To avoid over-fitting the model, only these five variables were included. Possible multicollinearity and all possible two-way interaction terms were checked one by one with main effect. Goodness-of-fit statistics were used to assess the fit of the regression model against actual outcomes. Two-sided P values < 0.05 were considered statistically significant. Statistical Package Social Sciences (SPSS) statistical software version 24 was used for the analysis.

The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained from the National Medical Research Registry, Ministry of Health Malaysia (registration number NMRR-20–720–54598). The requirement for written informed consent was waived given the context of an emerging infectious disease.

RESULTS

In total, 1287 laboratory-confirmed cases of COVID-19 in Selangor were included in the analysis. Of these, 750 patients (58.3%) were male and most (74.0%) were of Malay ethnicity. The median age was 36 years, and the highest percentage of cases were in people aged 18–29 years. The most commonly reported comorbidities were hypertension (15.5%) and diabetes (11.0%). More than one third of cases presented with fever (43.8%) or cough (37.1%); only 5.5% experienced dyspnoea, and 6.1% were lethargic (**Table 1**).

Table 1. **Socio-demographic characteristics, comorbidity and clinical presentation of COVID-19-positive cases in Selangor (*n* = 1287)**

Characteristic	COVID-19-positive cases
Sex, *n* (%)	
Male	750 (58.3)
Female	537 (41.7)
Age (years)	
Median (IQR)	36.0 (30.0)
Mean (SD)	38.8 (18.2)
Age groups, *n* (%)	
<18	116 (9.0)
18–29	366 (28.4)
30–39	239 (18.6)
40–49	151 (11.7)
50–59	214 (16.6)
≥60	201 (15.6)
Ethnicity, *n* (%)	
Malay	952 (74.0)
Chinese	118 (9.2)
Indian	43 (3.3)
Other	174 (13.5)
Nationality, *n* (%)	
Malaysian	1122 (87.2)
Non-Malaysian	165 (12.8)
Comorbid conditions, *n* (%)	
Hypertension	200 (15.5)
Diabetes	141 (11.0)
Heart disease or other problem	50 (3.9)
Chronic respiratory disease	40 (3.1)
Chronic kidney disease	18 (1.4)
Cancer	7 (0.5)
Current smoker	57 (4.4)
Symptoms, *n* (%)	
Fever	564 (43.8)
Cough	477 (37.1)
Lethargy	78 (6.1)
Dyspnoea	71 (5.5)
Headache	71 (5.5)
Myalgia	53 (4.1)
Diarrhoea	41 (3.3)
Arthralgia	31 (2.4)
Hospital admission (*n* = 1156), *n* (%)	
Intubated (invasive ventilator support)	25 (2.2)
Not intubated	1131 (97.9)

Of the 1156 patients who were hospitalized, 25 (2.2%) were admitted to the ICU and required intubation/mechanical ventilation. Of these 25 cases, 14 were aged ≥60 years, 17 had hypertension, 10 had diabetes, 22 presented with fever, 14 with cough, 10 with dyspnoea and 11 with lethargy (**Table 2**).

The final multivariate model demonstrated that the odds of COVID-19 cases that required intubation/mechanical ventilation being older (≥60 years) were 4.2 times (aOR: 4.24, 95% CI: 1.59–11.34) higher than the odds of all other cases being older, after controlling for sex, comorbidities and presenting symptoms. COVID-19 cases that required intubation/mechanical ventilation also had 6.0 times higher odds of having underlying hypertension (aOR: 5.97, 95% CI: 2.27–15.72) and presenting with the symptoms of fever (aOR: 7.91, 95% CI: 2.18–28.73), dyspnoea (aOR: 8.47, 95% CI: 3.08–23.29) or lethargy (aOR: 7.57, 95% CI: 2.89–19.86), compared with the odds for these risk factors in all other cases (Table 3). When age was used as a continuous variable in the same regression model, every 1-year increase in age increased the odds of requiring intubation/mechanical ventilation by 8% (aOR: 1.08, 95% CI: 1.03–1.12).

Univariable analyses were also conducted for cancer, chronic kidney disease, current smoker, chronic respiratory disease and symptoms at presentation such as diarrhoea, arthralgia, myalgia and headache. The results are not presented in the table because the small sample sizes did not give meaningful ORs and CIs.

DISCUSSION

In this study, the proportion of COVID-19 cases requiring intubation/mechanical ventilation in Selangor, Malaysia (2.2%) was similar to studies in China (2.3–3.0%)[10,15] but lower than that in the United States of America (20.2–22.3%).[16,17] These differences may be due to differences in guidelines for intubation and mechanical ventilation as well as ICU bed capacity. We also found that underlying hypertension and diabetes were the most common comorbidities in all COVID-19 cases, consistent with the findings in Wuhan[18] and in a meta-analysis of the prevalence of comorbidities in COVID-19 patients.[19] Bornstein et al.[20] reported that hypertension and type-II diabetes were the most common comorbidities in infected COVID-19 patients,

Table 2. **Numbers of intubated cases of COVID-19 by socio-demographic, NCD comorbidity and clinical presentation**

Variables	Intubated (invasive mechanical ventilation) (*n* = 25)	Not intubated (*n* = 1262)
Sex, *n* (%)		
Male	18 (72.9)	732 (58.0)
Female	7 (28.0)	530 (42.0)
Age group, *n* (%)		
<60	11 (44.0)	1075 (85.2)
≥60	14 (56.0)	187 (14.8)
Comorbid conditions, *n* (%)		
Hypertension	17 (68.0)	183 (14.5)
Diabetes	10 (40.0)	131 (10.4)
Heart disease	4 (16.0)	46 (3.6)
Chronic respiratory disease	0 (0.0)	40 (3.2)
Chronic kidney disease	3 (12.0)	15 (1.2)
Cancer	0 (0.0)	7 (0.6)
Current smoker	1 (4.0)	56 (4.4)
Symptoms, *n* (%)		
Fever	22 (88.0)	542 (42.9)
Cough	14 (56.0)	463 (36.7)
Lethargy	11 (44.0)	67 (5.3)
Dyspnoea	10 (40.0)	61 (4.8)
Diarrhoea	3 (12.0)	38 (3.0)
Arthralgia	1 (4.0)	30 (2.4)
Myalgia	1 (4.0)	52 (4.1)
Headache	0 (0.0)	71 (5.6)

due to metabolic inflammation caused by the infection, which compromises the immune system. Diabetes and hypertension were also reported as the most common comorbidities with other coronaviruses, such as SARS-CoV and MERS-CoV.[21]

Older age and underlying comorbidities are predictors of severe outcomes in viral infections generally,[22,23] and we found that the proportion of COVID-19 patients who required intubation/mechanical ventilation increased with age. The regression model showed that the odds of requiring intubation/mechanical ventilation was 4.2 times higher for adults aged ≥60 years after controlling for comorbidities and presenting symptoms. As in other studies, the risk for a severe outcome is higher for older people. Data from China indicate that older adults with severe underlying health conditions are at higher risk for severe COVID-19-associated illness and death.[24] Reports from Italy also suggested that the risk factors for severe disease include older age and the presence of at least one underlying health condition among COVID-19 cases.[11]

Preliminary findings from the United States of America suggested that people with underlying health conditions are at higher risk for severe disease from COVID-19.[25] A study in China showed that almost 70% of COVID-19 patients who were admitted to an ICU had comorbidities.[26] Our study shows that COVID-19 patients with underlying hypertension contributed to a high percentage of ICU admissions requiring intubation/mechanical ventilation. Cases that required intubation/mechanical ventilation also had six times the odds of having underlying hypertension after adjustment for age, other comorbidities and clinical presentation. Hypertension was the most common comorbidity that predicted a poor prognosis in patients with COVID-19. In a systematic review and meta-analysis by Yang et al.,[26] the pooled odds of hypertension in patients with severe, as compared with non-severe disease, was 2.36 (95% CI: 1.46–3.83).

Other than age and underlying hypertension, the presenting symptoms of COVID-19 infection also predict a severe outcome. As in other studies, the most common

Table 3. **Factors associated with intubation among positive COVID-19 cases in a binary logistic regression model (*n* = 1287)**

Risk factor	Simple logistic regression			Multiple logistic regression		
	b	Crude OR (95% CI)	*P*	*b*	Adjusted OR* (95% CI)	*P*
Sex						
Male		1				
Female	–0.62	0.54 (0.22–1.30)	0.166			
Age group (years)						
< 60		1			1	
≥ 60	1.99	7.32 (3.27–16.36)	< 0.001	1.45	4.24 (1.59–11.34)	0.004
Hypertension						
No		1			1	
Yes	2.53	12.53 (5.33–29.46)	< 0.001	1.79	5.97 (2.27–15.72)	< 0.001
Diabetes						
No		1			1	
Yes	1.75	5.76 (2.53–13.07)	< 0.001			
Heart disease						
No		1			1	
Yes	1.62	5.04 (1.66–15.26)	0.004			
Fever at presentation						
No		1			1	
Yes	2.28	9.74 (2.90–32.72)	< 0.001	2.07	7.91 (2.18–28.73)	0.002
Cough at presentation						
No		1			1	-
Yes	0.787	2.20 (0.99–4.88)	0.053			
Dyspnoea at presentation						
No		1			1	
Yes	2.58	13.13 (5.66–30.42)	< 0.001	2.14	8.47 (3.08–23.29)	< 0.001
Lethargy at presentation						
No		1			1	
Yes	2.64	14.01 (6.13–32.05)	< 0.001	2.03	7.57 (2.89–19.86)	< 0.001

* Backwards multiple logistic regression was applied. Multicollinearity and interactions were checked and not found. Hosmer Lameshow test $P = 0.808$, classification table (overall correctly classified percentage = 98.0%) and area under ROC curve = 94.3% were used to check model fitness.

Univariable analyses were also conducted for cancer, chronic kidney disease, current smoker, chronic respiratory disease and symptoms at presentation such as diarrhoea, arthralgia, myalgia and headache. The results are not presented in the table because small cell sizes did not give meaningful ORs and CIs.

presenting symptoms in this study were fever, cough, dyspnoea and lethargy.[10,15,18,28,29] Our findings indicate that symptomatic COVID-19 patients with fever, dyspnoea and lethargy have a strong, significant risk for intubation/mechanical ventilation. Li et al.[30] demonstrated significant differences in clinical symptoms and computed tomography scan manifestation between patients with or without severe or critical COVID-19 after control for age and comorbidities. This finding is important for clinicians in stratifying risk for their patients according to presenting symptoms. Although dyspnoea is a known risk factor for intubation/mechanical ventilation, patients presenting with fever or lethargy should also be closely monitored.

Our study has some notable limitations. First, the number of cases requiring intubation/mechanical ventilation was small at 25 cases (2.2%). Furthermore, the data were derived from a report from a single state in Malaysia and may not represent the national population. Data on ICU admissions, comorbidities and outcomes were missing for <20% of patients. Despite these limitations, our results are consistent with previous studies of COVID-19 cases.

CONCLUSION

COVID-19 cases that were intubated and ventilated had higher odds of being aged ≥60 years, having hypertension and presenting with fever, dyspnoea or lethargy compared with all other COVID-19 cases. Older people and those with comorbidities such as hypertension should be prioritised for hospital care as they are more vulnerable to severe disease and progression when infected with SARS-CoV-2.

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Conflict of interest

None declared.

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COVID-19 is moving to high-density, poor residential areas in Metropolitan Manila, Philippines

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We note three successive waves of coronavirus disease 2019 (COVID-19) cases in the National Capital Region (Metropolitan Manila), Philippines: the first was from imported cases among Chinese nationals; the second was from infections among Filipinos residing in less densely populated areas; and the third was from infections among Filipinos residing in high-density, poor areas. We support these observations with data from San Lazaro Hospital, the national infectious diseases hospital, which serves a low-income population in Manila City, the most densely populated city within Metropolitan Manila (**Fig. 1**).

The first two confirmed cases of COVID-19 in the Philippines were among Chinese nationals on vacation, both of whom were admitted to San Lazaro Hospital on 25 January 2020, with confirmation on 31 January and 1 February.[1] A third imported case from China was confirmed on 3 February 2020.[2] Despite concerns that all three individuals had travelled widely within the Philippines, no secondary infections arising from these cases were confirmed.

The next person with confirmed COVID-19 was admitted to San Lazaro Hospital more than one month later, on 8 March. During the following 10 days, a further 17 confirmed cases were reported at the hospital. In contrast to the first individuals with confirmed COVID-19, these individuals were all Filipinos, with seven reporting recent travel to areas affected by COVID-19. None of these patients resided in the densely populated catchment area of the hospital. From 19 to 29 March, a further 16 cases were confirmed at the hospital. In contrast to the previous wave, all patients except for one resided in Manila City, with only one reporting a significant history of international travel.

The occurrence of confirmed COVID-19 in Manila City is concerning given that it has an estimated population density of 71 263 persons per square kilometre. In the Philippines overall, there were 9223 confirmed cases as of 3 May.[2] The true number of cases is likely to be much higher given that until late March testing was conducted by only one laboratory in the country. Significant community transmission cannot be excluded due to the lack of laboratory surveillance data. The establishment of subnational laboratories across the Philippines, including at San Lazaro Hospital, is timely and welcome. In Manila City, increased community testing and monitoring of individuals presenting to hospitals with respiratory symptoms could detect increased COVID-19 transmission.

At-home isolation for 14 days is now recommended for people with mild COVID-19;[3] however, for people living in high-density or slum areas, it will be challenging to ensure that they are able to adequately isolate to avoid further transmission. The planned establishment of designated isolation facilities and expansion of testing should help reduce community transmission.[4]

A surge of severe or high-risk cases in Manila City is likely to put enormous pressure on health-care facilities, which are already experiencing significant infections among health-care workers and shortages of personal protective equipment. Bed shortages may become more acute if other infectious disease outbreaks occur, such as measles, dengue or leptospirosis.

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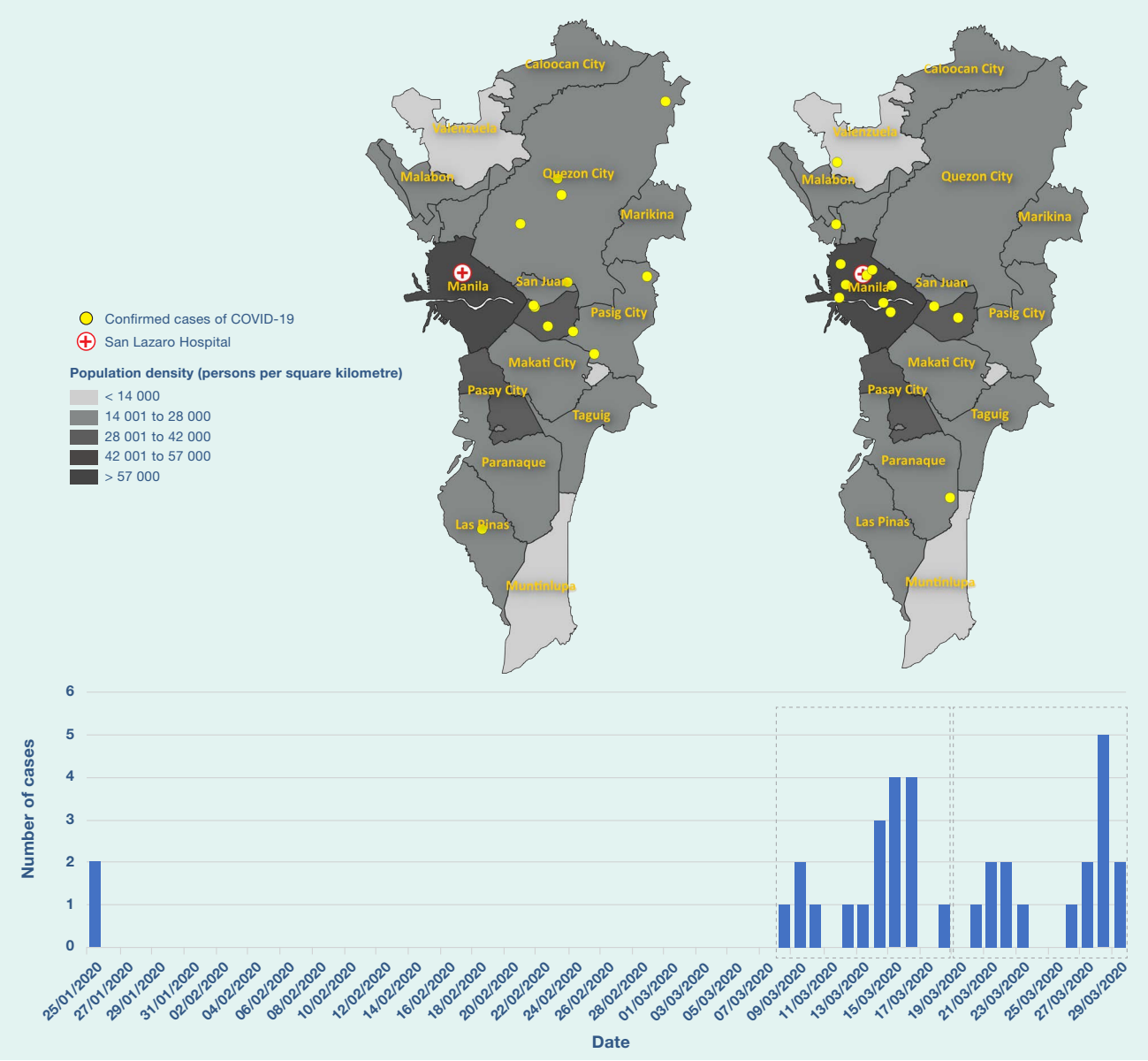
Fig. 1. **Timeline of cases with confirmed COVID-19 admitted to San Lazaro Hospital, from 25 January to 29 March 2020. Maps show the residence of patients in the National Capital Region (Metropolitan Manila) admitted during 8–18 March (left) and 19–29 March (right).**



Luzon island has been under community quarantine since 15 March 2020.[5] People living in high-density areas, such as Manila City, are likely to be more vulnerable to the negative consequences of community quarantine, such as economic difficulties, food insecurity and domestic violence. It is hoped that the quarantine measures will flatten the epidemic curve and result in fewer overall infections, but they may be difficult to sustain for a long period.

Conflicts of interest

The authors declare that they have no competing interests.

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Early response to COVID-19 in the Philippines

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Low- and middle-income countries (LMICs) with weak health systems are especially vulnerable during the COVID-19 pandemic. In this paper, we describe the challenges and early response of the Philippine Government, focusing on travel restrictions, community interventions, risk communication and testing, from 30 January 2020 when the first case was reported, to 21 March 2020. Our narrative provides a better understanding of the specific limitations of the Philippines and other LMICs, which could serve as basis for future action to improve national strategies for current and future public health outbreaks and emergencies.

THE PHILIPPINE HEALTH SYSTEM AND THE THREAT OF PUBLIC HEALTH EMERGENCIES

Despite improvements during the past decade, the Philippines continues to face challenges in responding to public health emergencies because of poorly distributed resources and capacity. The Philippines has 10 hospital beds and six physicians per 10 000 people.[1,2] and only about 2335 critical care beds nationwide.[3] The available resources are concentrated in urban areas, and rural areas have only one physician for populations up to 20 000 people and only one bed for a population of 1000.[4] Disease surveillance capacity is also unevenly distributed among regions and provinces. The primary care system comprises health centres and community health workers, but these are generally ill-equipped and poorly resourced, with limited surge capacity, as evidenced by lack of laboratory testing capacity, limited equipment and medical supplies, and lack of personal protective equipment for health workers in both primary care units and hospitals.[5] Local government disaster preparedness plans are designed for natural disasters and not for epidemics.

Inadequate, poorly distributed resources and capacity nationally and subnationally have made it difficult to respond adequately to public health emergencies in the past, as in the case of typhoon Haiyan in 2013.[6] The typhoon affected 13.3 million people, overwhelming the Government's capacity to mobilize human and financial resources rapidly to affected areas.[7] Failure to deliver basic needs and health services resulted in disease outbreaks, including a community outbreak of gastroenteritis.[8] Access to care has improved in recent years due to an increase in the number of private hospital beds;[5] however, improvements in private sector facilities mainly benefit people who can afford them, in both urban and rural areas.

In this paper, we describe the challenges and early response of the Philippine Government, focusing on travel restrictions, community interventions, risk communication and testing, from 30 January 2020 when the first case was reported, to 21 March 2020.

EARLY RESPONSE TO COVID-19

Travel restrictions

Travel restrictions in the Philippines were imposed as early as 28 January, before the first confirmed case was reported on 30 January (**Fig. 1a**).[9] After the first few COVID-19 cases and deaths, the Government conducted contact tracing and imposed additional travel restrictions,[10] with arrivals from restricted countries subject to 14-day quarantine and testing. While

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Fig. 1a. **New cases of COVID-19 in the Philippines, 30 January–21 March 2020**

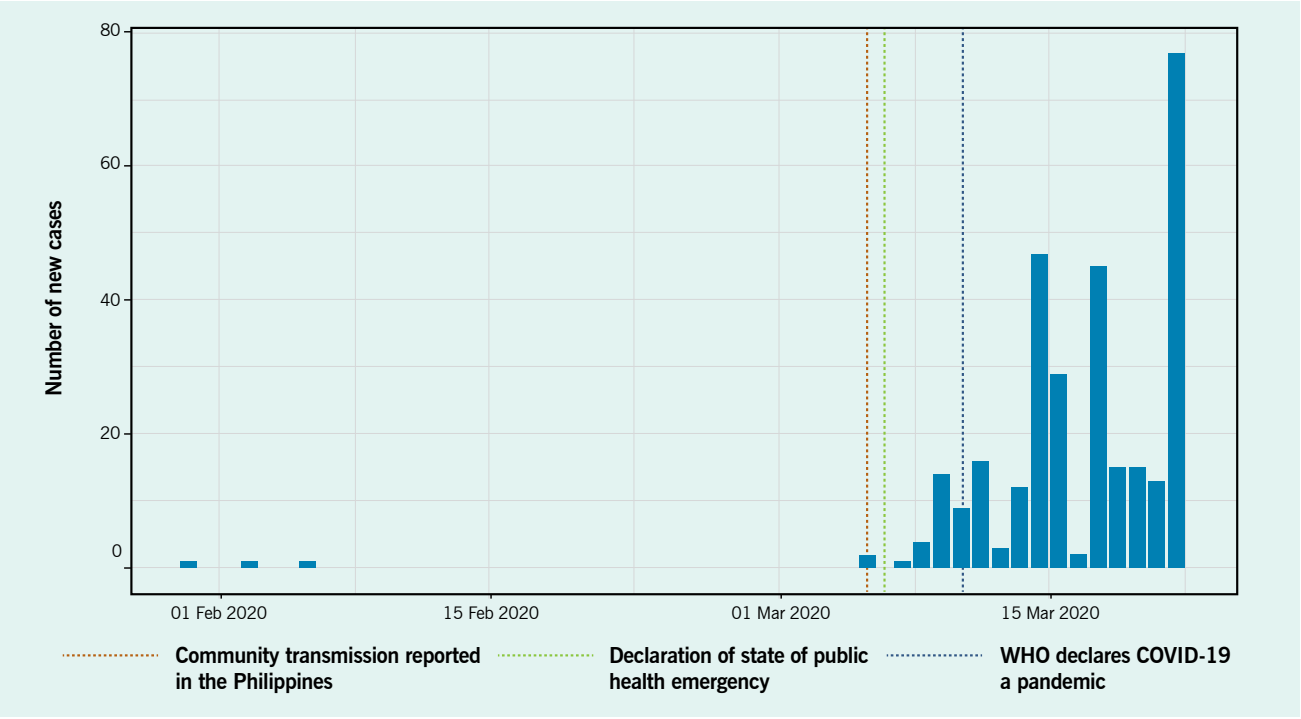
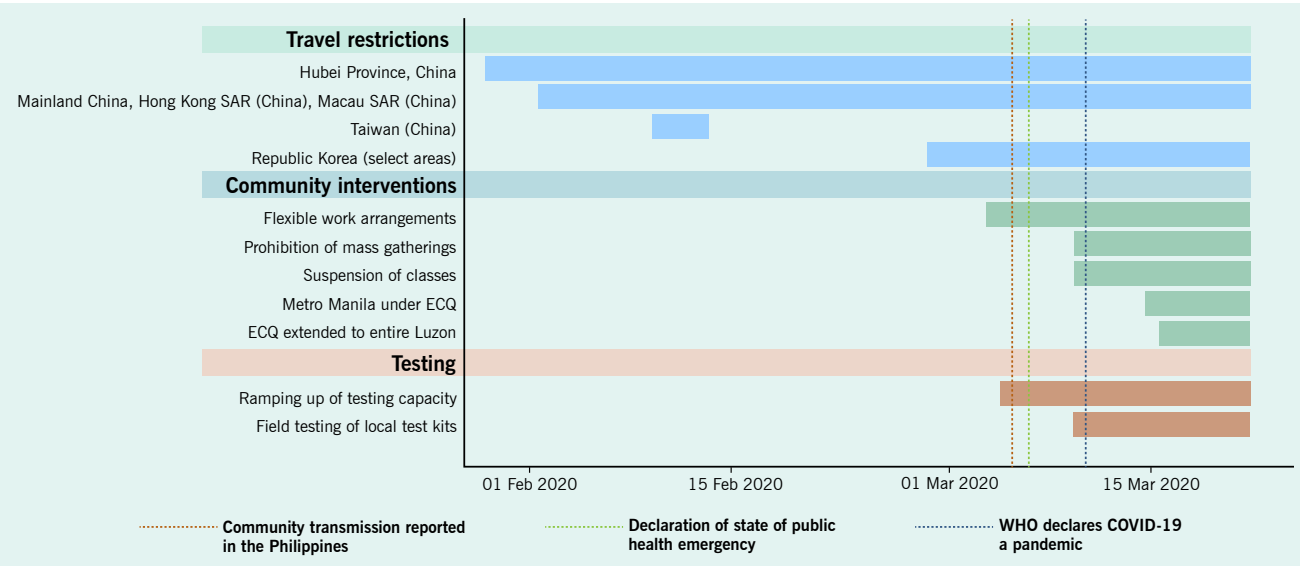
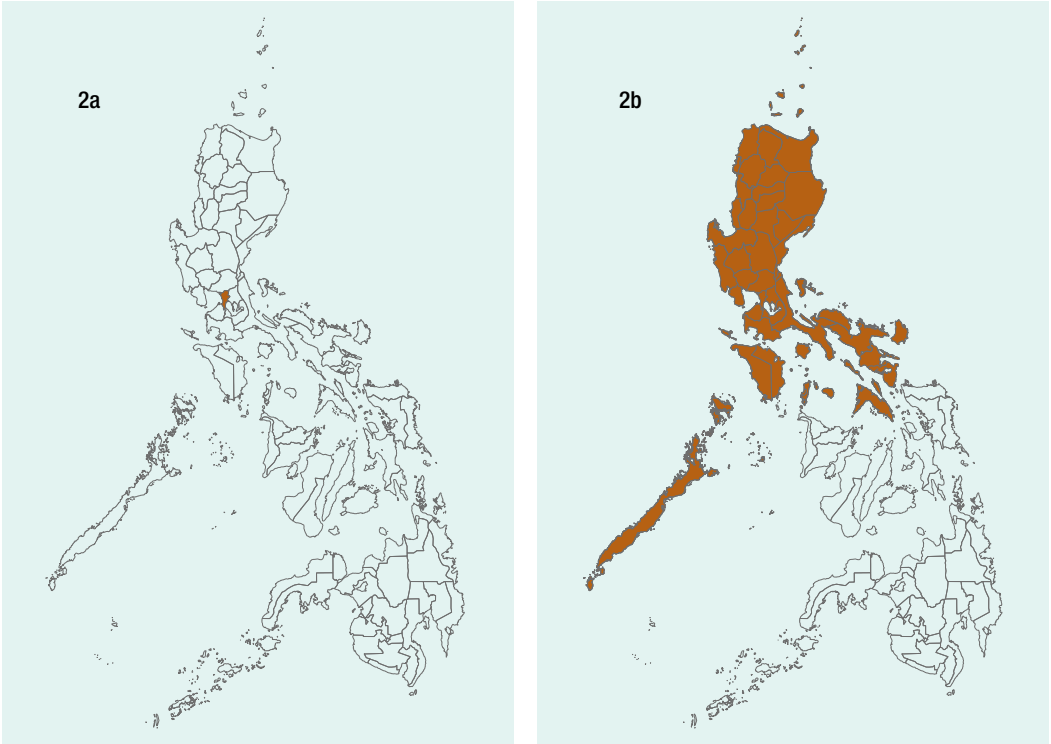


Fig. 1b. **Timeline of key events and developments in the Philippines, 30 January–21 March 2020**



travel restrictions in the early phase of the COVID-19 response prevented spread of the disease by potentially infected people, travellers from countries not on the list of restricted countries were not subject to the same screening and quarantine protocols. The restrictions were successful in delaying the spread of the disease only briefly, as the number of confirmed cases increased in the weeks that followed.[11] **Fig. 1b** shows all interventions, including travel restrictions undertaken before 6 March, when the Government declared the occurrence of community spread, and after 11 March, when WHO declared COVID-19 a pandemic.

Fig. 2. **Provinces placed under enhanced community quarantine (ECQ). (2a) The Government declared ECQ in Metro Manila effective 15 March 2020; (2b) The Government declared ECQ on the entire island of Luzon effective 17 March 2020.**



Community interventions

The Government declared "enhanced community quarantine" (ECQ) for Metro Manila between 15 March and 14 April (**Fig. 2a**), which was subsequently extended to the whole island of Luzon (**Fig. 2b**). The quarantine consisted of: strict home quarantine in all households, physical distancing, suspension of classes and introduction of work from home, closure of public transport and non-essential business establishments, prohibition of mass gatherings and non-essential public events, regulation of the provision of food and essential health services, curfews and bans on sale of liquor and a heightened presence of uniformed personnel to enforce the quarantine procedures.[12] ECQ – an unprecedented move in the country's history – was modelled on the lockdown in Hubei, China, which was reported to have slowed disease transmission.[13] Region-wide disease control interventions, such as quarantining of the entire Luzon island, were challenging to implement because of their scale and social and economic impacts, but they were deemed necessary to "flatten the curve" so that health systems were not overwhelmed.[14] While the lockdown implemented by the Government applied only to the island of Luzon, local governments in other parts of the country followed this example and also locked down. The ECQ gave the country the opportunity to mobilize resources and organize its pandemic response, which was especially important in a country with poorly distributed, scarce resources and capacity.

Risk communication

The Government strengthened and implemented national risk communication plans to provide information on the new disease. The Government conducted daily press briefings, sponsored health-related television and Internet advertisements and circulated infographics on social media. Misinformation and conspiracy theories about COVID-19 were nevertheless a challenge for a population that spends more than 10 hours a day on the Internet.[15,16] These spread quickly and became increasingly difficult to correct. Furthermore, the Government's messages did not reach all households, despite access

to health services and information, resulting in limited knowledge of preventive practices, except for handwashing.[17]

Testing

Testing is key to controlling the pandemic but was done on a small scale in the Philippines. As of 19 March, fewer than 1200 individuals had been tested,[11] as only the Research Institute for Tropical Medicine located in Metro Manila performed tests and assisted subnational reference laboratories in testing.[18] No positivity rates for RT-PCR tests were reported until early April 2020. Because of the limited capacity for testing at the start of the pandemic, the Department of Health imposed strict protocols in order to ration testing resources while ramping up testing capacity. Most tests were conducted for individuals in urban areas, where the incidence was highest.[19]

CONCLUSIONS

At the start of the COVID-19 pandemic, the country's initial response lacked organizational preparedness to counter the public health threat. The Philippines' disease surveillance system could conduct contact tracing, but this was overwhelmed in the early phases of outbreak response. Similarly, in February, only one laboratory could conduct reverse transcriptase polymerase chain reaction (RT–PCR) testing, so the country could not rapidly deploy extensive laboratory testing for infected cases. In addition, the primary care system of the Philippines did not serve as a primary line of defence, as people went straight to hospitals in urban areas, overwhelming critical care capacity in the early stages of the COVID-19 pandemic.

In response to the early phase of the pandemic, the Government of the Philippines implemented travel restrictions, community quarantine, risk communication and testing; however, the slow ramping up of capacities particularly on testing contributed to unbridled disease transmission. By 15 October, the number of confirmed cases had exponentially grown to 340,000 of which 13.8% were deemed active.[11] The lack of pandemic preparedness had left the country poorly defended against the new virus and its devastating effects. Investing diligently and consistently in pandemic preparedness, surveillance and testing capacity in particular is a lesson that the Philippines and other LMICs should learn from COVID-19.

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Conflict of interests

None reported

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Lessons from COVID-19-free Vanuatu: intensive health operations for Phase 1 of repatriation and quarantine, May–July 2020

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International borders to Vanuatu closed on 23 March 2020 due to the global COVID-19 pandemic. In May–July 2020, the Government of Vanuatu focused on the safe and timely return of citizens and residents while ensuring Vanuatu remained COVID-19 free. Under Phase 1 of repatriation, between 27 May and 23 June 2020, 1522 people arrived in the capital, Port Vila, and were placed in compulsory government-mandated 14-day quarantine in 15 hotels. Pre-arrival health operations included collection of repatriate information, quarantine facility assessments, training for personnel supporting the process, and tabletop and functional exercises with live scenario simulations. During quarantine, health monitoring, mental health assessments and psychosocial support were provided. All repatriates completed 14 days of quarantine. One person developed symptoms consistent with COVID-19 during quarantine but tested negative. Overall health operations were considered a success despite logistical and resource challenges.

Lessons learnt were documented during a health sector after-action review held on 22 July 2020. Key recommendations for improvement were to obtain timely receipt of repatriate information before travel, limit the number of repatriates received and avoid the mixing of "travel cohorts", ensure sufficient human resources are available to support operations while maintaining other essential services, establish a command and control structure for health operations, develop training packages and deliver them to all personnel supporting operations, and coordinate better with other sectors to ensure health aspects are considered. These recommendations were applied to further improve health operations for subsequent repatriation and quarantine, with Phase 2 commencing on 1 August 2020.

PROBLEM

Vanuatu, in the South Pacific, comprises 83 islands with a total population of around 307 000. As of 1 August 2020, it was one of the few countries with no confirmed cases of coronavirus disease 2019 (COVID-19),[1] mainly due to international border restriction measures implemented from late January 2020 and full border closure from 23 March 2020. A State of Emergency (SoE) was declared on 26 March 2020[2] to strengthen prevention and containment measures in response to the COVID-19 global pandemic (**Fig. 1**). The SoE was extended to include Tropical Cyclone Harold, which struck Vanuatu on 6–7 April 2020,[3] and was subsequently extended to 31 December 2020.[4]

Many Vanuatu citizens and residents travel or reside overseas, particularly under seasonal work programmes in Australia and New Zealand, or for study in Fiji and New Caledonia. As the global COVID-19 pandemic affected work and study abroad, many of these expressed interest in being repatriated to Vanuatu.

CONTEXT

The Government of Vanuatu undertook bilateral negotiations to ensure the safe and timely return of priority citizens and residents. Phase 1 of the operations (May–July 2020) aimed to ensure that priority repatriation and quarantine were completed ahead of the celebrations for the 40th anniversary of independence (23–31 July 2020). Phase 2 of the operations started after these celebrations.

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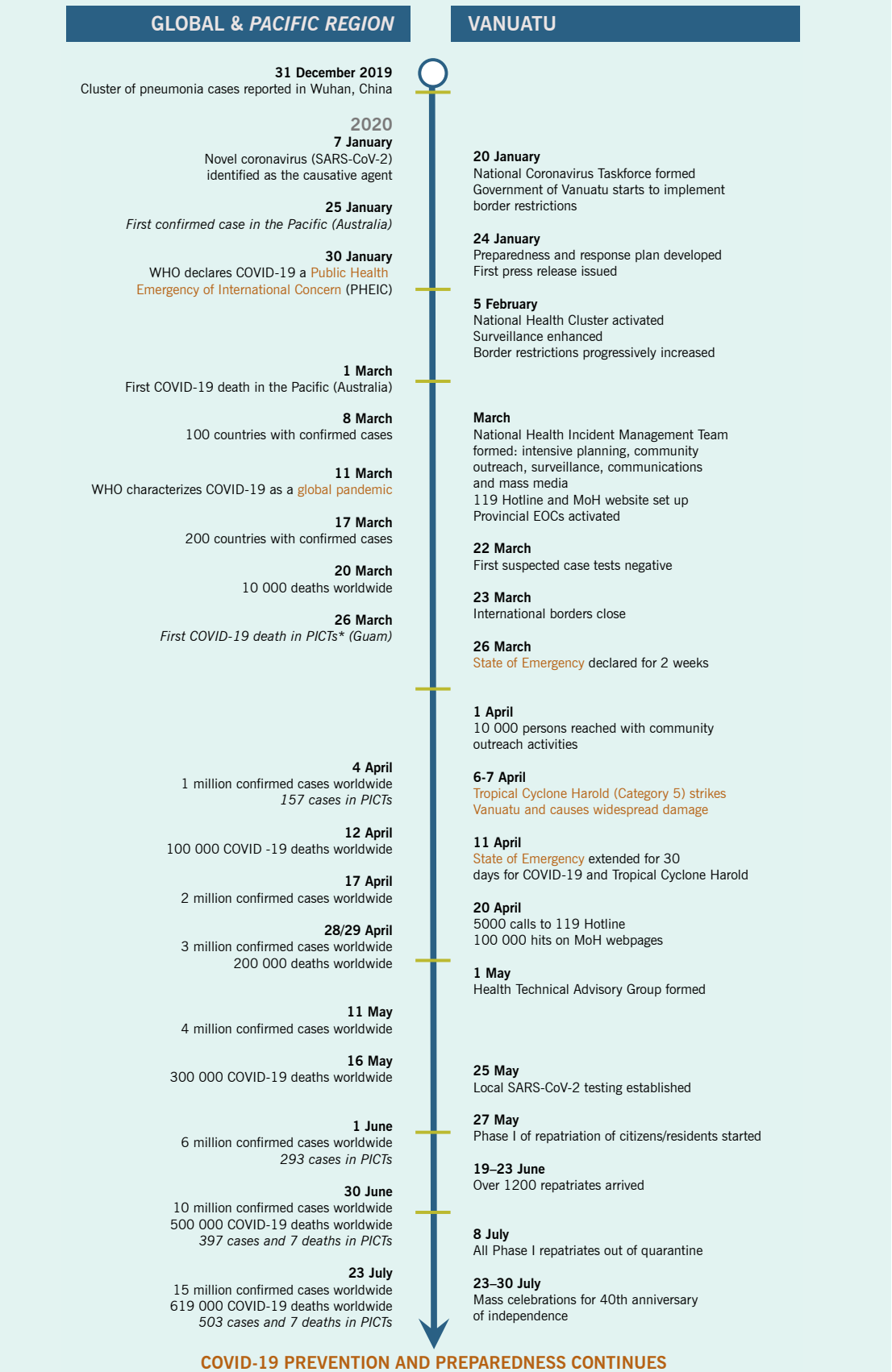
Fig. 1. **Timeline of the COVID-19 pandemic globally, in the Pacific and in Vanuatu and beyond, 31 December 2019 to 30 July 2020**



EOC: emergency operations centre; MoH: Ministry of Health; PICT: Pacific island country or territory; WHO: World Health Organization.

ACTIONS

Between 27 May and 23 June 2020, 1522 returning citizens and residents arrived through the Phase 1 repatriation operation. Fourteen flights were received in the capital, Port Vila, from Solomon Islands (1), Fiji (1), the Philippines (1), New Zealand (8), New Caledonia (1) and Australia (2), with 11 of these flights arriving between 19 and 23 June 2020.

In accordance with the Vanuatu Public Health Act [Cap. 234],[5] mandatory quarantine in government-designated hotel facilities was instituted for all arriving repatriates. Quarantine was for a 14-day period, based on technical recommendations from the Vanuatu Health Technical Advisory Group[6] and the incubation period of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The health operation activities are summarized in **Table 1** and **Fig. 2**.

Twenty people involved in Phase 1 of the health operations from the Ministry of Health (MoH) and development partner organizations participated in an after-action review (AAR), held on 22 July 2020. The AAR was facilitated by the World Health Organization (WHO) Vanuatu Country Liaison Office, with five observers (WHO staff and senior MoH staff) and three rapporteurs. This report presents the main observations and lessons learnt from Phase 1.

Main observations and lessons learnt

Coordination and staffing

The health operations team comprised staff from the MoH and development partner organizations, with existing staff repositioned or additional personnel contracted to meet critical gaps. A total of 34 provincial public health staff (public health officers, nurses and medical officers) were involved in daily monitoring across the 15 government-designated quarantine facilities, with staff redeployed from other services. The team was highly motivated to support the quarantine process during Phase 1, and continual improvements were made. However, the rapid influx of repatriates over a 5-day period, and the requirement to register and then monitor each person daily with in-person temperature and symptom checks, added a considerable burden to the public health system. The AAR therefore recommended that, for Phase 2, human resource requirements to support operations should be clearly mapped out and options should be identified for surge capacity (e.g. those working in provincial offices, retired staff or new recruits), with opportunities provided for upskilling. The AAR strongly recommended limiting the number of arriving repatriates and those in quarantine to a manageable number, based on staff numbers and availability of quarantine facilities.

During Phase 1, separate daily meetings were held at both the MoH and Shefa Community Health Services, during which staff provided updates on operations, identified or were notified about current health issues, and determined the actions required. The AAR highlighted the need to strengthen coordination of health operations between the MoH and provincial health offices, to avoid replication and undue burden on managers, and to ensure joint daily briefings, debriefings and production of consolidated situation reports. Tabletop and functional exercises with live scenario simulation exercises were conducted with national and provincial staff throughout Phase 1, in parallel with ongoing repatriation operations. They covered arrival, transfer from airport to quarantine facilitiess and registration – lessons learnt were fed back for continuous improvement.

Pre-arrival preparations

In Phase 1, the MoH requested repatriate information (e.g. age, sex, health issues, medical conditions and required medication) from foreign missions in advance of travel, but little information was provided. This constrained preparatory work by the health operations team (e.g. pre-arrival quarantine facility allocations). The AAR recommended that the MoH develop an electronic system to collect repatriate information 72 hours before travel to enable MoH assessment of epidemiological risk and health approval before travel; preparation for quarantine, including pre-allocation to quarantine facilities based on health and medical needs; and systematic registration and tracking of all arriving repatriates.

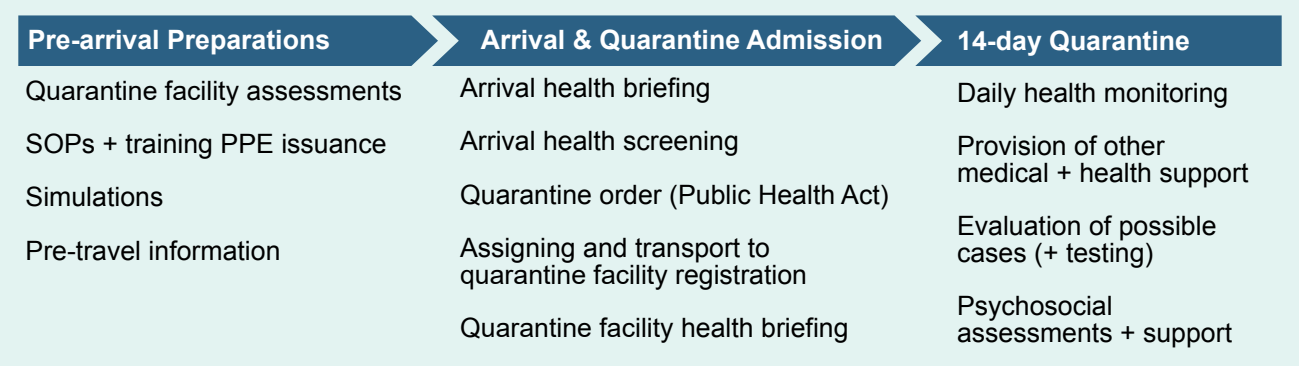
The AAR also highlighted the need to strengthen coordination with the other agencies involved in repatria-

Table 1. **Purpose and description of health operation activities for Phase 1 of repatriation and quarantine in Vanuatu, May–July 2020**

Stage/activity	Purpose
Coordination and staffing	
Operations coordination	To ensure coordination and communication across teams involved in health operations through daily meetings, debriefings and situation reports.
Pre-arrival preparations	
Quarantine facility assessments	To ensure quarantine facilities selected meet minimum MoH/WHO standards to support compliance while maintaining good health and well-being of repatriates.
Quarantine facility training and information	To educate managers and staff on quarantine SOPs, including appropriate use of PPE.
Other training	To educate others supporting the repatriation and quarantine process (border security, police, drivers and others) on general COVID-19 information and quarantine SOPs.
Tabletop and live scenario simulations	To replicate processes to identify potential issues and areas for improvement, including pre-arrival, transfer from airport to quarantine facilities and registration.
Procurement and issuance of PPE	To provide PPE (gloves, masks, gowns, eye protection and hand sanitizer) to those who require it, in accordance with MoH guidance.
Before departure from origin	
Information to repatriates	To enable appropriate preparation for travel and quarantine.
Information to MoH	To inform health operations team preparations based on passenger information (age, pre-existing health issues or medical conditions, and medication requirements).
Pre-boarding screening	To collect (through a passenger health declaration form) travel history and ensure repatriates are fit to travel.
Upon arrival at the airport in Vanuatu	
Information to repatriates at border	To provide further educational information, including through videos screened in the arrival hall.
Health screening	To check for signs or symptoms of COVID-19 and review information on passenger health declaration forms before transferring them to quarantine facilities.
Assigning to quarantine facilities	To ensure all those who may require specialized medical or health support can access it.
Luggage and transportation logistics	To support smooth operations and ensure the comfort of repatriates (including access to required medication).
Check-in to quarantine facilities	
Quarantine order	To provide medical authorization for placing persons in quarantine through quarantine admission letters.
Quarantine facility registration	To collect health and other information to enable admission to quarantine, including through interviews and forms used for subsequent daily health assessments and health clearance.
Orientation briefing	To provide repatriates with additional information to support the quarantine process, including advisories from health, hotel and security staff.
During quarantine	
Daily health screening	To rapidly detect any COVID-19 symptoms (including fevers through measurement of temperature) or other medical issues throughout the quarantine period.
Other health and medical support	To provide repatriates with any additional support needed for health and well-being, with a 24/7 nurse and doctor on roster.
Evaluation of possible COVID-19 cases	To ensure the detection of COVID-19 cases by testing repatriates who fulfilled the WHO case definition (or others in exceptional circumstances).
Psychosocial surveys and support	To detect or assess any mental health or other issues to provide timely support, through surveys including an adapted Kessler Psychological Distress Scale on days 3 and 7 of quarantine.
Other support	To provide further support to children or others in quarantine with additional needs (e.g. providing activity packs for children and other services such as currency exchange).
Incident reports and health risk assessments	To facilitate rapid reporting of any incidents and inform follow-up or mitigating actions through a standard online incident log system and health risk assessment process.
Quarantine discharge	
Health clearance letters	To provide medical authorization for discharge from quarantine following 14 days of monitoring, with clearance by a medical officer.
Pre-discharge debriefing	To provide final health and other information to repatriates before their departure from quarantine.

MoH: Ministry of Health; PPE: personal protective equipment; SOP: standard operating procedure; WHO: World Health Organization.

Fig. 2. **Overview of health operation activities for Phase 1 of repatriation and quarantine in Vanuatu, May–July 2020**



PPE: personal protective equipment; QF: quarantine facility; SOP: standard operating procedure.

tion planning and execution, such as the Department of Foreign Affairs and the National Disaster Management Office (NDMO).

In Phase 1, the MoH developed selection criteria to guide the identification of suitable quarantine facilities. Criteria included status of services (running water, hot water, electricity, phone, Internet and television) and spacing between beds, potential to open windows for airflow, pathways around the quarantine facility, and outdoor space available for movement and exercise, accessibility to emergency or other medical care, and logistics for daily monitoring. However, the selection of facilities was led by the NDMO rather than the MoH. The AAR recommended that the MoH define clear selection criteria for quarantine facilities and decide which facilities would be appropriate for Phase 2.

To minimize costs, one to six people were allocated to a room in Phase 1, with people from different travel origins sometimes housed together, which the MoH identified as an elevated transmission risk. The AAR therefore recommended that, for Phase 2, no more than two people should share a room, and "travel cohorts" should be maintained by allocating people from a particular travel origin and plane to a single quarantine facility (unless access to specialized medical care was needed).

The issues identified with quarantine facility selection and room allocation highlighted the importance of multisectoral coordination, and the need for the MoH to actively engage with the NDMO, to enable appropriate planning and operations that consider health risk factors, logistics and cost.

Before departure from origin

Information on the process, requirements and restrictions for quarantine was provided to repatriates in a pre-travel information note issued by the Director of Public Health, enabling repatriates to adequately prepare mentally and logistically for quarantine. However, surveys conducted during quarantine indicated that not all repatriates received adequate information before departure, and people were frustrated, mainly due to unclear or conflicting information on access to tobacco and alcohol products, and kava. The information was provided primarily through Vanuatu overseas missions, which may not have received accurate information and which were not available in some countries from which people travelled. The AAR therefore recommended that consistent pre-travel information be issued to repatriates well in advance of travel, to clearly communicate quarantine rationale, processes and restrictions, and consequences of non-compliance.

Upon arrival at the airport in Vanuatu

Quarantine admission letters were issued by the Director of Public Health, in line with the Public Health Act.[5] In Phase 1, arriving repatriates completed a paper passenger health declaration form, providing information on travel or contact history, signs and symptoms of COVID-19 or any other health issues or conditions. Completed forms were evaluated by Shefa Community Health Services to determine whether repatriates required specialized quarantine conditions, although the criteria for such exceptions were unclear. Feedback from the health operations team highlighted the lack of a clear

process if a repatriate with no symptoms was found to have a temperature over a pre-established threshold. The AAR therefore recommended updating standard operating procedures for arrival health screening.

Upon arrival or registration, issues were identified for 42 people; these included medication requirements (41), pregnancy (14), allergies (30), addiction[5] and disability.[3] The AAR recommended that allocation to quarantine facilities consider pre-existing health conditions or issues, travel origin and travel history.

Check-in to quarantine facilities

Data from passenger health declaration forms were later entered into a database; this process led to delays in data availability and constrained use of the data for quarantine operations. Separate registration forms were required for check-in to quarantine facilities and were again reviewed by Shefa Community Health Services. The AAR recommended improving information collection and management by using tablets for onsite data entry, updating online forms, and developing dashboards for rapid and clear communication and action.

During quarantine

Daily health screenings included assessment of self-reported symptoms and measurement of temporal temperature by infrared thermometer to detect fever. In Phase 1, only one person was identified with symptoms consistent with the WHO case definition for COVID-19 at the time.[7] A nasopharyngeal swab was found to be negative for SARS-CoV-2; the person was discharged following 14 days of quarantine and was later reclassified as not having been a suspected case. Health screenings also identified other health issues (e.g. foodborne illness and dental issues). All those in quarantine were cleared for discharge on day 15 after their arrival (to ensure a full 14 days in quarantine).

A total of 2480 quarantine-experience surveys and 2098 Kessler Psychological Distress Scale assessments were conducted around days 3 and 7 of quarantine. The aim was to conduct two surveys for each individual, but limited numbers of trained health staff meant this was not always possible. Pooled results indicated that quarantine was "easy" for 78%, "a bit difficult" for 20% and "very difficult" for 2% of respondents. Overall, eight individuals showed signs of moderate or severe distress. At some facilities, there was dissatisfaction with the amount of time allocated for exercise or physical activity, or with special dietary requirements (e.g. food allergies or religion) not being adequately met. Almost all (99%) repatriates felt safe during quarantine and 92% knew who to contact for any health issues, but 16% were worried about their safety after discharge from quarantine. Consultations were held with community leaders in areas to which repatriates were to return, to address concerns and promote understanding that those discharged from quarantine did not pose a health risk to the population. The AAR recommended proactive community engagement to reduce stigma towards those discharged from quarantine, and follow-up psychosocial monitoring for those discharged from quarantine.

A total of 43 incidents were logged using the MoH system. Most were related to non-health incidents (e.g. losses or delays with luggage); others related to the absence or behaviour of quarantine support staff, including non-compliance with quarantine restrictions. Two instances of breaches of procedures and protocols by quarantine staff triggered health risk assessments. Both incidents led to hotel staff being quarantined, even though this was not in line with MoH recommendations. The AAR noted that a streamlined quarantine facility incident reporting and health risk assessment system is imperative to address issues rapidly and to mitigate risks. The AAR also recommended that the Public Health Act be revised to adequately reflect directed quarantine, and to enable penalties for breaches of quarantine directives, either by those in quarantine or by other members of the public.

Personal protective equipment (PPE), including gloves, masks, gowns, eye protection and alcohol sanitizer, were issued in accordance with MoH guidelines to all staff working in quarantine facilities and airports and to drivers and boat operators involved in transporting repatriates to quaratine facilities. There were some reports of inappropriate use of this PPE (e.g. unnecessary use of gloves). Although 695 people attended some 29 formal training sessions, not everyone supporting repatriation and quarantine processes received training; this led to differences in how protocols were applied and standards were maintained (e.g. PPE use and the amount of time allowed for daily exercise). The AAR therefore recommended that a full and comprehensive training package

be developed to include content tailored for various staff supporting the quarantine process.

Other support during quarantine included provision of activity and entertainment packs to children and services such as exchange of currency and shopping. The health operations team also liaised with hotel management on health-related issues; the AAR recommended that this additional role be clearly defined for Phase 2.

Quarantine discharge

Some delays were experienced as repatriates went through health clearance and discharge from quarantine, due mainly to the limited availability of medical officers to appraise health data. The AAR therefore recommended improved quarantine discharge and additional registered medical officers to assess and sign discharge summaries. Before discharge, repatriates were debriefed on actions to take if COVID-19 signs and symptoms were observed, and to thank them for their cooperation that enabled a successful quarantine process.

CONCLUSION

Health operations instituted in Vanuatu to support government-managed repatriation and quarantine from May to July 2020 were successful. Challenges included a lack of information to guide health planning, high volumes of arrivals, insufficient health staff, poor consideration of health factors for quarantine facility selection and allocations, and inadequate multisectoral coordination. Lessons learnt from health operations in Phase 1 were documented during an AAR in late July 2020. The recommendations will be applied to Phase 2 (from August 2020).

ETHICS STATEMENT

The Vanuatu Health Ethics and Research Committee advised that ethics approval was not required because data were collected as part of the pandemic response and in line with the Vanuatu Public Health Act of 1994, with only non-identifiable data collated.

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Conflicts of interest

All authors declare no conflicts of interest.

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Seroepidemiology of SARS-CoV-2, Yamagata, Japan, June 2020

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In Japan, the first case of coronavirus disease 2019 (COVID-19) was identified in mid-January 2020, and cases peaked in the spring at 720 cases per day on 11 April. Thereafter, the number of reported cases per day declined to 50 on 15 May and remained low until mid-June, when numbers again started to increase. On 5 August, 1234 cases were reported, giving a cumulative total of 40 485 cases, with a case fatality proportion of 2.5% (1021 deaths).[1] Although COVID-19 is designated as a reportable disease in Japan, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing capacity was limited in the early stage of the pandemic. It took up to 4 days for specimens to be tested by reverse transcription polymerase chain reaction (RT-PCR). The Japanese Government recommended that anyone with mild illness symptoms should stay at home, to avoid overwhelming health-care facilities. SARS-CoV-2 testing was prioritized for hospitalized patients and those with chronic comorbidities. Thus, the true number of symptomatic cases of COVID-19 in Japan is likely to be far greater than the number of reported cases.

In one Chinese study, SARS-CoV-2-specific immunoglobulin IgG and IgM were detected in serum samples from most patients (asymptomatic or symptomatic) who were diagnosed with SARS-CoV-2 by RT-PCR.[2] This finding implies that seroepidemiological studies can be used to estimate the infection rate of SARS-CoV-2 in a population. Estimating the point prevalence of SARS-CoV-2 infections might be helpful in assessing population susceptibility, and in balancing public health control measures with the reopening of social and economic activities. Results from several seroepidemiological studies have been published, with seroprevalence reported from Spain (5%), Switzerland (10.8%) and the United States of America (1–6.9%, 4.65% and 14%).[3–7] These studies were performed in countries where the incidence of COVID-19 was high. In countries in the Asia-Pacific, where COVID-19 incidence was low, a few SARS-CoV-2 seroepidemiology studies have been conducted that are not population based. Among these studies, seroprevalence was 7.6% from a single-centre study of outpatients and their guardians in the Republic of Korea, and 0.4% in a study using residual sera collected at a single hospital in Malaysia.[8,9]

We conducted a cross-sectional seroepidemiological study in Yamagata Prefecture, an urban–rural area in northern Japan, where the incidence of reported COVID-19 cases was 0.007% (i.e. 76 cases among a population of about 1.07 million, as of 5 August 2020).[1] This is lower than the overall incidence of COVID-19 cases reported throughout Japan (0.034%), and lower than in most Japanese prefectures and the Tokyo metropolitan area (0.102%); however, it is higher than in some low-incidence prefectures (0–0.002%).[1] Residual sera obtained from patients who visited the outpatient clinic of Yamagata University Hospital for any acute medical condition during 1–4 June 2020 were tested for SARS-CoV-2 antibody. Blood samples were collected for clinical diagnostic purposes and, after use, were de-identified before serological testing was performed. Because samples were de-identified, individual consent was not obtained. This study was approved by the Ethics Committee of Yamagata University School of Medicine.

Serological testing was performed using an electrochemiluminescence immunoassay (ECLIA) Elecsys® Anti-SARS-CoV-2 on Cobas® e601 module (Roche Diagnostics, Basel, Switzerland). This qualitative assay detects total antibody – primarily IgG, but also IgM and

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IgA antibody – to the nucleocapsid protein of SARS-CoV-2. A cut-off optical density (OD) index value of 1.0 was used to define a seropositive result. According to the manufacturer's fact sheet, the specificity of the serological assay is 99.80% (i.e. 21 false positives among the 10 453 specimens collected before December 2019).[10]

Among 1009 samples tested, five specimens were positive for SARS-CoV-2 antibody. The estimated seroprevalence of SARS-CoV-2 infections was 0.50% (95% confidence interval [CI]: 0.062–0.93%). The OD values of five seropositive specimens varied substantially; two had OD values close to the cut-off index value (1.3 and 1.6), suggesting low antibody titres, and three were above 5.0. Using the 95% CI for the seroprevalence estimate of 0.50%, we estimated that the Yamagata Prefecture population had 670–10 000 SARS-CoV-2 antibody-positive individuals.

Our study has several limitations. First, sera used in this study were obtained from patients visiting our hospital's outpatient acute care clinic; hence, this sample is probably not representative of the general population of Yamagata Prefecture. Also, because the serum specimens were de-identified, we did not have any demographic data to determine representation across age groups. Second, the specificity of the assay suggests an anticipated false positive rate of 0.20%, which may affect the reliability of the estimated seroprevalence in our study. Third, in a population with a low prevalence of SARS-CoV-2 infections, as was the case in Yamagata, false positives are more likely than in a population with high prevalence. Slight modification of the assay seropositive cut-off index value (e.g. from 1.0 to 1.6) would reduce the estimated seroprevalence. For example, if only the three strongly positive serum samples were considered to be true seropositive results, the estimated seroprevalence would be 0.30% (95% CI: 0–0.63%).

This cross-sectional seroepidemiological study in Yamagata Prefecture, Japan, identified low seroprevalence of SARS-CoV-2 antibody, suggesting that the population is highly susceptible to SARS-CoV-2. Additional studies with population-based sampling are needed to assess the impact of SARS-CoV-2 in this population over time.

Ethical statement

Because samples were de-identified, individual consent was not obtained. This study was approved by the Ethics Committee of Yamagata University School of Medicine.

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Conflict of interest

We have nothing to declare.

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