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How can we better support the public health emergency response workforce during crises?

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The public health emergency response workforce has experienced unrelenting pressure during the past decade. Countries in the Western Pacific Region have responded to significant outbreaks of avian influenza, Zika virus disease, Middle East respiratory syndrome, vaccine-derived poliovirus, measles and the coronavirus disease 2019 (COVID-19) pandemic, as well as natural disasters; they also supported the response to Ebola virus disease in West Africa during 2014–2016.[1] For public health responses to be effective, we must continue to identify optimal mechanisms to support people working in challenging public health responses.

Health systems strengthening, in particular for workforce support, is fundamental to achieving the core capacity required under the International Health Regulations (2005).[2] The Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III) recognizes that a skilled, experienced local public health workforce must be developed and maintained to prevent the escalation and spread of emergencies.[3]

The IHR Joint External Evaluations show that work remains to be done to strengthen public health workforces so that they can manage health security events.[4] The COVID-19 pandemic has clearly demonstrated that large public health events require responders with skills and expertise to address the crisis appropriately. In May 2021, the World Health Assembly recommended investment in the health workforce for better management of the COVID-19 pandemic.[5]

In the Western Pacific Region, field epidemiology training programmes (FETPs) are a key activity for strengthening health security by developing vital technical expertise in the existing workforce.[3,6] The programmes are based on the principle of "learning through doing" with guidance from experienced epidemiologists.[6] Such support, however, often stops at graduation. A guiding principle of APSED III is "continuous learning and improvement".[3] Thus, preparedness before a crisis is an integral component, but professional support to the health workforce during crises would be feasible for consolidating what has been learnt.

In 2019, we interviewed public health emergency response experts on topics that included workforce support. The experts discussed the challenge of inexperience and noted that an emergency response surge workforce was frequently based on availability rather than appropriate skills and experience.[7] Less experienced epidemiologists were often readily available for rapid deployment, but emergency response was considered not to be an ideal training setting. The experts stated that less experienced responders could be considered suitable if they were guided.[7]

To support the technical and leadership needs of the surge workforce during the COVID-19 pandemic in Australia, the Public Health Association of Australia and the Australasian Epidemiological Association rapidly established a pilot mentorship programme for surge responders, in which mentors provided both professional and personal support to mentees remotely.[8,9] Subsequent evaluation showed that the programme effectively supported a workforce with limited prior public health experience to work in a stressful environment during a national crisis. The mentors were found to improve the confidence of the mentees in conducting their work by sharing their professional skills in areas such as leadership and decision-making. Importantly, the mentors supported the well-being of the mentees by acting as a confidential

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sounding board and guiding them in navigating political and otherwise complex environments.[8,9]

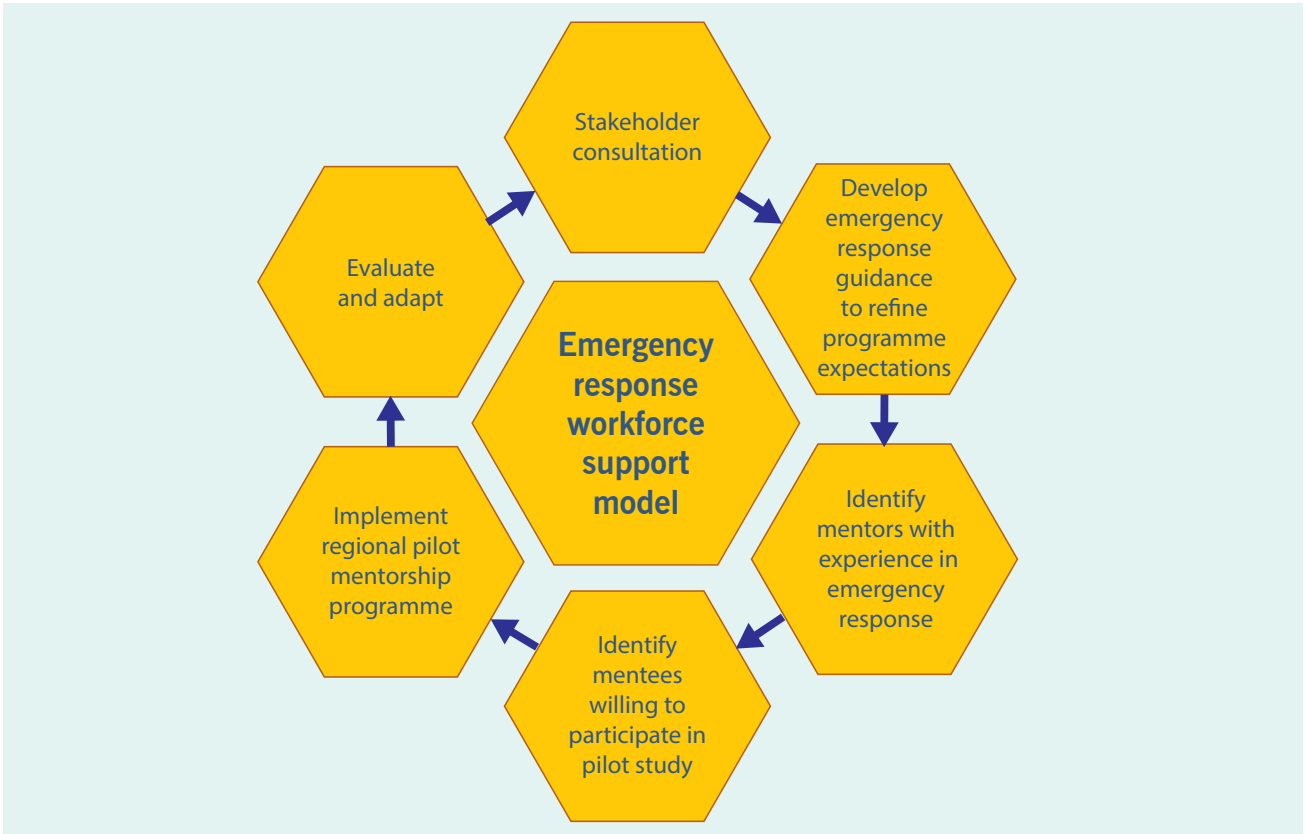
The Australian mentorship programme supported front-line pandemic surge response workers at a time of great need. The main recommendation of the evaluation was to design a purpose-built programme for supporting emergency response workers.[8,9] Difficulties associated with such support include the fact that people are involved in a response for only short periods and are often new to the context or organization in which they are working. Provision of support during emergencies can also be limited by lack of time and cross-cultural challenges.

A similar programme in the Western Pacific Region, based on the experience of the Australian programme,[8,9] could provide support for the COVID-19 response and also an opportunity to learn and prepare for future public health emergencies. Stakeholders such as partners in the Global Outbreak Alert and Response Network should be consulted to design an all-purpose emergency response support model and materials and to pilot-test the programme and evaluate comprehensively what works and how. The recommended steps in establishing a pilot programme are illustrated in **Fig. 1**.

Such a support programme could be used in public health emergency response both locally and globally. It could increase the effectiveness of the workforce, add to professional knowledge, provide less experienced responders with skills and reduce stress and burn-out.[8] The proposed pilot programme would also benefit long-term national and regional preparedness, providing individuals and countries with peer-supported learning and experience.

The first objective of the WHO Global Strategy on Human Resources for Health is to optimize the quality of performance and the impact of the workforce.[10] This should be based on emerging evidence on strengthening and continuing to support the health workforce during crises. To ensure that the Region becomes "the healthiest and safest",[11] high-quality, longer-term programmes will be necessary, such as FETPs to ensure sustained

Fig. 1. **Recommended steps for establishing an emergency response workforce support model**



Source: based on evaluation findings, Australian National University[8]

workforce development. In crises, however, a mentoring-like programme might foster consistent support for and empowerment of the workforce.

Conflicts of interest

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

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Emergence of influenza B/Victoria in the Micronesian US-affiliated Pacific Islands, spring 2019

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Data collected through routine syndromic surveillance for influenza-like illness in the Micronesian United States-affiliated Pacific Islands highlighted out-of-season influenza outbreaks in the spring of 2019. This report describes the data collected through the World Health Organization's Pacific Syndromic Surveillance System for the Commonwealth of the Northern Mariana Islands (CNMI), Guam, the Federated States of Micronesia (FSM) and the Republic of the Marshall Islands (RMI). Compared with historical data, more cases of influenza-like illness were observed in all four islands described here, with the highest number reported in Guam in week 9, CNMI and FSM in week 15, and RMI in week 19. The outbreaks predominantly affected those aged <20 years, with evidence from CNMI and RMI suggesting higher attack rates among those who were unvaccinated. Cases confirmed by laboratory testing suggested that influenza B was predominant, with 83% (99/120) of subtyped specimens classified as influenza B/Victoria during January–May 2019. These outbreaks occurred after the usual influenza season and were consistent with transmission patterns in Eastern Asia rather than those in Oceania or the United States of America, the areas typically associated with the United States-affiliated Pacific Islands due to their geographical proximity to Oceania and political affiliation with the United States of America. A plausible epidemiological route of introduction may be the high levels of international tourism from Eastern Asian countries recorded during these periods of increased influenza B/Victoria circulation. This report demonstrates the value of year-round surveillance for communicable diseases and underscores the importance of seasonal influenza vaccination, particularly among younger age groups.

The United States-affiliated Pacific Islands are a group of six countries and territories spread across the Pacific. In spring 2019, unusual increases in influenza-like illness (ILI) were reported in four of these Micronesian islands: the Commonwealth of the Northern Mariana Islands (CNMI); the Federated States of Micronesia (FSM), comprising the states of Chuuk, Kosrae, Pohnpei and Yap; Guam; and the Republic of the Marshall Islands (RMI) (**Fig. 1**).

These islands are part of the World Health Organization's (WHO's) Pacific Syndromic Surveillance System, which monitors ILIs and other syndromes and distributes weekly reports with data from 23 participating Pacific island countries and territories.[1] Despite inclusion in surveillance system dispatches, these 23 countries and territories have low representation in broader regional reports, partly because of their limited diagnostic testing capacity as well as their small populations, which are dwarfed by other members of WHO's Western Pacific Region. Data from these US-affiliated islands also generally do not appear in United States influenza surveillance reports. As a result, surveillance of the burden, distribution and type of influenza impacting the Pacific island countries and territories may be incomplete. This report uses surveillance data from four

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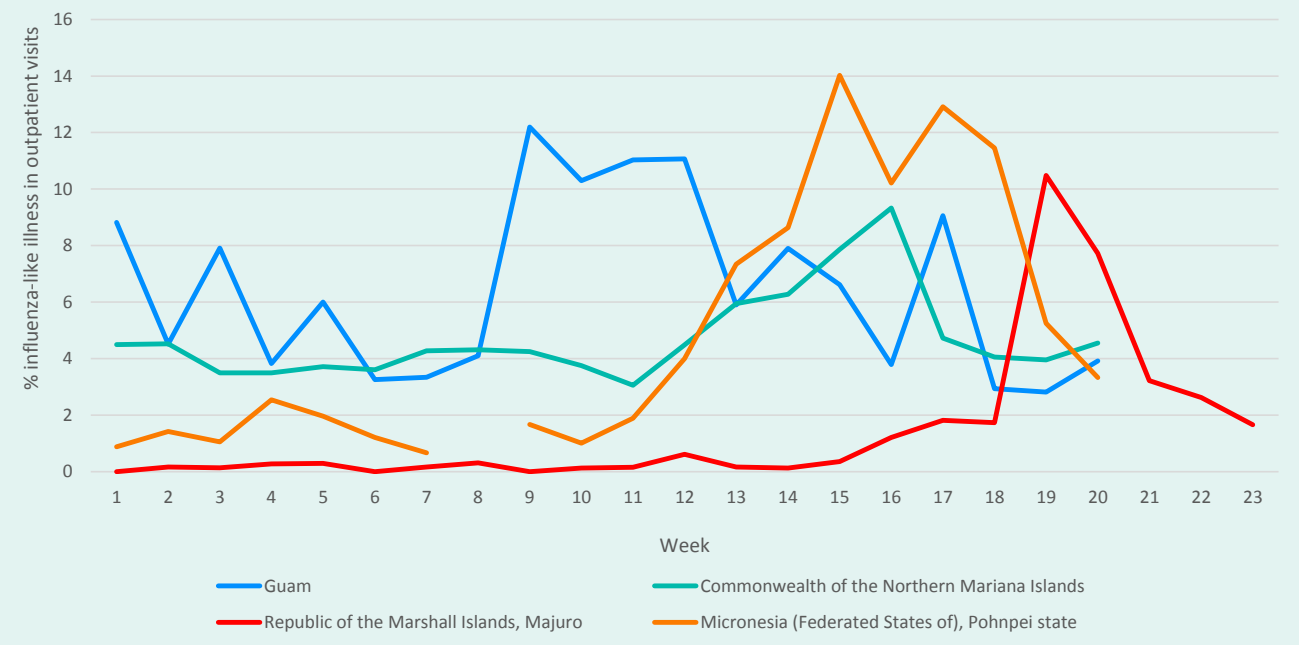
Fig. 1. **Number of cases of influenza-like illness reported in four of the US-affiliated Pacific Islands: the Commonwealth of the Northern Mariana Islands, the Federated States of Micronesia, Guam and the Republic of the Marshall Islands, weeks 1–23, 2019**



of the Micronesian islands affiliated with the United States to expand understanding of how these islands fit into broader regional and global influenza transmission trends.

Ethics statement

This project was determined to be exempt from review by the Emory University Institutional Review Board.

METHODS

This surveillance report describes trends in ILI and influenza for weeks 1–20 of 2019 from data reported to the surveillance system from the following four US-affiliated islands: CNMI, FSM, Guam and RMI. Although the primary focus is on the time from January through mid-May, data are provided through June for RMI, which experienced a later outbreak.

ILI counts were collected as part of routine surveillance system reporting, which defines ILI as the acute onset of fever (38 °C/100.4 °F) accompanied by cough or sore throat, or both.[1] CNMI routinely calculates ILI rates as a percentage of total outpatient encounters; rates were calculated retrospectively for Guam, FSM and RMI.

Cases were confirmed by nasopharyngeal swab testing, which is implemented routinely on a selection of patients presenting with flu-like symptoms. Testing is done at the health-care provider's discretion but may be more likely when providers are aware of increased circulation of influenza. A small number of nasopharyngeal swab specimens from CNMI, FSM and RMI were subtyped using reverse transcription polymerase chain reaction (RT-PCR) analyses (Applied Biosystems 7500 Fast Dx Real-Time PCR, ThermoFisher Scientific, Carlsbad, CA, USA) conducted by the Guam Public Health Laboratory and the Hawaii State Laboratories Division. The laboratory in Guam routinely selects at least four nasopharyngeal swab specimens for surveillance each week.

A confirmed influenza case was defined as infection in a patient with symptoms of ILI and a nasopharyngeal swab specimen positive for influenza by rapid or RT-PCR testing. Cases were considered probable if not confirmed through nasopharyngeal swab testing.

Data from CNMI came from seven sentinel sites on the three permanently inhabited Northern Mariana Islands. Forty-two facilities representing the four states of FSM contributed syndromic data, but ILI rates

reported here are from only the eight sentinel sites in Pohnpei, which had the most complete data about total encounters. Syndromic data from Guam were collected at the island's only public hospital, and confirmed cases were detected through electronic laboratory reports and morbidity reports from health-care facilities across the island. The RMI system is composed of hospitals and clinics located on Ebeye Island, Majuro and the Outer Islands, although the data presented here are drawn only from Majuro's three sentinel sites due to constraints on data access. For each jurisdiction, vaccination rates were calculated based on immunization programme records, where available.

Regional trends were assessed based on information from FluNet, WHO's online platform that aggregates influenza counts from the Global Influenza Surveillance and Response System (GISRS).[2]

RESULTS

Guam

In late February and most of March 2019, Guam experienced an increase in rates of ILI (**Fig. 2**) not expected based on historical data. In weeks 8 and 9, the rate of ILI increased nearly threefold to reach 12.2% (35/287) of outpatient encounters, and it remained above 10% through week 12 (31/301, 30/272 and 29/262 in weeks 10, 11 and 12, respectively). A total of 107 specimens were randomly selected for serotyping from week 1 to 20. Although influenza A(H3N2) and A(H1N1)pdm09 were detected early in the year, the number of confirmed cases caused by influenza A generally declined beginning in late January. Cases caused by influenza A viruses reached a low just as the number of confirmed cases caused by influenza B viruses began to increase in week 6, when they represented 71% (24/34) of confirmed cases. By the peak of the outbreak in week 13, influenza B viruses accounted for 88% (77/88) of confirmed cases. Influenza B/Victoria was present in 100% of specimens tested by RT-PCR during weeks 10–20. During the full study period, 80% (86/107) of confirmed cases were caused by the Victoria lineage (**Table 1**). No influenza B/Yamagata viruses were detected.

The majority of cases of ILI occurred among those aged <20 years. From week 6 onwards, 61% (172/280) of ILI encounters were with those aged 0–4 years, and 19% (52/280) were with those aged 5–19 years. Among confirmed influenza B cases of known age, 70% (163/232) were 5–19 years, 20% (46/232) were <5 years and 1 was >50 years. Altogether, 35% (30/86) of confirmed cases classified as caused by influenza B/Victoria occurred in persons aged <5 years, and 55% (47/86) occurred in persons aged 5–19 years.

There were six hospitalizations for confirmed cases of influenza B in weeks 5–17, with two in week 9. Five of these confirmed cases were aged ≤6 years, and one of these passed away after admission.

Commonwealth of the Northern Mariana Islands

Two weeks after cases of ILI peaked in Guam, the rate of ILI in CNMI began to increase, nearly doubling in 2 weeks (**Fig. 3**). The ILI rate increased consistently through week 16, reaching 9.3% (117/1254) of outpatient encounters. The number of confirmed cases rose from week 11 onwards, peaking during week 15 at 50 cases. Much like Guam, CNMI started the year with a higher number of confirmed cases caused by influenza A. In week 8, however, the number of confirmed cases caused by influenza B viruses for the first time exceeded the confirmed cases caused by influenza A. From week 7 to 20, 87% (293/338) of confirmed cases were caused by influenza B. Four specimens collected during weeks 16–17 were sent to the Guam Public Health Laboratory for serotyping, and all were identified as influenza B/Victoria (**Table 2**).

The age range among confirmed cases of influenza B/Victoria was 7 months to 11 years, consistent with the range in Guam. Those aged <20 years accounted for 76% (770/1007) of cases of ILI from week 7 to 20. During that period, 46% (462/1007) of ILI cases occurred among people aged 5–19 years, with weekly percentages of ILI occurring in this age group ranging from 31% (19/62) to 57% (36/63). Only 5% (48/1007) of ILI cases occurred in those aged ≥50 years.

The population-wide vaccination rate in CNMI from August 2018 through week 20 of 2019 was 35% among those younger than 5 years (CNMI Commonwealth Healthcare Corporation, Division of Public Health Services Immunization Program, unpublished data, 2019). However, this is likely an overestimation, as it does not include those who received the second dose recommended

Fig. 2. **Number of cases of influenza-like illness reported and confirmed influenza, by virus type and rate, Guam, weeks 1–20, 2019**

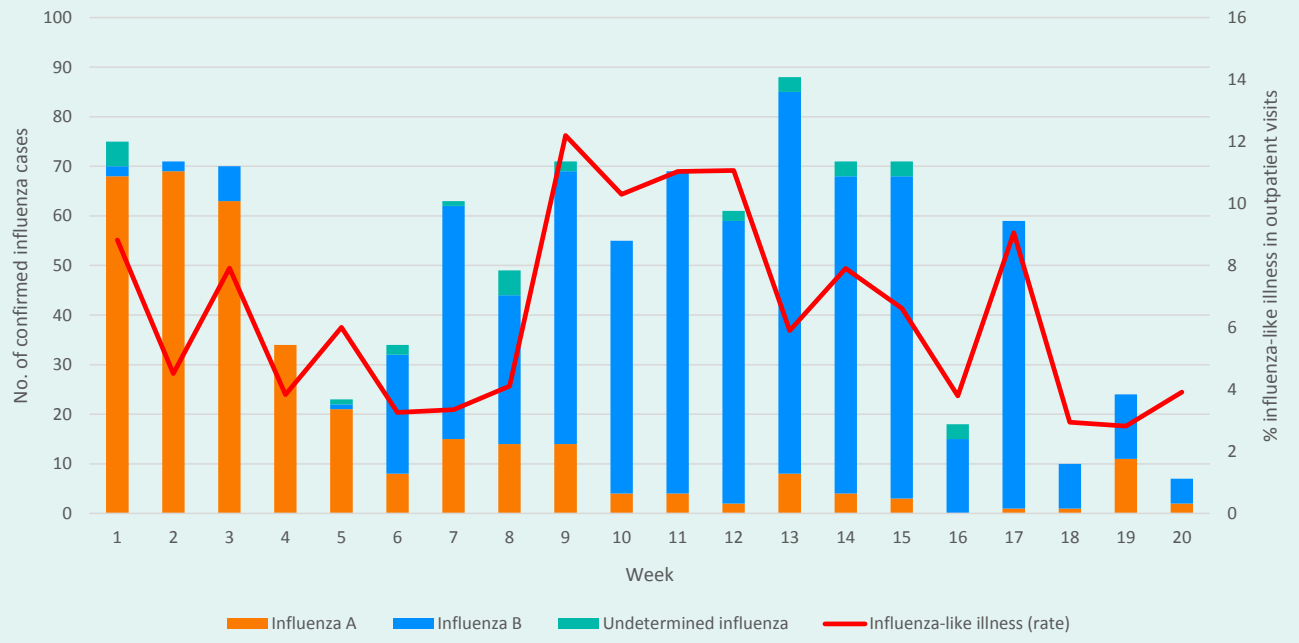


Table 1. **Number of positive influenza specimens by subtype, Guam, weeks 1–20, 2019**[a]

Week	Influenza type		Total no. of specimens tested
	A(H1N1)pdm09 and A(H3N2)	B/Victoria	
1	8	0	8
2	–	–	–
3	–	–	–
4	–	–	–
5	4	0	4
6	5	3	8
7	0	11	11
8	1	8	9
9	3	6	9
10	0	6	6
11	0	7	7
12	0	6	6
13	0	5	5
14	0	6	6
15	0	6	6
16	0	4	4
17	0	5	5
18	0	4	4
19	0	5	5
20	0	4	4
Total	**21**	**86**	**107**

[a] The Guam Public Health Laboratory subtypes a random selection of nasopharyngeal swab specimens each week for routine influenza surveillance. No testing was conducted during weeks 2–4, indicated by –.

Fig. 3. **Number of cases of influenza-like illness reported and confirmed influenza, by virus type and rate, Commonwealth of the Northern Mariana Islands, weeks 1–20, 2019, with rates for 2018 and 2019 (2018 rate included for comparison)**

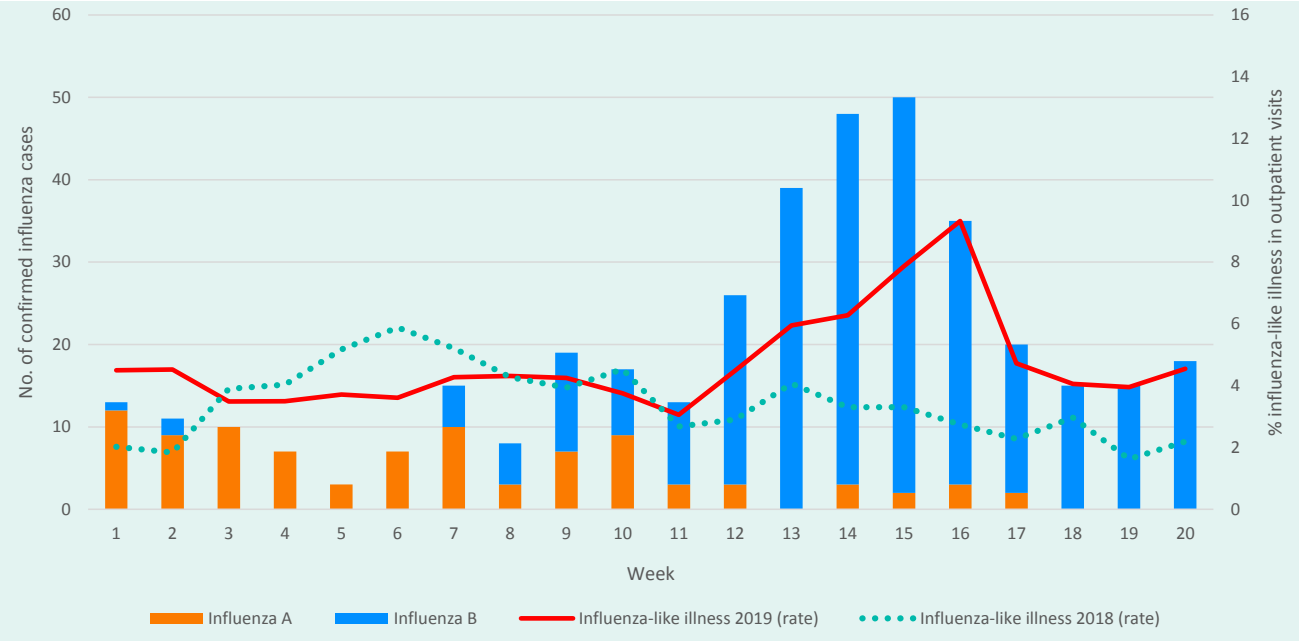


Table 2. **Number of positive influenza specimens submitted for further testing, by lineage, US-affiliated Pacific Islands, weeks 1–20, 2019**

Jurisdiction	Influenza type		Total no. of specimens tested
	A(H1N1)pdm09 and A(H3N2)	B/Victoria	
Commonwealth of the Northern Mariana Islands	0	4	4
Micronesia (Federated States of)	0	2	2
Republic of the Marshall Islands	0	7	7

for younger children. Among confirmed cases aged 0–4 years detected during weeks 8–18, 95% (84/88) were unvaccinated, although 14% (12/84) of these were too young for vaccination. Among cases aged 5–19 years, 86% (110/128) were unvaccinated.

Federated States of Micronesia

Data from FSM indicate similar patterns to those in Guam and CNMI. The number of ILI encounters increased from week 11 to 15, when encounters peaked at 370, or approximately 2.7 times the year-to-date average of 136 ILI encounters per week. In week 14, there were 294 cases of ILI, approximately 1.8 times the 4-week average of 167 cases. For weeks 12–18, cases of ILI were above the year-to-date average. There were six confirmed cases: three of influenza A and three of influenza B. The influenza B viruses were all detected during weeks 14–15 in cases with an age range of 8–29 years. Of the two specimens from Yap subtyped by the Guam Public Health Laboratory, both were influenza B/Victoria (**Table 2**).

The increase in ILI cases in FSM appears to have been driven primarily by increased cases in Pohnpei, although this may have been amplified by missing data from other states. Pohnpei reported 67% (2068/3066) of FSM's cases during weeks 1–20. Pohnpei's ILI encounters nearly doubled from week 12 to 13, reaching 7.3% of outpatient encounters (153/2085). The ILI rate was above 10% for most of April and peaked at 14%

(314/2239) in week 15. While ILI rates were not available for states other than Pohnpei, the number of ILI cases in Yap exceeded the threshold indicating heightened ILI activity during weeks 14–16.

Republic of the Marshall Islands

Influenza cases were reported in RMI later than in the other US-affiliated Pacific Islands and exceeded the expected ILI threshold only on the main island of Majuro. Only Majuro is connected to RMI's health information system, which may impact the capacity to detect outbreaks. Within Majuro, the ILI rate remained <1% until week 16 (**Fig. 4**). At the outbreak's peak in week 19, the rate of ILI in outpatient encounters increased to 10.5% (111/1059), with 49% (54/111) of cases occurring among children aged <5 years and 35% (39/111) among those aged 5–19 years. Only 3% (3/111) occurred among people aged ≥50 years. The rate of ILI detected in the outpatient department was 8% (40/497) in week 19 and 6.2% (29/467) the following week. Consistent with the age range affected by the outbreak, ILI rates were significantly higher in the Public Health/Maternal and Child Health Department, at 27.1% (69/255) in week 19 and 17% (38/224) in week 20.

There were 131 probable cases of influenza detected on Majuro during weeks 16–23. Among these, 61% (80/131) were among children aged <5 years and 20% (26/131) were among those aged 5–19 years. Seven confirmed cases from week 19 were subtyped as influenza B/Victoria by the Hawaii State Laboratories Division (**Table 2**), with these confirmed cases ranging in age from 8 to 54 years.

Based on data extracted from the RMI national immunization information system, influenza vaccine coverage during the 2018–2019 season for Majuro was 66% for those aged <20 years. Among the probable and confirmed cases, the overall vaccination rate was 5%, with a slightly higher rate (12%) among those aged 5–19 years.

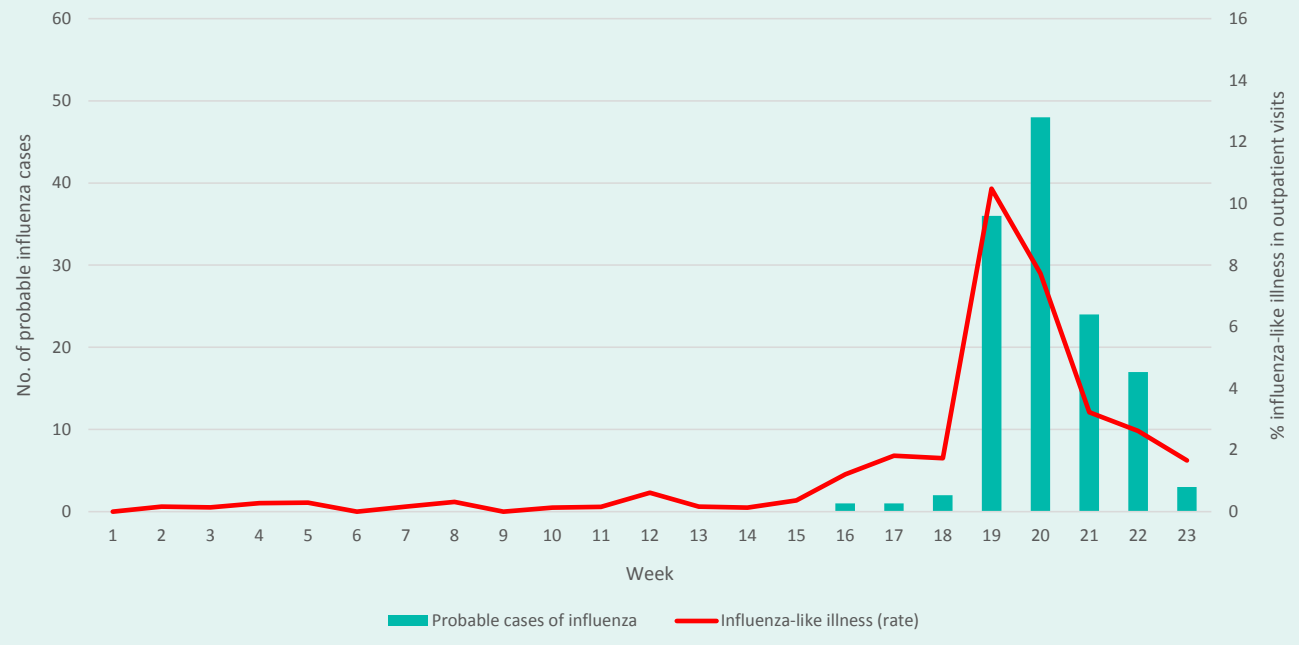
DISCUSSION

Surveillance data identified unseasonal outbreaks of influenza during the spring of 2019 in four US-affiliated Pacific Islands: CNMI, FSM, Guam and RMI. Although historical data are limited, the number of cases of ILI reported at their peak in FSM in 2019 was three times higher than during the same week the previous year (104 cases in 2018 versus 322 in 2019), and the 4-week average at the height of the outbreak was 65% higher than during the same period in 2018 (103 in 2018 and 170 in 2019). Data from CNMI provide further evidence that the increase in ILI cases observed in 2019 was not consistent with recent regional trends, with the peak ILI encounter rate of 9.3% in spring 2019 for CNMI more than triple that during the same week in 2018 (2.7%). During the spring 2019 peak, the 4-week average for ILI encounters (106 encounters) was more than twice as high as during the same time in the previous year (43 encounters).

Of the 107 confirmed cases reported from Guam during 2019, 80% were influenza B/Victoria. Although only a few specimens from patients with ILI in CNMI, FSM and RMI were subtyped, all were found to be influenza B/Victoria. The timing and age distribution of these confirmed cases were also consistent with the confirmed cases from Guam. Previous studies have found higher rates of influenza B/Victoria than influenza B/Yamagata in younger age groups, with some highlighting that those of school age are at increased risk.[3–5] Contributing factors may include molecular differences and higher levels of genetic diversity in influenza B/Victoria viruses, which allow them to target younger people with less prior viral exposure.[5] Widespread circulation of both influenza B subtypes has been documented in the Pacific, with influenza B/Victoria predominant during 2010–2012 and 2016, and with influenza B/Yamagata predominant in 2013–2015 and 2017.[6] The outbreaks reported here perhaps indicate a resurgence of influenza B/Victoria over influenza B/Yamagata.

The four US-affiliated Pacific Islands in this report all lie in the tropical region between the equator and the 20th parallel north. Although the timing of these influenza outbreaks in these Micronesian islands was consistent with northern temperate climates, where influenza activity spikes in the winter months,[6] the emergence of influenza B/Victoria did not match the patterns of viruses circulating in the US mainland. During weeks 1–20, only 5% of influenza cases reported by the US to GISRS were caused by influenza B viruses.[7] The Oceania–Melanesia–Polynesia influenza transmission zone, of which all US-affiliated Pacific Islands are members, had similarly low levels of influenza B cases, according to the global reporting system.[7] Patterns of confirmed influenza cases in the broader WHO Western Pacific Region, driven in

Fig. 4. **Number of reported cases of influenza-like illness and probable influenza, with rate of influenza-like illness, Majuro, Republic of the Marshall Islands, weeks 1–23, 2019**



large part by data from China, were similar to those noted in this report: a decline in influenza A cases starting in January and influenza B increasing in early March, overtaking influenza A by the end of the month and remaining dominant through week 20.[7] Overall, 20% of cases reported to GISRS from WHO's Western Pacific Region were influenza B, and 88% of these were influenza B/Victoria.[7]

The high volume of travellers to the US-affiliated Pacific Islands during the spring of 2019 could explain the distinct influenza peaks recorded. The rise of influenza B in Guam and CNMI that began around week 7 corresponded to high levels of visitors from Eastern Asian countries,[8,9] offering a plausible route of introduction. A total of 667 784 visitors arrived on Guam from January to May, mostly from the Republic of Korea (44%) and Japan (42%).[9] During that period, CNMI recorded 188 147 visitors, 47% from China and 42% from the Republic of Korea.[9]

China reported 87% of the influenza cases in GISRS from WHO's Western Pacific Region and exhibited trends similar to those of the islands reported here.[7] In mid-February, influenza B cases began to increase in China, and comprised 82% of cases by week 20.[7] Influenza B began appearing around the same time in the Republic of Korea, increasing to account for more than 90% of confirmed influenza cases during weeks 18–20.[7] No data were available on subtyped influenza B viruses from the Republic of Korea, but 92% of specimens from China were identified as influenza B/Victoria and only 2% were influenza B/Yamagata.[7]

The increase in influenza B cases observed later in 2019 in FSM and RMI compared with CNMI and Guam may be partially attributable to the lack of direct flights from Eastern Asia. RMI received 2049 visitors during January–March 2019, with arrivals peaking in March.[10] Data from previous years suggest that most visitors to RMI come from other Pacific Islands and North America,[11] and FSM's visitors are primarily from the US.[12] However, Guam serves as a primary air transport hub for both FSM and RMI, which may have provided an opportunity for the introduction of influenza B. This would help explain the delays in peak activity, with Guam's burden highest in week 13, followed by that in FSM in week 15 and in RMI in week 20.

The epidemiological evidence provided on the vaccination status of influenza cases has implications for immunization policy. The high attack rate among those aged <20 years underscores the vulnerability of the young to seasonal influenza and reinforces the need for concentrated efforts to vaccinate this population. All four US-affiliated Pacific Islands in this report used influenza

vaccines approved for the northern hemisphere that included a B/Victoria/2/87 virus (B/Colorado/06/2017-like) in both the trivalent and quadrivalent formulations.[13] Further testing would be needed to determine whether any differences between the vaccine formulation and the circulating strain could partially explain the higher attack rate among those aged <20 years. Low vaccination rates in this age group are likely a contributing factor. The availability of data about the vaccination status of cases in CNMI and RMI provides support for the effectiveness of the vaccine, with 12–14% of cases aged 5–19 years having received the vaccine in those jurisdictions.

There were some limitations to our analysis. The data presented in this report were drawn from surveillance systems in four different US-affiliated Pacific Islands, each with unique data collection procedures. Although the Pacific Syndromic Surveillance System provides a standard definition of ILI, the way in which that definition is operationalized locally may result in disparate levels of data integrity. While surveillance based on WHO definitions distinguishes ILI from severe acute respiratory infection based on whether the case was hospitalized,[14] it is possible that some cases of severe acute respiratory infection were reported as ILI.

Because the jurisdictions represented in this report are characterized by their relatively remote locations, in some cases, limited public health infrastructure and completeness of reporting may have influenced the findings. It is possible that resource availability and physical distance from larger hubs reduced reporting from outer islands.

Those presenting with ILI were not systematically selected for rapid influenza testing, but were selected at the provider's discretion. Heightened awareness of influenza activity may have influenced providers' decisions to test and report patients presenting with ILI. However, consistent patterns of age distribution and influenza type in CNMI, where a large portion of ILI encounters were followed up with nasopharyngeal swabs, provide evidence that overall trends may not have been significantly impacted by nonrandom selection.

Classifying influenza cases into either influenza A or B was made possible through rapid testing, but only a small fraction of specimens was subtyped, and most of the subtyped specimens were from Guam. Beyond its lineage as an influenza B/Victoria virus, isolation of the exact strain circulating was not possible, which precludes determination of whether the virus was contained in the 2018–2019 influenza vaccine as well as precluding confirmation that the viruses were similar to those circulating in China, Japan or the Republic of Korea. Analyses based on the immunization status of cases were limited because this information was not routinely reported for ILI encounters in all jurisdictions.

CONCLUSIONS

The ability of the sentinel surveillance system to detect influenza outbreaks in four US-affiliated Pacific Islands is a testament to the value of year-round surveillance for ILI because it ensures that clinical teams are informed about circulating respiratory infections. Epidemiological analysis identified the age groups most at risk, aiding both clinical and public health responses. Although influenza B viruses are not considered to have pandemic potential, identifying circulating strains is important, as demonstrated by the increased burden seen in younger age groups. Understanding changing influenza patterns helps in evaluating immunization effectiveness and gaps in coverage to protect the population from an undue burden of disease.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

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Enhanced event-based surveillance for imported diseases during the Tokyo 2020 Olympic and Paralympic Games

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In 2021, the National Institute of Infectious Diseases, Japan, undertook enhanced event-based surveillance (EBS) for infectious diseases occurring overseas that have potential for importation (excluding coronavirus disease 2019 [COVID-19]) for the Tokyo 2020 Olympic and Paralympic Summer Games (the Games). The pre-existing EBS system was enhanced using the World Health Organization Epidemic Intelligence from Open Sources system and the BlueDot Epidemic Intelligence platform. The enhanced EBS before and during the Games did not detect any major public health event that would warrant action for the Games. However, information from multiple sources helped us identify events, characterize risk and improve confidence in risk assessment. The collaboration also reduced the surveillance workload of the host country, while ensuring the quality of surveillance, even during the COVID-19 pandemic.

Due to the coronavirus disease 2019 (COVID-19) pandemic, the Tokyo 2020 Olympic and Paralympic Games (the Games) were rescheduled for 23 July to 5 September 2021. The attendance of spectators from abroad was not permitted; however, several tens of thousands of people associated with the Games were expected to visit Japan from more than 200 countries and regions. The visitors included national Olympic and Paralympic team members, media crews and sponsors. Since international mass gatherings have high potential to disseminate communicable diseases to several countries,[1] it was important during the Games to monitor infectious diseases occurring overseas that have potential for importation.

Event-based surveillance (EBS) is the organized and rapid capture of information about events that are a potential risk to public health.[2] Official and unofficial information sources can be used for EBS, and the information obtained should be used to rapidly assess the risk that the event poses to public health, so that a timely response can be taken. As stated in the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III),[3] various information sources for EBS are useful for assessing contextual vulnerabilities and creating risk assessments to develop response strategies.

In the past, new EBS systems have often been created for international mass gatherings to respond to complex and evolving situations. However, this was not practical for the Games, owing to the burden of the COVID-19 pandemic on national surveillance and response teams. Therefore, to address the high demand on local resources, we used external resources in our enhanced EBS for imported infectious diseases. This paper describes the methodology and preliminary results of the enhanced EBS for infectious diseases occurring overseas (excluding COVID-19) that have potential for importation before and during the Games.

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METHODS

The enhanced EBS for the Games was conducted at the National Institute of Infectious Diseases (NIID), Japan, which houses the country's Field Epidemiology Training Programme (FETP). Three staff members and 15 FETP fellows were engaged in EBS from 1 July to 19 September 2021, 7 days a week. The initial period (1–10 July) was a test run, during which EBS was conducted in the same way as for the actual operation (from 11 July). Each day, two fellows and one staff member oversaw the daily EBS. Concurrent national disease surveillance systems, including those for COVID-19 and EBS for domestic events, are not described here.

The enhanced EBS systems supplemented an existing surveillance system targeting 69 diseases in 80 countries, not including Japan (**Table 1**). The priority diseases were pre-selected based on their epidemic status, severity and unfamiliarity among physicians in Japan (a factor that may cause delays in diagnosis and treatment). The countries and regions to be monitored were selected from among those that have previously participated in the Games with the highest numbers of estimated participants and officials present. The enhanced EBS for infectious diseases occurring overseas (other than COVID-19) comprised the pre-existing EBS system plus two external systems – the World Health Organization (WHO) Epidemic Intelligence from Open Sources (EIOS) system and the BlueDot Epidemic Intelligence (EI) platform, a surveillance and risk assessment platform that leverages both artificial intelligence and human intelligence (**Fig. 1**).[4,5]

Pre-existing EBS sources included International Health Regulations (2005) notifications and information publicly available via the Internet. Sources included official information from international organizations such as WHO and national health authorities, and unofficial information from news aggregators, blogs, expert groups and other systems such as ProMED, the Center for Infectious Disease Research and Policy at the University of Minnesota and HealthMap. From these sources, we screened for events each day based on our screening criteria (**Box 1**).

The WHO EIOS system is a web-based system designed to augment and accelerate global public health intelligence activities.[6] It collects articles each day from a broad range of online official and unofficial sources and publishes the categorized information through its user interface, which is accessible only to authorized individuals. The WHO Regional Office for the Western Pacific conducted screening based on their standardized approach and emailed NIID a list of detected signals once a day.[4] This screening report provided a summary of signals, including the number of reports, affected population characteristics, reporting period, reporting region, baseline data and actions taken. The Regional Office also provided their qualitative assessment of the risk of importation into Japan during the Games and of further spread within the country, as well as the potential significant impact on society. These signals were defined as events.

BlueDot's web-based EI platform shows quantitative risk assessments based on modelling that calculates the importation risk based on air travel data and local infectious disease epidemiological data.[7,8] BlueDot obtained local disease activity hourly from online sources such as international organizations and public health agencies, ProMED-mail and Global Database of Events, Language and Tone. The information was first scanned by BlueDot's artificial intelligence system and then screened and verified by their experts. Users could select a disease on the

Box 1. Screening criteria for pre-existing event-based surveillance, Japan, 2021

- Events related to emerging infectious diseases that should be monitored:
  - sustained human-to-human transmission of a known emerging infectious disease
  - outbreaks with undiagnosed symptoms.
- Events of concern that have potential impact on Japan:
  - events with potential impact on Japanese travellers
  - events with potential for disease importation (occurrence above baseline, unexpected outbreaks of fatal infectious diseases)
  - events with contaminated food distributed to Japan
  - potential for dispatch of international emergency relief teams from Japan
  - potential need to review response and countermeasures (e.g. update of case definitions, update of epidemiological investigation guidelines).
- Events posted on WHO event information site

Table 1. **List of priority infectious diseases (other than coronavirus disease 2019) for event-based surveillance during the Tokyo 2020 Olympic and Paralympic Games, Japan (n = 80)**

Mode of transmission	Surveillance-priority infectious diseases
Human-to-human	Diphtheria, poliomyelitis, tuberculosis,[a] hepatitis B,[a] varicella, pertussis, measles, rubella, sexually transmitted infections (HIV, syphilis, chlamydia, gonorrhoea),[a] meningococcal disease, seasonal influenza, acute gastroenteritis, mumps, bacterial meningitisa
Foodborne	Enterohaemorrhagic Escherichia coli infection,[a] cholera, shigellosis,[a] typhoid/paratyphoid, hepatitis A, hepatitis E, botulism, amoebiasis,[a] cryptosporidiosis,[a] giardiasis,[a] listeriosis
Soil/waterborne	Coccidioidomycosis, leptospirosis, Legionnaires' disease, melioidosis, tetanus, Cryptococcus gattii infection,[a] strongyloidiasis, histoplasmosis
Animal-borne	Middle East respiratory syndrome coronavirus, lassa fever, South American haemorrhagic fever, avian influenza, Q fever, rabies, anthrax, hantavirus infection, brucellosis, hendra virus disease, Rift Valley fever, tularaemia, lyssavirus infection[a]
Mosquito-borne	Japanese encephalitis, West Nile virus infection, yellow fever, Zika virus disease, chikungunya virus disease, Western equine encephalitis, Eastern equine encephalitis, dengue, malaria, St. Louis encephalitis, La Crosse encephalitis, Ross River virus disease, Barmah Forest virus disease, Oropouche fever
Tick-borne	Severe fever with thrombocytopenia syndrome virus infection, Crimean-Congo haemorrhagic fever, tick-borne encephalitis, Lyme disease, Omsk haemorrhagic fever, recurrent fever, Kyasanur Forest disease, Colorado tick fever, Rocky Mountain spotted fever, African tick-bite fever,[a] Queensland tick typhus,[a] Mediterranean spotted fever, other spotted fever group rickettsioses,[a] Powassan virus disease, anaplasmosis, ehrlichiosis
Other arthropod-borne	Plague, scrub typhus, leishmaniasis, Chagas disease

[a] Diseases not included in the BlueDot system.

platform and see the risk of importation from every other country to Japan. The risk of importation was defined by BlueDot as at least one infected person entering Japan by plane and was classified as high or higher risk if it was greater than 50%. We checked the platform for updates at a set time each day and defined events as those that were newly flagged as high or higher risk.

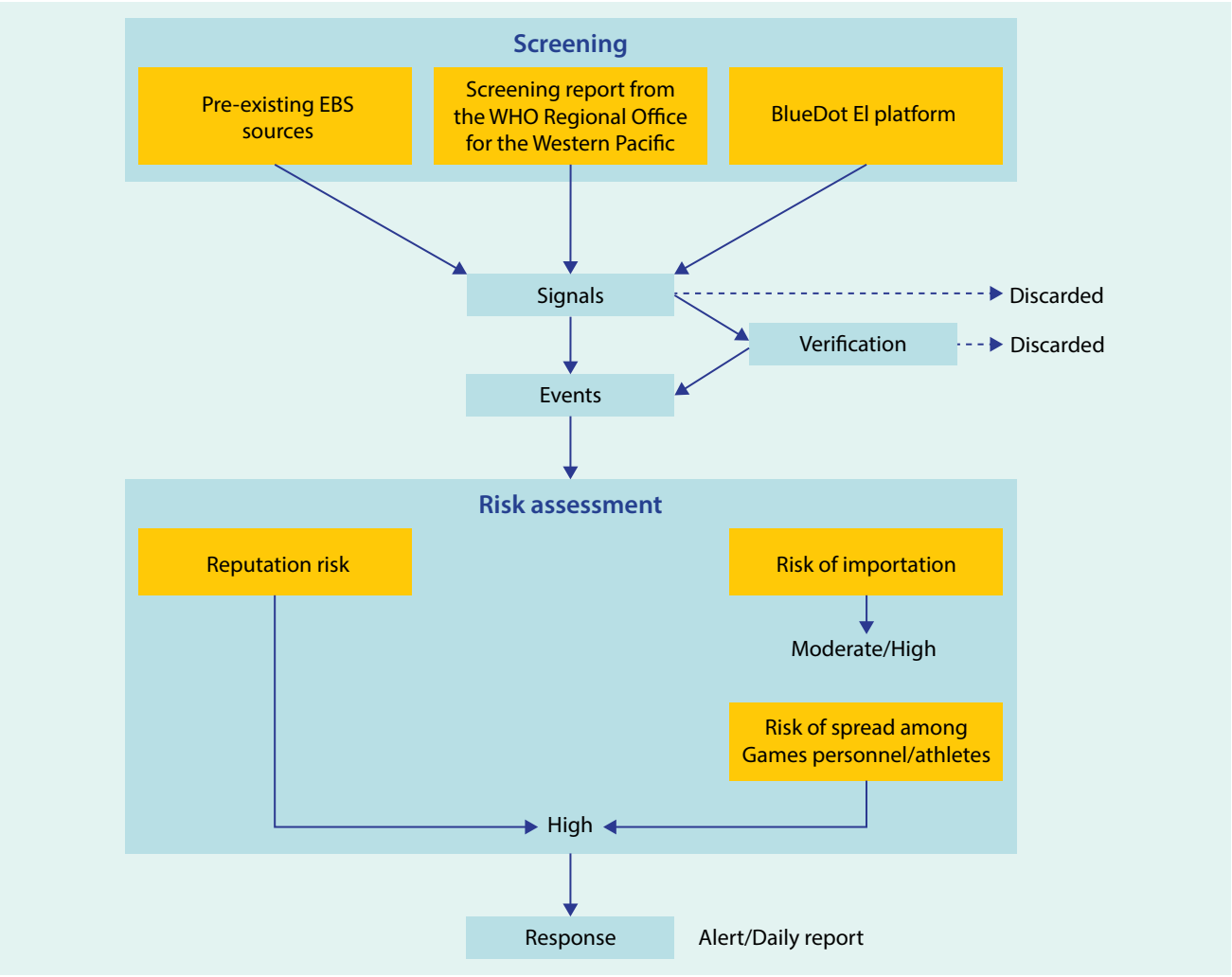
For signals or events with uncertain information, verification was conducted by referring to official sources or by combining multiple sources. After verification, we recorded all events in the EBS database and conducted risk assessments to determine their risk of association with the Games (**Box 2**). First, we assessed the potential risk of importation of diseases to Japan in relation to the Games by referring to previous national surveillance data of imported cases to Japan,[9–11] WHO epidemiological reports, the number of previous visitors to Japan[12] and the number of estimated Games participants. Second, if an importation risk related to the Games existed, the consequent risk of transmission among Games personnel and athletes was evaluated. We also assessed whether events posed a potential risk to the Games. The level of risk was discussed between staff and FETP fellows and was qualitatively determined as high, medium or low by consensus.

Box 2. **Risk assessment criteria for publishing events in the daily National Institute of Infectious Diseases report, Japan, 2021**

- Does the event have a high probability of importation of infectious diseases?
  - Do the infectious diseases have a high probability of transmission among Games personnel?
  - Do the infectious diseases have a high probability of transmission from Games personnel to the community?
- Does the event have a reputational risk among Games personnel and relevant stakeholders?

Through these processes, events that were considered to pose a high risk to the Games were posted in daily reports with summaries and assessments. They

Fig. 1. **Overview of event-based surveillance for infectious diseases occurring overseas[a] during the Tokyo 2020 Olympic and Paralympic Games, Japan**



EBS: event-based surveillance; EI: epidemic intelligence; WHO: World Health Organization.

[a] Excludes coronavirus disease 2019.

were distributed to local governments and the Tokyo Organising Committee of the Olympic and Paralympic Games through the Ministry of Health, Labour and Welfare, to alert them and help them to respond in a timely manner.

RESULTS

Overall, 140 events and 20 diseases were identified by the enhanced EBS system during the provisional period of 11 July to 8 August 2021; that is, from the end of the 10-day test run to the closing day of the Olympics (**Table 2**). A total of 17 events and 10 diseases were detected by the pre-existing system, 121 events and 11 diseases by the EIOS system, and two events and two diseases by the BlueDot platform. The median number of events per day was 5 (range, 1–9).

All identified events were evaluated for risk, with none meeting the high-risk criteria for publishing in the daily report (**Table 3**). The time required to conduct EBS using the three systems was less than 60 minutes per FETP fellow per day.

DISCUSSION

Enhanced EBS of infectious diseases occurring overseas that have potential for importation, other than COVID-19, was conducted for the Tokyo 2020 Olympic and Paralympic Games using the pre-existing EBS system

Table 2. **Number of events and diseases detected by event-based surveillance of infectious diseases occurring overseas[a] before and during the Tokyo 2020 Olympic Games, Japan, 11 July to 8 August 2021**

	Pre-existing EBS	Screening report from the WHO Regional Office for the Western Pacific	BlueDot EI platform	Total
Number of events	17	121	2	140
Number of diseases	10	11	2	20
Disease	Avian influenza B virus infection, Cyclospora infection, cholera, dengue, Japanese encephalitis, Middle East respiratory syndrome, monkeypox, plague, typhoid fever	Acute gastroenteritis, chikungunya, dengue, hepatitis A, hepatitis B, Middle East respiratory syndrome, sexually transmitted infections, unknown disease, West Nile virus infection, yellow fever, Zika virus disease	Dengue, malaria	

EBS: event-based surveillance; EI: epidemic intelligence; WHO: World Health Organization.

[a] Excludes coronavirus disease 2019.

Table 3. **Examples of risk assessment for events detected in event-based surveillance before and during the Tokyo 2020 Olympic Games, Japan, 11 July to 8 August 2021**

Date of recording	EBS system/disease/source	Event summary	Risk assessment
29 July	EIOS/hepatitis A/media	495 cases associated with a national hepatitis A outbreak have been reported in North Carolina, USA, since 1 January 2021.	The USA has been experiencing nationwide outbreaks of hepatitis A since 2017, spread through person-to-person contact. The number of imported cases detected in Japan from the USA over recent years has been 0–2 per year. The number of people entering Japan from the USA has significantly decreased, and the risk of travellers, including Games personnel, importing the virus into Japan is low.
29 July	Pre-existing EBS/monkeypox/WHO Disease Outbreak News	A patient who developed monkeypox travelled from the USA to Nigeria on 25 June. He returned to the USA on 9 July after disease onset and was quarantined on 13 July. Possible community and health-care contacts are being monitored. The source of infection for this case is unknown.	The risk of importation from Nigeria to Japan is low due to a significant decrease in the number of travellers and the low number of Games participants from Nigeria. The risk of spread of infection in the USA is low because contacts in the USA had been identified and were monitored during the incubation period after their last contact date. Therefore, the risk of importation into Japan is low.
3 August	BlueDot EI platform/malaria/media	377 599 new cases of malaria were recorded in the northern Angolan province of Malanje in the first half of 2021, resulting in the deaths of 268 people. This is an increase in cases, but a reduction in deaths, compared with the same period in 2020.	The actual increase in cases cannot be determined because data for previous years were not available. There have been no imported malaria cases from Angola in the past 5 years, the number of travellers has decreased significantly from recent years, and the number of Games participants from Angola is less than 50. Therefore, the risk of importation into Japan is low.

EBS: event-based surveillance; EI: epidemic intelligence; USA: United States of America; WHO: World Health Organization.

and external EBS systems. The provisional results revealed that no events occurring overseas were assessed as high risk for importation during the Games and none qualified to be published in the daily report. The absence of such events during the Games may be due to reports of imported infectious diseases decreasing during the pandemic.[13] Although travellers entered Japan for the Games, overall arrivals were substantially lower than before the COVID-19 pandemic, which may have led to an overall decrease in importation risk. In addition, infection control measures in place against COVID-19 may have decreased the risk of disease importation.

The enhanced EBS for the Games resulted in more reliable risk assessments because the framework incorporated data triangulation among three sources – the pre-existing EBS system in Japan, the WHO EIOS system and the BlueDot web-based EI platform. The same signals, obtained from multiple articles and different sources, were often reported from each system; such consistency in signals coming from sources with different timeliness, representativeness, sensitivity and completeness may increase the validity of risk assessments. Furthermore, the intelligence obtained from different sources was complementary, providing more detailed information about the event than relying on a single source, which may have contributed to appropriate risk assessment.[3]

Using three EBS systems also prevented public health events from being missed. For example, signals obtained from one system were not picked up as events in the other systems. This was partly due to differences in the initial assessment (e.g. BlueDot could conduct quantitative risk assessment using more accurate travel data, whereas the EIOS-based screening report qualitatively assessed the risk associated with the Games).

Incorporating external surveillance systems had the potential to reduce the time and effort required for signal screening for the Games. The EIOS system is a useful tool to deliver extensive and prompt information, but its informative nature makes it time consuming. Previously, the EIOS system was used for the 2019 Rugby World Cup in Japan, with 79 infectious diseases across 30 countries targeted for surveillance; it required one staff member and two FETP fellows to work for 3 hours each day.[14] For the Games, a larger number of countries were targeted; however, the time required was less than 1 hour per day per FETP fellow. This reduction in time was largely due to events being triaged by the Regional Office and BlueDot, which allowed NIID staff to rapidly initiate an assessment based on information provided. Globally, public health resources have been limited during the COVID-19 pandemic; hence, the technical support from external resources was vital for implementing enhanced surveillance for the Games. During future mass gatherings, the use of external platforms may make EBS more efficient for local governments and facilities with limited human resources.

There were limitations to this enhanced EBS in terms of data triangulation. First, many of the information sources used by the three systems overlapped because they obtained information through existing informal or formal channels such as social media or ProMED. Second, since the newly adopted systems were outsourced, there was a time lag between the signal screening and our detection. These limitations need to be considered if the assessment and response are required immediately, in which case, the system would need to be based at the relevant internal institution.

EBS to monitor infectious diseases occurring overseas, apart from COVID-19, for the Games in Japan was enhanced by working with external organizations. The triangulation of information provided reliable risk assessments without missing significant events. Furthermore, the collaboration helped to reduce the effort required to screen a wide range of sources internally while maintaining the quality of surveillance, especially for this event that occurred during the COVID-19 pandemic.

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Conflict of interest

None

Ethics statement

As this work is a report on daily event-based surveillance activities and does not involve human research, ethical clearance was not sought.

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Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* in the Philippines, 2012–2018

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Objective: Data are scarce on the prevailing *Streptococcus pneumoniae* serotypes in the Philippines, including the relative antimicrobial resistance (AMR) of these bacteria. This study is designed to fill that gap by describing the serotype distribution and AMR of *S. pneumoniae* in the Philippines from 2012 to 2018.

Methods: *S. pneumoniae* isolates from clinical specimens were collected through the Philippine Department of Health Antimicrobial Resistance Surveillance Program from 1 January 2012 to 31 December 2018. Identification and antimicrobial susceptibility testing (AST) were performed using conventional and automated methods (Vitek2 Compact Automated Machine). AST for penicillin, erythromycin, co-trimoxazole, ceftriaxone and levofloxacin was done following the Clinical and Laboratory Standard Institute recommendations. Serotyping was done through slide agglutination following the Denka Seiken slide agglutination method.

Results: From a total of 307 isolates of *S. pneumoniae*, 32 serotypes were identified; the most frequently occurring were serotypes 1, 3, 5, 4, 18, 19A, 6B, 15 and 14. Many (n=113, 36.53%) of the isolates were from those aged ≤5 years. Pneumococcal conjugate vaccine (PCV) coverage was as follows: PCV7 (32.69%), PCV10 (54.16%) and PCV13 (69.23%). The overall AMR of invasive *S. pneumoniae* isolates was low. Penicillin-resistant serotypes were 14, 19, 24, 4, 5, 1, 15, 6 and 32.

Discussion: With the inclusion of PCV13 in the National Immunization Program, continued monitoring of the prevailing serotypes of *S. pneumoniae* isolates in the Philippines is needed to guide disease and AMR control measures.

Streptococcus pneumoniae poses a serious public health concern because it causes a wide range of diseases including otitis media, septicaemia, meningitis and pneumonia. The World Health Organization (WHO) reports that pneumonia accounted for 15% of mortalities among children aged ≤5 years globally in 2017.[1] *S. pneumoniae* was identified as one of the leading causes of pneumonia in the 2016 Global Burden of Disease report.[2] Invasive pneumococcal disease (IPD), defined as infection of normally sterile sites of the body with *S. pneumoniae*, most frequently affects children aged <2 years, adults aged ≥65 years and immunocompromised patients.[3,4] In the Philippines, a study in Regions VI, VII and VIII determined that there were 89 221 children aged <5 years with pneumonia who were seen and 85 923 who were given medication from January to December 2012.[5]

At present, more than 94 different pneumococcal serotypes have been classified based on the unique polysaccharide characteristics and composition expressed in the capsule.[6] Serotype 19A was the most commonly identified serotype in the regions of East Africa, Asia Pacific, United States of America (USA), Europe and North America in 2007–2015.[7] Serotypes 6B, 14 and 19F were the predominant causes of IPD among children in the Africa–Eastern Mediterranean region, whereas serotypes 1 and 14 were prevalent in Europe and Latin America.

The threat of emerging antimicrobial resistance (AMR) among *S. pneumoniae* serotypes worldwide was recognized as early as the 1980s. Antimicrobial susceptibility profiling of *S. pneumoniae* has played a significant role in the treatment of patients and in

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mapping AMR for large-scale epidemiology studies. Specific *S. pneumoniae* serotypes have been associated with resistance to specific antimicrobial agents; for example, serotypes 19F, 14, 23F, 9V and 6B have been found to be resistant to penicillin and macrolides.[3]

Data are lacking on the prevailing pneumococcal serotypes in the Philippines, including their resistance to specific antimicrobials. This study therefore describes the distribution and AMR of *S. pneumoniae* serotypes in the Philippines from 2012 to 2018.

METHODS

Bacterial isolates

S. pneumoniae isolates from invasive clinical specimens were collected through the Philippine Department of Health Antimicrobial Resistance Surveillance Program (DOH-ARSP) from 1 January 2012 to 31 December 2018. The DOH-ARSP is a laboratory-based AMR surveillance programme with 24 sentinel sites representing 16 of the 17 geopolitical regions in the country. There are two private hospitals among the eight sentinel sites in the National Capital Region, but all other sentinel sites are regional government hospitals that cater to their respective geopolitical regions. All are tertiary hospitals with bed capacity ranging from 50 to 1500, with many being in the 300–500 range.

Case finding for DOH-ARSP is based on priority specimens sent routinely to sentinel site laboratories for clinical purposes. Thus, sampling in the present study is largely based on diagnostic practices of the sentinel site clinicians. All *S. pneumoniae* isolates grown from invasive clinical specimens were included in the present study. Cumulative overall analyses were done for all isolates, with a focus on the most vulnerable age groups, that is, those aged ≤5 years and those aged ≥65 years.

Bacterial identification and antimicrobial susceptibility testing

S. pneumoniae isolates were cultured by the sentinel sites from invasive clinical samples based on the WHO Manual for the laboratory identification and antimicrobial susceptibility testing of bacterial pathogens of public health importance in the developing world.[8] Isolates were then sent to the implementing laboratory of the DOH-ARSP for confirmation of identification and antimicrobial susceptibility testing (AST) and for serotyping. Confirmation of identification and AST of isolates were performed using the Vitek2 Compact Automated Machine (bioMérieux). AST for penicillin, erythromycin, co-trimoxazole, ceftriaxone and levofloxacin was done following the method described by the Clinical and Laboratory Standard Institute (CLSI).[9] Results were managed and analysed using WHONET 5.6, a Windows-based database software that facilitates analysis of AST. In computing percentage resistance, only the first isolate per patient per calendar year was included.

Serotyping

S. pneumoniae isolates were serotyped through slide agglutination following the Denka Seiken slide agglutination method as described by Denka Seiken Co., Ltd.[10] Because of local unavailability of factor sera, typing within serogroups that contained multiple serotypes was not done.

RESULTS

IPD serotype distribution

A total of 307 isolates of *S. pneumoniae* were collected from patients with IPD in the 7-year study period. The age range was 0–93 years. Most of the isolates were from blood (n=286, 93.15%) and cerebrospinal fluid (n=21, 6.84%). About a third (n=113, 36.80%) of the isolates were from the ≤5 years age group followed by the age groups 18–64 years (n=111, 36.15%), ≥65 years (n=55, 17.91%) and 6–17 years (n=28, 9.12%).

Thirty-two serotypes were identified, with the most frequently occurring being serotypes 1, 6, 3, 5, 4, 18, 23, 12, 15 and 2 (**Table 1**). These 10 serotypes made up 71% of the total isolates. Due to local unavailability of typing sera, no typing was done for serogroups 6, 18, 19 and 23.

The overall PCV coverages of the serogroups identified in this study were as follows: PCV7 (39.73%), PCV10 (59.60%) and PCV13 (68.07%). There were 37 isolates (12%) with serotypes not included in PCVs and PPVs (non-vaccine types) (**Table 1**).

Table 1. **Frequency of *Streptococcus pneumoniae* serotypes in the Philippines, 2012–2018 (*N*=307)**

Serotype	2012 *n*=7	2013 *n*=20	2014 *n*=33	2015 *n*=51	2016 *n*=63	2017 *n*=59	2018 *n*=74	TOTAL	%
4	1	1	4	5	3	3	6	23	7.49
6		1	5	8	7	3	3	27	8.79
9			1		4		3	8	2.61
14	2	2		1		5	3	13	4.23
18		1	2	5	1	8	4	21	6.84
19				1	4	0	4	9	2.93
23	1	2	2	2	4	6	4	21	6.84
1		5	5	7	9	6	6	38	12.37
5	2	2	8	2	3	1	5	23	7.49
7				1	3	1	1	6	1.95
3		1	1	3	4	9	8	26	8.46
2	1	2	1	2	4	1	1	12	3.90
10				1		1	3	5	1.63
11				2	1			3	0.98
12				2	1	1	1	5	1.63
15			1	2	6	2	2	13	4.23
20			1	1	1	1	3	7	2.28
22					3	1	1	5	1.63
33		1		1	2			4	1.3
16						2	5	7	2.28
21						1		1	0.33
24					2		2	4	1.3
25				1		1	1	3	0.98
28				1		1		2	0.65
29				2		2	2	6	1.95
31				1	1			2	0.65
32		1						1	0.33
34		1	1				3	5	1.63
35							2	2	0.65
39						1		1	0.33
40			1			2		2	0.65
46						2		1	0.33
TOTAL								**307**	

Legend:		
	PCV7	Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F
	PCV10	Serotypes: PCV7 + 1, 5, 7F
	PCV13	Serotypes: PCV10 + 3, 6A, 19A
	PPSV23	Serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

Among patients aged ≤5 years, the most common serotypes were 6 (*n*=16, 14.15%), 18 (*n*=12, 10.61%) and 14 (*n*=10, 8.85%), all covered by PCVs. The overall PCV coverages of serotypes from this age group were 54.86% for PCV7, 66.37% for PCV10 and 70.79% for PCV13. A total of 11% of the isolates among this age group were non-vaccine serotypes.

Among isolates from older adults, those aged ≥65 years, the most frequent were serotypes 3 (*n*=10, 18.18%), 4 (*n*=5, 9.09%) and 1 (*n*=5, 9.09%), which are all covered by PCV. Serotype 3 (present in PCV13 but not in PCV7 and PCV10) was consistently seen in this age group from 2014 to 2018. The overall vaccine coverages in this age group were PCV7 (29.09%), PCV10 (50.90%), PCV13 (69.09%) and PPV23 (89.09%). Only 7% (4/55) were non-vaccine serotypes.

There were only 28 isolates from patients aged 6–17 years, with the most common being serotypes 1 (*n*=5, 17.85%) and 18 (*n*=4, 14.28%), both covered by the conjugate vaccines. Among the isolates from patients aged 18–64 years, the most common were serotypes 1 (*n*=21, 18.91%), 4 (*n*=12, 10.81%) and 23 (11, 9.90%), all of which were covered by PCVs. Only 15% (11/111) were non-vaccine serotypes.

The overall cumulative resistance rate to antibiotics of interest among the invasive *S. pneumoniae* isolates in this study was low. Resistance to penicillin (meningitis breakpoint) was highest at 14.57%, followed by co-trimoxazole (9.06%), erythromycin (2.7%) and ceftriaxone (0.31%). No resistance to levofloxacin was seen in this study. The only distinct trend in yearly AMR rates was seen for penicillin, with a 2-year successive increase in 2017 and 2018. However, given the relatively low number of isolates, these increases were not statistically significant (**Fig. 1**).

Antimicrobial resistance

There were 34 penicillin-resistant isolates in the study, of which 56% (19/34) were from patients aged ≤5 years and were of serotypes 14 (*n*=8, 42%), 19 (*n*=4, 21%), 6 (*n*=2, 10%), 1, 4, 15, 33 and 24 (*n*=1 each, 5% each). PCV coverage of penicillin-resistant isolates from this age group was 84%, with three non-PCV serotypes: serotypes 15, 33 and 24. Serotypes of penicillin-resistant isolates from other age groups are shown in **Table 2**.

Of the 21 isolates resistant to co-trimoxazole, most (*n*=13, 62%) were from patients aged ≤5 years and were of serotypes 6, 14, 19, 23 and 5. PCV coverage of such isolates in this age group was 100%.

There were few erythromycin-resistant isolates in this study, with most (4/7, 57%) coming from the adult population (18–64 years) and only two isolates from children aged ≤5 years. The erythromycin-resistant isolates were of serotypes 6, 1, 23 and 24, with the non-vaccine serotype 24 being the most common type (3/7, 43%).

One serotype 24 isolate from a male child aged 6 months was reported in 2015 to be resistant to ceftriaxone. This non-vaccine type isolate was noted to also be resistant to erythromycin and penicillin. There was no report of any similarly resistant phenotype in the succeeding years.

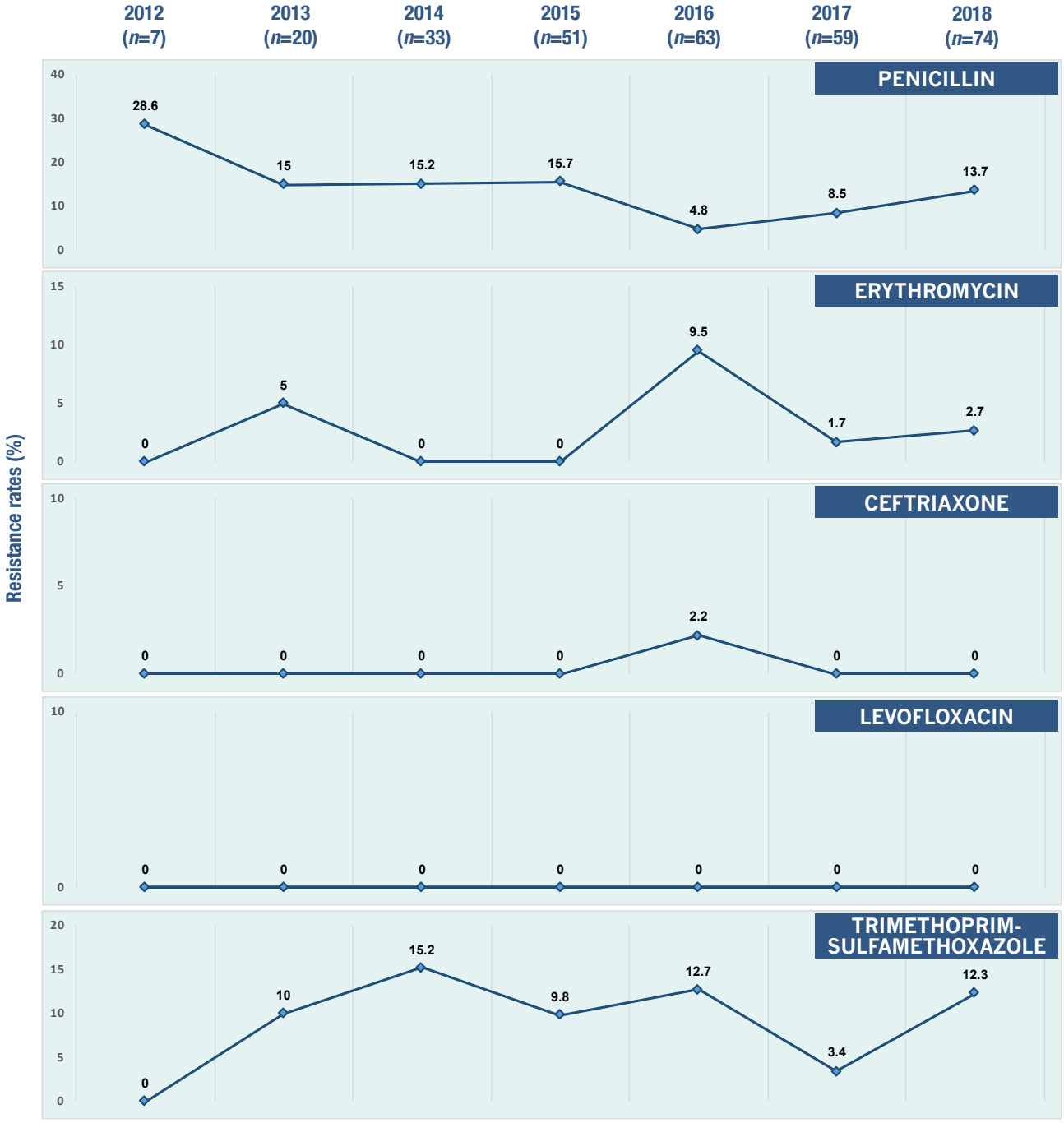
Among the 10 serotype 14 isolates from patients aged ≤5 years, eight (80%) were penicillin-resistant. Further, of the nine serotype 19 isolates, six (67%) were penicillin-resistant, with four of these isolated from patients aged ≤5 years.

DISCUSSION

IPD serotype distribution

Pneumococcal serotypes vary in prevalence, age group infected, geographical distribution and AMR pattern. Local IPD serotypes identified in this study (serotypes 1, 3, 4, 6, 14, 18 and 23) resemble the dominant IPD serotypes worldwide, including 1, 3, 4, 14, 6A, 6B, 7F, 8, 18C, 19F, 9V and 23F.[11] Serotype 1 was present yearly in all age groups and accounted for the greatest number of isolates across each age group. Serotypes 4 and 5 were also observed in all age groups and were present in each year of the study period. Of the 32 serotypes identified in this study, seven have not been reported previously in local studies: serotypes 10 and 11, which are covered by PPV, and five non-vaccine types, 21, 32, 35, 40 and 46. The IPD serotype distribution in this study relies on the diagnostic practices of sentinel site clinicians. This study does not provide data on the proportion of IPD cases that had isolates for testing; however, it does provide information on the serotype distribution and AMR of *S. pneumoniae* in the Philippines.

Fig. 1. **Yearly antimicrobial resistance rate of penicillin, erythromycin, ceftriaxone, levofloxacin and trimethoprim-sulfamethoxazole in the Philippines, 2012–2018**



Following the introduction of PCV13 in Asian countries in 2009, the pattern of vaccine serotype coverage and predominant IPD serotypes detected has changed. PCV7 serotype coverage reduction was noted to be 30–34% in the Republic of Korea, Hong Kong SAR (China) and Taiwan (China).[12] In the PCV13 period, the most prevailing serotype was 19A in Japan, 3 in Taiwan (China) and 15 in China. This is in contrast with the results of the present study where serotypes 1 (*n*=38, 12.37%) and 6 (*n*=27, 8.79%) predominated. The difference in the prevailing serotypes across the region could be influenced by the presence of antibiotic-resistant strains, immunogenicity of each conjugate in different populations and a mismatch between serotype variants present in a country and the available strains used in vaccine preparation.[12]

Table 2. **Distribution of penicillin-resistant isolates by age and serotype**

Age group	Number of isolates	Serotypes
≤5	19 (55.9%)	4, 6, 14, 19, 1, 15, 33, 24
6–17	2 (5.9%)	14, 5
18–64	10 (29.4%)	4, 19, 1, 5, 15, 24
≥65	3 (8.8%)	19, 5, 32
Total	34	

The overall PCV13 coverage of 68.07% in the present study is lower than was found in a previous local 8-year study (2004–2011), where it was 73.8%.[13] This may be due to the larger number of isolates in the present study. The overall PCV13 coverage among isolates from patients aged ≤5 years in the present study was 70.79% – lower than the reported 80.4% in Hong Kong SAR (China) and 93.1% in Taiwan (China).[12]

PCV13 was included in the country's National Immunization Program for children aged ≤5 years in 2015, with low vaccination coverage ranging from 30% to 60% in 2015–2019.[1] However, there was no noted decrease in PCV13 coverage among the isolates from this age group in 2015, with PCV13 coverage ranging from 68% in 2016 to 79% in 2018. Continuous surveillance of *S. pneumoniae* serotypes can track changes to prevailing serotypes, especially if vaccination coverage improves.

Among the isolates from those aged ≥65 years, serotypes included in PCV13 (3, 1, 4, 18, 6) were the most common. These findings support the 2018 local immunization recommendation of administering PCV13 to this age group.[15]

Antimicrobial resistance

The cumulative resistance rates of pneumococci in the present study were low, ranging from 0% for levofloxacin to 14.57% for penicillin. This is lower than reported elsewhere in Asia, including values for penicillin resistance among pneumococci causing IPD in 17 Chinese cities of 51.6% (455/881) and erythromycin resistance of 95.2% (839/881) during 2011–2016.[16] A study from the Asian Network for Surveillance of Resistant Pathogens reported pneumococci resistance rates of 1.7%, 0.4%, 1.5% and 13.4% for levofloxacin, moxifloxacin, gatifloxacin and ciprofloxacin, respectively.[17] The resistance rates to ceftriaxone among 10 hospitals in China were 8.2% and 18.1% among non-meningeal and meningeal isolates, respectively.[18] A medical research institute in Malaysia reported that 35.9% of the total pneumococcal isolates (663/1847) from a paediatric population was resistant to co-trimoxazole.[19]

The most common multidrug resistance pattern observed in this study was a penicillin-erythromycin-co-trimoxazole combination (n=3). This combination was also found in 6/125 resistance patterns in a multicentre retrospective study in China.[20]

Serotypes and AMR

Specific pneumococcal serotypes are known to be associated with certain antibacterial resistance.[20] Worldwide, penicillin resistance was observed among serotypes 6A, 6B, 9V, 14, 19A, 19F, 23A and 35B, with the most resistant serotypes being 19A (28.1%), 19F (19.0%) and 35 (16.7%).[22,23] Three of these serotypes were identified among the penicillin-resistant isolates in the present study – 6, 14 and 19A – all of which are covered by PCV13. With four of the six isolates from patients aged ≤5 years, vaccination with PCV13 could prevent penicillin resistance among pneumococci in this age group. Interestingly, all four of the serotype 24 isolates – a non-vaccine type – from the ≤5 year and the 16–84 year age groups in this study were penicillin-resistant. Monitoring this serotype is recommended to guide control measures against the spread of penicillin-resistant pneumococci.

Erythromycin resistance has been observed among serotypes 6A, 6B, 9V, 14, 15A, 19A and 19F,[21] and for serotypes 6 (21.8%) and 14 (41.9%) among children aged ≤5 years.[20] Results from this study differ, with serotypes 1 (2.6%), 6 (7.4%), 23 (14%) and 24 (100%) being erythromycin-resistant isolates. Co-trimoxazole-re-

sistant isolates in the present study were from serotypes 6 (45%) and 19 (19.35%), similar to results reported for co-trimoxazole-resistant serotypes (serotype 6B) from Malaysia.[23]

Although particular serogroups have been associated with resistance to specific antibiotics recently, it is possible that serotype profiles of resistant pneumococci will change through the years because the genes encoding the capsular serotype can be exchanged and acquired.[24] This, as well as the potential for serotype replacement and switching serotypes within the conjugate vaccines, suggests that monitoring pneumococci serotypes is required in the Philippines. Whole genome sequencing could also be considered for monitoring pneumococci serotypes, given that AMR among pneumococci is usually clonal in origin.

CONCLUSION

The *S. pneumoniae* serotypes in the present study are largely similar to those prevailing worldwide. The most common serotypes and serogroups observed in this study were serotypes 1, 6, 3, 5, 4, 18, 23, 15, 14 and 2. PCV coverage among patients aged ≤5 years across the 7-year study has not decreased, even after the inclusion of PCV13 in the National Immunization Program. The AMR rates of *S. pneumoniae* to penicillin, erythromycin, ceftriaxone, co-trimoxazole and levofloxacin remained low. The specific antibiotic-resistant serotypes observed in this study were similar to those in other Asian countries. All serotype 24 isolates, a non-vaccine type, were found to be resistant to penicillin and erythromycin. With the inclusion of PCV13 in the National Immunization Program, continued monitoring of the prevailing serotypes of *S. pneumoniae* isolates in the Philippines is needed to guide disease and AMR control measures.

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Conflict of interest

All authors declared no conflict of interest in the conduct of this study.

Ethics statement

This study was submitted to and approved by the Institutional Review Board of the Research Institute for Tropical Medicine (2019–35).

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Capacity and use of diagnostics and treatment for patients with severe acute respiratory infections in the pre-COVID-19 era in district and provincial hospitals in Viet Nam

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Objective: To describe the burden of severe acute respiratory infection (SARI) and the infrastructure and current practices of SARI management in hospitals in Viet Nam.

Methods: We conducted a short observational study at critical care units (CCUs) in 32 district hospitals and 16 provincial hospitals in five provinces in Viet Nam from March to July 2019. We collected data on hospital equipment and medicines used in SARI management. At the patient level, data were collected for 14 consecutive days on all patients presenting to CCUs, including information on demographics, intervention and treatment within 24 hours of CCU admission and 7-day outcome.

Results: There were significant differences between district and provincial hospitals in the availability of microbial culture, rapid influenza diagnostic tests, inflammatory markers and mechanical ventilation. Among 1722 eligible patients admitted to CCUs, there were 395 (22.9%) patients with SARI. The median age of SARI patients was 74 (interquartile range: 58–84) years; 49.1% were male. Although systemic antibiotics were available in all hospitals and were empirically given to 93.4% of patients, oseltamivir was available in 25% of hospitals, and only 0.5% of patients received empiric oseltamivir within 24 hours of admission. The 7-day mortality was 6.6% (26/395). Independent factors associated with 7-day mortality were septic shock and requiring respiratory support within 24 hours of admission.

Discussion: SARI is a major burden on CCUs in Viet Nam. Barriers to delivering quality care include the limited availability of diagnostics and medication and non-protocolized management of SARI in CCUs.

Severe acute respiratory infection (SARI) remains a substantial burden on health care systems worldwide, with more than 2.5 million deaths in 2017, when it was ranked the fourth leading cause of death for all ages globally.[1] During the first two decades of the 21st century, the emergence of novel respiratory infections such as severe acute respiratory syndrome virus (SARS), avian influenza, Middle East respiratory syndrome (MERS) and novel H1N1 pandemic influenza posed significant threats to humans, particularly in Asia.[2] In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen that causes coronavirus disease 2019 (COVID-19), was first identified in Wuhan, China; it rapidly spread across the world and was declared a pandemic in March 2020.[3]

Lower- and middle-income countries (LMICs) are more vulnerable to infectious diseases, especially epidemic- and pandemic-prone SARI, owing to the lack of preparedness required for critical care services, including health care worker training, infrastructure and supplies.[4,5] Delivering high-quality care in critical care units

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(CCUs) in LMICs is challenged by a relative lack of epidemiologic data, context-specific effective interventions and resources.[6–8] In addition, during outbreaks, health care systems and CCUs are under a greater burden.[9,10] However, protocolization of critical care in LMICs is limited, and the use of available diagnostics and treatment in this setting is not well known.[11]

Viet Nam is an LMIC that has experienced many outbreaks of emerging infectious respiratory diseases such as SARS-CoV, avian influenza A(H5N1) and SARS-CoV-2.[12–14] Most of the SARI studies in Viet Nam mainly describe clinical and pathological characteristics but give little information about the concordance between clinical management capacity and the availability of medical supplies in association with patient outcome.[15–17] Our previous assessment of health care infrastructure capacity to respond to SARI indicated enormous limitations on relevant structural and human resources in selected district and provincial hospitals in Viet Nam.[18] This study describes current practices in SARI case management and the burden to CCUs on medical resources in district and provincial hospitals in Viet Nam in the months leading up to the COVID-19 pandemic.

METHODS

Study design

This was a multi-centre, prospective, observational study to evaluate the management and outcomes of patients with SARI who were admitted to CCUs in Viet Nam. As of 2019, Viet Nam had 63 provinces divided into six administrative regions, with a population of 96.5 million.[19] Per 10 000 inhabitants, Viet Nam had 28.5 hospital beds and 8.8 medical doctors.[19] In this study, we used convenience sampling to select five provinces from different administrative regions. In each province, we invited all hospitals at the provincial and district levels to participate in the study. In each participating hospital, we excluded surgical CCUs and paediatric CCUs. Between March and July 2019, all participating hospitals underwent a 14-day observational period. During the first 7 days, all patients aged ≥18 years admitted to the eligible CCUs were enrolled in the study, and all were observed for outcomes for 7 days from their enrolment.

Data collection

SARI cases were defined as: 1) a history of fever or measured fever ≥38 °C, 2) cough, 3) symptom onset within the past 10 days and 4) requiring hospitalization.[20] Patient outcomes were evaluated at 7 days after admission to the CCU, or when the patient was discharged or transferred to another hospital, whichever came first.

We collected data related to clinical management of SARI in the CCUs from hospital administration records and the patients' medical records. Data from hospital administration records included information on the availability or use of laboratory tests and medication given to the patients to manage SARI and sepsis that follow international and national guidelines.[21,22] Demographic characteristics, onset of symptoms and medical history were collected using a modified standardized questionnaire on arrival to the CCU.[23] Relevant comorbidities included chronic cardiac disease, chronic renal disease, chronic liver disease and chronic respiratory disease, according to World Health Organization definitions of pre-existing conditions associated with increased risk of severe influenza or death.[24] We calculated the quick sequential organ failure assessment (qSOFA) score within the first 24 hours of admission, giving one point for each of three criteria: respiratory rate ≥22 breaths/minute, altered mentation and systolic blood pressure ≤100 mmHg.[22] For each patient, information on relevant treatments and interventions during the first 24 hours of admission and early mortality (within 7 days of CCU admission) was also extracted from patients' medical records.

Ethics

This study was approved by the Institutional Review Board of Hanoi Medical University (approval number 59/GCN-DDNCYSH-DHYHN). All participants or legal guardians were informed about the study's purpose and gave their verbal consent for use of their data. The need for written consent was waived by the Institutional Review Board because the data collected were extracted from medical records as part of routine clinical care, with minimal risk of harm to the participants.

Statistical analysis

Data collected on paper case report forms were entered into an electronic database (EpiData, Odense, Denmark). The proportion of patients who received laboratory tests was calculated as the number of patients who received a test divided by the total patients admitted to all CCUs in which the test was available. Statistical analysis was performed using R software version 3.6.1. All categorical data were calculated as frequencies and compared using chi-squared or Fisher's exact test, as appropriate. Continuous variables were given as medians with interquartile range (IQR), and comparisons between groups were performed using the Mann-Whitney U test or Kruskal-Wallis test, as appropriate. Cox proportional hazards regression was used to identify variables that predicted 7-day mortality. *P* values <0.05 were considered statistically significant.

RESULTS

Of the 51 hospitals invited to participate in the study, 48 responded (94% response rate). A total of 1759 patients were admitted to the 48 participating CCUs between March and July 2019 (**Appendix Fig. 1**). We excluded from this analysis 37 (2.1%) patients with no information on diagnosis or date of symptom onset. Among the 1722 eligible patients admitted to CCUs, 395 (22.9%) met the definition of SARI and 1327 (77.1%) had other diagnoses (non-SARI) on admission. The numbers of patients presenting to district hospital CCUs and provincial hospital CCUs were 929 (53.9%) and 793 (46.1%), respectively. The proportion of SARI cases among patients admitted to district CCUs was significantly higher than among those admitted to provincial CCUs (247/929 [26.6%] vs 148/793 [18.7%], $P < 0.001$).

Descriptive baseline characteristics of patients admitted to CCUs are displayed in **Table 1**. The median age of SARI patients was 74 (58–84) years, compared with 67 (53–79) years in non-SARI patients ($P < 0.001$). Among SARI patients, 151 (38.2%) had one comorbidity and 155 (39.2%) had at least two comorbidities. The most common comorbidity among the SARI patients was chronic cardiac disease (166/395 [42.0%]), followed by chronic respiratory disease (154/395 [39.0%]) and diabetes (47/395 [11.9%]). Median time from symptom onset to hospitalization was 2 (IQR: 1–3) days in patients with SARI and 1 (IQR: 1–3) day in patients with non-SARI ($P = 0.001$).

The SARI patients in district and provincial hospitals were similar in terms of the proportions of male gender (45.7% vs 54.9%, $P = 0.1$) and age (median age, 74 [IQR: 58–85] vs 73 [IQR: 59–83], respectively, $P = 0.82$) (**Table 1**). However, the duration from symptom onset to hospitalization was higher in patients with SARI presenting to district CCUs than in those presenting to provincial CCUs (median, 2 days vs 1 day, respectively).

Most district and provincial hospitals had the essential supplies and equipment to conduct diagnostic testing (e.g. chest X-ray and complete blood count) and to treat patients with SARI and sepsis. However, specific laboratory testing capacity was more available in provincial hospitals than in district hospitals, for example, for blood and sputum culture, inflammatory markers (C-reactive protein and procalcitonin), lactate, arterial blood gas and influenza A and B antigen detection (**Table 2**).

To further elucidate the impact of testing deficiency on the frequency of indicated investigations, we evaluated the association between the percentage of test availability and the proportion of SARI patients who received the corresponding test at each hospital level (**Fig. 1a**). In district hospitals, the frequency of patients who received each specific laboratory test was limited in terms of testing capacity, expressed by a significantly positive correlation ($r = 0.96$, $P < 0.001$). Meanwhile, in provincial hospitals, the relationship between testing capacity and frequency of testing displayed a positive trend ($r = 0.36$, $P = 0.09$) (**Fig. 1a**). Noticeably, among patients with SARI, 95.5% of patients in district and 62.8% of patients in provincial hospitals had no microbiological testing for etiology (**Fig. 1c**).

Among the 395 patients who met the case definition of SARI, 340 (86.1%) underwent chest X-ray, of whom 225 (66.2%) had X-ray confirmed pneumonia. However, only 8/395 patients (2%) received rapid influenza diagnostic tests, 32/395 (8.1%) received blood cultures and 44/395 (11.1%) received sputum cultures to identify the etiology of SARI. No patients were tested via polymerase chain reaction (PCR) assay for respiratory viruses, including influenza, which could be due to a deficiency of PCR machines in the participating hospitals: only three of 48 hospitals (6.3%) had the capacity to perform on-site PCR testing. In all patients with SARI diagnosis on admission, 88.4% (349/395) received empiric intravenous antibiotics within 24 hours of admission, whereas only

Table 1. **Characteristics of patients admitted to CCUs in 32 district hospitals and 16 provincial hospitals in Viet Nam, March–July 2019**

Characteristics	Patients with SARI (n = 395)	Patients with other diagnosis (n = 1327)	P	Patients with SARI in district hospitals (n = 247)	Patients with SARI in provincial hospitals (n = 148)	P
Male gender, n (%)	194/395 (49.1)	780/1327 (58.8)	**< 0.001**	115/247 (45.7)	79/148 (54.9)	0.1
Age (years), median (IQR)	74 (58–84)	67 (53–79)	**< 0.001**	74 (58–85)	73 (59–83)	0.82
Days to seek care, median (range)	2 (1–3)	1 (1–3)	**< 0.001**	2 (1–3)	1 (0–3)	**< 0.001**
qSOFA score, n (%)						
0–1	205/395 (51.9)	886/1327 (66.8)	**< 0.001**	148/247 (59.9)	57/148 (38.5)	**< 0.001**
≥2	190/395 (48.1)	441/1327 (33.2)		99/247 (40.1)	91/148 (61.5)	
Comorbidities						
Chronic respiratory disease	154/395 (39.0)	399/1327 (30.1)	**< 0.001**	109/247 (44.1)	45/148 (30.4)	**< 0.01**
Chronic cardiac disease	166/395 (42.0)	467/1327 (35.2)	**0.01**	100/247 (40.5)	66/148 (44.6)	0.64
Diabetes	47/395 (11.9)	135/1327 (10.2)	0.33	21/247 (8.5)	26/148 (17.6)	**0.01**
Chronic liver disease	11/395 (2.8)	69/1327 (5.2)	0.045	3/247 (1.2)	8/148 (5.4)	**0.02**
Chronic kidney disease	20/395 (5.1)	51/1327 (3.8)	0.28	10/247 (4.0)	10/148 (6.8)	0.34

Statistically significant *P* values are shown in bold.

0.5% (2/395) received empiric oseltamivir treatment. The proportions of patients with SARI requiring oxygen therapy, invasive mechanical ventilation or vasopressors were 73.2% (289/395), 7.3% (29/395) and 4.8% (19/395), respectively, and the proportions were higher in provincial CCUs than in district CCUs (**Table 3**). The median age of patients receiving oxygen therapy and mechanical ventilation within 24 hours of admission was 76 (IQR: 63–85) and 77 (IQR: 65–88), respectively. Use of corticosteroids was common in patients with SARI (238/395 [60.3%]), particularly in district CCUs (**Table 3**). The overall rate of corticosteroid use in patients needing supplementary oxygen or invasive mechanical ventilation was 63.3% (183/289) and 65.5% (19/29), respectively, compared with 50% (51/102) in patients without respiratory support.

The overall 7-day mortality in patients presenting to CCUs was 6.6% (26/395) (**Appendix Fig. 1**). The 7-day mortalities in patients initially admitted to district and provincial CCUs were 10/247 (4%) and 16/148 (10.8%), respectively ($P < 0.001$). The 7-day mortality of all SARI cases was similar to the mortality of those with other diagnoses (26/395 [6.6%] vs 79/1327 [6.0%], respectively, $P = 0.65$). The median age of patients who died was 74 (IQR: 60–84) for SARI cases and 72 (IQR: 59–84) for patients with non-SARI diagnoses.

The median time to death for SARI cases was 3 days (IQR: 2–5). Multivariate Cox proportional hazard regression analysis indicated that septic shock (hazard ratio [HR]: 3.5, 95% confidence interval [CI]: 1.23–9.96) and qSOFA score ≥2 (HR: 3.41, 95% CI: 1.25–9.34) within the first 24 hours of CCU admission were associated with death (**Table 4**).

DISCUSSION

Our study shows that SARI remains a burden on the Vietnamese health care system. A considerable proportion of SARI cases (22.9%) were admitted to CCUs, and 7-day mortality (6.6%) was not negligible in the pre-COVID-19 era. Laboratory testing for SARI was severely limited in the district hospitals and underused in the provincial hospitals included in this study.

Previous studies in developing countries demonstrated that SARI was common among patients admitted to emergency departments (range of about 20–30%).[25,26] In a surveillance study of 15 sites in Viet Nam during 2006–2010, the hospital admission rates in outpatients presenting with influenza-like illness (ILI) – defined as a measured temperature of 38 °C or more and cough and/or sore throat – was 9.3%. Of 6516 outpatients with ILI tested for influenza by PCR, 22% were positive.[27] In a study of hospital admissions in a tertiary paediatric hospital in Hanoi during 2007–2014, pneumonia and bronchitis were the leading causes and accounted for 24.5% and 19.1% of all emergency visits, respectively.[28] In 2016, SARI surveillance on 4003 specimens revealed

Table 2. **Availability of supplies and intervention for management of SARI in study hospitals in Viet Nam, March–July 2019**

Supply and intervention	All hospitals (n = 48)	District hospitals (n = 32)	Provincial hospitals (n = 16)	P
Chest X-ray (%)	48/48 (100)	32/32 (100)	16/16 (100)	-
Blood culture (%)	16/48 (33.3)	3/32 (9.4)	13/16 (81.2)	**< 0.001**
Sputum culture (%)	22/48 (45.8)	9/32 (28.1)	13/16 (81.2)	**0.001**
Rapid influenza diagnostic tests (%)	21/48 (43.8)	8/32 (25.0)	13/16 (81.2)	**< 0.001**
Influenza RT-PCR test	3/48 (6.3)	0/32 (0)	3/16 (18.8)	**0.03**
Complete blood count (%)	48/48 (100)	32/32 (100)	16/16 (100)	-
C-reactive protein (%)	26/48 (54.2)	10/32 (31.2)	16/16 (100)	**< 0.001**
Procalcitonin (%)	12/48 (25.0)	1/32 (3.1)	11/16 (68.8)	**< 0.001**
Lactate (%)	18/48 (37.5)	6/32 (18.8)	12/16 (75)	**< 0.001**
Arterial blood gas (%)	19/48 (39.6)	8/32 (25)	11/16 (68.8)	**< 0.001**
Antimicrobials (%)				
Carbapenem	21/48 (43.8)	7/32 (21.9)	14/16 (87.5)	**0.04**
Cephalosporin	48/48 (100)	32/32 (100)	16/16 (100)	-
Aminoglycoside	41/48 (85.4)	26/32 (81.2)	15/16 (93.8)	0.4
Quinolone	48/48 (100)	32/32 (100)	16/16 (100)	-
Oseltamivir	12/48 (25.0)	6/32 (18.8)	6/16 (37.5)	0.29
Vasopressor (%)				
Adrenalin	48/48 (100)	32/32 (100)	16/16 (100)	-
Noradrenalin	30/48 (62.5)	14/32 (43.8)	16/16 (100)	**< 0.001**
Dopamine	41/48 (85.4)	25/32 (78.1)	16/16 (100)	0.08
Dobutamine	30/48 (62.5)	14/32 (43.8)	16/16 (100)	**< 0.001**
Corticosteroids (%)				
Hydrocortisone	27/48 (56.2)	14/32 (43.8)	13/16 (81.2)	**0.02**
Dexamethasone	27/48 (56.2)	14/32 (43.8)	13/16 (81.2)	**0.02**
Methylprednisolone	46/48 (95.8)	30/32 (93.8)	16/16 (100)	0.55
Prednisolone	31/48 (64.6)	21/32 (65.6)	10/16 (62.5)	0.83
Oxygen therapy (%)	48/48 (100)	32/32 (100)	16/16 (100)	-
Mechanical ventilation (%)	29/48 (60.4)	13/32 (40.6)	16/16 (100)	**< 0.001**
Proton pump inhibitor	44/48 (91.7)	28/32 (87.5)	16/16 (100)	0.29
Heparin	44/48 (91.7)	28/32 (87.5)	16/16 (100)	0.29

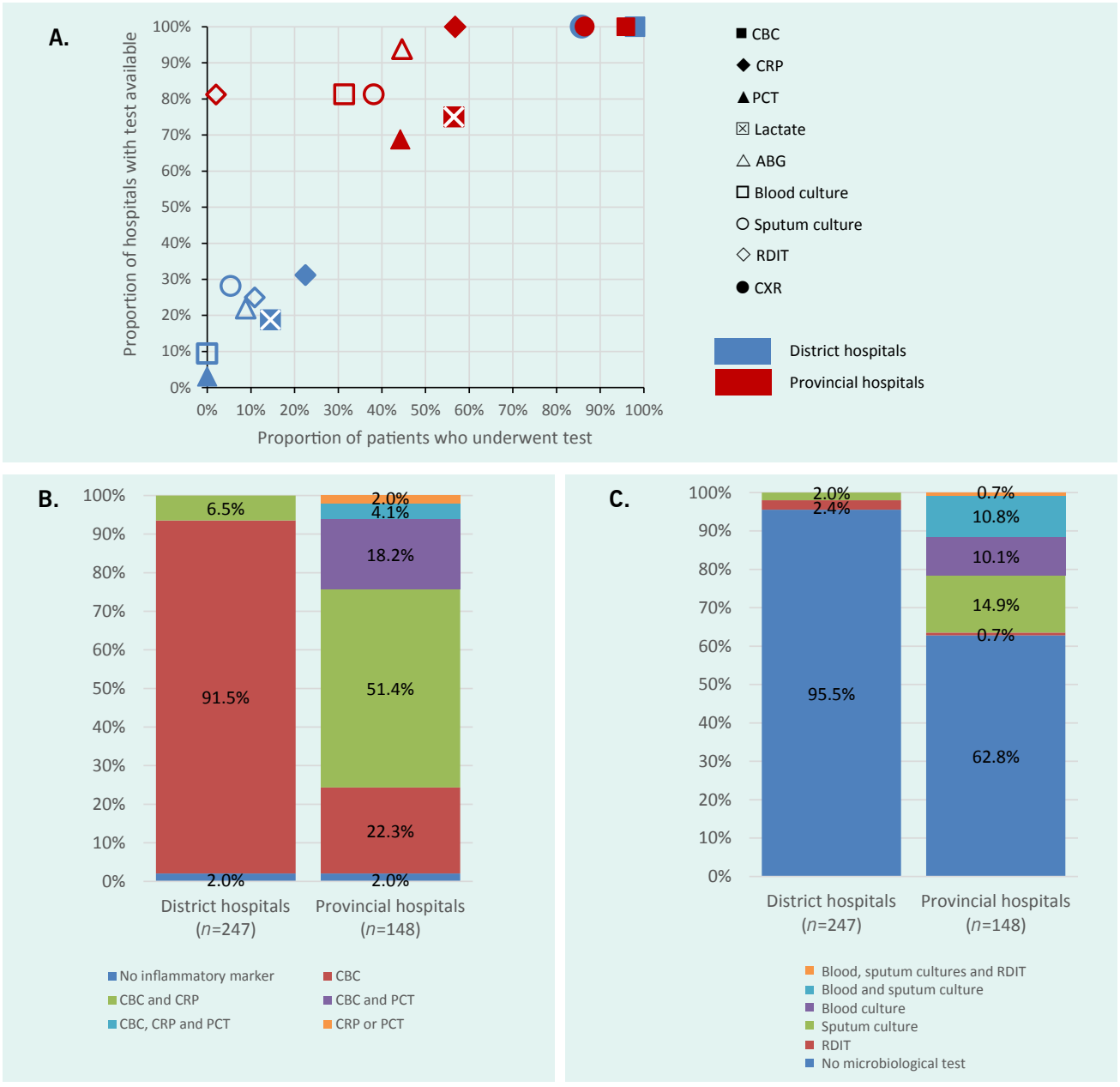
Statistically significant P values are shown in bold.

that 20.2% were positive for influenza virus and 41.8% were positive for at least one non-influenza respiratory virus (including 16.2% respiratory syncytial virus, 13.4% rhinovirus, and 9.6% adenovirus and other viruses).[15] During the study period, the participating hospitals were not actively involved in SARI sentinel surveillance, and no data were reported.

One study conducted at a provincial hospital in Viet Nam in 2009–2010 demonstrated a case mortality rate of 9.8% among hospitalized patients with community-acquired pneumonia.[17] In our study, the number of SARI cases admitted to CCUs was higher, but the mortality rate was lower at 6.6%. This may be due to the greater number of patients in district hospitals, where the clinical severity of cases tends to be milder, and to early mortality being assessed at day 7 after admission, which can lead to underestimation of the mortality rate in CCUs and hospitals.

In our study, SARI cases tended to be older and had more chronic cardiovascular and respiratory comorbidities than the general population. This is concordant with previous studies in which SARI cases tended to be associated with risk factors including older age and underlying heart and pulmonary diseases.[29,30]

Fig. 1. **Availability and use of diagnostic tests among patients admitted to CCUs in 32 district hospitals and 16 provincial hospitals in Viet Nam, March–July 2019. A) Association between test availability and SARI patients who received each test in CCUs in district and provincial hospitals. B) Frequency of biomarker indications in patients with SARI admitted to CCUs. C) Frequency of microbiological diagnostic indications in patients with SARI admitted to CCUs**



ABG: arterial blood gas; CBC: complete blood count; CRP: C-reactive protein; CXR: chest X-ray; PCT: procalcitonin; RIDT: rapid influenza diagnostic tests.

We found an apparent disparity in laboratory testing capacity between district and provincial hospitals in Viet Nam. Although the diagnosis of respiratory infections is more commonly based on physical examination, chest imaging and identification of pathogens are key to clinical management, especially in critically ill patients. Laboratory testing also contributes to identifying and preventing issues with antimicrobial resistance.[31,32] A SARI surveillance study in Egypt demonstrated that patients for whom pathogens were identified had a significantly lower rate of intensive care unit admission, length of hospital stay and overall mortality than those with unknown etiology.[33] Although the predominant pathogens in SARI cases are presumably viruses, especially influenza (up to 50% of tested respiratory samples from previous surveillance in Viet Nam),[15,27,34] strengthening laboratory capacity in

Table 3. **Management of patients with SARI admitted to CCUs in 32 district hospitals and 16 provincial hospitals in Viet Nam, March–July 2019**

	All patients (n = 395)	District hospitals (n = 247)	Provincial hospitals (n = 148)	*P*
Antibiotics, *n* (%)				
None	26/395 (6.6)	15/247 (6.9)	9/148 (6.1)	
Oral route	20/395 (5.1)	11/247 (4.5)	9/148 (6.1)	0.75
Intravenous route	349/395 (88.4)	219/247 (88.7)	130/148 (87.8)	
Oseltamivir, *n* (%)	2/395 (0.5)	2/247 (0.8)	0/148 (0)	0.53
Vasopressors, *n* (%)	19/395 (4.8)	2/247 (0.8)	17/148 (11.5)	**< 0.001**
Corticosteroids, *n* (%)	238/395 (60.3)	168/247 (68.0)	70/148 (47.3)	**< 0.001**
Oxygen therapy, *n* (%)	289/395 (73.2)	160/247 (64.8)	129/148 (87.2)	**< 0.001**
Mechanical ventilation, *n* (%)	29/395 (7.3)	7/247 (2.8)	22/148 (14.9)	**< 0.001**
Heparin, *n* (%)	27/395 (6.8)	7/247 (2.8)	20/148 (13.5)	**< 0.001**
Proton pump inhibitors, *n* (%)	174/395 (44.1)	92/247 (37.2)	82/148 (55.4)	**< 0.001**

Statistically significant *P* values are shown in bold.

Table 4. **Cox proportional hazards model of factors associated with 7-day mortality among SARI patients admitted to CCUs in 32 district hospitals and 16 provincial hospitals in Viet Nam, March–July 2019**

Variable	Hazard ratio (95% CI)	*P*
Age (1-year increment)	1 (0.97–1.02)	0.78
Male gender	0.59 (0.26–1.31)	0.19
Initial admission at secondary hospitals	1.59 (0.67–3.75)	0.29
Comorbidities	6.21 (0.78–49.44)	0.08
Septic shock within first 24 hours of admission	3.5 (1.23–9.96)	**0.02**
Oxygen or mechanical ventilation within first 24 hours of admission	1.17 (0.31–4.48)	0.82
qSOFA on admission ≥2	3.41 (1.25–9.34)	**0.02**
X-ray confirmed pneumonia	0.69 (0.29–1.62)	0.39

Statistically significant *P* values are shown in bold.

order to identify causal pathogens is critically important for the management of not only SARI but also of other emerging and re-emerging diseases, considering the current burden of SARI cases in CCUs in Viet Nam. In regards to laboratory testing, in addition to microbiological identification tests (blood culture, sputum culture or viral PCR for respiratory tract specimens), other investigations recommended for severity assessment, antibiotic de-escalation and mortality prediction in SARI include blood gas analysis or inflammatory and sepsis markers (C-reactive protein, procalcitonin and lactate).[35–39] The shortage and underuse of these tests in our study reinforces the need to develop a care bundle for SARI management to further improve the quality of care in LMICs.

We found that 93.4% of patients in our study were given empiric antibiotics within the first 24 hours of admission, but only a small number of patients received antiviral drugs. For patients with SARI presenting to CCUs, the use of empiric antimicrobials on admission is reasonable and recommended.[31] Corticosteroids were more commonly used in district hospitals than in provincial hospitals, although international guidelines advise against routinely using corticosteroid therapy in patients with community-acquired pneumonia.[31]

In our 2017 survey, we noted a shortage of supplies and equipment in the district hospitals compared with provincial hospitals and a lack of ventilators at both hospi-

tal levels.[18] In this study, we reaffirmed that – in addition to the availability of equipment – supply of and access to laboratory tests for critical care in district hospitals were still insufficient for SARI management. The current SARS-CoV-2 pandemic has highlighted vulnerabilities of the critical care system for SARI management caused by a shortage of supplies, especially ventilators, even in developed countries.[40] Under the current situation of COVID-19, accurate diagnosis of SARS-CoV-2 is solely based on nucleic acid amplification tests, which have major capacity constraints in almost all CCUs in district hospitals. Hence, both the limitations of laboratory and supply capacities are major obstacles for CCUs in district hospitals in Viet Nam to cope with COVID-19.

There were several limitations in our study. First, because the study hospitals were selected by convenience sampling, the findings were not representative of the capacity of the health care system nationwide, although we believe it reflected the general situation in Viet Nam. Second, for the purposes of this study, SARI was defined using clinical symptoms. Without a doctor's justification, there may have been bias in actual diagnosis and indications for investigations (i.e. the hospital doctors may have another differential diagnosis that indicated different practices for laboratory test orders).

In conclusion, our study reported a high rate of CCU admission among SARI patients in selected district and provincial hospitals in Viet Nam. With the current insufficiencies in diagnostic and treatment capacity in district hospitals and underuse in provincial hospitals, it is recommended that a standardized protocol for SARI management in resource-constrained settings be developed to improve quality of care.

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Conflicts of interest

The authors declare that they have no competing interests.

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Strengthening national, regional and global health capacity through the WHO Western Pacific Region's Field Epidemiology Fellowship Programme

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Objective: The World Health Organization's (WHO's) Field Epidemiology Fellowship Programme in the Western Pacific Region aims to strengthen countries' capacities for surveillance and risk assessment and build a workforce to tackle public health emergencies. A survey was conducted to assess the on-the-job training experience of the Regional Fellows, evaluate the strengths of the Programme and gain feedback on areas for improvement.

Methods: Between 25 September and 25 October 2018, an online survey was sent to Regional Fellows who had participated in the Programme between July 2006 and September 2018. The survey was shared with WHO country offices in the Western Pacific Region and directly with graduates of the Programme. Responses were recorded electronically and analysed.

Results: A total of 53 former Regional Fellows responded (54% response rate; 53/98). At the time of Programme participation, the Fellows' median age was 35, 62% (33/53) were female and 72% (38/53) were affiliated with a national or subnational health department. Fellows gained experience in event-based surveillance and risk assessment and worked among a diverse group of professionals in various Member States. Altogether, 77% (41/53) of respondents believed that the Programme had helped them move into a better career position with greater responsibility. Ninety-four percent (50/53) would recommend the Programme to their colleagues.

Discussion: Alumni from the Western Pacific Region's Field Epidemiology Fellowship Programme perform key health security roles, particularly within governmental systems, and directly contribute to managing health emergencies in their countries, in the Region and globally. The Programme is building a workforce with surge capacity to ensure that public health events in the Region can be addressed. Furthermore, connections developed through the Programme are helping to develop an alumni network, and enhance communications among Member States and between Member States and WHO.

Public health emergencies, such as outbreaks of emerging infectious diseases and natural disasters, pose threats to health security and economies in the World Health Organization's (WHO's) Western Pacific Region.[1,2] Although the occurrence of such events is unpredictable, preparedness, prompt detection and rapid responses can reduce their impacts. In health emergencies, field epidemiologists play vital roles in the detection, verification, risk assessment, response and communication of events at the local, national and regional levels.[3] A sufficient pool of competent field epidemiologists is necessary to respond to these events in a timely manner. Field Epidemiology Training Programmes (FETP) and modified Field Epidemiology Training (FET) are implemented by countries, depending on a Member State's situation, capacity and needs.[4]

The WHO Western Pacific Region's Field Epidemiology Fellowship Programme is an applied epidemiology training programme provided by WHO's Regional Office for the Western Pacific; for simplicity, participants are referred to throughout this paper as Regional Fellows. The objectives of this Programme are to (i) strengthen countries' capacities for surveillance and risk assessment, (ii) build a workforce to address public health

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emergencies, (iii) provide the staff needed for surge capacity responses to public health emergencies, (iv) contribute to and improve WHO's regional and global event-based surveillance and response systems, and (v) establish a regional network of Programme alumni to facilitate information sharing and collaboration to enhance health security. The Programme achieves these objectives by inviting FETP and FET trainees and graduates in the Region to work with the WHO Health Emergency Information Management and Risk Assessment team in the Health Emergencies Programme, usually for 7 to 9 weeks.

Regional Fellows undergo on-the-job training in a multicultural and diverse work environment, improving their skills by applying an all-hazards approach to event- and indicator-based surveillance; risk assessment; health emergency information management; and responses to emerging infectious diseases, disasters and other unexpected events. Upon completion of the Programme, which may include a field deployment, the Regional Fellows return to their country and are expected to use their new knowledge and skills to contribute towards strengthening national and regional epidemiological and field capacity.

Originally published in 2006, the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies (APSED III) is the third iteration of a regional framework aimed at implementing, maintaining and advancing the International Health Regulations (IHR) 2005 core capacities in the Asia Pacific. The Western Pacific Region's Fellowship Programme was established in 2006 to strengthen the capacities of Member States and WHO to rapidly detect and respond to emerging infectious diseases and other acute public health events in the region. This is consistent with developing core capacities under IHR (2005).[5]

From 2006 to 2018, more than 130 public health officials, interns and volunteers from 13 Member States participated in the Region's Fellowship Programme. In 2011, the Programme changed from an individual, mentorship-based experience to a more structured format where Regional Fellows joined a public health intelligence team focused on event-based surveillance, signal verification, risk assessment and response.

Until now, the experiences of the Regional Fellows and their feedback on the Programme had not been systematically evaluated. The objectives of this survey were to capture the on-the-job training experience of the Fellows, evaluate the usefulness and strengths of the Programme as an opportunity for Fellows to develop competencies in surveillance and responding to health emergencies, and gain feedback on areas in which the Programme could be strengthened.

METHODS

Definitions

For the purposes of this paper, "FET/P" is defined as FET, FETP or equivalent programmes that are implemented in individual countries. FETP is a two-year "learning by doing" training programme for field epidemiology. A modified version of the FETP is the FET, which is usually shorter and adapted to the country's situation and needs while maintaining on-the-job mentorship and training. We differentiate these FET/Ps from those of the Regional Fellows participating in the WHO Western Pacific Region's Field Epidemiology Fellowship Programme.

Survey development and platform

The survey was developed with the online platform KoBoToolbox, a tool developed by the Harvard Humanitarian Initiative.[6] KoBoToolbox was selected because it was the most accessible platform for all countries in the Western Pacific Region. The survey consisted of 34 questions, with 5 question types: binary choice, multiple choice, Likert scale, ranking and free text. One question at the beginning of the survey was optional (name).

Eligibility and survey dissemination

The Western Pacific Region's database of Regional Fellows was used to select those who had participated in the Programme between July 2006 and September 2018. The URL for the survey was shared via email with WHO country offices in Brunei Darussalam, Cambodia, China, the Lao People's Democratic Republic, Malaysia, Mongolia, the Philippines, Singapore and Viet Nam. Focal points for the WHO Health Emergencies Programme in these countries disseminated the survey to graduates of the Programme in their countries. Alumni from Australia, Japan and the Republic of Korea were contacted directly by the survey team. These two methods were used because not all countries in the Region have a

WHO country office. Eligible alumni who did not respond were sent up to two reminder emails by the team. The survey link was open for 1 month, from 25 September to 25 October 2018.

A total of 144 fellows were initially identified in the database. Not all participants in the Region's Fellowship Programme were in FET/Ps at the time of the survey or had previously participated in FET/Ps. Interns and volunteers were not eligible to participate in the survey because their learning needs and career trajectories may differ from those of alumni who were affiliated with Member States' governmental or other institutions. After removing duplicates, interns, volunteers and Regional Fellows whose active email addresses could not be determined, 98 former Fellows were asked to participate in the survey.

Analysis

Survey responses were collected via the online platform. After the survey deadline passed, responses were analysed using Microsoft Excel and R statistical software, version 3.1.3. For binary, multiple choice and Likert scale questions, the frequency and percentage of responses were calculated. For ranking questions, responses were calculated using standard methods for weighted averages – that is, weighted average = (W1X1 + W2X2 + …)/(total number of responses), where W is the weight according to rank (with the highest rank given the highest weight, the lowest rank given the lowest weight) and X is the number of responses. Weighted averages are relative values that are used to compare responses. Open-ended questions were analysed thematically and classified by theme.

RESULTS

A total of 135 Regional Fellows from 12 Member States participated in the Western Pacific Region's Field Epidemiology Fellowship Programme, of whom 20% (27/135) participated during 2006–2010, 37% (50/135) during 2011–2014 and 42% (57/135) during 2015–2018; for <1% (1/135) the year of participation was unknown. Of these 135 Regional Fellows, 98 were contacted and 53 responded (54% response rate) from 11 countries in the Region (**Fig. 1** and **2**). Responses were received from former Regional Fellows who participated in the Programme between 2007 and 2018. A majority of respondents were female (62%; 33/53), affiliated with a national or subnational ministry or department of health (72%; 38/53), an FET/P graduate at the time of the attachment (53%; 28/53) and attached to the Regional Office for the Western Pacific for between 7 and 9 weeks (57%; 30/53); 77% (41/53) of respondents self-identified as having a background in epidemiology and public health (**Table 1**).

The majority of Fellows (66%; 35/53) indicated they thought the duration of the Programme was of an appropriate length: of these, 21 participated for 7–9 weeks, 4 participated for 4–6 weeks, 8 participated for 10–12 weeks, 1 participated for >12 weeks and 1 participant did not provide a response for this question. Among the 23% (12/53) of participants who indicated that the duration was too short, 6 participated for 8 weeks, 4 participated for 4 weeks, 1 participated for 6 weeks and 1 participated for 10 weeks. Three Fellows (6%; 3/53) indicated that the Programme was too long, all of whom participated for 8 weeks. Three Fellows (6%, 3/53) did not provide a response for this question.

Assessment of the Western Pacific Region's Field Epidemiology Fellowship Programme

The skills gained during the Programme that helped Regional Fellows most in their current position were, in order of importance, (i) event-based surveillance (signal detection and screening); (ii) risk assessment; (iii) IHR (2005)-related communications and other communications, including signal verification; (iv) ability to work with a diverse group of professionals and with professionals from different countries; (v) knowledge of WHO's role and function in health emergencies; and (vi) oral presentation skills in English.

A majority of respondents agreed (53%; 28/53) or somewhat agreed (32%; 17/53) that they were given clear guidance and supervision during the Programme. By year of participation, 67% (6/9) of those who participated in the individual mentorship-based Programme between 2007 and 2010 and 94% (33/35) of those who participated in the structured Programme between 2011 and 2018 agreed or somewhat agreed that they were given clear guidance and supervision during the Programme. Regional Fellows expected to gain experience and knowledge in the areas of (i) risk assessment (25%; 13/53), (ii) event-based surveillance (21%;

Fig. 1. **Indentification of eligible respondents for the 2018 survey of former Fellows in WHO's Western Pacific Region Field Epidemiology Fellowship Programme**

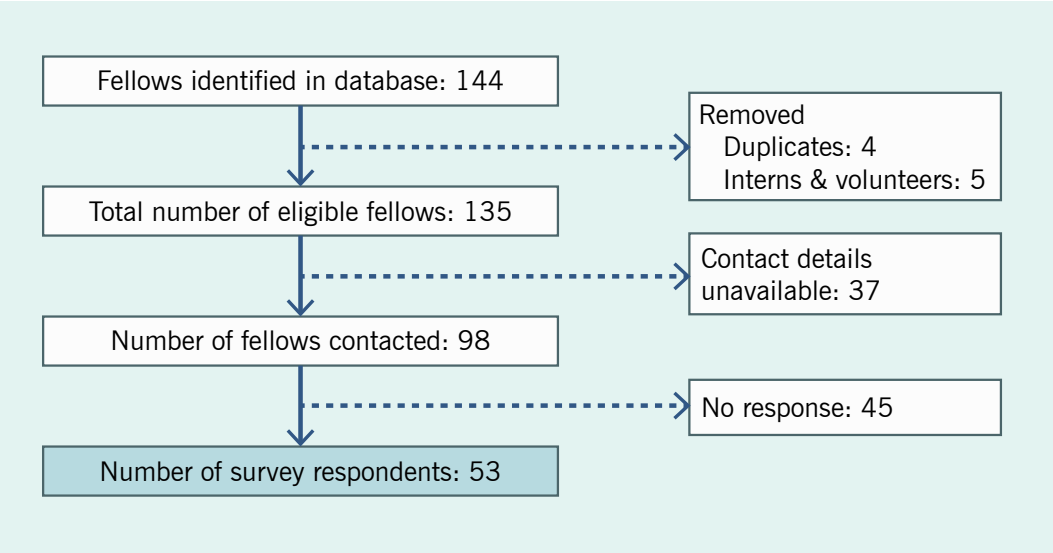
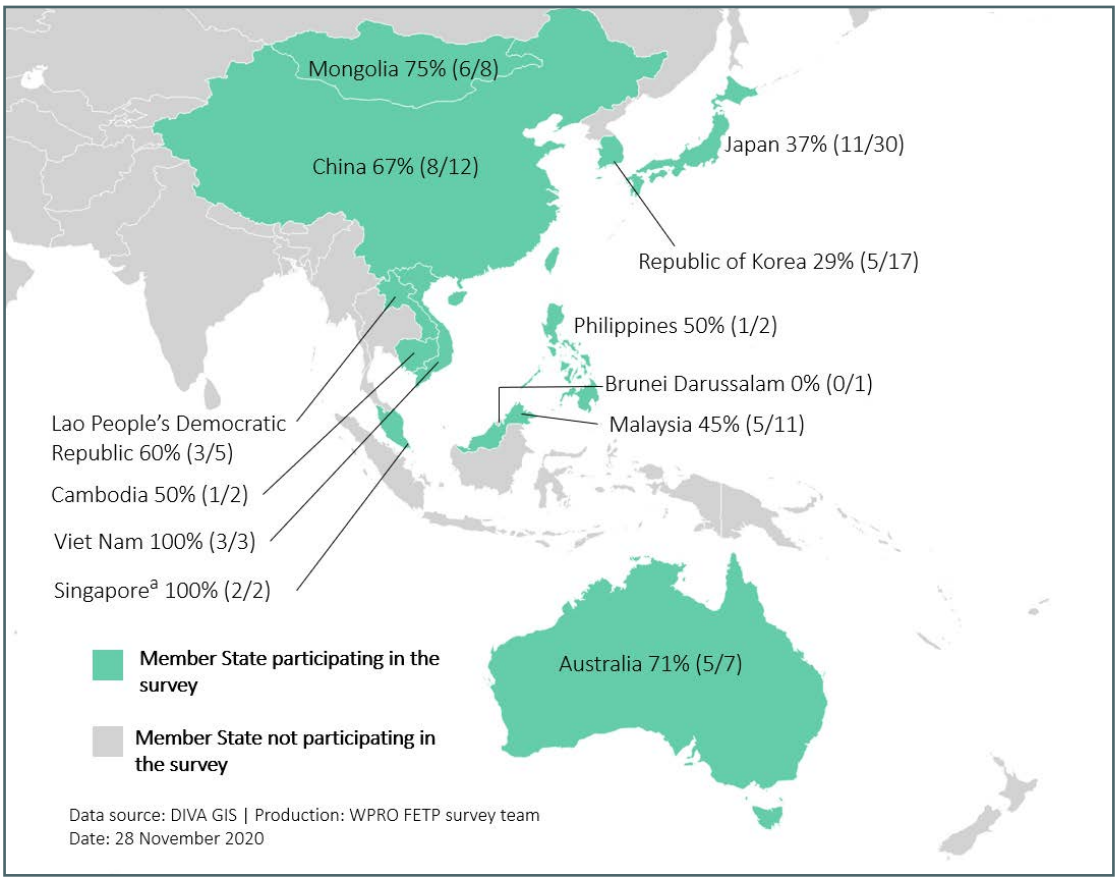


Fig. 2. **Response rate to the 2018 survey of Fellows from WHO's Western Pacific Region Field Epidemiology Fellowship Programme, by Member State. The numerators are the number of respondents from each country; the denominators are the total number of participants in the Programme from each country during July 2006 to September 2018. (The number of respondents does not sum to 53 because three respondents did not provide information for this specific question.)**



[a] For Singapore, one alumnus was identified in the database, but two alumni responded.

Table 1. **Demographic information about respondents to the 2018 survey of Fellows from WHO's Western Pacific Region Field Epidemiology Fellowship Programme**

Characteristic	Number	%
Respondents	**53**	**100**
Female	33	62
Median age (range)	35 (26 to 48)	
Affiliation at time of attachment		
National ministry or department of health	29	55
Subnational health department office	9	17
University or research institute	7	13
Health care facility (clinical practice)	3	6
Other government sector, including agriculture, veterinary, environment, security	2	4
No institutional affiliation or no response	3	6
Affiliation with FET/P[a] at the time of attachment (multiple selections possible)		
FET/P graduate	28	53
FET/P fellow	18	34
FET/P supervisor or mentor	6	11
FET/P programme coordinator	2	4
Other[b] or no response	6	11
Duration of attachment		
4–6 weeks	10	19
7–9 weeks	30	57
10–12 weeks	9	17
>12 weeks	1	2
No response	3	6
Self-identified professional background (multiple selections possible)		
Epidemiology and public health	41	77
Medicine	13	25
International development	3	6
Nursing	2	4
Veterinary medicine	2	4
Laboratory science	2	4
Pharmacology	1	2

[a] FET/P is defined as FET, FETP or equivalent programmes that are implemented in individual countries.

[b] "Other" included one international FET/P candidate in Thailand who was also a graduate of FET/P China, one staff at Chinese Center for Disease Control and Prevention working closely with FET/P China, and one respondent who indicated no institutional affiliation.

11/53), (iii) the structure and function of WHO in health emergencies (19%; 10/53), and (iv) outbreak and emergency responses (15%; 8/53). A majority of former Fellows agreed (55%; 29/53) or somewhat agreed (32%; 17/53) that their expectations of the Programme had been met. Some reasons why expectations were not considered to have been met included a lack of field deployment, having to take on a teaching role for other Fellows which impeded their own learning, and difficulty understanding the context of the risk assessment.

Career progression and FET/P affiliation

Most former Regional Fellows were currently based in the country in which they had completed their FET/P (87%; 46/53), indicating a high retention rate in the country in which they were trained.

Their affiliations at the time of the survey in 2018 were a national ministry or department of health (55%; 29/53), subnational health department (17%; 9/53)

or a university or research institute (13%; 7/53). Two former Regional Fellows worked at WHO, one as a staff member and one through an epidemiology consulting company.

Altogether, 64% (34/53) did not change their affiliation from when they joined the Western Pacific Region's Fellowship Programme to when they participated in the survey. Among those who changed affiliations, five changed from a national or subnational health department to a university, research institute or other organization; one moved from a subnational to a national health department; one moved from a national to a subnational health department; and four moved from a university, research institute or other organization to a governmental institution.

Former Regional Fellows currently engage in surveillance and risk assessment (81%; 43/53), outbreak management (66%; 35/53), rapid response activities in their country (60%; 32/53), health emergency events (57%; 30/53) and rapid response activities outside of their country (25%; 13/53). It was reported that the Programme had helped 77% (41/53) of respondents move to a better career position with greater responsibility. Stratified by the year of participation, the Programme helped 87% (13/15) of Regional Fellows who had participated between 2007 and 2012 and 69% (20/29) of those who had participated between 2013 and 2018 in their career progression.

A majority (61%, 11/18) of those who were FET/P fellows, 64% (18/28) of those who were FET/P graduates and all (100%, 6/6) of those who were FET/P supervisors or mentors at the time they were Regional Fellows continued to be involved in FET/P programmes in various leadership roles (**Table 2**). Altogether, 3 of 11 former FET/P fellows; 5 of 18 FET/P graduates (another 5 of 18 did not indicate their years of participation); and 3 of 6 former FET/P supervisors or mentors who were affiliated with FET/Ps at the time of the survey were Regional Fellows between 2007 and 2012.

Almost all respondents were available and willing to take part in response activities to address outbreaks or public health emergencies within (98%; 52/53) or outside of (79%; 42/53) the country in which they were based. Only 40% (21/53) had engaged in such response activities outside of their country since completing the Regional Fellowship at the time of the survey. All but one alumni (98%; 52/53) indicated that they have epidemiological expertise in public health emergencies, and 53% (28/53) have expertise in infection prevention and control.

Feedback and recommendations

The top three aspects that the Regional Fellows most liked about the Programme were (i) working in a diverse team with a good professional support system; (ii) gaining insight into the WHO system and response systems in other countries; and (iii) learning about surveillance – that is, about collecting information, and verifying, analysing and managing it, and conducting risk assessments.

When Regional Fellows were asked about the shortcomings of the Programme, the top three responses were (i) the need for extended working hours at times; (ii) the need to start tasks early in the day; and (iii) challenges with the team structure and mentoring. When asked which technical aspects could be improved, the top three concerns were (i) the lack of, or limited, time allocated for field work in countries; (ii) the limited number of analytical or in-depth projects; and (iii) limited learning or discussion sessions. Respondents suggested providing more opportunities for field work or field investigation (n = 5), developing a structure to allow for continued collaboration and networking among Regional Fellows after completion of the Programme (n = 5), reducing the workload of WHO staff to ensure they have more time for mentoring (n = 3) and providing more opportunities for in-depth projects, such as analytical tasks and programme assessments (n = 3). Other suggestions included enrolling more participants from developing countries; ensuring that information about the objectives, setting and scope of the Programme are shared with potential Fellows prior to them enrolling; and providing Regional Fellows with opportunities to interact with other teams and divisions at the Regional Office for the Western Pacific.

Almost all former Regional Fellows (96%; 51/53) wished to stay in contact with the Fellowship Programme and other former Fellows. Overall, 94% (50/53) of former Fellows would either highly recommend or recommend the Programme to their colleagues.

Table 2. **Changes in the affiliations of Regional Fellows who had an association with FET/Ps from the time of participation in WHO's Western Pacific Region Field Epidemiology Fellowship Programme to the time of the survey in 2018**

Position in FET/P at the time of Regional Fellowship[a]	Affiliated with FET/P at the time of the 2018 survey[b]					
	n	In any capacity	FET/P supervisor	FET/P teacher, trainer, lecturer	FET/P programme coordinator or facilitator	Host for overseas FET/P fellows
FET/P fellow	18	11	5	5	3	N/A
FET/P graduate	28	18	11	10	2	1
FET/P supervisor or mentor	6	6	5	2	3	N/A

[a] Four respondents indicated they had more than one role at the time of their Regional Fellowship (i.e. FET/P graduate AND FET/P supervisor or mentor), and therefore are counted twice in this table.

[b] Respondents who were affiliated with FET/Ps at the time of the survey were able to select multiple roles as applicable (e.g. FET/P supervisor and FET/P teacher, trainer, lecturer).

DISCUSSION

The Western Pacific Region's Field Epidemiology Fellowship Programme is unique within WHO and is designed to build capacity for detecting and responding to emerging infectious diseases and other acute public health events in the Region, in keeping with the objectives of APSED III.[1] Our findings provide insights into the experience of the Regional Fellows who have completed the Programme. We found that these experiences were positive and that Regional Fellows felt they had gained new skills and knowledge that have enabled them to progress in their careers. Alumni of the Regional Fellowship Programme perform key health security roles, particularly within governmental systems, and directly contribute to managing health emergencies within their countries, in the Region and globally.

Individuals who participated in the Programme continue to be involved in national FET/Ps in their home countries in supervisory, coordinating or teaching roles. The guidance from alumni in leadership roles who have gained technical and interpersonal skills through the Programme plays a key role in providing good mentorship to trainees and implementing a successful FET/P.[7,8] Through mentoring, teaching, training, supervising and directly working with FET/Ps, there are opportunities for competencies gained through the Regional Fellowship to be passed down to the next generation of trainees, which could further contribute to strengthening countries' capacities to address health emergencies.

The Regional Fellowship Programme is helping to maintain connections and communication among Member States, and between Member States and WHO, because it is uniquely designed to bring together professionals from a variety of disciplines, nations and experiences. This diversity enriches the Regional Fellows' experiences through mutual learning and cross-cultural interaction, and it helps them gain competencies to respond to health emergencies in various contexts.[9] Former Fellows ranked the team's diversity as the most important characteristic of the Programme, and almost all Fellows wished to stay in contact with the Programme and other Fellows through a more structured channel, in addition to personal communications. The Regional Office for the Western Pacific responded to this feedback and brought Fellowship alumni together for the first alumni meeting in Tokyo, Japan, in November 2018 to continue fostering robust and long-term relationships among alumni in the Region.[10]

In combination with official platforms and communication channels, this alumni network could act as an incubator for catalysing new ideas and implementing innovative tools in the Region. For example, the network could play a key role in familiarizing public health officials with and supporting implementation of useful tools such as epidemic analysis for response decision-making, which aims to utilize multisource data for decision-making during an emergency response,[11] thereby facilitating timely detection and rapid responses.

The Western Pacific Region's Field Epidemiology Fellowship Programme has trained a pool of experts who can be recruited to respond to health emergencies, as evidenced by the response to the novel coronavirus disease 2019 pandemic. From January to October 2020,

seven former graduates contributed to the pandemic response as part of WHO's Incident Management Support Team at the Regional Office and at WHO headquarters, according to an internal tally; many more alumni are contributing to the response through their respective governments.[12] The Regional Fellowship is fulfilling one of its objectives by building a workforce to provide surge capacity for public health emergencies in the Region.

Alumni highlighted a desire to gain field experience and the need for opportunities for more in-depth analytical and project-based work. In this regard, the Regional Fellows' training experiences could be augmented by work with national FET/Ps, such as through field investigations and epidemiological analyses. Additionally, in response to suggestions from this survey, the Regional Office has modified the daily team schedule to allow Regional Fellows to complete tasks without working extended hours. Sharing information about the objectives, setting and scope of the Programme before participants apply to and participate in it is key to setting expectations for incoming Fellows.

There are limitations to this survey, such as the relatively low response rate and small sample size. Nevertheless, it is the first study to comprehensively summarize the outcomes of the Regional Fellowship Programme. The findings of this survey have been and will be used to continually improve the Programme.

Within the APSED III framework, the Regional Fellowship Programme is effective for training future leaders in field epidemiology to respond to health emergencies, developing professional relationships among Member States in the Region, and strengthening national and regional capacities. The Regional Fellowship model may be applicable to similar settings.

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Conflicts of interest

None

Ethics statement

This work was considered a routine continuous quality improvement activity of the WHO Regional Office for the Western Pacific. As such, ethical clearance from a health research ethical review committee was not obtained. All collected data were de-identified prior to analysis, and only aggregated results have been shared to protect the confidentiality of survey participants.

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None

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Genomic surveillance of *Acinetobacter baumannii* in the Philippines, 2013–2014

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Objective: *Acinetobacter baumannii* is an opportunistic nosocomial pathogen that has increasingly become resistant to carbapenems worldwide. In the Philippines, rates of carbapenem resistance and multidrug resistance are above 50%. We undertook a genomic study of carbapenem-resistant *A. baumannii* in the Philippines to characterize the population diversity and antimicrobial resistance mechanisms.

Methods: We sequenced the whole genomes of 117 *A. baumannii* isolates recovered by 16 hospitals in the Philippines between 2013 and 2014. From the genome sequences, we determined the multilocus sequence type, presence of acquired determinants of antimicrobial resistance and relatedness between isolates. We also compared the phenotypic and genotypic resistance results.

Results: Carbapenem resistance was mainly explained by acquisition of the class-D β-lactamase gene bla_{OXA-23}. The concordance between phenotypic and genotypic resistance to imipenem was 98.15%, and it was 94.97% overall for the seven antibiotics analysed. Twenty-two different sequence types were identified, including 7 novel types. The population was dominated by the high-risk international clone 2 (i.e. clonal complex 92), in particular by ST195 and ST208 and their single locus variants. Using whole-genome sequencing, we identified local clusters representing potentially undetected nosocomial outbreaks, as well as multi-hospital clusters that indicated interhospital dissemination. Comparison with global genomes suggested that the establishment of carbapenem-resistant international clone 2 in the Philippines is likely the result of clonal expansion and geographical dissemination, and at least partly explained by inadequate hospital infection control and prevention.

Discussion: This is the first extensive genomic study of carbapenem-resistant *A. baumannii* in the Philippines, and it underscores the importance of hospital infection control and prevention measures to contain high-risk clones.

Hospital-acquired *Acinetobacter baumannii* infections are some of the most challenging to treat due to the bacterium's ability to acquire resistance to different groups of antimicrobials and to survive for long periods on dry surfaces, making eradication in health care facilities difficult once it has become endemic.[1] A previous surveillance study in the Asia–Pacific area showed that Acinetobacter spp. was the organism most frequently isolated in ventilator-associated pneumonia,[2] while in recent years the Philippines Antimicrobial Resistance Surveillance Program (ARSP) has consistently reported *A. baumannii* as the second and third most commonly isolated organism from, respectively, cerebrospinal fluid and respiratory specimens.[3]

During the past two decades, *A. baumannii* has become increasingly resistant to carbapenems worldwide, with resistance rates of >40% reported across several countries in the Asia–Pacific area, which is the highest prevalence of carbapenem resistance among important nosocomial Gram-negative pathogens.[4,5] This pattern is also observed in the Philippines, where the annual resistance rates for several antibiotics, including carbapenems,

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have been increasing, in 2017 reaching 56% for meropenem and 57% for imipenem (**Fig. 1A–C**). In addition, the ARSP has reported rates of multidrug resistance of 63% for all isolates and 47% for blood isolates, with combined resistance to aminoglycosides, fluoroquinolones, carbapenems and ampicillin-sulbactam.[3] Importantly, bacteraemia due to multidrug-resistant (MDR) *A. baumannii* has been shown to result in additional hospitalization and costs compared with bacteraemia due to non-MDR *A. baumannii*.[6]

Molecular typing methods have shown that clinical isolates of *A. baumannii* with an MDR phenotype belong mostly to two globally disseminated lineages: global clone (GC) 1 and GC2, also known as international clones (ICs) 1 and 2. Clonal complex 92 (CC92), corresponding to GC2, was the most prevalent in a previous study in nine Asian countries that included two isolates from the Philippines.[7]

The ARSP has been conducting surveillance of drug-resistant *A. baumannii* using phenotypic detection methods for bacterial identification and antimicrobial susceptibility testing. Whole-genome sequencing (WGS) can provide information on antimicrobial resistance (AMR) and genotyping with a single assay and with additional resolution to aid outbreak investigations.[8] Understanding the molecular epidemiology and AMR mechanisms of *A. baumannii* by monitoring the presence of international clones and the emergence of novel lineages in the Philippines can aid in the control of AMR. This report provides baseline data on the molecular epidemiology of *A. baumannii* in the Philippines, with a focus on the predominant circulating lineages and AMR mechanisms.

METHODS

Bacterial isolates

A total of 5254 *A. baumannii* isolates were collected and tested for antimicrobial susceptibility by the ARSP's sentinel sites from January 2013 to December 2014. Isolates resistant to carbapenems were subsequently referred to the Antimicrobial Resistance Surveillance Reference Laboratory for confirmation. Out of the 445 carbapenem-resistant *A. baumannii* isolates referred (155 in 2013 and 290 in 2014), 117 from 16 sentinel sites were selected for WGS according to the following criteria (previously described in detail):[9] (i) isolate was referred to the Reference Laboratory during 2013–2014; (ii) complete antimicrobial susceptibility data were available (i.e. a resistance profile); (iii) the overall prevalence of the resistance profile was in the ARSP database (including both referred and non-referred isolates); (iv) geographical representation of the different sentinel sites was present; (v) invasive isolates (i.e. from blood or cerebrospinal, joint, pleural or pericardial fluids) were selected when both invasive and non-invasive isolates were available for a combination of resistance profile, sentinel site and year of collection (**Table 1**). We utilized a proxy definition for "infection origin" whereby patients' isolates collected on either of the first 2 days of hospitalization were categorized as from community-acquired infections, while isolates collected on hospital day 3 or later were categorized as from hospital-acquired infections.

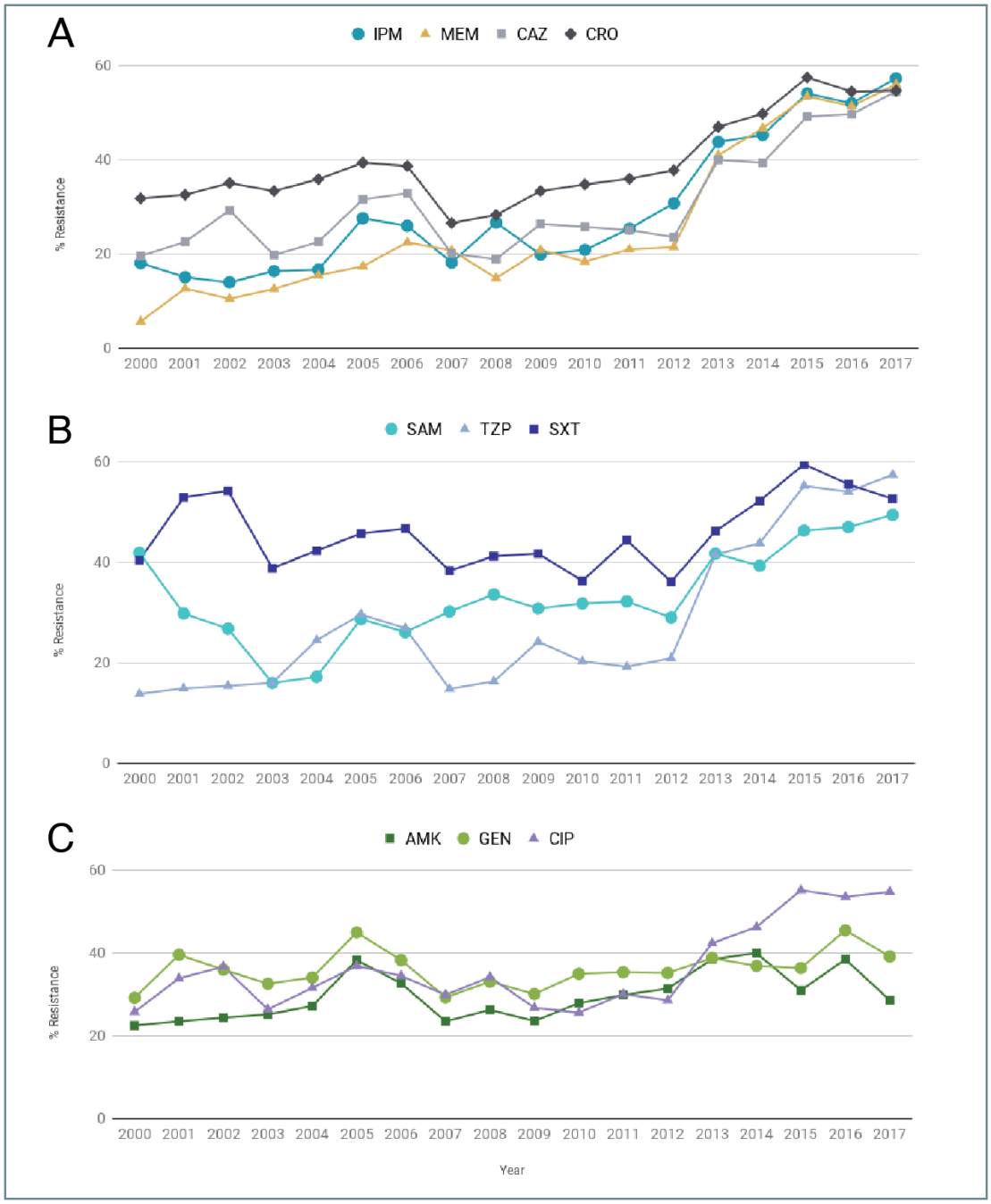
Antimicrobial susceptibility testing

All *A. baumannii* isolates included in this study were tested for antimicrobial susceptibility to nine antibiotics representing six different classes: ceftazidime (CAZ), ceftriaxone (CRO), imipenem (IPM), ampicillin-sulbactam (SAM), piperacillin-tazobactam (TZP), gentamicin (GEN), amikacin (AMK), ciprofloxacin (CIP) and sulfamethoxazole-trimethoprim (SXT) (**Table 1**). Antimicrobial susceptibility was determined at the Reference Laboratory using one or a combination of the following methods: Kirby–Bauer disk diffusion; a gradient method, such as the E-Test (bioMérieux; Marcy-l'Étoile, France); or the Vitek 2 Compact automated system (bioMérieux; Marcy-l'Étoile, France). The zone of inhibition and minimum inhibitory concentration obtained were interpreted according to the twenty-sixth edition of the Clinical and Laboratory Standards Institute guidelines[10] to determine the resistance profile of the isolates as a list of antimicrobials to which the organism was not susceptible. MDR phenotypes were defined as nonsusceptibility to ≥1 agent in ≥3 antimicrobial categories, and extensively drug-resistant (XDR) phenotypes were defined as nonsusceptibility to ≥1 agent in all but ≥2 classes.

DNA extraction and whole-genome sequencing

DNA was extracted from a single colony of each of the 117 *A. baumannii* isolates using the QIAamp 96 DNA QIAcube HT Kit and the QIAcube HT system (Qiagen; Hilden, Germany). DNA extracts were multiplexed and sequenced on the Illumina HiSeq platform (Illumina;

Fig. 1. **Annual resistance rates of *Acinetobacter baumannii* to different antibiotics, 2000–2017**



A. IPM: imipenem; MEM: meropenem; CAZ: ceftazidime; CRO: ceftriaxone. **B**. SAM: ampicillin-sulbactam; TZP: piperacillin-tazobactam; SXT: sulfamethoxazole-trimethoprim. **C**. AMK: amikacin; GEN: gentamicin; CIP: ciprofloxacin.

San Diego, CA, USA) with 100–base pair paired-end reads. Raw sequence data were deposited in the European Nucleotide Archive under the study accession PRJEB17615. Run accessions are provided through the links to Microreact projects in the figure legends.

Bioinformatics analysis

Genome quality was assessed based on metrics produced for assemblies, annotation files and the alignment of the reads to the reference genome *A. baumannii* strain ATCC 17978 (GenBank accession CP000521), as previously described.[9] Annotated assemblies were produced from short-read Illumina data as previously described.[11]

We derived in silico the multilocus sequence type of the isolates from WGS. The sequence types were determined from assemblies using Pathogenwatch (https://pathogen.watch/) or from sequence reads using ARIBA[12] and the *A. baumannii* database hosted

Table 1. **Total number of *A. baumannii* isolates analysed by the Antimicrobial Resistance Surveillance Program (ARSP) and referred to the Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL) during 2013 and 2014, isolates submitted for whole-genome sequencing, and high-quality *A. baumannii* genomes obtained, discriminated by sentinel site and AMR profile.**

	Number of isolates		
	2013	**2014**	**Total**
***A. baumannii* total ARSP**	2327	2927	5254
***A. baumannii* referred to ARSRL**	155	290	445
***A. baumannii* submitted for WGS**	59	58	117
***A. baumannii* high-quality genomes**	58	50	108
By sentinel site[a]			
BGH	4	6	10
CMC	0	1	1
CVM	1	0	1
DMC	6	2	8
FEU	0	1	1
GMH	5	1	6
JLM	0	2	2
MAR	11	3	14
MMH	2	4	6
NKI	1	1	2
NMC	1	1	2
RMC	1	0	1
SLH	0	2	2
STU	3	3	6
VSM	13	19	32
ZMC	10	4	14
By AMR profile[b]			
CAZ CRO IPM SAM TZP GEN AMK CIP SXT	48	36	84
CAZ CRO IPM SAM TZP GEN AMK CIP	0	6	6
CRO IPM SAM TZP AMK	3	1	4
CAZ CRO IPM SAM TZP GEN CIP	0	3	3
Susceptible	1	1	2
CAZ CRO SAM TZP GEN CIP SXT	1	0	1
IPM	0	1	1
CAZ CRO IPM SAM TZP AMK CIP SXT	1	0	1
CRO IPM TZP AMK	1	0	1
CAZ CRO SAM TZP GEN AMK	1	0	1
IPM TZP	0	1	1
CAZ CRO IPM SAM TZP GEN CIP SXT	1	0	1
CAZ CRO IPM SAM TZP	1	0	1
CAZ CRO IPM TZP	0	1	1

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

[b] AMK: amikacin; CAZ: ceftazidime; CIP: ciprofloxacin; CRO: ceftriaxone; GEN: gentamicin; IPM: imipenem; SAM: ampicillin-sulbactam; SXT: trimethoprim-sulfamethoxazole; TZP: piperacillin-tazobactam.

at PubMLST.org.[13] The isolates were assigned to international clones based on their sequence types, as previously described.[14–17]

Evolutionary relationships between isolates were inferred from single-nucleotide polymorphisms (SNPs) by mapping the paired-end reads to the reference genomes of *A. baumannii* strain A1 (accession CP010781) or AC29 (ST195, CC92, accession CP007535), as described in detail previously.[9] Mobile genetic elements were masked in the alignment of pseudogenomes with a script available at https://github.com/sanger-pathogens/remove_blocks_from_aln. Alignments of SNP positions were inferred with SNP-sites v. 2.4.1 (https://github.com/sanger-pathogens/snp-sites).[18] For the phylogenies of CC92 genomes, recombination regions detected with Gubbins[19] in the alignment of pseudogenomes were also removed. Maximum likelihood phylogenetic trees were generated with RAxML v. 8.28,[20] based on the generalised time reversible model with the GAMMA method of correction for among-site rate variation and 100 bootstrap replications. Pairwise SNP differences between primary isolates belonging to the same or different hospitals were calculated from alignments of SNP positions with a script available at https://github.com/simonrharris/pairwise_difference_count.

To contextualize the Philippine genomes, global *A. baumannii* genomes with geolocation data and an isolation date mainly between 2007 and 2017, for which raw Illumina paired-end sequence data were available at the European Nucleotide Archive, were downloaded, assembled and underwent quality control as described above. Evolutionary relationships between global genomes and those from this study were inferred from an alignment of SNP positions obtained after mapping the reads to the complete genome of strain A1 and masking regions with mobile genetic elements, as described above. The tree of 977 genomes was obtained using an approximately maximum–likelihood phylogenetic method with FastTree.[21] The tree of 573 global CC92 genomes was inferred with RAxML from an alignment of SNP sites obtained after mapping the genomes to the complete genome of strain AC29 and removing mobile genetic elements and recombination regions, as described above.

Known AMR determinants were identified from raw sequence reads using ARIBA[12] and two different AMR databases, a curated database of acquired resistance genes[22] and the Comprehensive Antibiotic Resistance Database (CARD).[23] Point mutations were identified on gyrase and topoisomerase genes with CARD and ARIBA, and corroborated with a literature search. The presence of the insertion sequences IS*Aba1* (GenBank accession AY758396) and IS*Aba125* (GenBank accession AY751533) upstream of the *ampC* gene was examined with ISMapper v. 2.0.1 (24) using the reference genome of *A. baumannii* A1 (GenBank accession CP010781) and default parameters. Genomic predictions of resistance were derived from the presence of known AMR genes and mutations identified in the genome sequences. The genomic predictions of AMR (the test) were compared with the phenotypic results (the reference), and the concordance between the two methods was computed for each of 7 antibiotics (756 total comparisons). For comparison purposes, isolates with either a resistant or an intermediate phenotype were considered nonsusceptible. An isolate with the same outcome for both the test and the reference (i.e. both susceptible or both nonsusceptible) was counted as a concordant isolate. The concordance was the number of concordant isolates over the total number of isolates assessed (expressed as a percentage).

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

RESULTS

Demographic and clinical characteristics of the isolates

Out of the 117 *A. baumannii* genomes sequenced, 7 were excluded based on their quality, and 2 were identified in silico as *Acinetobacter pittii* (**Table 1**). The demographic and clinical characteristics of the remaining 108 *A. baumannii* isolates are summarized in **Table 2**. The age of the patients ranged from <1 year to 92 years old, with 31.48% of the isolates (n = 34) from patients aged ≥65 years. Altogether 62.03% of the isolates (n = 67) were from males. The majority of the isolates were from inpatients (99.07%; n = 107) and were classified as being from a hospital-acquired infection (76.85%; n = 83). Respiratory samples (tracheal aspirates and sputum) accounted for 55.56% of the specimens (n = 60).

Concordance between phenotypic and genotypic antimicrobial resistance

The genotypic predictions of AMR were highly concordant with the phenotypic results (overall concordance, 94.97%; **Table 3**). The concordance for imipenem was 98.15%, and of the 104 resistant isolates, 97 isolates from 14 hospitals (93.26%) carried the class D β-lactamase gene bla_{OXA-23} alone or in combination with $bla_{OXA-235}$ (n = 1). The remaining isolates carried bla_{NDM-6} (n = 3), bla_{NDM-1} (n = 2) or bla_{OXA-72} (n = 2). One isolate had no known acquired carbapenemase. Of the 104 isolates resistant to imipenem, 89 (85.58%) were classified as XDR and 13 (12.50%) as MDR; also noted were the presence of the *armA* gene encoding a 16S ribosomal RNA methyltransferase, conferring broad-spectrum resistance to aminoglycosides in 54 isolates, and the co-occurrence of mutations in *gyrA* and *parC*, conferring resistance to fluoroquinolones in 95 isolates (**Table 3**). The mobilized colistin resistance gene (*mcr*) was not detected.

The isolates that were nonsusceptible to the third-generation cephalosporins ceftazidime (n = 99) or ceftriaxone (n = 104), or both, carried either the insertion sequence IS*Aba1* upstream of the chromosomal bla_{ampC} gene (n = 67), two or three copies of the bla_{ampC} gene (n = 22), the extended-spectrum β-lactamase genes bla_{PER-1} (n = 4) and $bla_{CTX-M-15}$ (n = 1) or the carbapenemase gene bla_{NDM} (n = 5). Most of the false negative calls for ceftazidime (n = 3) and ceftriaxone (n = 8) (**Table 3**), for which no resistance mechanism was detected, coincided with intermediate susceptibility (n = 2 and n = 5, respectively).

Genotypic findings

In silico genotyping

Multilocus sequence type was predicted in silico from the WGS data of the 108 *A. baumannii* isolates. A total of 22 different sequence types were identified from this data set as per the Oxford scheme,[19] 7 of which were novel and are now identified as ST2197, 2199, 2220, 2317, 2318, 2319 and 2320. The population was dominated by CC92 (n = 61), represented mainly by ST195 (n = 29) and ST208 (n = 23). CC92 was found at 13 of the 16 sentinel sites, with ST195 and ST208 spread geographically across 8 and 7 sentinel sites, respectively. In contrast, ST369 (n = 5) was found in only one site. The *armA* gene was found only in isolates belonging to CC92 (n = 54) and from 11 hospitals. Seven of the eight hospitals represented by six or more sequenced isolates showed clonal diversity, with at least two different circulating sequence types (**Table 4**), albeit with similar or identical resistance profiles. In contrast, all isolates collected by the Baguio General Hospital and Medical Center (BGH) belonged to sequence type 208.

Population structure of A. baumannii *in the Philippines*

The phylogenetic tree of 108 *A. baumannii* genomes showed that the population was composed of well-defined clades that matched the distribution of the sequence types. The two main clonal groups were IC1 and IC2 (i.e. CC92; **Fig. 2a**), with a minor representation of IC8 and IC7. Isolates belonging to international clones were mostly XDR and are known to be responsible for disseminating AMR globally. The carbapenemase gene bla_{OXA-23} was found consistently in IC1 and IC2 genomes, and more sporadically in IC8 and nonclonal genomes. In contrast, the carbapenemase gene bla_{NDM-6} was found exclusively in three IC8 genomes from Corazon Locsin Montelibano Memorial Regional Hospital (MMH), while bla_{NDM-1} and bla_{OXA-72} were found only sporadically. Notably, isolates carrying IS*Aba1* inserted in the promoter of bla_{ampC} belonged to ST449 (IC1) or to CC92 (IC2), while isolates carrying two or three copies of the bla_{ampC} gene all belonged to a novel sequence type (now ST2199) found in the Vicente Sotto Memorial Medical Center (VSM) in the Visayas region and the Zamboanga City Medical Center in the Mindanao region (**Fig. 2a**).

The phylogenetic tree of 61 genomes from the prevalent XDR CC92 clone showed that most isolates were grouped into two clades represented by ST208 and single locus variant ST425 (bootstrap support, 96%) and by ST195 and single locus variant ST369 (bootstrap support, 100%) (**Fig. 2b**). Both ST208–ST425 and ST195–ST369 were found in hospitals from all three island groups (Luzon in the north, Visayas in the centre and Mindanao in the south), but their geographical distribution showed little overlap. The phylogeographical signal suggested there were both local outbreaks and interhospital dissemination (**Fig. 2b**). We investigated this further by counting the number of pairwise, nonrecombinant SNP differences between primary isolates from the same or different hospitals. First, we

Table 2. **Demographic and clinical characteristics of 108 sequenced and confirmed *A. baumannii* isolates collected from 16 ARSP sites**

Characteristic	No. Isolates
Sex	
Male	67
Female	41
Age (in years)	
<1	6
1–4	11
5–14	3
15–24	6
25–34	7
35–44	9
45–54	12
55–64	20
65–80	26
≥81	8
Patient Type	
In-patient	107
Out-patient	1
Specimen Origin	
Community-acquired	25
Hospital-acquired	83
Submitted As*	
Carbapenem-resistant	104
Non carbapenem-resistant	4
Specimen Type	
Aspirate	1
Blood**	21
Bone	1
Catheter	1
Catheter, central	1
Cerebrospinal fluid**	13
Sputum	10
Tracheal aspirate	50
Ulcer	1
Urine	4
Wound	5

* Specimen Origin is computed based on admission date of the patient

** Specimen types considered as Invasive isolates.

identified three intrahospital clusters (bootstrap support, 100%) of closely related isolates from BGH (ST208, 2–35 pairwise SNPs; $n = 9$), Southern Philippines Medical Center (DMC, ST208–ST425, 1–6 pairwise SNPs; $n = 8$) and Mariano Marcos Memorial Hospital and Medical Center (MAR, ST195, 0–3 pairwise SNPs; $n = 6$). The isolates within each of the three clusters carried identical or almost identical repertoires of resistance determinants, further supporting their clonal relationship. The isolation dates spanning more than 12 months suggested that these clonal lineages are possibly endemic to the hospitals, although regular introduction by colonized patients cannot be ruled out.

Next, we identified two clusters of closely related isolates from two or more hospitals. One cluster contained nine ST195 genomes from two hospitals in the Visayas region (MMH and VSM), with a median of only 5 pairwise SNP differences (range, 1–17) between isolates from different hospitals. The second one contained 18 ST195–ST369 genomes from six hospitals across three different regions, with a median of 25 pairwise SNP differences (range, 1–53). The clonal relationship between isolates from different hospitals within these two clusters is also supported by a similar complement of resistance determinants.

A. baumannii *from the Philippines in the global context*

To place the retrospective collection of *A. baumannii* isolates from the Philippines in the context of the global population of this pathogen, we compared our genomes to 931 genomes publicly available from sequence data archives that have linked geographical and temporal information. The isolates were collected between 1982 and 2016, with 94.7% of the isolates collected from 2007 onwards. The public genomes belonged to 16 countries and were assigned to 154 sequence types. The population represented by the global genomes was substantially skewed towards genomes from the United States (40.5%) and belonging to CC92 (58.6%). The Philippine genomes were found in multiple branches of the tree, as expected by the diversity of sequence types, but

Table 3. **Comparison between antimicrobial susceptibility testing results and genotypic resistance for 108 *A. baumannii* isolates.**

Antibiotic class	Antibiotic	Isolates tested	Resistant isolates	False positive	False negative	% Concordance	Resistance genes/SNPs
3rd gen cephalosporin	Ceftazidime	108	99	0	3	97.22	IS*Aba1*-bla_{ampC}, 2+ copies of bla_{ampC}, $bla_{CTX\text{-}M\text{-}15}$, $bla_{PER\text{-}1}$, $bla_{NDM\text{-}1/6}$
3rd gen cephalosporin	Ceftriaxone	108	104	0	8	92.59	
Carbapenem	Imipenem	108	104	1	1	98.15	$bla_{OXA\text{-}23}$, $bla_{NDM\text{-}1/6}$, $bla_{OXA\text{-}235}$, $bla_{OXA\text{-}72}$
Aminoglycoside	Gentamicin	108	96	0	10	90.74	*aac(3')-Ia, aac(3')-II, ant(2'')-Ia, armA*
Aminoglycoside	Amikacin	108	97	6	0	94.44	*aac(6')-Ib, aph(3)-VI, armA*
Fluoroquinolone	Ciprofloxacin	108	96	0	1	99.07	*gyrA*_S81L, *parC*_S84L, *qnrA1*
Folate pathway antagonist	Trimethoprim-sulfamethoxazole	108	87	1	7	92.59	*sul1, sul2, dfrA14, dfrA18*

they mostly formed discreet clusters within each branch without genomes from other countries interspersed (**Fig. 3a**). This suggests that the establishment of each clone in the Philippines is the result of one or only a few founding events.

To investigate in more detail the relationship to global genomes within CC92, a tree of 573 genomes was inferred from the alignment of nonrecombinant SNPs (**Fig. 3b**). The ST195–ST369 genomes from the Philippines clustered with genomes from China, Malaysia, Singapore, the United States and Viet Nam, while the ST208–ST425 genomes were related to genomes from China, Puerto Rico and the United States. However, the strong phylogeographical signal displayed by both the ST195–ST369 and the ST208–ST425 subtrees suggested a single founder event in the Philippines for each clone, followed by their expansion.

DISCUSSION

This study reports on the combined genomic and laboratory-based surveillance of *A. baumannii* in the Philippines during 2013–2014. The prevalence of carbapenem-resistant *A. baumannii* during this period was above 40%, and we therefore focused on characterizing these organisms. In *A. baumannii*, only low-level carbapenem resistance is mediated by the chromosomal OXA-51-like carbapenemase. The class D OXA-23 carbapenemase was the most prevalent acquired carbapenem resistance mechanism identified in this study, in line with global trends.[25] We also detected representatives from the OXA-235-like ($bla_{OXA\text{-}235}$) and the OXA-40-like ($bla_{OXA\text{-}72}$) groups, albeit in low frequency. No OXA-58-like carbapenemases were detected, as previously reported from other Asia–Pacific nations.[26] Importantly, we also detected the presence of the class B metallo-β-lactamases NDM-1 and NDM-6, which, unlike OXA-23, confer resistance to extended-spectrum cephalosporins as well as carbapenems. *A. baumannii* harbouring NDM-1 has been sporadically reported previously from other countries,[27–29] but NDM-6-carrying *A. baumannii* has only recently been reported from Spain.[30] Resistance to extended-spectrum cephalosporins was mainly explained by the insertion of IS*Aba1* in the promoter of the intrinsic gene bla_{ampC}, which has been shown to lead to increased expression of the encoded cephalosporinase.[31] Identification of this mechanism represents an additional in silico query of the genomes, which is burdensome in the context of a public health reference laboratory, but omitting it would lead to high major error rates for genomic predictions of resistance to extended-spectrum cephalosporins.

Both IC1 and IC2, which are responsible for the spread of MDR and XDR phenotypes worldwide,[25,32] were found in the Philippines. However, IC2 was the predominant clonal type of *A. baumannii* in our study population, with ST195 and ST208 and their respective single locus variants found throughout the country. The global phylogenetic tree showed that these two lineages diverged before their establishment in the Philippines. The genetic relatedness of isolates from different hospitals and their similar complements of resistance determinants

Table 4. **The summary of distribution, sequence types (ST), resistance profiles and antimicrobial resistance genes and mutations of the 108 isolates collected from 16 Antimicrobial Resistance Surveillance Program sentinel sites.**

Site[a]	No. of isolates	No. of STs	ST (*n*)	Resistance profiles[b] (*n*)	Acquired resistance mechanisms (*n*)
BGH	10	1	208 (10)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (9)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, aph(3')-VI, armA, gyrA*_S81L, *parC*_S84L, *sul1, sul2* (6)
					IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, aph(3')-VI, armA, gyrA*_S81L, *parC*_S84L, *sul1* (2)
					IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, armA, gyrA*_S81L, *parC*_S84L, *sul1, sul2* (1)
				CAZ CRO IPM SAM TZP AMK CIP SXT (1)	*ISAba1*-bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul2* (1)
CMC	1	1	2319 (1)	CAZ CRO IPM TZP (1)	bla_{OXA-72} (1)
CVM	1	1	957 (1)	CAZ CRO SAM TZP GEN AMK (1)	bla_{PER-1}, *aac(3)-II, aph(3')-VI, sul1* (1)
DMC	8	2	208 (7)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (7)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, armA, gyrA*_S81L, *parC*_S84L, *sul1* (7)
			425 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, armA, gyrA*_S81L, *parC*_S84L, *sul1* (1)
FEU	1	1	208	CAZ CRO IPM SAM TZP GEN CIP (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *gyrA*_S81L, *parC*_S84L (1)
GMH	6	6	2174 (1)	CRO IPM SAM TZP AMK (1)	bla_{OXA-23}, *aph(3')-VI* (1)
			2197 (1)	CRO IPM SAM TZP AMK	bla_{OXA-23}, *aph(3')-VI* (1)
			2318 (1)	CRO IPM SAM TZP AMK	bla_{OXA-23}, *aph(3')-VI* (1)
			2320 (1)	CRO IPM SAM TZP AMK	bla_{OXA-23}, *aph(3')-VI* (1)
			2317 (1)	CRO IPM TZP AMK	bla_{OXA-23}, *aph(3')-VI* (1)
			ND (1)	CAZ CRO IPM SAM TZP	bla_{NDM-1}, *aph(3')-VI* (1)
JLM	2	2	195 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (1)
			208 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(6')-Ib, armA, gyrA*_S81L, parC_S84L, sul1 (1)
MAR	14	5	195 (6)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (6)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (5)
					ISAba1-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (1)
			449 (5)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (5)	*ISAba1*-bla_{ampC}, bla_{OXA-23}, *ant(2'')-Ia, aph(3')-VI, gyrA*_S81L, *sul1* (5)
			447 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	bla_{NDM-1}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul2* (1)
			391* (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	$bla_{CTX-M-15}$, bla_{PER-1}, bla_{OXA-23}, *aac(3)-II, aac(6')-Ib, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *qnrA1, sul1, sul2, dfrA14* (1)
			2197 (1)	Susceptible	bla_{OXA-23}, *aph(3')-VI* (1)
MMH	6	2	195 (3)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (3)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (3)
			642 (3)	CAZ CRO IPM SAM TZP GEN AMK CIP (2)	bla_{NDM-6}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L (2)
				CAZ CRO IPM SAM TZP GEN CIP	bla_{NDM-6}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L
NKI	2	2	195 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (1)
			208 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, armA, gyrA*_S81L, *parC*_S84L, *sul2* (1)

Site[a]	No. of isolates	No. of STs	ST (*n*)	Resistance profiles[b] (*n*)	Acquired resistance mechanisms (*n*)
NMC	2	1	208	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul2* (1)
				CAZ CRO SAM TZP GEN CIP SXT (1)	IS*Aba1*-bla_{ampC}, *aac(3)-Ia, gyrA*_S81L, *parC*_S84L, *sul1, sul2* (1)
RMC	1	1	1128	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, armA, gyrA*_S81L, *parC*_S84L, *sul1, sul2* (1)
SLH	2	2	195 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (1)
			642 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	bla_{OXA-23}, $bla_{OXA-235}$, *aac(6')-Ib, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1, sul2, dfrA18* (1)
STU	6	3	195 (3)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (3)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (2)
					IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul1, sul2* (1)
			1289 (2)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (2)	IS*Aba1*-bla_{ampC}, bla_{PER-1}, bla_{OXA-23}, *aac(3)-Ia, aac(6')-Ib, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1, sul2, dfrA18* (1)
					IS*Aba1*-bla_{ampC}, bla_{PER-1}, bla_{OXA-23}, *aac(3)-Ia, aac(6')-Ib, gyrA*_S81L, *parC*_S84L, *sul1, sul2, dfrA18* (1)
			449 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *ant(2'')-Ia, aph(3')-VI, gyrA*_S81L, *sul1* (1)
VSM	32	6	2199 (20)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (19)	2 copies of bla_{ampC}, bla_{OXA-23}, *aac(3)-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1* (15)
					2 copies of bla_{ampC}, bla_{OXA-23}, *aac(3)-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1* (2)
					2 copies of bla_{ampC}, *aac(3)-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1* (1)
					2 copies of bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1* (1)
				CAZ CRO IPM SAM TZP GEN CIP SXT (1)	2 copies of bla_{ampC}, bla_{OXA-23}, *aac(3)-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1* (1)
			195 (7)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (4)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (2)
					IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aac(3)-Ia, armA, gyrA*_S81L, *parC*_S84L, *sul1* (1)
					IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (1)
				CAZ CRO IPM SAM TZP GEN AMK CIP (2)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (2)
				CAZ CRO IPM SAM TZP GEN CIP (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L (1)
			310 (2)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	bla_{OXA-23}, *aph(3')-VI* (1)
				IPM TZP (1)	bla_{OXA-23}, *aph(3')-VI* (1)
			208 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (1)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul2* (1)
			229 (1)	IPM (1)	bla_{OXA-72} (1)
			1418 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP (1)	2 copies of bla_{ampC}, bla_{OXA-23}, *ant(2'')-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L (1)

Site[a]	No. of isolates	No. of STs	ST (*n*)	Resistance profiles[b] (*n*)	Acquired resistance mechanisms (*n*)
ZMC	14	3	195 (7)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (7)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (7)
			369 (5)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT (5)	IS*Aba1*-bla_{ampC}, bla_{OXA-23}, *armA, gyrA*_S81L, *parC*_S84L, *sul2* (5)
			2199 (1)	CAZ CRO IPM SAM TZP GEN AMK CIP SXT	2 copies of bla_{ampC}, bla_{OXA-23}, *aac(3)-Ia, aph(3')-VI, gyrA*_S81L, *parC*_S84L, *sul1*
			2220 (1)	Susceptible	None detected

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

[b] AMK: amikacin; CAZ: ceftazidime; CIP: ciprofloxacin; CRO: ceftriaxone; GEN: gentamicin; IPM: imipenem; SAM: ampicillin-sulbactam; SXT: trimethoprim-sulfamethoxazole; TZP: piperacillin-tazobactam.

support the notion that their subsequent success was the result of clonal expansion and in-country geographical dissemination, rather than multiple introductions. This highlights the need for concerted infection prevention and control measures to contain the spread of high-risk clones. However, the limited number and disparate sampling of genomes from other countries in the region and the selective referral of carbapenem-resistant isolates to the reference laboratory by the sentinel sites limited our ability to capture the dynamics of these clones.

We also identified three ST195 and ST208 intrahospital clusters spanning more than 12 months each. Resistance to antimicrobial drugs and to desiccation contribute to the survival of *A. baumannii* in the hospital environment,[1] and cross-contamination of hospital surfaces with MDR strains has been documented, particularly in the areas surrounding colonized or infected patients.[33,34] The ARSP does not currently include environmental samples, and thus it was not possible to connect the persistence of the intrahospital clusters to environmental contamination, which is a limitation of our study. Outbreaks of *A. baumannii* with bla_{OXA-23}, including of ST195 and ST208, have been reported from several countries,[35–37] and our study identified potential hospital outbreaks retrospectively. The resolution afforded by WGS was in stark contrast to the uniform resistance profiles of the isolates in our study, thus making cluster detection based on WGS rather than resistance profiles, of particular utility for carbapenem-resistant *A. baumannii*.

The assignment of isolates to an outbreak based on their genetic distance is key for effective patient containment and infection control during an ongoing investigation. Out of the three intrahospital IC2 clusters detected, the ST208 cluster from BGH displayed more genetic diversity than the other two, based on the number of pairwise SNP differences, opening the possibility that more than one closely related strain was circulating in the hospital. However, the absence of data on patient movement precluded the epidemiological investigation that would have aided in delineating the outbreaks, another limitation of our study. In addition, while the pairwise SNP differences are similar to those reported in other studies,[36,38–40] SNP thresholds are difficult to assess by comparison due to methodological differences, such as the use of core- versus whole-genome SNPs, the choice of reference genome for reference-based mapping of short reads, and the inclusion or exclusion of SNPs associated with recombination regions.

In conclusion, our retrospective genomic epidemiology study of carbapenem-resistant *A. baumannii* in the Philippines revealed that IC2 with OXA-23 is the main source of the increasing carbapenem resistance in the Philippines and that breaches in infection control and prevention likely contributed to its dissemination. WGS proved a useful tool for improving surveillance of *A. baumannii*.

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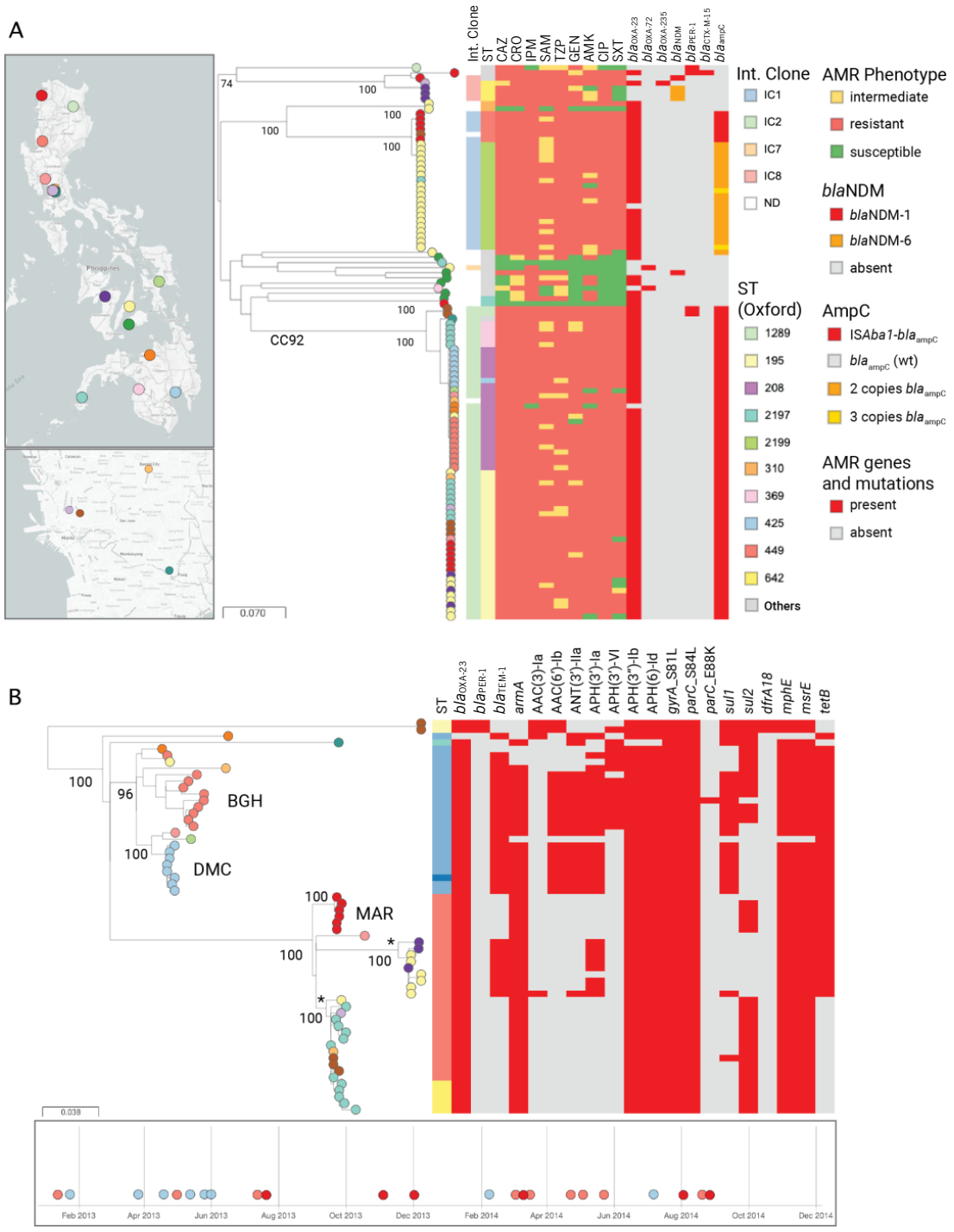
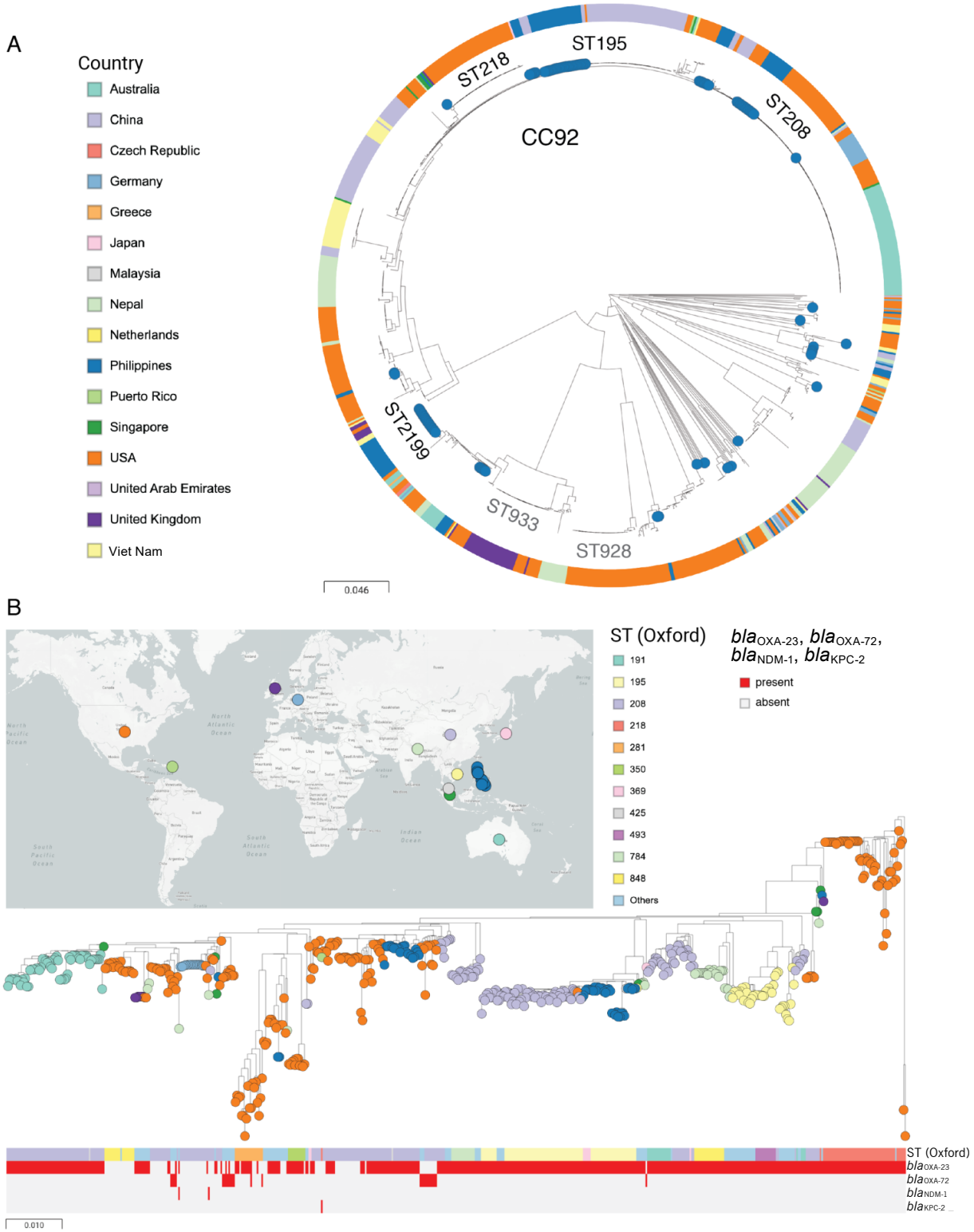
Fig. 2. **Genomic surveillance of *A. baumannii* from the Philippines, 2013–2014**



A) Phylogenetic tree of 108 isolates inferred from an alignment of 168 916 single nucleotide polymorphism (SNP) sites obtained after mapping the genomes to the complete genome of strain A1 and masking mobile genetic elements from the alignment. The tree leaves are coloured by sentinel site and indicated on the map (top: Philippines; bottom: detail of the National Capital Region). The tree is annotated with the isolates assigned to international clones and sequence types, the results of susceptibility testing and the presence of acquired carbapenemase genes. AMK: amikacin; AMR: antimicrobial resistance; CAZ: ceftazidime; CIP: ciprofloxacin; CRO: ceftriaxone; GEN: gentamicin; IC: international clone; IPM: imipenem; SAM: ampicillin-sulbactam; ST: sequence type; SXT: sulfamethoxazole-trimethoprim; TZP: piperacillin-tazobactam. The full data are available at https://microreact.org/project/ARSP_ABA_2013-2014.

B) Phylogenetic tree of 61 clonal complex 92 (CC92) genomes, inferred from an alignment of 618 SNP sites after mapping the genomes to reference AC29 and removing mobile genetic elements and recombination regions. The tree leaves are coloured by sentinel site, as indicated on the map in panel (a). The tree blocks represent the distribution of STs and of acquired resistance genes and mutations. Three hospital clusters are annotated on the tree with the hospital code (BGH: Baguio General Hospital and Medical Center; DMC: Southern Philippines Medical Center; MAR: Mariano Marcos Memorial Hospital and Medical Center), and their isolation dates are indicated on the timeline. Two multihospital clusters are annotated with an asterisk. The full data are available at https://microreact.org/project/ARSP_ABA_CC92_2013-2014. The scale bars represent the number of SNPs per variable site.

Fig. 3. ***A. baumannii* from the Philippines in global context**



A) Phylogenetic tree of 977 isolates from the Philippines (blue nodes) and from 15 other countries inferred from 305 031 SNP positions. The major STs and CCs are labelled in black if represented by genomes of this study, or in grey if they are not. The data are available at https://microreact.org/project/ARSP_ABA_Global.

B) Phylogenetic tree of 573 CC92 isolates inferred from an alignment of 5890 SNP positions. The tree leaves are coloured by country as indicated on the map. The tree is annotated with the distribution of acquired carbapenemase genes (red: present, grey: absent). The data are available at https://microreact.org/project/ARSP_CC92_Global. The scale bars represent the number of SNPs per variable site.

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Conflicts of Interest

The authors have no conflicting affiliations or financial or non-financial interests in the subject matter discussed in this manuscript.

Ethics Statement

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

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How Iwate Prefecture in Japan maintained a low COVID-19 infection rate

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The first case of coronavirus disease 2019 (COVID-19) in Japan was confirmed on 16 January 2020. The first wave of cases peaked on 10 April 2020 (n = 710) and the second on 7 August 2020 (n = 1595). Iwate Prefecture in north-eastern Japan was the last prefecture to confirm a case of COVID-19, on 29 July 2020, 110 days after all other prefectures had confirmed cases. No cases were reported during the first wave.[1] As of 21 September 2021, there had been 3469 cases (282.8/100 000 population) and 52 deaths (1.50% fatality rate) in Iwate and 1.7 million cases (1333.2/100 000 population) and 17 294 deaths (1.03% fatality rate) in Japan overall. This article discusses possible reasons for the low number of COVID-19 cases in Iwate.

Geographical characteristics and population movement

Iwate Prefecture is 500 km from Tokyo and is bordered by mountains to the west and the sea to the east. It has a low population density (83.8 persons/km^2). Population movement into and within Iwate decreased after the initial COVID-19 cases were reported in Japan. After a national state of emergency was declared on 16 April 2020, the transient population of Morioka City, the capital of Iwate, decreased by 30–60%.[2] During the national Golden Week holiday in 2020, held at the end of April, for example, travel on trains to major train stations in Iwate was 70-80% lower than in 2019.[3] A survey showed that two thirds of Iwate residents did not want contact with people from other prefectures,[4] and people from other prefectures avoided going to Iwate to avoid discrimination. Thus, geographical barriers and decreased movement into Iwate may have contributed to the low transmission.

Miyagi Prefecture neighbours Iwate to the south. Although its historical, demographic, socioeconomic and cultural characteristics are similar to those of Iwate, it had 149 notifications of COVID-19 as of 28 July 2020, while Iwate had none. Miyagi Prefecture is closer to Tokyo, at 300 km, and is also the largest prefecture in the Tohoku region in terms of population and economy. Miyagi Prefecture also had to take in COVID-19 patients who were infected on board the Diamond Princess cruise ship without adequate preparation.[5] These factors may have contributed to a higher rate of contact between people and more cases.

Lessons learnt from responding to the 2011 Great East Japan Earthquake and Tsunami

Countermeasures for infectious diseases were established in Iwate to respond to the 2011 Great East Japan Earthquake and Tsunami. These included use of infection control assistance teams for daily surveillance, training in hand hygiene and providing information on infection control.[6] The teams were used in the early response to COVID-19 in Iwate and provided advice and information to decision-makers for infection control.

Countermeasures adopted by the Iwate prefectural government

The Iwate prefectural government took appropriate local actions at each stage of the COVID-19 pandemic. It established a countermeasure headquarters headed by the governor in February 2020, with the first phase of countermeasures beginning on 23 April when a state of emergency was declared. Although there were no local cases during this phase, the strategy was to limit the risk

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of transmission by physical distancing. Businesses stayed open, but the government requested people to avoid "unnecessary and non-urgent" outings.[7] Schools were closed from 2 to 25 March and from 29 April to 6 May. Staff were recruited for disaster medical assistance teams to coordinate the work of hospitals. Testing and treatment centres and support systems, such as call centres for travellers, were quickly established.

During the second phase, from after the state of emergency in Iwate was lifted on 14 May to 7 June, the prefectural government continued to prevent transmission while maintaining the local economy. Although the national government established restrictions on large-scale events, in Iwate, which had still not reported a COVID-19 case, all schools and businesses (including bars, night clubs and restaurants) remained open, except between 29 April and 6 May, when all recreational facilities, night clubs or establishments that served food and beverages were closed. The prefectural government requested residents not to travel between prefectures, but this request was relaxed on 1 June.

The goal during the third phase was to provide information about the current situation and establish plans for when the first confirmed COVID-19 case occurred. As the period with no confirmed cases in Iwate became longer, residents feared becoming the first case. The prefectural government promised to provide sufficient contact tracing and isolation and publicly appealed that no blame be placed on cases.

Strong leadership throughout the response included clear, consistent messaging by government officials about preventive measures, such as avoiding the "three Cs" (confined spaces with poor ventilation, gathering in crowded areas and close contact with others), frequent hand-washing and physical distancing.[7]

The Iwate prefectural government also provided direct support to businesses affected by the COVID-19 restrictions.[8] After declaration of the first national state of emergency in late April 2020, many companies experienced financial difficulties; however, as of late July 2020, only two companies in Iwate had closed due to the pandemic. The unemployment rate in Iwate hardly changed (2.1% in 2019 vs 2.4% in 2020).[9]

Cultural characteristics of Iwate residents

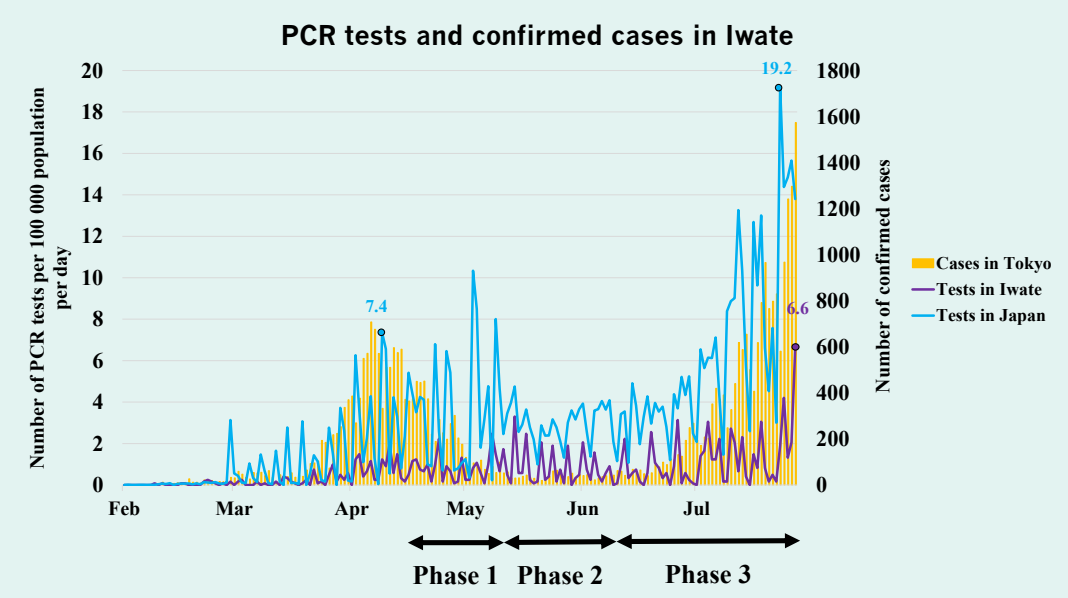
The Japanese custom of physical distancing during greetings is often cited as a factor in preventing transmission of infectious diseases.[10] Another characteristic of Iwate residents, which may also prevent transmission of respiratory infections, is that they do not raise their voices during conversation. Widespread awareness of being the last prefecture in Japan without a confirmed case of COVID-19 might also have led to further effort to avoid infection.

Limited testing early in the response

Another possible reason for the low number of COVID-19 cases in Iwate is limited testing, as polymerase chain reaction (PCR) tests were initially used only for patients with symptoms of pneumonia.[11] As of 28 July 2020, 1438 diagnostic tests had been conducted in Iwate, a rate of 118.4 per 100 000 population, as compared with 515.7 per 100 000 in Japan overall and 1297.7 per 100 000 in Tokyo (**Fig. 1**).[12–14] Therefore, asymptomatic cases of COVID-19 might have been missed, in particular among younger people.[15] As resources for testing increased in Japan, tests were conducted not only for symptomatic patients but also for asymptomatic suspected cases.[16] By July 2020, Japan had acquired sufficient testing capacity. Therefore, if cases of infection had been missed due to lack of testing or undetected asymptomatic cases, there should have been a large increase in the number of cases of COVID-19 once testing was increased.[17] This was not the case.

This article summarizes the characteristics of Iwate Prefecture, its population and local government actions that may have contributed to the delay in cases of COVID-19 infection. The extra time allowed the local government to strengthen health-care capabilities and raise residents' level of awareness. These countermeasures might have contributed to the smaller number of reported COVID-19 cases in Iwate, which has continued into the second year of the pandemic.

Fig. 1. **Number of PCR tests conducted and COVID-19 cases confirmed in Iwate and Japan, February–July 2020**[a]



[a] The purple line represents Iwate, and the blue line represents all of Japan.
No cases of COVID-19 were confirmed in Iwate through 28 July 2020.

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Conflicts of interest

None

Ethics approval

As this research was a secondary analysis of public data from Japan, the study was exempt from review by an internal review board.

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Virological characteristics of cases of COVID-19 in northern Viet Nam, January–May 2020

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Background: Viet Nam confirmed its first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on 23 January 2020 among travellers from Wuhan, China, and experienced several clusters of community transmission until September. Viet Nam implemented an aggressive testing, isolation, contact tracing and quarantine strategy in response to all laboratory-confirmed cases. We report the results of SARS-CoV-2 testing during the first half of 2020 in northern Viet Nam.

Methods: Between January and May 2020, 15 650 upper respiratory tract specimens were collected from 14 470 suspected cases and contacts in northern Viet Nam. All were tested for SARS-CoV-2 by real-time RT-PCR. Individuals with positive specimens were tested every three days until two tests were negative. Positive specimens from 81 individuals were cultured.

Results: Among 14 470 tested individuals, 158 (1.1%) cases of SARS-CoV-2 infection were confirmed; 89 were imported and 69 were associated with community transmission. Most patients (122, 77%) had negative results after two tests, while 11 and 4 still tested positive when sampled a third and fourth time, respectively. SARS-CoV-2 was isolated from 29 of 81 specimens (36%) with a cycle threshold (Ct) value <30. Seven patients who tested positive again after testing negative had Ct values >30 and negative cultures.

Conclusion: Early, widespread testing for SARS-CoV-2 in northern Viet Nam identified very few cases, which, when combined with other aggressive strategies, may have dramatically contained the epidemic. We observed rapid viral clearance and very few positive results after clearance. Large-scale molecular diagnostic testing is a critical part of early detection and containment of COVID-19 in Viet Nam and will remain necessary until vaccination is widely implemented.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China, in late December 2019. As of September 2020, SARS-CoV-2 was responsible for over 25 million cases and nearly 1 million deaths.[1]

Viet Nam is a country of 97 million people, which, despite its lower- to middle-income status, has managed to limit the spread of SARS-CoV-2, requiring 8 months to reach 1000 cases and 7 months to record its first fatality. Strategies for prevention, detection and control have included the key response measures of early detection, testing and treatment, required for all persons entering the country from affected countries, starting in early February 2020.[2] The early days of the pandemic in Viet Nam were marked primarily by cases imported from China, whereas the second cluster was characterized by cases mainly imported from Europe.[2–6]

Viet Nam hosts two national influenza centres, including one at the National Institute of Hygiene and Epidemiology (NIHE). The Institute coordinates influenza surveillance in northern Viet Nam and has played a critical role in responding to the COVID-19 pandemic. In its role as a reference laboratory for the entire country, NIHE received some of the earliest specimens from cases of suspected COVID-19. We describe herein the virological characteristics of specimens received for COVID-19 testing between January and April 2020.

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METHODS

Viet Nam established a National Steering Committee on Prevention and Control of COVID-19 on 28 January 2020, 6 days after the first cases of COVID-19 were identified in the country.[3] Subsequent guidelines issued by the Steering Committee on 19 February 2020 called for the collection of nasopharyngeal and oropharyngeal (NP/OP) swabs from suspected cases and close contacts of confirmed cases; the guidelines were harmonized with those of the World Health Organization (WHO) in March 2020.[1] Additional samples were obtained from travellers in quarantine, who were required to provide upper respiratory specimens for testing upon arrival and before the end of the 14-day quarantine. Specimens were submitted by hospitals, provincial centres for disease control or quarantine facilities, with forms to indicate the reason for testing. Confirmed cases of COVID-19 were sampled every 3 days during hospitalization until they recovered clinically and had at least two negative results by real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2.

Real-time RT-PCR testing

NP/OP swabs were placed into a viral transport medium and maintained at 4 °C during transport to the national influenza centre at NIHE for 24–48 hours.[7] RNA was isolated from the swabs with the viral RNA extraction kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions in biosafety level 3 containment laboratories. Real-time RT-PCR was conducted with the SuperScript III One-step RT-PCR system with Platinum Taq High Fidelity DNA Polymerase (Invitrogen, Carlsbad, CA, USA), with targets of E, RdRp and N genes according to WHO recommendations. We defined confirmed cases as those with cycle threshold (Ct) values <37 for at least two of the target genes.[8]

Viral isolation

Vero E6 cells were maintained in Eagle's minimal essential medium containing 5% (v/v) newborn calf serum; 100 μL of real-time RT-PCR-positive samples were inoculated onto Vero E6 cells and incubated at 37 °C. Viral growth was monitored by daily observation of cytopathic effect. All experiments with SARS-CoV-2 viruses were performed in biosafety level 3 containment laboratories.[9]

Data analysis

Laboratory and epidemiological data collected in this study were entered into a FileMaker Pro 19 Advanced database and analysed. Summary data were reported to the Minister of Health daily and fed back to each sender 24–48 hours after reception of samples.

RESULTS

Characteristics of specimens received

Between 23 January and 25 May, the national influenza centre received 15 650 NP/OP specimens from 14 470 suspected cases in 28 cities and provinces in northern Viet Nam. Samples were submitted from two types of suspected cases: 6420 people who entered Viet Nam from abroad (China during the first cluster and other countries during the second cluster) and 8050 from people who were contacts of suspected or confirmed cases. During the first cluster (23 January–25 February 2020), 1741 specimens (11% of all specimens) were collected from people arriving from Wuhan, China, their families and their close contacts. During the second cluster of cases (7 March–25 May 2020), we received an additional 13 909 (88.9%) samples; nearly two thirds were received from four locations (Hanoi, 5366; Ha Giang, 1603; Thai Binh, 1118; Lai Chau, 1011) (**Table 1**).

Detection of SARS-CoV-2 by real-time RT-PCR

Among 14 470 tested samples, 158 (1.14%) cases of SARS-CoV-2 were confirmed (**Table 1**). Eighty-nine (56%) of these were detected among suspected cases imported from other countries and the remaining 69 (44%) among community contacts of confirmed cases (**Table 2**).

Thirteen cases were confirmed during the first cluster among people returning from China or their close contacts. Of the 158 confirmed cases, 143 (91%) were Vietnamese nationals and 96 (61%) were female, although we observed a significant difference in the distribution of gender between imported cases (44/89 or 49% female) and cases among community contacts (52/69, or 75% female, $P < 0.0009$ by the chi-squared test). The median age was 41 years (interquartile range [IQR]: 3 months–88 years) for community contacts and 33 years (IQR: 10–74 years) for imported cases. Eleven

Table 1. **Epidemiological features of suspected cases tested for SARS-CoV-2, northern Viet Nam, January–May 2020**

Dates	Source of suspected cases	No. of suspected cases	Gender, *n* (%)		Mean (IQR)	No. of positive cases (%)
			Male	Female		
23 January–25 February	Travellers from China	1123	516 (45.9)	607 (54.1)	30 (1 month–87 years)	6 (0.5)
	Community contacts	118	54 (45.8)	64 (54.2)	35 (4 months–58 years)	7 (5.9)
7 March–25 May	Travellers from other countries	5297	2436 (45.9)	2861 (54.1)	38 (1 month–96 years)	83 (1.6)
	Community contacts	7932	3648 (46.0)	4284 (54.0)	33 (1 month–90 years)	62 (0.8)
	Total	14 470	6654 (45.9)	7816 (54.1)	34 (1 month–96 years)	158 (1.1)

Table 2. **Epidemiological features of confirmed cases of COVID-19, northern Viet Nam, January–May 2020**

Group	All cases, *n* (%)	Gender, *n* (%)		Nationality, *n* (%)		Mean (IQR)	Re-positive, *n* (%)
		Male	Female	Viet Nam	Others		
Imported cases	89 (56)	45 (51)	44 (49)	74 (83)	15 (17)	33 (10–74 years)	6 (3.8)
Community contacts	69 (44)	17 (25)	52 (75)	69 (100)	0 (0)	41 (3 months–88 years)	1 (0.6)

(12%) of the 89 imported cases were detected only at second sampling while in quarantine.

The Ministry of Health guidelines require that laboratory-confirmed cases undergo follow-up testing until at least two consecutive tests are negative. Most cases required three or four subsequent tests to meet this criterion, but we also observed some cases after the collection of 10–15 subsequent specimens (**Table 3**).

Correlation between Ct value, date of illness / days since first positive sample and viral culture results

We analysed the Ct values of 158 confirmed cases of SARS-CoV-2 infection by serial sampling during hospitalization until two consecutive negative results were obtained. The proportion of cases that tested positive decreased with the number of times they were sampled. Among the 652 samples collected, 167 (26%) had Ct values <30, of which 105 (63%) were identified at the first sampling. Among cases that were sampled a third and fourth time, only 12/124 (10%) and 6/71 (8%) cases, respectively, had Ct values <30 (**Table 3**).

We identified 99 positive specimens with Ct values >30, including seven cases that tested positive again after having tested negative ("re-positives"). The pattern was similar to that of cases with Ct values <30: for 84 (85%) cases, only the first three samples were positive, and an additional 10 (11%) cases had positive results for one of the next three samples. One case was sampled 15 times with no positive results after the 10th sampling.

For 81/158 (51%) confirmed cases, the samples had been appropriately stored and were of a sufficient volume to be inoculated onto Vero E6 cells, from which we obtained 29 (36%) SARS-CoV-2 isolates. Of these, 20 samples had detectable cytopathic effects between 72 and 96 hours, and an additional 9 isolates were harvested after a second blind passage. We identified 28 samples with Ct values <20, and, of these, 18 (64%) yielded culturable virus (**Table 4**). An additional 20 cases had Ct values of 20–25, and we successfully cultured virus from 10 (50%) of these. The additional nine isolates recovered during the second passage had Ct values of 25–30, suggesting a low load of viable virus. No viral isolates were recovered from samples with Ct values >30 (n = 20).

DISCUSSION

During the first 5 months of the COVID-19 epidemic in Viet Nam, we characterized all upper respiratory tract specimens received by NIHE from cities and provinces

Table 3. **Relations between cycle threshold (Ct) values and specimen positivity over time for 158 confirmed cases of COVID-19, northern Viet Nam, February–May 2020.**

No. of tests for each suspected case	<30		≥30		Positive		Negative	Total
	n	%	*n*	%	*n*	%	*n*	*n*
1	105	71	42	29	147	93	11[a]	158
2	42	62	26	38	68	53	61	129
3	12	43	16	57	28	23	96	124
4	6	55	5	45	11	15	60	71
5	0	0	4	100	4	8	45	49
6	1	50	1	50	2	5	40	42
7	0	NA	0	0	0	0	31	31
8	0	0	2	100	2	10	19	21
9	1	50	1	50	2	17	10	12
10	0	0	2	100	2	25	6	8
11	0	0	0	0	0	0	3	3
12	0	0	0	0	0	0	1	1
13	0	0	0	0	0	0	1	1
14	0	0	0	0	0	0	1	1
15	0	0	0	0	0	0	1	1
Total	167	63	99	37	266	69	386	652

[a] The first samples from these cases were negative, but the second samples were positive. All were from travellers from countries other than China.

in northern Viet Nam. During that time, two clusters of SARS-CoV-2 infection occurred with community transmission. Just over 1% of all samples yielded positive results by real-time RT-PCR and, by the end of May 2020, fewer than 400 cases had been identified in Viet Nam, with no deaths.

Rapid scaling up and decentralization of testing were key components of Viet Nam's strategy to minimize entry and transmission of SARS-CoV-2. We identified 89 laboratory-confirmed cases in travellers by testing during centralized quarantine. Of them, 78 (88%) were positive on their first sampling, and 11 were positive during their quarantine. This suggests that testing in quarantine centres at entry and throughout quarantine can prevent transmission of SARS-CoV-2 in a country. Our results provided critical support for evaluating the COVID-19 prevention and control strategy in Viet Nam.

Table 4. **Relations between Ct value and culturable SARS-CoV-2 virus, northern Viet Nam, February–May 2020.**

Ct value	No. of clinical samples	Isolates recovered, *n* (%)
≤20	28	18 (64)
21–25	20	10 (50)
26–30	20	1 (5)
>30	13	0 (0)
Total	81	29 (36)

Although viral culture is the gold standard for confirmation of viral infection, real-time RT-PCR is the accepted gold standard for detecting SARS-CoV-2 for the purposes of isolation and contact tracing because of the shorter turnaround time and greater sensitivity. Semi-quantification of viral nucleic acids from the Ct value can be used to select samples for virus isolation.[3,9–11] We observed a strong correlation between Ct values and cell culture positivity rate, suggesting that viral load may be used as a proxy for the infectivity of infected patients.

Among the 158 confirmed COVID-19 cases, seven had positive real-time RT-PCR results after two consecutive negative results within 15 days. Prolonged viral nucleic acid detection in samples from patients who have recovered from COVID-19 has been a concern, as the large majority of these samples, both in the

literature and in our collection, have high Ct values, yet attempts to culture these viruses have been unsuccessful.[4,10] The virus could not be cultured from specimens from the seven cases in this study, all of which had Ct values >30, suggesting that these cases represent viral remnants rather than infectious virus. These findings are consistent with those from China and the Republic of Korea.[11–14] This observation supports the hypothesis that prolonged shedding or re-positivity of samples is not associated with continued replication but is rather an indicator of removal of damaged lung tissue containing intact stretches of viral RNA by coughing or ciliary transport.[13–14] Positive real-time RT-PCR results can be confusing for patients and hospital staff who understandably wish to prevent continued transmission, either among patients and health-care workers or in the general community. These findings should provide reassurance that patients with positive real-time RT-PCR results with Ct values >30 more than 10 days after onset or first positive result and after having had a negative result are at extremely low risk of transmission. These findings also support a strategy of testing based on signs of clinical recovery, rather than a "test-of-cure" strategy.

This study had several limitations. First, the specimens we received were collected as part of the national strategy for prevention and control of COVID-19 without accompanying systematic clinical metadata, and we were thus unable to stratify asymptomatic, mild and severe cases. Second, we could not systematically assess the possible duration of viral shedding because most of our cases were detected upon arrival, through contact tracing and in quarantine. Thus, sampling times were determined by disease control staff in the field rather than in the context of a rigorously designed study. Third, the specimens for viral isolation were only from the upper respiratory tract. We did not receive any sputum or tracheal aspirate fluids, which might have different characteristics in terms of Ct values or culturable virus.

In summary, we describe here the virology and epidemiology of cases of laboratory-confirmed COVID-19 in northern Viet Nam in two clusters of cases during the first 5 months of the pandemic. Most cases that were laboratory-confirmed were confirmed within the first few samplings. We also determined that most cases that are positive very late in their clinical course are unlikely to represent active infection but, rather, remnants of viral RNA. These results have provided valuable information for improving technical guidelines for molecular testing, viral isolation and clinical management of COVID-19 in Viet Nam.

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Conflicts of interest

The authors declare no conflicts of interest related to this work.

Ethics statement

The ethics committee of the National Institute of Hygiene and Epidemiology, Viet Nam, approved the protocol of this study.

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Clinical characteristics and outcomes of COVID-19 patients in a tertiary hospital in Baguio City, Philippines

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Objective: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily targets the respiratory system. This study describes the characteristics associated with mortality among patients infected with SARS-CoV-2 at a single hospital in Baguio City, Philippines.

Methods: We reviewed medical records (including history, laboratory results and treatment regimen) of 280 confirmed COVID-19 patients admitted to a single hospital during March–October 2020. Clinical characteristics and outcomes (frequency and type of complication, recovery rate and mortality) were evaluated. Multiple logistic regression was used to analyse factors associated with mortality.

Results: The mean age of COVID-19 patients was 48.4 years and the female-to-male ratio was 1.8:1. Hypertension, cardiovascular disease (CVD) and diabetes were the most frequent comorbidities reported. Common presenting symptoms were respiratory and constitutional, with 41% of patients not reporting symptoms on admission. Patients with moderate, severe and critical disease comprised 45%, 8% and 4%, respectively. A total of 15% had complications, health care-associated pneumonia being the most frequent complication. The recovery rate was 95%; 5% of patients died, with multiorgan failure being the most common cause. The presence of CVD, chronic kidney disease, prolonged prothrombin time and elevated lactate dehydrogenase (LDH) were associated with mortality.

Discussion: Most COVID-19 patients in our population had asymptomatic to moderate disease on admission. Mortality from COVID-19 was associated with having CVD, chronic kidney disease, elevated LDH and prolonged prothrombin time. Based on these results, we emphasize that people should take all necessary precautions to avoid infection with SARS-CoV-2.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily targets the respiratory system. In December 2019, an epidemiological alert was released in China following a rise in cases of pneumonia of unknown cause. The Philippines announced its first confirmed case on 31 January 2020.[1,2] The World Health Organization (WHO) officially declared a global pandemic on 11 March 2020, by which time the Philippines already had 49 confirmed cases, largely in the National Capital Region.[2]

Baguio City is located north of Manila, within the Cordillera Central mountain range in northern Luzon. The estimated population is 345 000, with adults (aged 19–60 years) and those aged over 60 years comprising 52% and 6.6% of the population, respectively.[3] Leading causes of morbidity include hypertension, diabetes, bronchitis and asthma.[4]

The first confirmed case in Baguio City was recorded on the city's ninth day of quarantine during March 2020, with local sustained transmission declared six months later.[5] Worldwide, by the end of October 2020, there were 43 623 111 confirmed cases and 1 161 311 deaths. At that time in the Philippines, cases had risen to 373 144 and deaths to 7053. Baguio City comprised 0.53% of confirmed cases and 0.37% of deaths nation-

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wide.[6–8] COVID-19 patients in Baguio City were admitted and treated in six local hospitals and three community isolation units.

Many reports describing the characteristics and outcomes of COVID-19 in different settings are being published. In this study, we describe the clinical characteristics and outcomes of COVID-19 patients and the characteristics associated with mortality at one hospital in Baguio City, Philippines.

METHODS

We conducted a retrospective study of all patients aged over 18 years with COVID-19, confirmed by reverse transcription polymerase chain reaction (RT-PCR), who were admitted to a tertiary hospital that was one of the government-mandated COVID-19 referral hospitals in Baguio City, Philippines from 1 March to 27 October 2020.

A total of 371 patients were admitted during this period. Paediatric cases (n = 80) and cases dead on arrival (n = 9) were excluded. Charts were excluded if they lacked information on age, sex, travel history or exposure, official RT-PCR result, complete blood count or chest radiography (n = 2), leaving 280 charts for analysis. The following data were extracted: patient history, exposure, initial laboratory results, treatment and outcome.

Baseline routine blood examinations included complete blood count, high-sensitivity C-reactive protein, procalcitonin, lactate dehydrogenase (LDH), creatinine, aspartate aminotransferase, alanine transaminase, ferritin, prothrombin time, partial thromboplastin and D-dimer. Radiography and computerized tomography were used for chest imaging. On admission, each patient was scored for quick sequential organ failure assessment (qSOFA), Glasgow coma score and neutrophil-lymphocyte ratio.[9,10]

Standard of care was based on national guidelines that were continuously being updated during the study period.[11] Medications such as antiviral drugs and immunomodulators were not consistently available.

The severity of COVID-19 disease was categorized as asymptomatic, mild, moderate, severe and critical. Patients were labelled "asymptomatic" if they had no symptoms; "mild" if they had constitutional and nonspecific symptoms; "moderate" if they had pneumonia but did not require oxygen; "severe" if they had pneumonia plus hypoxemia, tachypnoea or hypotension; and "critical" if they had worsening pneumonia, sepsis or septic shock.[11]

In our analysis, we explored clinical characteristics and outcomes (frequency and type of complication, recovery rate and mortality) and identified factors associated with mortality in COVID-19 patients. Median, means, standard deviations and proportions were used to summarize the data. The t-test and chi-squared test were used to test for differences in means and proportions, respectively. The Mann-Whitney U test was used to compare differences in median values. Fisher's exact test or the chi-squared test was used to examine differences between categorical data. A stepwise analysis model using multiple logistic regression was used to determine which variables were associated with mortality. Variables that were statistically significant ($P < 0.05$) in the univariate analysis were selected. Although both disease severity and qSOFA were statistically significant at the univariate level, only the former was included in the final model because these two variables had overlapping definitions. EPI-Info version 7.2.4.0 was used to process the data.

RESULTS

Characteristic of cases at hospital admission

The mean age of the 280 COVID-19 patients was 48.4 years and the majority (64%) were females. Two thirds (63%) were aged under 60 years. More than half (62%) had exposure to a known case through either travel or close contact. The majority (58%, 161/280) of cases had at least one comorbidity, and 34% (94/280) had two or more comorbidities, with hypertension, cardiovascular disease (CVD) and diabetes being the most frequent. Pregnant patients comprised 16% of the cases and health care workers 23% (**Table 1A**). Among pregnant patients, 71% were in their third trimester of pregnancy.

Upon admission, 59% of patients complained of symptoms, most commonly respiratory (cough, cold or dyspnoea) and constitutional (fever or malaise) in nature. The other 41% did not report symptoms on admission. Twenty-one per cent of patients were observed to have tachypnoea, hypotension or altered mental state. Six patients (2.2%) had a qSOFA score of at least 2 (**Table 1A**).

Table 1A. **Demographic characteristics of adult COVID-19 patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**

Clinical characteristics	Total, *n* (%)	Recovered, *n* (%)	Died, *n* (%)	*P*
Total number of patients	280	267	13	
Age, years				
Mean ± SD	48.4 ± 18.5	47.7 ± 18.5	62.2 ± 13.5	0.71
18–44	131 (46.8)	129 (48.3)	2 (15.3)	*0.01*
45–59	44 (15.7)	43 (16.1)	1 (7.7)	
60–79	98 (35.0)	88 (33.0)	10 (76.9)	
≥80	7 (2.5)	7 (2.6)	-	
Sex				
Female	179 (64.0)	174 (65.2)	5 (38.5)	0.05
Male	101 (36.1)	93 (34.8)	8 (61.5)	
Comorbidities	161 (57.5)	148 (55.4)	13 (100)	*<0.01*
Hypertension	124 (44.3)	114 (42.7)	10 (76.9)	0.02
Diabetes mellitus	47 (17.0)	45 (16.9)	2 (15.4)	0.62
Cardiovascular disease	34 (12.1)	26 (9.7)	8 (61.5)	*<0.01*
Bronchial asthma	17 (6.1)	16 (6.0)	1 (7.7)	0.57
Malignancy	12 (4.3)	12 (4.5)	-	
Chronic kidney disease	4 (1.4)	1 (0.4)	3 (23.1)	*<0.01*
Chronic obstructive pulmonary disease	3 (1.1)	3 (1.1)	-	
Number of comorbidities				
0	119 (42.5)	119 (44.6)	-	*<0.01*
1	68 (24.3)	65 (24.3)	3 (23.1)	
2	66 (23.6)	59 (22.1)	7 (53.9)	
>2	27 (9.6)	24 (9.0)	3 (23.1)	
Patient reported symptoms	164 (58.6)	153 (57.3)	11 (84.6)	0.04
Cough	111 (39.6)	101 (37.8)	10 (76.9)	*<0.01*
Cold	49 (17.5)	48 (18.0)	1 (7.7)	0.30
Fever	40 (14.3)	35 (13.1)	5 (38.5)	0.03
Malaise	37 (13.2)	31 (11.6)	6 (46.2)	*<0.01*
Dyspnoea	35 (12.5)	28 (10.5)	7 (53.9)	0.27
Sore throat	26 (9.3)	26 (9.7)	-	
Headache	24 (8.6)	24 (9.0)	-	
Anosmia	17 (6.1)	17 (6.4)	-	
Dysgeusia	14 (5.0)	14 (5.2)	-	
Anorexia	12 (4.3)	10 (3.8)	2 (15.4)	0.10
Diarrhoea	11 (3.9)	11 (4.1)	-	
Chills	4 (1.4)	2 (0.8)	2 (15.4)	*0.01*
Seizure	2 (0.7)	2 (0.8)	-	
Disease severity at admission based on national COVID-19 case definitions				
Asymptomatic	43 (15.4)	43 (16.1)	-	
Mild	77 (27.5)	76 (28.5)	1 (7.1)	*<0.01*
Moderate	126 (45.0)	123 (46.1)	3 (23.1)	
Severe	23 (8.2)	21 (7.9)	2 (15.4)	
Critical	11 (3.9)	4 (1.5)	7 (53.8)	

Clinical characteristics	Total, *n* (%)	Recovered, *n* (%)	Died, *n* (%)	*P*
Quick sequential organ failure assessment (qSOFA) score				
0	228 (81.4)	225 (84.3)	3 (23.1)	*<0.01*
1	46 (16.4)	39 (14.6)	7 (53.9)	
2	5 (1.8)	3 (1.1)	2 (15.4)	
3	1 (0.4)	0 (0.0)	1 (7.7)	
Glasgow coma score <15	4 (1.4)	1 (0.4)	3 (23.1)	*<0.01*
Respiratory rate ≥22 breaths/min	32 (11.4)	24 (9.0)	8 (61.5)	*<0.01*
Systolic blood pressure ≤100 mmHg	23 (8.2)	20 (7.5)	3 (23.1)	0.08

P values <0.05 are italicized.

Forty-five per cent of patients were assessed against the national case definitions as having moderate disease. Concomitant non-pulmonary syndromes such as stroke and myocardial infarction were noted (**Table 1A**).

Most patients (93.6%) had procalcitonin <0.5 ng/mL. Many had high-sensitivity C-reactive protein >10 ng/mL (37%) and ferritin >341 ng/mL (42%). A few had elevations in other inflammatory markers such as LDH, aspartate aminotransferase, alanine transaminase and D-dimer, whereas anaemia, leukopenia and thrombocytopenia were not typical (**Table 1B**).

More than half of the population had chest radiography findings, with infiltrates being the most common. Computed tomography was available to two thirds (62%) of patients. Findings were noted in 71%, ground glass opacity being the most common (**Table 1B**).

Illness outcomes

The overall recovery rate was 95% (267/280), with most recovered cases having asymptomatic to moderate disease on admission. All health care workers and pregnant patients recovered. Mortality occurred in 5% (13/280) of patients, with the most common cause of death being multiorgan failure (39%, 5/13). Among those who died, most were males in the 60–79-year age group with at least one comorbidity, respiratory symptoms on admission, a qSOFA score ≥1 and bilateral lung involvement. Nine were assessed as having severe to critical disease at admission (**Fig. 1**).

The mean time from illness onset to discharge from hospital for recovered patients was 15.5 days (range: 4.0–54.0) with the mean hospital stay being 11.7 (±5.6) days (range: 3.0–49.0). For cases who died, the mean time from illness to death was 11.5 days (range: 4.0–29.0) (**Fig. 2**).

Forty-two (15%) cases had complications, most of whom had moderate to critical disease on admission (32/42) (**Table 2**, **Fig. 2**). Health care-associated pneumonia was the most frequent complication. Among the 14 patients who developed acute kidney injury, six underwent haemodialysis and none of those six survived. Among patients with complications, 30 (71%) recovered and 12 (29%) died. Among those who died, many had cardiovascular or renal complications or secondary infections (**Table 2**).

Treatment of cases

Antibiotics were prescribed for 73% of cases and antiviral drugs for 55% of cases (**Table 3**). The most common antiviral drugs used were oseltamivir (83/154), favipiravir (54/154), remdesivir (16/154) and lopinavir-ritonavir (1/154). Hydroxychloroquine was administered during March–May 2020, while steroids, particularly dexamethasone, were prescribed to patients from August 2020. Supplemental oxygen was used in 11% of cases (**Table 3**). Among the seven cases who underwent renal replacement therapy, only one had underlying chronic kidney disease. Patients with extrapulmonary syndrome such as stroke, myocardial infarction and seizure were treated according to guidelines for the general population.

Mortality from COVID-19

Using multiple logistic regression with a stepwise analysis model, factors associated with mortality in patients with COVID-19 were chronic kidney disease, CVD, prothrombin time >15.3 seconds and LDH >400 (**Table 4**).

Table 1B. **Pertinent baseline diagnostic test results of adult COVID-19 patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**

Diagnostic test	Reference range	Total *n* (range/%)	Recovered *n* (range/%)	Died *n* (range/%)	*P*
Serum					
Haemoglobin (g/L) (*n* = 280)	120–160	141 (131–152)	141 (131–152)	140 (124–142)	0.56
<120		21 (7.5)	20 (7.5)	1 (7.7)	0.65
Haematocrit (L/L) (*n* = 280)	0.37–0.47	0.4 (0.4–0.5)	0.4 (0.4–0.5)	0.4 (0.38–0.41)	0.37
≥0.47		46 (16.4)	45 (16.9)	1 (7.7)	0.34
Leukocytes (10^9/L) (*n* = 280)	5–10	7.5 (5.8–9.8)	7.5 (5.8–9.7)	8.0 (6.3–10.9)	0.47
<4		14 (5.0)	14 (5.2)	–	
Neutrophil–lymphocyte ratio	1–3	2.5 (1.6–22.8)	2.4 (1.6–3.5)	4.4 (3.2–8.6)	*<0.01*
≤3		185 (66.1)	182 (68.2)	3 (23.1)	*<0.01*
>3 to <9		83 (29.6)	76 (28.5)	7 (53.9)	0.05
≥9		12 (4.3)	9 (3.4)	3 (23.1)	*0.01*
Platelets (*n* = 279)	150–400	253.0 (198–313)	257.0 (202–316)	196.0 (158.5–211.5)	*<0.01*
<125		5 (1.8)	4 (1.5)	1 (8.3)	0.20
High-sensitivity C-reactive protein (mg/L) (*n* = 264)	<5	5.0 (1.5–18.7)	4.7 (1.5–16.0)	83.6 (33.4–131.5)	*<0.01*
5–10		33 (12.5)	33 (13.1)	–	
>10		98 (37.1)	87 (34.5)	11 (91.7)	*<0.01*
Procalcitonin (ng/mL) (*n* = 236)		0.05 (0.02–0.12)	0.05 (0.02–0.11)	1.17 (0.13–1.81)	*<0.01*
<0.5		221 (93.6)	217 (96.4)	4 (36.4)	*<0.01*
Lactate dehydrogenase (U/L) (*n* = 263)	<247	216.3 (174.6–285.8)	214.9 (174.3–278.9)	407.6 (236.5–657.3)	*<0.01*
>400		19 (7.2)	12 (4.8)	7 (53.9)	*<0.01*
Creatinine (mg/dL) (*n* = 278)	0.55–1.02	0.71 (0.60–0.86)	0.71 (0.60–0.85)	0.76 (0.71–2.6)	*0.04*
>1.02		36 (13.0)	30 (11.3)	6 (46.2)	*<0.01*
Aspartate aminotransferase (U/L) (*n* = 277)	<35	29.3 (23.2–40.0)	28.8 (22.9–39.0)	52.1 (33.7–86.0)	*<0.01*
>95		12 (4.3)	9 (3.4)	3 (23.1)	*0.01*
Alanine transaminase (U/L) (*n* = 278)	<35	29.6 (17.8–46.0)	28.8 (17.4–44.1)	42.9 (25.0–49.4)	0.09
>95		17 (6.1)	15 (5.7)	2 (15.4)	0.18
Ferritin (ng/mL) (*n* = 190)	4–341	295.0 (68.1–653.7)	281.1 (63.5–604.8)	982.1 (238.7–1611.0)	*0.04*
>341		80 (42.1)	75 (41.0)	5 (71.4)	0.11
Prothrombin time (seconds) (*n* = 266)		12.1 (11.5–12.8)	12.1 (11.4–12.7)	12.8 (12.3–18.7)	*<0.01*
>15.3		7 (2.6)	2 (0.8)	5 (38.5)	*<0.01*
Partial thromboplastin time (seconds) (*n* = 263)		29.6 (27.7–31.8)	29.5 (27.7–31.8)	33.2 (27.1–39.7)	0.12
>35		24 (9.1)	20 (8.0)	4 (33.3)	*0.02*
D-dimer (μg/mL) (*n* = 260)	<0.5	0.54 (0.18–1.19)	0.52 (0.34–1.17)	0.94 (0.63–5.36)	*0.03*
>1		61 (29.6)	57 (28.8)	4 (50.0)	0.18

Diagnostic test	Reference range	Total *n* (range/%)	Recovered *n* (range/%)	Died *n* (range/%)	*P*
Imaging					
Chest radiograph		*N* = 276	*N* = 263	*N* = 13	
Patients with findings		151 (54.7)	140 (53.2)	11 (84.6)	*0.04*
Infiltrates		147 (97.4)	139 (99.3)	8 (72.7)	*<0.01*
Effusion		2 (1.3)	1 (0.7)	1 (9.1)	0.11
Consolidation		3 (2.0)	1 (0.7)	2 (18.2)	*0.01*
Computed tomography		*N* = 174	*N* = 166	*N* = 8	
Patients with findings		124 (71.3)	118 (71.1)	6 (75.0)	1.00
Ground glass opacity		111 (89.5)	105 (89.0)	6 (100)	1.00

P values <0.05 are italicized.

SD: standard deviation.

Table 2. **Frequency of complications in adult COVID-19 patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**

Complications	Total *n* (%)	Recovered *n* (%)	Died *n* (%)	*P*
Total number of patients	280	267	13	
Number of patients with complications	42 (15.0)	30 (11.2)	12 (92.3)	*<0.01*
Secondary infection	22 (7.9)	16 (6.0)	6 (46.2)	*<0.01*
HCAP	17 (6.1)	13 (4.9)	4 (30.8)	*<0.01*
Septic shock	6 (2.1)	2 (0.8)	4 (30.8)	*<0.01*
Bacteraemia	3 (1.1)	3 (1.1)	-	
CAUTI	1 (0.4)	-	1 (7.7)	
Acute kidney injury	14 (5.0)	5 (1.9)	9 (69.2)	*<0.01*
Cardiovascular	11 (3.9)	2 (0.8)	9 (69.2)	*<0.01*
Myocardial infarction	7 (2.5)	1 (0.4)	6 (46.2)	*<0.01*
Fatal arrhythmia	7 (2.5)	1 (0.4)	6 (45.2)	*<0.01*
Transaminitis	11 (3.9)	10 (3.8)	1 (7.7)	0.41
Haematologic/immunologic	8 (2.9)	4 (1.5)	4 (30.8)	*<0.01*
Cytokine storm	4 (1.4)	2 (0.8)	2 (15.4)	*0.01*
Thrombocytopenia	3 (1.1)	1 (0.4)	2 (15.4)	*0.01*
Leukopenia	1 (0.4)	1 (0.4)	-	
Neurological	2 (0.7)	-	2 (15.4)	
Seizure	1 (0.4)	-	1 (7.7)	
Stroke (ischaemic)	2 (0.7)	-	2 (15.4)	

P values <0.05 are italicized.

CAUTI: catheter-associated urinary tract infection; HCAP: health care-associated pneumonia.

Table 3. **Treatment modalities of adult COVID-19 patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**

Treatment	Total *n* (%)	Recovered *n* (%)	Died *n* (%)	*P*
Total number of patients	280	267	13	
Antibiotics	203 (72.5)	192 (71.9)	11 (84.6)	0.26
Antivirals	154 (55.0)	149 (55.8)	5 (38.5)	0.17
Immunomodulators	70 (25.0)	61 (22.9)	9 (69.2)	*<0.01*
Hydroxychloroquine	25 (8.9)	24 (9.0)	1 (7.7)	0.67
Corticosteroids	45 (16.1)	37 (13.9)	8 (61.5)	*<0.01*
Intravenous immunoglobulin	4 (1.4)	3 (1.1)	1 (7.7)	0.17
Tocilizumab	3 (1.1)	2 (0.8)	1 (7.7)	0.13
Oxygen support	32 (11.4)	24 (9.0)	8 (2.9)	*<0.01*
Nasal cannula	24 (8.6)	21 (7.9)	3 (23.1)	0.09
Face mask	3 (1.1)	1 (0.4)	2 (15.4)	*0.01*
Invasive mechanical ventilation	5 (1.8)	2 (0.8)	3 (23.1)	*<0.01*
Renal replacement therapy	7 (2.5)	1 (0.4)	6 (46.2)	*<0.01*
Haemodialysis	5 (1.8)	1 (0.4)	4 (30.8)	*<0.01*
Haemodialysis with haemoperfusion	2 (0.7)	-	2 (15.4)	

P values <0.05 are italicized.

Fig. 1. **Outcomes of adult patients with COVID-19 based on disease severity on admission to Baguio General Hospital and Medical Center (*n* = 280)**

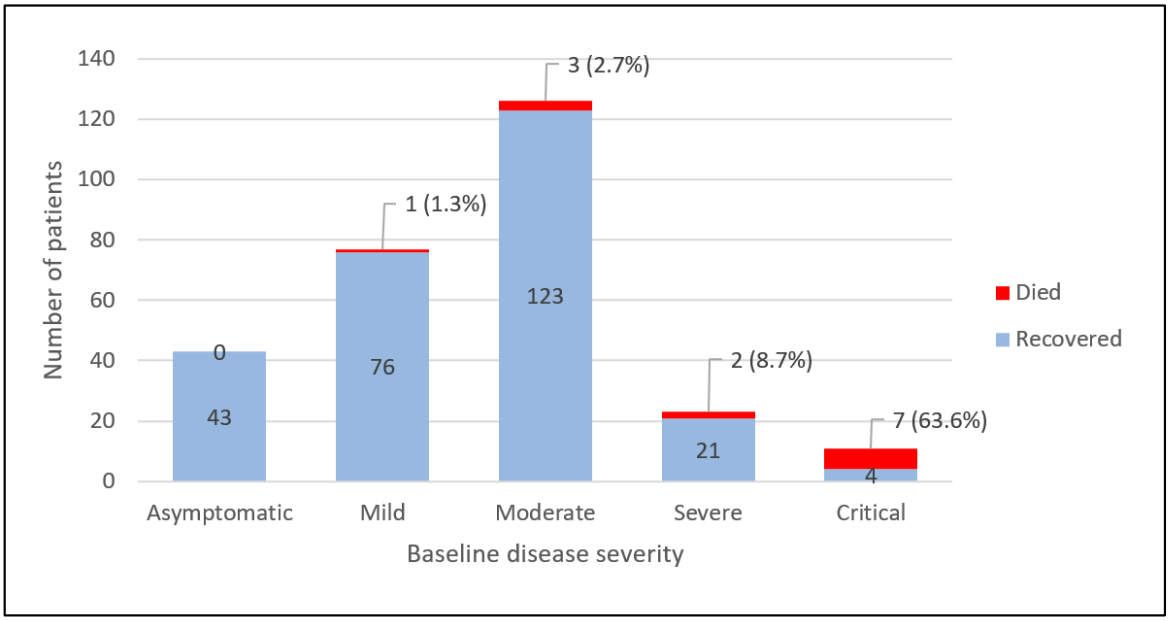
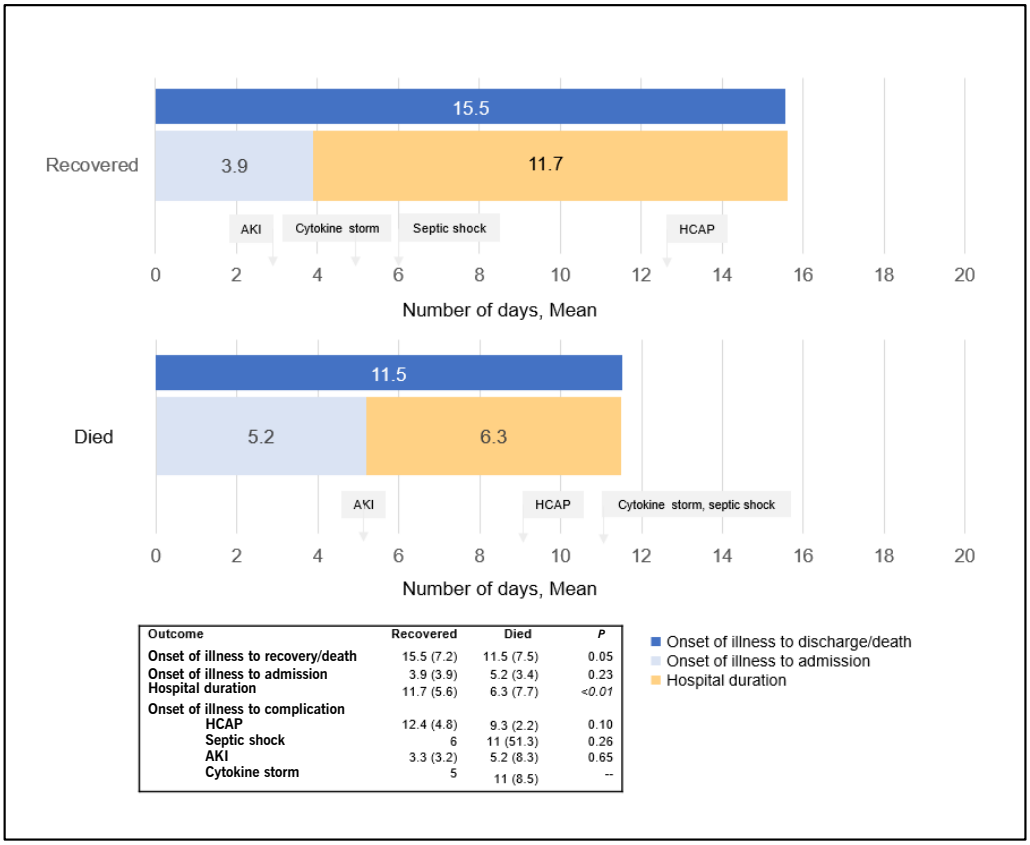


Table 4. **Factors associated with mortality of adult COVID-19 patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**

Variables	Adjusted odds ratios	95% confidence interval	*P* value
Presence of chronic kidney disease	324.7	12.5 to 8456.4	*0.001*
Presence of cardiovascular disease	10.6	1.7 to 66.8	*0.012*
Prothrombin time ≥15.3 sec	74.6	3.6 to 1562.6	*0.006*
Lactate dehydrogenase >400	26.4	3.8 to 184.6	*0.001*

P values <0.05 are italicized.

Fig. 2. **Mean duration (in days) of illness to admission, hospital duration, and onset of complications among patients admitted to Baguio General Hospital and Medical Center from 1 March to 27 October 2020**



Outcome	Recovered	Died	*P*
Onset of illness to recovery/death	15.5 (7.2)	11.5 (7.5)	0.05
Onset of illness to admission	3.9 (3.9)	5.2 (3.4)	0.23
Hospital duration	11.7 (5.6)	6.3 (7.7)	*<0.01*
Onset of illness to complication			
HCAP	12.4 (4.8)	9.3 (2.2)	0.10
Septic shock	6	11 (51.3)	0.26
AKI	3.3 (3.2)	5.2 (8.3)	0.65
Cytokine storm	5	11 (8.5)	--

AKI: acute kidney injury; HCAP: health care-associated pneumonia.

DISCUSSION

Our study assessed the clinical profile and outcomes of hospitalized adult COVID-19 patients in a single hospital in Baguio City, Philippines. The COVID-19 cases comprised mostly female patients with a mean age of 48.4 years. Moderate, severe and critical disease made up 45%, 8% and 4% of the COVID-19 patients, respectively. The recovery rate was 95% and mortality was associated with having chronic kidney disease, CVD, elevated LDH and prolonged prothrombin time at hospital admission.

The female-to-male ratio in our study was 1.8:1, yet 62% of cases that died were male. Several other studies have shown a male predominance of COVID-19 cases,[12,13] and a recent meta-analysis showed that male sex was significantly associated with severe disease.[14] However, in our study, there was no significant difference

in sex between the cases that recovered and those that died. The high female-to-male ratio in our study may have been due to the former outnumbering the latter in all age groups except for those aged 1–4 years in Baguio City.[4]

In our study, 77% of COVID-19 cases that died were aged 60–79 years, reflecting national data, whereby 60% of confirmed deaths were males aged at least 60 years.[15] Old age is a known risk factor for severe COVID-19, for reasons not yet fully understood.[16,17] Changes in the immune system and prevalence of comorbidities in this age group contribute to the risk.

WHO recognizes that underlying comorbidities can negatively impact outcomes in COVID-19 patients,[18] with confirmed COVID-19 patients with comorbidities having increased admission rates to intensive care units and mortality.[19] Although all the cases in our study who died had at least one comorbidity, the presence of a comorbidity did not in itself significantly increase the likelihood of death. However, having chronic kidney disease and CVD were significantly associated with mortality. Chronic kidney disease is considered the most prevalent risk factor for severe COVID-19 worldwide, especially for patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2.[17,20] In addition to chronic kidney disease, a higher proportion of those who died also had acute renal complications warranting haemodialysis. It is hypothesized that kidney involvement is through direct cellular and immune-mediated damage due to the presence of the virus.[21] COVID-19 patients presenting with acute kidney injury have been shown to have a higher risk of death than patients with acute kidney injury from other conditions.[22] A recent meta-analysis found that pre-existing CVD is also an independent risk factor associated with poor outcomes from COVID-19.[23] Patients who have pre-existing comorbidities or present with complications should be closely monitored for severe outcomes. This, in combination with evidence relating to other complications during COVID-19 infection (e.g. hospital-acquired infections), supports the rapidly accumulating evidence that COVID-19 may have multisystemic affectations.

Our study found an association between mortality and prolonged prothrombin time (>15.3 seconds) and elevated LDH (>400). Several studies have shown that a prolonged prothrombin time is associated with a poorer outcome among COVID-19 patients.[24,25] Coagulation parameters not only reflect haemostasis but are also associated with the inflammation and organ dysfunction brought about by COVID-19 infection. In a pooled analysis, elevated LDH values were associated with a 6-fold increase in odds of severe COVID-19 disease and >16-fold increase in odds of mortality.[26] Since LDH is present in lung tissue, patients with severe COVID-19 infections who present with a severe form of interstitial pneumonia can be expected to release greater amounts of LDH in the circulation.

High baseline levels of inflammatory biomarkers (e.g. serum LDH, alanine transaminase and D-dimer) are considered poor prognostic factors that are associated with mortality, increased stay in the intensive care unit and severe disease.[11] Certain haematological abnormalities (e.g. decreased haemoglobin, white blood cell count and platelets), although not rare in COVID-19, are seen in severe disease.[27] Both scenarios were seen in a minority of our cases. This may relate to our population's low mortality rate. Meanwhile, a low or normal procalcitonin level, observed in a high number of patients in our study, is compatible with a viral infection. Elevated levels may be due to other non-viral, even non-infectious, causes.[11]

That 73% of our patients received antibiotics is a concern, although this was mainly as a preventive measure and due to many patients having a secondary infection, including hospital-acquired pneumonia, bacteraemia and complicated urinary tract infections. Secondary infections can contribute to a poorer outcome, and when faced with severely ill hospitalized patients where the diagnosis of a bacterial superinfection is uncertain, antibiotics are often started.[28] Because this study was in the early phase of the pandemic, hydroxychloroquine and lopinavir-ritonavir were included among the investigational drugs given to patients.

The most common symptoms in our COVID-19 patients were cough, cold, fever, dyspnoea and malaise. Although, in the univariate analysis, the proportions reporting cough, fever and malaise were significantly higher in cases that died than in those that recovered, these proportions were not associated with mortality in multivariate analysis. Other studies have identified various symptoms as prognosticators for mortality. Dyspnoea was consistently identified as a risk factor for mortality in multinational meta-analyses involving thousands of patients.[29,30] In contrast, a meta-analysis involving >50 000 patients in 13 countries showed that headache,

diarrhoea, vomiting and cough indicate a lower risk of death.[29] In addition, anosmia and dysgeusia are peripheral neurological symptoms of COVID-19 that have been investigated for their association with recovery, with studies on anosmia reporting it as being inversely associated with hospitalization and as a marker of milder COVID-19 disease.[31,32] Conversely, a meta-analysis showed that olfactory and taste dysfunction had no bearing on severity of COVID-19 disease.[33] In our study, all patients presenting with dysgeusia and anosmia recovered. Differences in study definitions, study methodologies and tools for detecting anosmia and dysgeusia may account for the differences in results.

Pregnancy is now recognized as a risk factor for contracting COVID-19. A weakened immune system during pregnancy confers a higher risk of infection with SARS-CoV-2.[34] In this study, 45 patients were pregnant but none died. Possible causes for this low mortality rate could be the lower age of pregnant patients as well as the lower rate of concomitant comorbidity in this subgroup.

Our study had some limitations. First, the study design was cross-sectional; causal inference and associations may be inherently difficult to make and interpret because the outcome, exposure and investigated risk factors were collected simultaneously. The frequency and type of complications seen in our patients cannot be wholly attributed to the effects of COVID-19. Second, the selection of our study population was non-randomized, and data analysis was non-stratified and non-matching. Although multiple logistic regression was used to identify risk factors associated with mortality, our sample size was small, leading to wide confidence intervals. Therefore, caution should be applied when interpreting the results. At the time of writing, the pandemic is ongoing and the clinical profile and prognosis of COVID-19 patients in our institution may change over time.

In conclusion, most of the patients in our population were classified with asymptomatic to moderate disease on admission and few had complications. Overall, 95% of cases recovered and 5% died. The presence of chronic kidney disease, CVD, elevated LDH and prolonged prothrombin time were associated with mortality in our population. Based on these results, we strongly recommend that patients with comorbidities, including pregnancy and those of older age, should take all necessary precautions to avoid getting infected with SARS-CoV-2.

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The year 2020 was truly a challenge in every community worldwide. We thank the first responders, front-line workers, essential workers, public health leaders, physicians and scientists who are continuing to work tirelessly to treat COVID-19 patients, protect vulnerable populations and prevent the spread of this virus.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

This study has been approved by the Ethics Review Board of Baguio General Hospital and Medical Center, Baguio City, Philippines.

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Re-positive testing, clinical evolution and clearance of infection: results from COVID-19 cases in isolation in Viet Nam

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Objective: Asymptomatic infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and test re-positivity after a negative test have raised concerns about the ability to effectively control the coronavirus disease 2019 (COVID-19) pandemic. We aimed to investigate the prevalence of COVID-19 asymptomatic and pre-symptomatic infections during the second wave of COVID-19 in Viet Nam, and to better understand the duration of SARS-CoV-2 infection and the dynamics between the evolution of clinical symptoms and SARS-CoV-2 test positivity among confirmed COVID-19 cases.

Methods: We conducted a cohort analysis on the first 50 confirmed cases during the second COVID-19 wave in Viet Nam using clinical, laboratory and epidemiological data collected from 9 March to 30 April 2020. Kaplan-Meier estimates were used to assess time to clearance of SARS-CoV-2 infection, and log-rank tests were used to explore factors related to time to SARS-CoV-2 infection clearance.

Results: Most cases (58%) had no typical signs or symptoms of COVID-19 at the time of diagnosis. Ten cases (20%) were re-positive for SARS-CoV-2 during infection. Eight cases (16%) experienced COVID-19 symptoms after testing negative for SARS-CoV-2. The median duration from symptom onset until clearance of infection was 14 days (range: 6–31); it was longer in re-positive and older patients and those with pre-existing conditions.

Conclusion: Asymptomatic and pre-symptomatic infections were common during the second wave of COVID-19 in Viet Nam. Re-positivity was frequent during hospitalization and led to a long duration of SARS-CoV-2 infection.

Coronavirus disease 2019 (COVID-19) is a respiratory disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 pandemic, first reported in Wuhan, China in December 2019,[1] spread quickly worldwide. As of mid-October 2021, there have been over 240 million confirmed cases and 4.9 million deaths.[2] The first case of COVID-19 in Viet Nam was recorded on 22 January 2020 in a person who had returned from Wuhan, and that case was linked to a further 15 cases related to Wuhan.[3] By the end of February, all 16 cases had recovered and Viet Nam remained clear of COVID-19 for the following 20 days. By early March, the world saw a major shift in the distribution of COVID-19 cases from China to Europe and the United States of America, while China's incidence decreased.[4] This sparked a second wave of imported COVID-19 cases in Viet Nam, of non-Chinese origin, starting on 6 March

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2020 when an international passenger arriving from the United Kingdom of Great Britain and Northern Ireland tested positive.[5]

Case investigations conducted during the second wave suggested the occurrence of cases without compatible signs or symptoms of COVID-19 at the time of the first positive test, raising concerns about the community spread of COVID-19 in Viet Nam. Some cases remained asymptomatic until discharge, whereas others developed symptom onset after testing positive (pre-symptomatic infections). Also seen at that time was reversion of test results in patients who had tested negative following a positive result, and then returned to positive (re-positivity). As in other settings, pre-symptomatic and fully asymptomatic infections were also recorded but not systematically investigated.[6,7]

Important evidence gaps remain for asymptomatic and pre-symptomatic cases, and for patients with re-positive test results.[8,9] In particular, the duration until clearance of infection and the dynamics between clinical symptoms and test positivity are poorly understood.[10,11] The testing and quarantine policy during the initial phase of the second wave of infections in Viet Nam provided us with a setting to investigate these questions. Using clinical, laboratory and epidemiological data of arriving air travel passengers to Viet Nam and their secondary cases during March and April 2020, we aimed to investigate the prevalence of asymptomatic and pre-symptomatic COVID-19 infections and to better understand the duration of SARS-CoV-2 infection and the dynamics between the evolution of clinical symptoms and SARS-CoV-2 test positivity.

METHODS

Design

A cohort analysis was conducted on the first 50 laboratory-confirmed cases during the second COVID-19 wave in Viet Nam using clinical, laboratory and epidemiological data collected as a part of the national epidemic response between 9 March and 30 April 2020.

Data sources

In Viet Nam, all hospitals reported clinical and treatment information and test results for COVID-19 cases to the National Institute of Hygiene and Epidemiology and the Medical Services Administration. Data included in this analysis were obtained from the National Institute of Hygiene and Epidemiology.

Case classification and definitions

This study used case definitions from guidelines developed by the Viet Nam Ministry of Health.[12] Case confirmation required a positive polymerase chain reaction (PCR) test for SARS-CoV-2. A symptomatic COVID-19 case was defined as a confirmed case showing any COVID-19 compatible symptom according to Ministry of Health guidelines, including cough, fever, muscle soreness, shortness of breath, sore throat, headache, nausea and fatigue with symptom onset within 14 days before the first positive PCR test result.[12] An *asymptomatic* case was a confirmed case without COVID-19 compatible symptoms throughout the incubation and infection period. This period was counted from 14 days before the first SARS-CoV-2 positive test result until the first negative PCR test, in a series of three negative PCR tests, with at least 24 hours between each test. A *pre-symptomatic* case was defined as a confirmed case without COVID-19 compatible symptoms at the time of the first positive PCR test but who then developed symptoms during the course of infection. A *re-positive* case was defined as a patient who had tested positive, then negative and then returned to positive.

A close contact was defined as a person with direct contact (≤2 metres distance) with a confirmed case.[13] In Viet Nam, if the confirmed case had a flight travel history within 14 days from the date of symptom onset or date of confirmation, whichever came first, all passengers on those flights were categorized as close contacts and were tested for SARS-CoV-2 infection.

As per Ministry of Health guidelines, case severity was categorized as mild, severe or critical.[13] A *mild* case was a patient with COVID-19 symptoms who was conscious and did not require oxygen support. A *severe* case was a symptomatic patient who was conscious but required oxygen support. A *critical* case was an unconscious patient either being treated with mechanical ventilation or receiving extracorporeal membrane oxygenation. Patients who had a chronic medical condition (e.g. cardiovascular disease, cancer, chronic respiratory diseases or diabetes) were defined as having pre-existing conditions at the time of infection.

Among confirmed cases, the status of being free from SARS-CoV-2 infection began on the date of the first of three consecutive negative SARS-CoV-2 tests before discharge. We used a sampling interval of 1 day between each test.

Case finding and management

Cases were identified through PCR testing at the time of arrival in Viet Nam, during self-presentation at health facilities because of health concerns (due to travel history to regions recording confirmed cases) or through active case-finding measures among passengers and their contacts. All passengers on incoming flights from COVID-19 affected areas were tested for SARS-CoV-2 upon arrival and entered a mandated 14-day quarantine, irrespective of test results or symptoms. (The evolving test and quarantine policies for passengers arriving from affected areas into Viet Nam are included in **Supplementary Table 1**.) During this period, passengers could leave the airport without testing or quarantine if they did not depart from defined designated areas, and passengers were only contacted when any co-passengers were confirmed to be positive for SARS-CoV-2.

Any person who presented to health facilities with symptoms compatible with COVID-19 and who reported a travel history to COVID-19 affected areas within the past 14 days was directly transferred to a reference hospital for SARS-CoV-2 testing and quarantine. Once SARS-CoV-2 infection was confirmed, an in-depth epidemiological investigation and contact tracing were conducted. All identified close contacts of confirmed cases were advised to self-quarantine immediately at their residence until contacted by local health authorities. They were then tested for SARS-CoV-2 by PCR and were placed into compulsory quarantine at a designated site for 14 days, irrespective of the test result. All quarantined individuals were tested at the start of their quarantine (day 0) and then systematically on days 3–5 and day 14. An additional test was undertaken if an individual developed symptoms. Anyone who tested positive or became symptomatic was transferred to a reference hospital for isolation and treatment.

Statistical analysis

Data were cleaned using Microsoft Excel and exported to the statistical software package R version 3.6.3 for analysis.[14] Frequencies and percentages were used to describe the number of cases of each type (asymptomatic, pre-symptomatic and symptomatic), demographics and clinical symptoms in the study's time range. Pearson's chi-squared and Fisher's exact test were applied to compare demographic and clinical characteristics between re-positive and non-re-positive cases, and between cases with a negative test presenting with COVID-19 symptoms versus those without COVID-19 symptoms. The Kaplan-Meier estimator was used to assess time to clearance of SARS-CoV-2 infection; that is, the time between the date of symptom onset and the date of the first of three consecutive negative SARS-CoV-2 tests. Asymptomatic cases were excluded from this analysis. Log-rank tests were applied to explore the relationship between time to SARS-CoV-2 infection clearance and patients' age, sex, pre-existing conditions, inconsistent PCR results and clinical severity.

RESULTS

Among the first 50 COVID-19 cases in the second wave in Viet Nam, the proportions of pre-symptomatic, symptomatic and asymptomatic cases were 38%, 42% and 20%, respectively. Male (54%) and female (46%) representation was approximately equal. Vietnamese nationals accounted for 64% of cases. The prevalence of people under 30 years old in pre-symptomatic, symptomatic and asymptomatic groups was 15.8%, 57.2% and 50%, respectively. Most of the asymptomatic and symptomatic cases were less likely than the pre-symptomatic cases to have a pre-existing condition (**Table 1**).

Two thirds of cases (n = 34, 68%) were international arrivals, with the remaining cases identified locally (n = 16, 32%). Among international passengers, 23% (n = 8) were detected through airport screening, 56% (n = 19) were detected through case-finding activities among flight passengers and 21% (n = 7) were detected during self-presentation at health facilities. All 16 local cases were close contacts of international passengers and were detected by case-finding activities (**Supplementary Fig. 1**).

Supplementary Table 2 illustrates symptoms at onset and total numbers of symptoms during infection (combining symptoms at onset and during treatment or isolation) for the 40 pre-symptomatic and symptomatic cases. The most common symptom at onset was cough (70%), followed by fever (25%) and sputum production

Table 1. **Characteristics of COVID-19 cases by symptomatic category (*n* = 50)**

	Total		Pre-symptomatic		Symptomatic		Asymptomatic	
	n = 50	%	*n* = 19	%	*n* = 21	%	*n* = 10	%
Age, mean (SD)	40.6 (19.2)		48.6 (18.2)		35.1 (16.7)		36.7 (22.5)	
<20	4	8	2	10.5	1	4.8	1	10
20–29	16	32	1	5.3	11	52.4	4	40
30–39	8	16	2	10.5	4	19	2	20
40–49	3	6	3	15.8	0	0	0	0
50–59	8	16	5	26.3	2	9.5	1	10
60–69	7	14	5	26.3	2	9.5	0	0
70+	4	8	1	5.3	1	4.8	2	20
Sex								
Male	27	54	12	63.2	11	52.4	4	40
Female	23	46	7	36.8	10	47.6	6	60
Nationality								
Vietnamese	32	64	10	52.6	15	71.4	7	70
Other	18	36	9	47.4	6	28.6	3	30
Pre-existing condition								
Yes	12	24	6	31.6	4	19	2	20
No	38	76	13	68.4	17	81	8	80

SD: standard deviation.

(15%). Most cases experienced multiple symptoms, with 70% having more than one symptom and 15% having six or more symptoms.

Fig. 1 presents the clinical evolution and PCR results of SARS-CoV-2 testing during treatment or isolation in symptomatic, pre-symptomatic and asymptomatic cases. Among 40 (80%) patients who experienced symptoms during infection, eight (20%) were clinically classified as severe and four (10%) as critical. Three of the four critical cases had pre-existing conditions, namely, vestibular disorder, type 2 diabetes and hypertension.

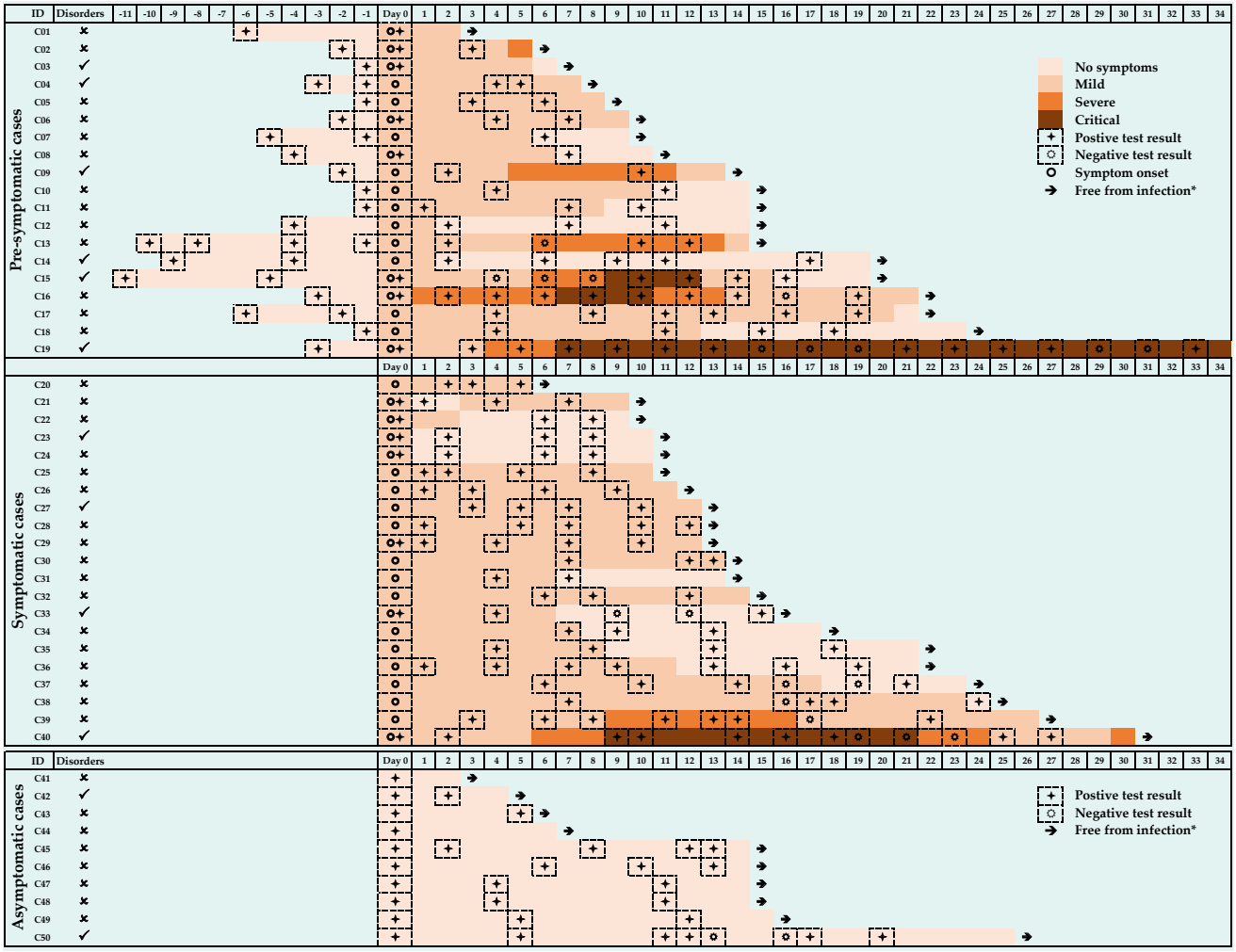
Ten cases (20%) returned a positive SARS-CoV-2 result after returning one or more negative result (re-positivity). The number of re-positive cases who were pre-symptomatic, symptomatic and asymptomatic was four, five and one, respectively. Most re-positive cases (90%) had one loop of reversion (i.e. one positive test after a negative test, then negative test results until being free from SARS-CoV-2). Only one re-positive case (case 19, who was pre-symptomatic at the time of testing) had more than one loop of reversion.

Eight cases (16%) still experienced COVID-19 symptoms after testing negative for SARS-CoV-2, among which four (50%) were symptomatic and four (50%) were pre-symptomatic at the time of testing.

The demographic and clinical characteristics of the 10 (20%) re-positive COVID-19 cases and eight (16%) cases who had COVID-19 symptoms after testing negative for SARS-CoV-2 are shown in **Table 2**. There was no significant difference in age, sex, nationality, pre-existing conditions and symptoms at onset between re-positive and non-re-positive cases. This was also observed among symptomatic cases who had a negative test versus cases without symptoms. Most re-positive cases and cases with COVID-19 symptoms after testing negative were categorized as severe or critical, and experienced more than two symptoms during infection.

The overall median duration from onset of symptoms to clearance of SARS-CoV-2 infection was 14 days (range: 6–31). Twenty days after symptom onset, 75% (30 cases) were free from SARS-CoV-2 infection (**Supplementary Fig. 2**).

Fig. 1. **The evolution of clinical symptoms and results of SARS-CoV-2 PCR tests during treatment of symptomatic, pre-symptomatic and asymptomatic cases in Viet Nam**



Cases are aligned by date of symptom onset for symptomatic and pre-symptomatic cases and date of first positive test for asymptomatic cases.

[a] "Free from infection" is defined as the date of the first of three consecutive negative SARS-CoV-2 tests before discharge, with a sampling interval of at least 1 day between each test.

Note: In the "Disorders" column, "✓": having at least one pre-existing condition and "×": free from pre-existing conditions.

The median duration until clearance of SARS-CoV-2 infection was 12 days (95% confidence interval [CI]: 11–20) for males and 14 days (95% CI: 13–22) for females ($P = 0.44$), and was higher in older people (14 days among all those aged 30 years and older, 10 days in those aged 30–44 years, 12.5 days in those aged 45–59 years, 20 days in those aged 60 years or more; $P < 0.001$) (**Fig. 2**).

The duration until SARS-CoV-2 clearance for re-positive cases was nearly double the duration for those without test conversion (22 days vs 13 days, $P = 0.00034$). Critical cases had a longer time to freedom from infection (26.5 days) than did mild cases (13 days) and severe cases (14 days) ($P = 0.015$) (**Fig. 3**).

DISCUSSION

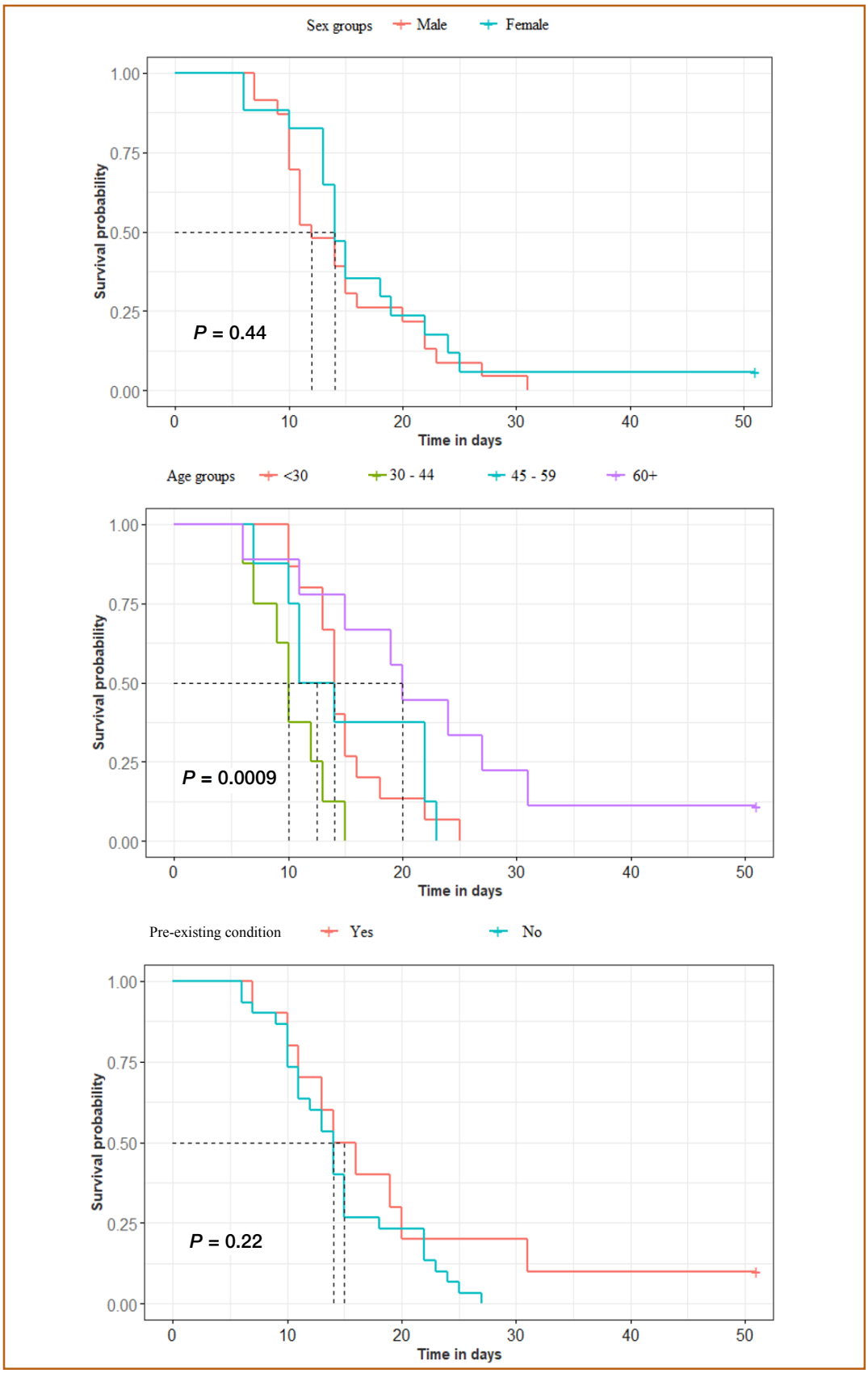
This study examined the clinical and laboratory findings of the first 50 SARS-CoV-2 confirmed cases at the start of the second COVID-19 wave in Viet Nam. There was a high prevalence of cases without compatible signs or symptoms of COVID-19 at the time of the first positive test (i.e. asymptomatic infections and pre-symptomatic infections). We found that 20% of cases tested positive following a negative result, and 16% of patients still experienced COVID-19 symptoms after testing negative for SARS-CoV-2. The median duration until clearance of SARS-CoV-2 infection was 14 days, with the duration being longer in older people, those with pre-existing conditions and re-positive cases.

Table 2. **Characteristics of COVID-19 cases with a re-positive PCR test and symptomatic cases with a negative PCR test (*n* = 50)**

Characteristics	Re-positive test		*P*†	Negative test with COVID-19 symptoms		*P*†
	No *n* (%)	Yes *n* (%)		No *n* (%)	Yes *n* (%)	
Demographics						
Age						
<45	26 (65)	3 (30)	0.10	28 (66.7)	1 (12.5)	0.01
45–64	8 (20)	5 (50)		8 (19)	5 (62.5)	
65+	6 (15)	2 (20)		6 (14.3)	2 (25)	
Sex						
Male	23 (57)	4 (40)	0.32	24 (57.1)	3 (37.5)	0.31
Female	17 (43)	6 (60)		18 (42.9)	5 (62.5)	
Nationality						
Vietnamese	25 (63)	7 (70)	0.66	27 (64.3)	5 (62.5)	0.92
Other	15 (38)	3 (30)		15 (35.7)	3 (37.5)	
Pre-existing condition						
Yes	7 (18.5)	5 (50)	0.03	9 (21.4)	3 (37.5)	0.33
No	33 (82.5)	5 (50)		33 (78.6)	5 (62.5)	
Disease characteristics						
Symptoms at onset						
Cough	23 (57.5)	5 (50)	--	23 (54.8)	5 (62.5)	--
Fever	7 (17.5)	3 (30)		7 (16.7)	3 (37.5)	
Headache	4 (10)	0 (0)		4 (9.5)	0 (0)	
Fatigue	4 (10)	0 (0)		4 (9.5)	0 (0)	
Sputum production	3 (7.5)	2 (20)		3 (7.1)	2 (25)	
Sore throat	2 (5)	2 (20)		3 (7.1)	1 (12.5)	
Chill	0 (0)	1 (10)		0 (0)	1 (12.5)	
Nasal congestion	0 (0)	1 (10)		1 (2.4)	0 (0)	
Diarrhoea	0 (0)	1 (10)		0 (0)	1 (12.5)	
Number of symptoms during infection						
1–2	24 (60)	6 (60)	1	26 (61.9)	4 (50)	0.53
>2	16 (40)	4 (40)		16 (38.1)	4 (50)	
Patient category						
Pre-symptomatic	15 (38)	4 (40)	0.66	15 (35.7)	4 (50)	0.3
Symptomatic	16 (40)	5 (50)		17 (40.5)	4 (50)	
Asymptomatic	9 (23)	1(10)		10 (23.8)	0 (0)	
Severity						
Asymptomatic	9 (23)	1 (10)	0.009	10 (23.8)	0 (0)	<0.001
Mild	28 (70)	4 (40)		29 (69)	3 (37.5)	
Severe	2 (5)	2 (20)		2 (4.8)	2 (25)	
Critical	1 (3)	3 (30)		1 (2.4)	3 (37.5)	

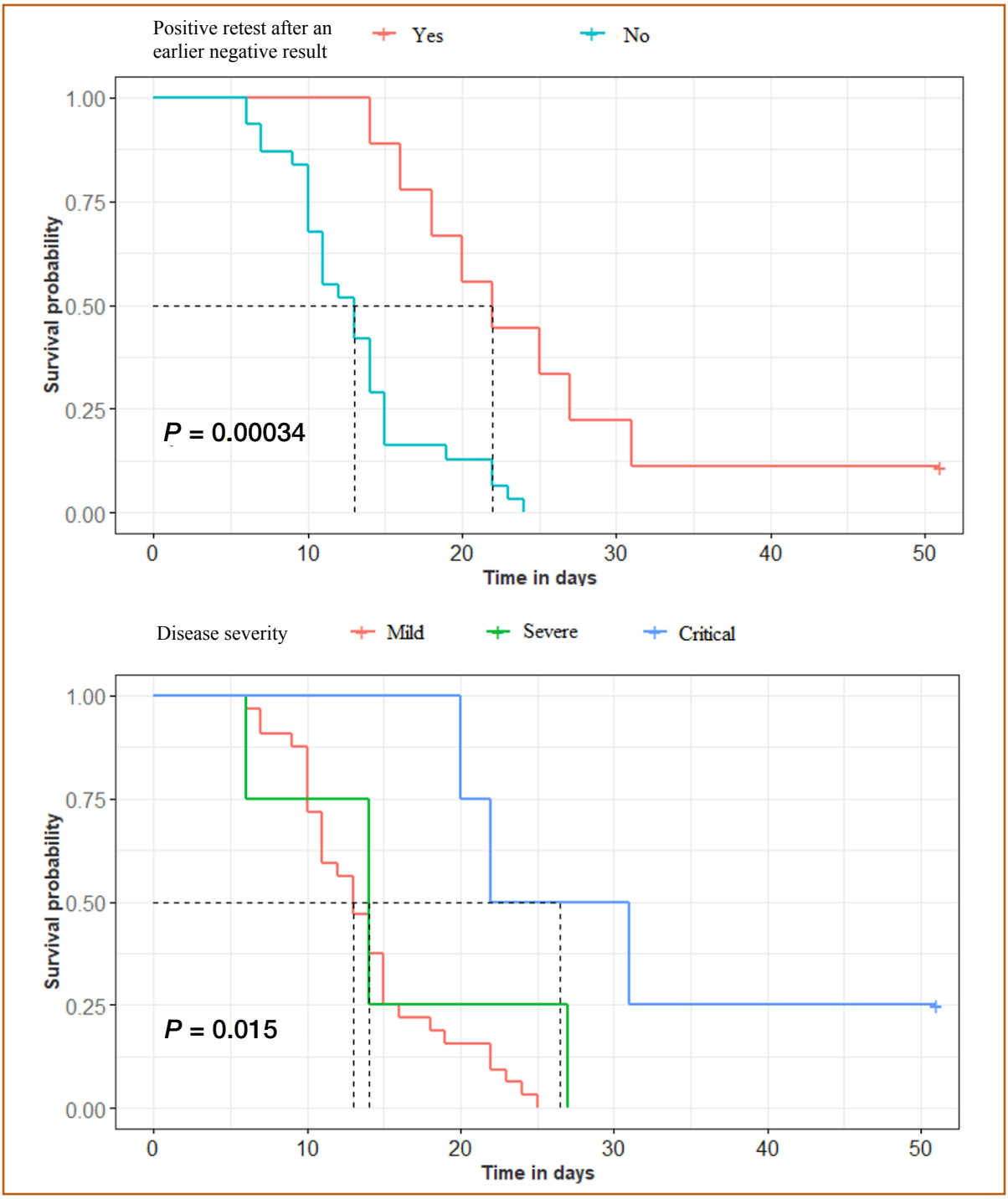
† Groups were compared using Pearson's chi-squared or Fisher's exact test.

Fig. 2. **Cumulative probability by sex, age and pre-existing condition of clearance of SARS-CoV-2 infection from the day of first positive laboratory test among 40 pre-symptomatic and symptomatic cases**



Survival probabilities were estimated using the Kaplan-Meier estimator and interpreted as the probability of clearance of SARS-CoV-2 infection (the probability of having the first of three consecutive negative SARS-CoV-2 tests). *P* values were calculated using log-rank tests.

Fig. 3. **Survival analysis by re-positivity and severity of 40 pre-symptomatic and symptomatic cases**



Survival probabilities were estimated using the Kaplan-Meier estimator and interpreted as the probability of clearance of SARS-CoV-2 infection (the probability of having the first of three consecutive negative SARS-CoV-2 tests). *P* values were calculated using log-rank tests.

The findings showed that 58% of cases did not exhibit compatible signs or symptoms of COVID-19 at the time of the first positive test, although fewer than half remained asymptomatic. This finding aligns with current published evidence of the expression of asymptomatic, symptomatic and pre-symptomatic cases.[15–17] The degree of SARS-CoV-2 transmission appears to vary among asymptomatic cases. A study in China showed that transmissibility from asymptomatic cases is comparable to that of symptomatic cases.[18] A study in Singapore suggested that people with asymptomatic COVID-19 might be less infectious than symptomatic cases.[19] Meanwhile, the World Health

Organization declared that asymptomatic cases are much less likely to transmit the virus than those who develop symptoms.[20] However, there is still a lack of comprehensive studies with representative samples on SARS-CoV-2 transmission during the asymptomatic period.

In our study, 20% of confirmed COVID-19 cases returned a positive SARS-CoV-2 result after one or more negative test result. Findings from China indicated that the prevalence of a positive test following a negative test was about 17% after discharge.[21,22] Most current evidence about re-positivity focuses on the recovery or post-discharge phase. However, re-positivity during hospitalization might contribute to the need for ongoing admission and repeat testing, and cause distress for both patients and health care staff, which has not been the focus of published studies to date. In this study, all critical cases returned to positivity during SARS-CoV-2 infection. Re-positive cases had a substantially longer duration until viral clearance, which aligned with current evidence.[21]

Although re-positive tests for SARS-CoV-2 in recovered COVID-19 patients are common, there is insufficient evidence about the underlying mechanism leading to a re-positive test.[23] Most reported re-positive results could not be explained as simple viral relapse or secondary infection.[24] Some potential reasons included virology (biological characteristics of the virus),[25] specimen issues (sample collection, processing, virus at the limit of detection)[26–28] or patient condition (underlying conditions, degree of infection, treatment methods).[29] A study in post-symptomatic individuals showed that persistent positivity is associated with elevated cellular immune responses, and thus the viral RNA may represent replicating virus.[30] However, transmission to close contacts was not observed. Other evidence suggested that re-positive cases are not infectious after an initial negative test, indicating that persistent PCR-positive individuals are not infectious at the post-symptomatic stage of infection.[11,31] However, further work is needed to understand the likelihood of transmission from these patients.

Our findings showed that several cases still experienced COVID-19 compatible symptoms after testing negative for the virus or even after meeting SARS-CoV-2 clearance criteria. Defining and measuring COVID-19 transmissibility should be more sophisticated than only checking for a negative test. It has been suggested that when determining criteria for discharge and ending isolation, health authorities should consider multiple factors such as symptom resolution, time elapsed since the onset of symptoms, disease severity, immune system response and evidence of viral RNA clearance from the upper respiratory tract.[32]

Viral shedding is used as a marker of infectivity when detected via an upper respiratory tract PCR sample a few days before symptom onset.[33] Viral shedding persists for varying periods of time, with a median duration of 11 days.[22] In our study, the median duration was 14 days. The viral shedding period in our study was defined as the day of diagnosis to the day of the first of three negative tests, each 24 hours apart; this excludes shedding before diagnosis. Although viral shedding has been identified during both the asymptomatic and symptomatic phases, its relation to transmissibility is unclear. Because real-time PCR cannot distinguish between infective virus and inactive virus, a positive PCR result does not necessarily represent the potential for viral transmission. The amount of viral RNA detected does not necessarily indicate greater infectivity.[33]

Older age and having pre-existing conditions have been reported as important independent predictors of worse outcomes in severe acute respiratory syndrome and Middle East respiratory syndrome.[34] Our results also confirmed that increased age and pre-existing conditions were associated with longer SARS-CoV-2 infection in COVID-19 patients, which is consistent with other findings.[35] Further in-depth studies are encouraged to explore additional factors related to the duration of SARS-CoV-2 infection.

We acknowledge that there were several limitations to this study. First, the relatively small number of cases and specific context might limit the generalizability of our study findings. Second, we acknowledge the lack of cycle threshold (Ct) values (the number of cycles necessary to detect the virus by PCR). Ct is a semi-quantitative value that categorizes the concentration of viral genetic material in a testing sample following PCR testing. This value indicates how much viral genetic material is in the sample: a low Ct indicates a high concentration of viral genetic material, which is typically associated with a high risk of infectivity and vice versa. Knowing this value might have helped us to understand re-positivity tests and to compare symptomatic, pre-symptomatic and asymptomatic

cases over time. Although Ct is important, this single value depends on several factors, including the quantity of specific gene targets and reagent variability, and other factors that do not reflect a person's infectivity in the absence of clinical context.[36] Large-scale, multicentre studies that include Ct values are required to explore the importance of this issue.

CONCLUSION

A high proportion of asymptomatic and pre-symptomatic infections were evident in the first 50 confirmed cases during the second wave of COVID-19 in Viet Nam. In this study, re-positive cases were common during hospitalization and had a long duration of SARS-CoV-2 infection. High-quality longitudinal studies to explore the transmissibility of re-positive and asymptomatic COVID-19 patients are needed.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics statement

The conduct of this analysis was approved by the National Institute of Hygiene and Epidemiology and was exempted by the institute's Institutional Review Board as part of routine outbreak investigation and response activities.

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COVID-19: Integrating genomic and epidemiological data to inform public health interventions and policy in Tasmania, Australia

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Objective: We undertook an integrated analysis of genomic and epidemiological data to investigate a large health-care-associated outbreak of coronavirus disease 2019 (COVID-19) and to better understand the epidemiology of COVID-19 cases in Tasmania, Australia.

Methods: Epidemiological data collected on COVID-19 cases notified in Tasmania between 2 March and 15 May 2020, and positive samples of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or RNA extracted from the samples were included. Sequencing was conducted by tiled amplicon polymerase chain reaction with ARTIC v1 or v3 primers and Illumina sequencing. Consensus sequences were generated, sequences were aligned to a reference sequence and phylogenetic analysis was performed. Genomic clusters were determined and integrated with epidemiological data to provide additional information.

Results: All 231 COVID-19 cases notified in Tasmania during the study period and 266 SARS-CoV-2-positive samples, representing 217/231 (94%) notified cases, were included; 184/217 (84%) were clustered, 21/217 (10%) were unique and 12/217 (6%) could not be sequenced. Genomics confirmed the presence of seven clusters already identified through epidemiological links, clarified transmission networks in which the epidemiology had been unclear and identified one cluster that had not previously been recognized.

Discussion: Genomic analysis provided useful additional information on COVID-19 in Tasmania, including evidence of a large health-care-associated outbreak linked to an overseas cruise, the probable source of infection in cases with no previously identified epidemiological link and confirmation that there was no identified community transmission from other imported cases. Genomic insights are an important component of the response to COVID-19, and continuing genomic surveillance is warranted.

Genomic sequencing for characterization of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was developed early during the coronavirus disease 2019 (COVID-19) pandemic.[1,2] Since then, genomics has been used internationally to understand the dynamics of viral transmission[3] and the genetic evolution of the virus.[4-6] Locally, genomic analysis has been used to analyse transmission routes, assign likely origins of infection, link outbreak cases and inform public health interventions and policies.[7–11]

Integrated analysis of genomic and epidemiological data provides additional benefits for public health investigations[12–14] and has been used during the COVID-19 pandemic.[9,14–16] Genomic sequencing of SARS-CoV-2 polymerase chain reaction (PCR)-positive diagnostic samples combined with epidemiological data has been shown to be beneficial in investigating health-care-associated infections,[9,17] monitoring community transmission,[8-10] informing public health responses[9,10,18] and understanding the pathology of the disease.[9,10,18]

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In Australia, integration of genomic sequencing into the response to COVID-19 has allowed clusters and outbreaks to be identified and transmission chains to be rapidly detected.[9] Genomic data enhance national surveillance data by clarifying the source of infection in outbreak settings and in cases with no known source of infection, by characterizing clusters of disease transmission[5] and by providing evidence of the introduction of lineages into Australia and any changes in cases acquired locally and overseas.[19]

Tasmania, an island state of Australia with a population of approximately 540 000, had one of Australia's first documented health-care-associated outbreaks of COVID-19. The first case of COVID-19 in Tasmania was notified on 2 March 2020. By 2 April 2020, a total of 80 cases had been notified, the distribution approximating the geographical distribution of the population throughout the state. Epidemiological investigations indicated that most infections had been acquired overseas (68/80, 85%), with a small number acquired locally after exposure to a known case (4/80, 5%) and 8 (10%) cases under investigation at the time (Internal reports, Department of Health Tasmania, 2020). On 3 April 2020, two cases were notified in health-care workers (HCWs) in a hospital in northwest Tasmania, and a third was notified the following day. These three cases signalled the beginning of a large outbreak that occurred among three health-care facilities and resulted in 138 cases.[20,21] At the time, the outbreak of COVID-19 was the largest to have occurred in a health-care facility in Australia, and public health investigations were critical to both control the outbreak and inform future public health actions.

To provide further evidence for the public health investigation and management of the outbreak in northwest Tasmania and to better understand the epidemiology of all COVID-19 cases in the state, the Tasmanian Department of Health in collaboration with the Microbiological Diagnostic Unit Public Health Laboratory (MDU) undertook an integrated analysis of genomic and epidemiological data for COVID-19 cases in Tasmania. This paper describes the findings.

METHODS

COVID-19 cases notified to the Tasmanian Department of Health between 2 March and 15 May 2020 were included in the analysis. PCR-positive samples for SARS-CoV-2, or extracted RNA if such samples were not available, were referred to the MDU with any epidemiological data that had been collected and were stored in the Tasmanian Government's COVID-19 database. Epidemiological clusters were defined as two or more COVID-19 cases that were linked by person, place and/or time, cases linked to an international cruise or cases linked to an interstate cluster.

The epidemiological data were analysed with STATA v14. They comprised demographics; onset date; whether the case resided in an aged-care facility or was a health or aged-care worker and, if so, whether they had worked in the 24 hours and/or 14 days before onset; whether the case was linked to a cluster and, if so, the outbreak code; whether they had travelled overseas or interstate and the countries or jurisdictions visited; whether they had had contact with a known case; and place of acquisition (if known) or whether no source was identified.

Sequencing and phylogenetic analyses were conducted as described by Seemann et al. Briefly, RNA extracted from SARS-CoV-2 reverse transcription PCR-positive samples underwent tiled amplicon PCR with ARTIC (version 1 or 3) primers. Sequencing libraries were prepared from amplicons with NexteraXT and sequenced on Illumina NextSeq. Reads were aligned against a SARS-CoV-2 reference genome (MN9008947.3 Wuhan Hu-1), and consensus sequences were generated. Quality control for consensus sequences included requiring 80% of the genome to be recovered, 25 single nucleotide polymorphisms from the reference genome and ≤300 ambiguous or missing bases. Sequences with 65–80% genome recovery were assessed for potential inclusion in the phylogenetic analysis. A maximum likelihood algorithm was used for phylogenetic reconstruction. Genomic clusters were determined with ClusterPicker and curated with the cleaned epidemiological data. Each confirmed case was assigned a genomic cluster identifier

which was uploaded onto the Tasmanian COVID-19 database. Further analysis was conducted with STATA v14 to compare epidemiological clusters with the identified genomic clusters, unique cases and those that could not be sequenced.

RESULTS

Epidemiological clusters

Twelve epidemiological clusters were identified in Tasmania before the genomic analysis. One was a cluster seeded from a returned international traveller (EC01), six were linked to separate overseas cruises (EC02–EC06, EC12), one was a case linked to an interstate cluster (EC07) and four were part of the northwest outbreak – the main outbreak of 129 cases and smaller linked clusters at an aged-care facility, within the community and at an additional hospital (EC08–EC11) (**Table 1**).

Genomic clusters

The 266 SARS-CoV-2-positive samples were referred to the MDU, representing 217 of the 231 cases (94% of all cases) notified during the study period. Fourteen samples were not referred because of insufficient sample volume or very high cycle threshold (correlated with low levels of virus in the sample). Of the 217, 184 were part of a genomic cluster, 21 were unique (singletons) and 12 could not be sequenced (i.e. did not meet the sequencing quality control criteria).

Eight genomic clusters were identified, clusters A–G (including two subclusters, A.1 and A.2), ranging in size from 2 to 149 cases (**Fig. 1**); all but one genomic cluster corresponded to epidemiological clusters or known travel partners (**Table 1**; **Fig. 2**).

Genomic cluster A

The largest genomic cluster, cluster A, corresponded to cases from overseas cruise A (EC02) and the large northwest outbreak (EC08-EC11), confirming that the northwest outbreak was seeded from infections originally acquired on overseas cruise A. Two travellers on this cruise were admitted to hospital A in northwest Tasmania and were in genomic cluster A – one in each of the subgroups A.1 and A.2. The ship had travelled from Sydney to New Zealand with approximately 2700 passengers, of whom approximately 900 subsequently developed COVID-19.[22] This genomic cluster had two subgroups (A.1 and A.2 below) with dates of onset of 8 and 17 March, respectively (**Fig. 1**). Clusters A.1 and A.2 were very closely related, separated by one cluster-defining single nucleotide polymorphism.

Genomic cluster A.1

Genomic cluster A.1 comprised 29 cases, including 17 returned overseas cruise A passengers (one of whom was admitted to hospital A and was thought to have been one of the index cases of the northwest outbreak), five HCWs from hospital A, six of their household contacts and a case not linked epidemiologically to the northwest outbreak. These corresponded to cases in EC02 and EC08.

Five cases in this cluster, all returned overseas cruise A passengers, were hospitalized (four at a hospital in southern Tasmania and one at hospital A), of whom two were admitted to an intensive care unit and two died. Three of the HCWs from hospital A reported having worked while symptomatic. The number of cases in cluster A.1 was highest in March, and cases continued to be detected until mid-April.

The unlinked case was a HCW from another hospital in northwest Tasmania, with no identifiable source of infection, despite extensive public health investigations. All HCWs who had worked at the hospital during their period of acquisition had done so before overseas cruise A docked in Sydney. The infection was thought to have been acquired during unidentified contact with a returned overseas cruise A passenger or a secondary case in the days before symptom onset. This case was not linked epidemiologically to any subsequent case.

Genomic cluster A.2

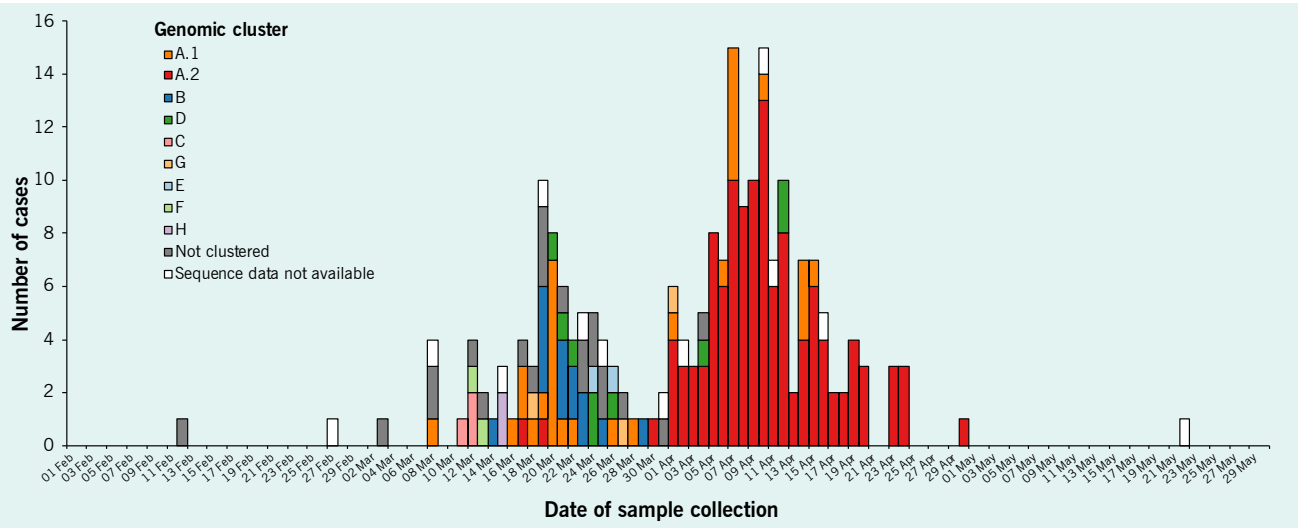
Genomic cluster A.2 comprised 120 cases and consisted of another overseas cruise A passenger who was also admitted to hospital A and 119 cases associated with the northwest outbreak. This subcluster comprised 72 staff members, 23 patients and 24 of their contacts (linked to hospital cases but who were not admitted to the hospital) and the one overseas cruise A case, corresponding to one case from EC02 and cases from the other northwest outbreak clusters (EC08–EC11).

Table 1. **Tasmanian COVID-19 epidemiological and genomic clusters, 2 March–15 May 2020**

Epidemiological cluster ID	Number of epidemiologically linked cases	Epidemiological links	Genomic cluster
EC01	3	Index case acquired overseas; transmission on local cruise	C
EC02	22	Overseas cruise A	A.1 and A.2
EC03	15 (14 on cruise plus one secondary case)	Overseas cruise B	B
EC04	1	Overseas cruise C	Not clustered
EC05	1	Overseas cruise D	Sequencing failed
EC06	9	Overseas cruise E	D
EC07	1	Local case linked to interstate cluster	G (one of the three cases in this genomic cluster)
EC08	129	Northwest outbreak	A.1
EC09	1	Northwest outbreak cluster 1; aged-care facility (index case in EC08)	A.2
EC10	6	Northwest outbreak cluster 2; community cluster (index case in EC08)	A.2
EC11	2	Northwest outbreak cluster 3; additional hospital (index case in EC08)	A.2
EC12	1	Overseas cruise F	Not clustered

Note: Not all cases linked to the epidemiological clusters were submitted for genomic analysis; therefore, the numbers of cases per epidemiological cluster do not always add up to the number by genomic cluster.

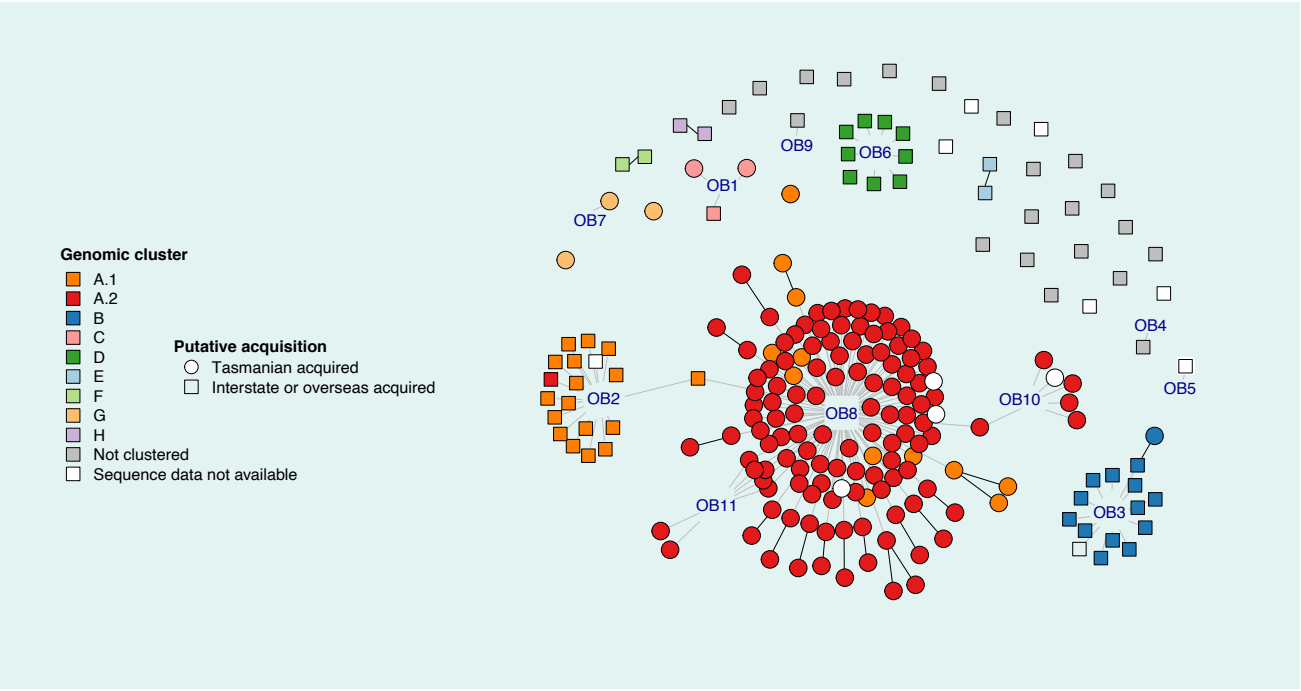
Fig. 1. **Epidemic curve of Tasmanian COVID-19 cases by genomic cluster**



Of the 72 staff members, 57 worked at hospital A, six at a co-located private hospital and two at the neighbouring hospital; seven staff worked at more than one of these facilities. Five cases were part of a community cluster linked to hospital A (EC10), two were part of a cluster at the neighbouring hospital (EC11) and one from an aged-care facility was linked to a case at hospital A (EC09). Cluster A.2 was first detected in mid-March, with the outbreak peaking in the second week of April.

Almost one quarter of the cases (n = 28; 23%) were hospitalized, although 19 were infected as inpatients at the hospital, and one was admitted to an intensive care unit. There were 10 deaths: the returned cruise passenger and nine inpatients. Most of the cases in this subcluster (n = 95; 79%) reported having had contact with a confirmed case, and 72 had been identified as contacts before infection. The first three notified cases were in HCWs who had had no direct contact with a case. Twelve

Fig. 2. **Tasmanian COVID-19 cases by epidemiological link, genomic cluster and putative source of acquisition, 2 March–15 May 2020**



cases associated with the outbreak, including 10 HCWs, were already experiencing symptoms of COVID-19 by the time the first two hospital-acquired cases were notified to the Tasmanian Department of Health.

Genomic clusters B–H

The remaining genomic clusters (B–H) ranged in size from 2 to 17 people, and, aside from cluster G, all had identified epidemiological links to specific sources, such as other cruise ships or travelling companions who had recently returned from interstate or overseas (**Tables 1** and **2**).

Genomic clusters B and D

These two genomic clusters were associated with two separate overseas cruises, comprising 14 and nine cases, respectively, and corresponded to EC03 and EC06. All but one case in cluster B acquired COVID-19 while on the cruise. The additional case in cluster B was a contact of a case from the cruise.

Genomic cluster C

This genomic cluster, comprising the cases from EC01, was associated with a group that travelled on a yacht tour of the east coast of Tasmania. The index case had just returned from an overseas trip to Canada, where they probably acquired COVID-19 infection. Two further cases were infected during the overnight tour.

Genomic cluster E

Cluster E comprised two co-travellers within Australia who were linked epidemiologically but not defined as an epidemiological cluster. The onset of the two cases occurred within two days; one case was hospitalized.

Genomic clusters F and H

Genomic clusters F and H also comprised two people each, who were co-travellers who had acquired their infection overseas. These two clusters were also linked epidemiologically but not defined as an epidemiological cluster. One couple had travelled to the USA and the other to Germany and the United Arab Emirates. None of these cases was hospitalized.

Genomic cluster G

Genomic cluster G contained three cases not epidemiologically linked before the genomic analysis. One case was epidemiologically linked to two travellers from Queensland while infectious and corresponded to EC07,

Table 2. **Characteristics of COVID-19 genomic clusters, Tasmania, 2020**

Genomic cluster ID (number of cases)	Onset date range (duration in days)	No. asymptomatic	No. in hospital	No. of COVID-19 deaths	No. of health-care workers[a]	Contact with COVID-19 case in 14 days before symptom onset	Identified as contact before infection	Place of acquisition
A.1 (n = 29)	8 March–14 April (38)	1	5 (all cruise), 2 in ICU	2 (cruise)	6	27 (5 HS, 6 non-hospital, 17 other)	27 (4 HS, 6 non-hospital, 17 other)	17 overseas 12 Tasmania
A.2 (n = 120)	17 March–24 April (39)	6	28 (6 HS, 20 patients)	10 (10 patients)	72	95 (56 HS, 16 patients, 23 other)	72 (41 HS, 10 patients, 20 non-hospital, 1 cruise)	1 overseas 119 Tasmania
B (n = 14)	14 March–25 March (12)	1	0	0	3	14	14	13 overseas 1 Tasmania
C (n = 3)	11 March–12 March (2)	0	2	0	0	3	2	1 overseas 2 Tasmania
D (n = 9)	20 March–4 April (26)	0	1	0	1	9	9	9 overseas
E (n = 2)	24 March–26 March (3)	0	1 ICU	0	0	1	1	2 Australia
F (n = 2)	12 March–13 March (2)	0	0	0	0	0	0	2 overseas
G (n = 3)	18 March–1 April (15)	0	0	0	0	1	1	3 Tasmania
H (n = 2)	15 March (1)	0	0	0	0	0	0	2 overseas
Non-clustered cases (n = 21)	12 February–4 April (NA)	0	2	0	2	6	2	2 cruise 18 overseas 1 Australia[b]
N/S (n = 12)	27 February–16 April (NA)	1	3 (2 NW outbreak)	1 (NW outbreak)	2	5	5 (2 cruise, 2 NW outbreak, 1 community cluster)	3 cruise 5 overseas 4 Australia[b]

N/S: sequencing not successful; HS: hospital staff; ICU: intensive care unit; NW: northwest

[a] Indicates whether the case is a HCW, not where their infection was acquired.

[b] Australia other than Tasmania

while the source of infection was not identified for the other two cases. Two of the cases were employed in jobs that required close contact with the public (taxi driver and tour bus driver), while the other was a tourist. All three were in the southern Tasmania area at the same time as the Queensland cases, although no clear epidemiological link was found between two of the cases and the Queensland travellers. Sequencing results uploaded to Australia's platform for real-time analysis of integrated pathogen genomic data for public health, AusTrakka,[23] have since confirmed that the cluster G cases were closely related to interstate samples from Queensland, Victoria, New South Wales and South Australia.

Non-clustered cases

There were 21 cases with unique genomic sequences and onset dates between 12 February and 4 April 2020. The group included four of the initial cases notified in Tasmania (**Fig. 1**). All were travel-related cases: two cases had travelled on different cruise ships (one each from EC04 and EC12), 18 had travelled internationally and one had travelled to Victoria. The cases had visited 15 different countries, and nine had travelled to several countries (**Table 2**, **Fig. 2**). Six cases (29%) reported having had contact with confirmed COVID-19 cases: two were household contacts and four were travel con-

tacts. All the cases were symptomatic, and two were hospitalized; there were no deaths.

There were two cases in the group that had travelled together, each initially nominated as a contact of the other. They had travelled to Europe (Austria, England and Italy); they had onset of infection days apart but had unrelated genomic sequences.

Cases that could not be sequenced

Samples from 12 cases could not be sequenced: seven were in the epidemiological clusters, and the remaining five had travelled overseas; none reported known contact with a confirmed COVID-19 case (**Fig. 2**). Those in known clusters included three from separate cruises (one each from EC02, EC03 and EC05) and four from the northwest outbreak (two patients and one staff member from EC08 and one that was part of the community cluster EC10). The onset dates ranged from 27 February to 16 April (**Fig. 1**).

DISCUSSION

We used genomic sequencing to add further evidence to the epidemiological data collected on COVID-19 cases in Tasmania, Australia. We were able to illustrate transmission routes within the state, from when the first case was notified through to when Tasmania effectively eliminated the virus. We found 31 groups of SARS-CoV-2 genomic sequences in 217 cases notified in Tasmania (eight genomic clusters, one split into two subclusters and 23 singletons unrelated to other cases by genomics), reflecting the broad travel histories associated with the cases.

The most valuable information provided by this study was that a large health-care-associated outbreak in northwest Tasmania was seeded from overseas cruise A, as initially hypothesized in the case series review.[20] Two separate transmission pathways were identified from overseas cruise A passengers admitted to hospital to HCWs, which then spread to two other hospital campuses, to close contacts of the HCW cases and to a limited extent into the community. This genomic cluster continued from early March to late April and ended after initiation of control measures, including hospital closure, cleaning and disinfection, a 14-day regional lockdown, quarantining of contacts and their households and screening of hospital staff before they returned to work.

Three cases linked by genomic analysis were not previously epidemiologically linked, suggesting limited community transmission relatively early in the outbreak in Tasmania (18 March to 1 April), when most other cases were in returned international travellers. These three cases were linked geographically and temporally and had exposures related to travel or tourists. More recent sequencing has shown that these cases are linked to interstate samples, demonstrating the importance and utility of sequence-sharing between jurisdictions for public health. Similarly, a previously unrelated case was linked to the first subcluster of the overseas cruise A/health-care-associated outbreak. After intensive review of the data, community transmission is also considered to be the most likely source of infection in this case.

Genomic analysis added value by quantifying the effectiveness of Tasmania's public health interventions. Aside from the transmission described above, genomic analysis found no evidence of community transmission in Tasmania by the other 113 cases in returned travellers, highlighting the success of quarantine, contact-tracing and testing procedures in the state.

Integration of genomic sequence data with epidemiological data improves understanding of SARS-CoV-2 transmission patterns and outbreak dynamics.[24] Routine inclusion of genomic data into public health surveillance can inform interventions and monitor their success,[9] indicate the likely source of infection in outbreaks or in cases with no known source and highlight patterns of transmission in populations.[25] The analyses were conducted retrospectively in Victoria; however, Tasmania has since developed genomic capacity locally, which will improve the timeliness of future outbreak investigations. Genomics can also play an important part in monitoring the evolution of SARS-CoV-2 over time and changes in its pathogenicity, immunogenicity or transmissibility.[25,26] Genomic surveillance will also be critical in monitoring selective pressure from vaccines as they are rolled out.[26,27]

A major strength of our study was our ability to combine genomic sequence with epidemiological data for 94% of the Tasmanian COVID-19 cases. A high rate of genomic sequencing was achieved because genomic surveillance programmes were already in place for other priority public health pathogens, with strong partnerships and capabilities among key organizations, providing the necessary infrastructure, governance and

referral arrangements and laboratory expertise for rapid development and scaling-up of genomic surveillance for COVID-19. These working relationships will be crucial to the success of continuous genomic surveillance, use of genomics in the prevention and control of future SARS-CoV-2 outbreaks[10] and the development of local genomics capacity.

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Conflicts of interest

As an editor of WPSAR is an author, another editor on the editorial team managed this publication.

Ethics statement

Epidemiological and genomics data were collected in accordance with the Tasmanian Public Health Act 1997. Ethical approval was received from the University of Tasmania Human Research Ethics Committee (project number 20079) and the University of Melbourne Human Research Ethics Committee (ID 1954615.3).

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Lessons learnt from the first large outbreak of COVID-19 in health-care settings in Tasmania, Australia

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Problem: One month after the initial case of coronavirus disease 2019 (COVID-19) in Tasmania, an island state of Australia, two health-care workers (HCWs) from a single regional hospital were notified to public health authorities following positive tests for SARS-CoV-2 nucleic acid. These were the first recognized cases in an outbreak that overwhelmed the hospital's ability to function.

Context: The outbreak originated from two index cases. Both had returned to Tasmania following travel on a cruise ship and required hospital admission for management of COVID-19. A total of 138 cases were subsequently linked to this outbreak: 81 HCWs (most being nurses) and 23 patients across three hospitals, one resident of an aged-care facility and 33 close contacts.

Action: The outbreak was controlled through the identification and isolation of cases, identification and quarantining of close contacts and their household members, closure of the affected facilities and community-level restrictions to reduce social mixing in the affected region.

Lessons learnt: Factors that were likely to have contributed to ongoing transmission in this setting included workplace practices that prevented adequate physical distancing, attending work while symptomatic, challenges in rapidly identifying contacts, mobility of staff and patients between facilities, and challenges in the implementation of infection control practices.

Discussion: Many commonly accepted hospital practices before the COVID-19 pandemic amplified the outbreak. The lessons learnt from this investigation changed work practices for HCWs and led to wider public health interventions in the management of potential primary and secondary contacts.

PROBLEM

On 19 March 2020, 2671 passengers and 1146 crew disembarked from a cruise ship after a 12-day international cruise that began and ended in Sydney, Australia; they then travelled on to other destinations.[1] Two thirds of the passengers were Australian; of these, 40% were subsequently diagnosed with coronavirus disease 2019 (COVID-19), including 18 who were diagnosed after returning to Tasmania, an island to the south of mainland Australia with a population of 528 000. Two of these Tasmanian cases were admitted to a regional public hospital on the northwest coast (Hospital 1) for management of their illness. Both were later identified as index cases of an outbreak that ultimately affected another 138 people comprising health-care workers (HCWs), patients and other close contacts. The outbreak led to the closure of Hospital 1; it also affected staff and patients at the co-located private hospital (Hospital 2), a smaller public hospital 56 km away (Hospital 3) and a residential aged-care facility 48 km away (**Fig. 1**). Here we describe the outbreak, possible transmission and lessons learnt from this early outbreak in Australia.

CONTEXT

The Tasmanian outbreak was the first large COVID-19 outbreak to occur in Australia within a health-care setting that demonstrated ongoing transmission between HCWs. Tasmania's initial COVID-19 case was notified on

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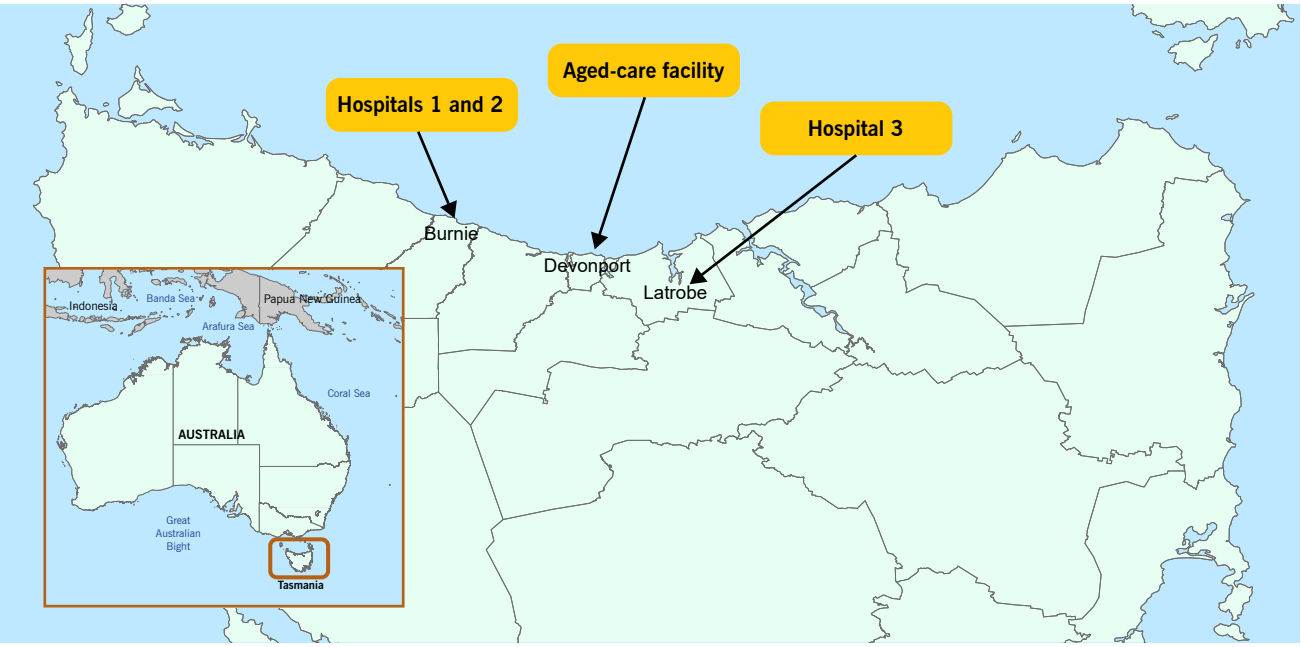
Fig. 1. **Map of Australia showing Tasmania (inset) and the northern coast of Tasmania showing the locations of the health-care facilities involved in the outbreak**



2 March 2020, and there was no community transmission in Tasmania at that time. HCWs are at risk of acquiring COVID-19 infection from their patients and of subsequently instigating or amplifying outbreaks within the health-care setting.[2,3] In recognition of the anticipated increased risk posed by the pandemic, hospitals in Tasmania had strengthened infection prevention and control procedures even though, before this outbreak, only nine patients with COVID-19 had been managed in a hospital in Tasmania.

Description of outbreak

Outbreak cases were defined in accordance with Australian national guidelines[4] as persons with laboratory confirmation of COVID-19 by nucleic acid testing from a deep nasopharyngeal swab, with onset of illness on or after 19 March 2020, who had a direct or indirect epidemiological link to any of the three health-care facilities (Hospitals 1–3) in the northwest region of Tasmania. All laboratory-confirmed cases were notified to Public Health Services (PHS), Tasmanian Department of Health, for public health response, as required by legislation. Cases were contacted to collect information about age, sex, occupation and risk factors for acquisition of infection, and to identify close contacts, as defined by the national guidelines.[4] Employment records were used to determine the number of staff by occupational group at Hospital 1 to estimate attack rates among clinical occupational groups.

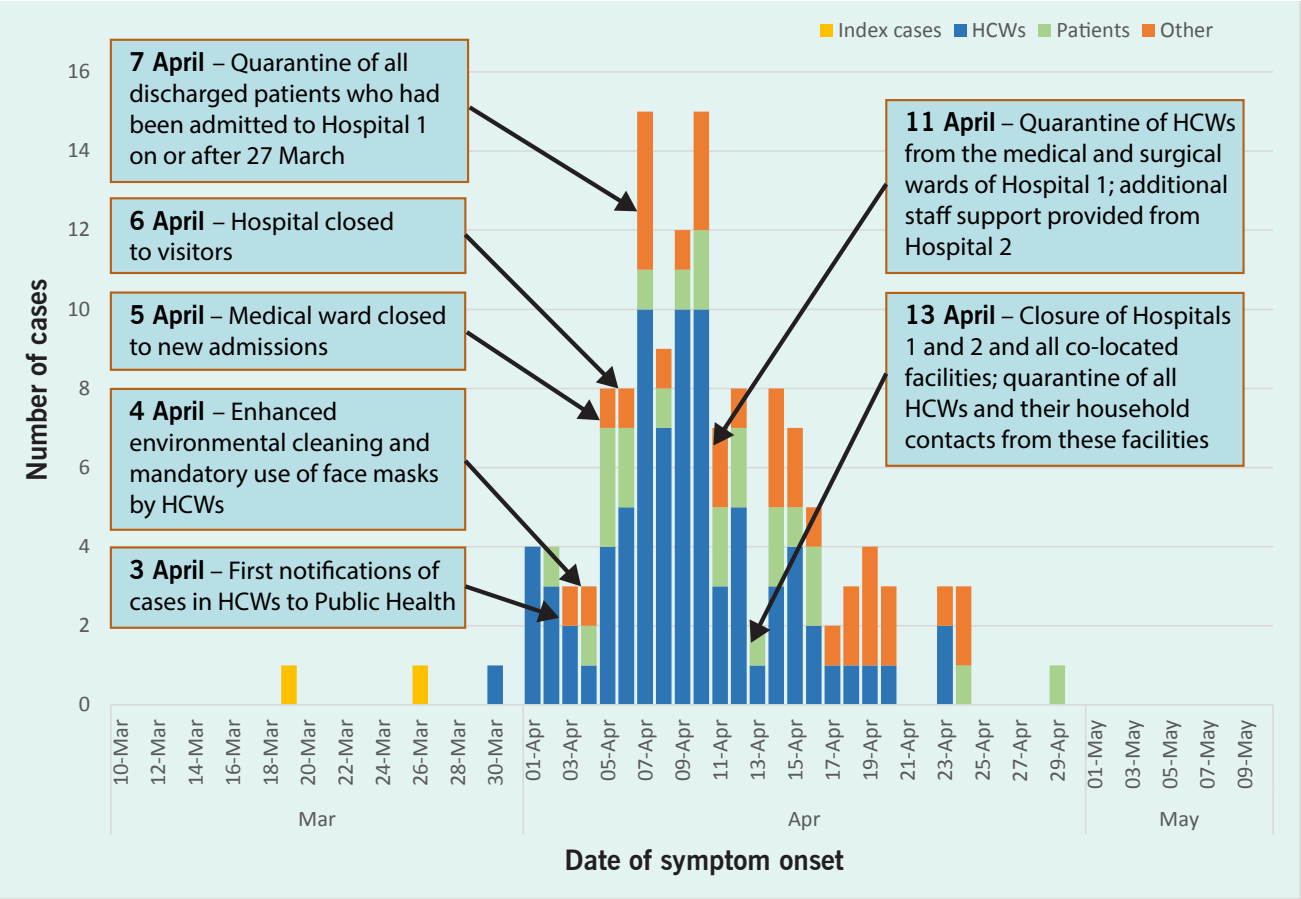
The two index cases were admitted to the medical ward of Hospital 1 for the management of COVID-19 on 20 and 26 March 2020. Their respective dates of diagnosis and notification to the Department of Health were 19 and 26 March. The two initial cases in HCWs were notified on 3 April 2020, with a third HCW case notified the following day. All three HCW cases worked on the medical ward of Hospital 1, although none provided direct care to the two index patients. Thereafter, daily COVID-19 case numbers increased rapidly for 10 days before declining (**Fig. 2**).

A total of 138 cases and 10 deaths were linked to the outbreak. Of the cases, 81 were HCWs, 23 were patients across the three hospitals, one was a resident of the aged-care facility and 33 were close contacts. The close contact cases included a small community cluster of six cases initiated from a discharged patient. The age and sex distributions of cases are shown in **Table 1**.

Cases among HCWs

Of the 81 cases among HCWs, 72 (89%) worked within Hospital 1, some of whom also worked at other facilities during the outbreak period, and 49 (60%) were nurses.

Fig. 2. **Epidemic curve of COVID-19 cases associated with the northwest outbreak in Tasmania, Australia, March to May 2020**



HCW: health-care worker (all HCWs including medical, nursing, allied health, administration, technical support and catering staff); Patients: people who acquired the illness while staying in one of the health-care facilities; Other: all other linked cases, mostly household contacts of HCWs.

Table 1. **Age and sex distribution of cases by group, hospitalization and death**

		All	Health-care workers	Patients[a]	Other[b]	Hospital cases[c]	Deaths
Total		138	81	24	33	29	10
Sex	Female	85	61	7	17	12	5
	Male	53	20	17	16	17	5
Age group (years)	0–19	6	–	–	6	–	–
	20–49	67	52	1	14	2	–
	50–69	41	28	5	8	9	–
	70+	24	1	18	5	18	10

[a] Includes people being treated in hospital or residents in an aged-care facility.

[b] Includes household and other close contacts of people with COVID-19 infection.

[c] Includes people who acquired the illness as inpatients and those who acquired the illness out of hospital but required admission for treatment of COVID-19.

Cases also occurred among medical and allied health practitioners, and among people working in maintenance, administrative and catering services, but none were identified among cleaning staff. The attack rates at Hospital 1 were 16/98 doctors (16%) and 43/393 nurses (11%). Seven HCWs required admission to hospital for management of their illness and all were subsequently discharged.

Affected HCWs worked across facilities in the co-located medical precinct of Hospitals 1 and 2 (including in pathology collection and outpatient services) and in health-care facilities in other locations. The median number of different clinical settings where individual staff worked during their infectious period was 1 (range 1–7). A total of 40 (49%) HCW cases did not attend work while symptomatic, 26 (32%) first had symptoms on their last day at work and 15 (19%) attended work while symptomatic for time periods of 1–7 days. Seven asymptomatic cases were identified during the outbreak, mostly through the requirement for testing before resuming work when Hospital 1 was reopened.

Pathways of transmission

The initial cases notified to PHS occurred in staff primarily working on the medical ward of Hospital 1. Ten HCWs had onset of symptoms between 30 March and 3 April, before identification of the first HCW cases, and at least two of these HCWs recalled providing direct care to one of the two index cases during their acquisition period. These early cases included medical, nursing and allied health staff who attended daily nursing and medical handover meetings conducted in confined spaces. Several other clusters among HCWs were identified among attendees of regular meetings, such as administrative or clinical planning meetings.

Cases also occurred in the co-located Hospital 2 (9 HCWs and 6 patients); among these cases, six (5 HCWs and 1 patient) had no link to other health-care facilities. Fourteen cases were associated with Hospital 3 (4 HCWs and 10 patients), of whom three (2 HCWs and 1 patient) could only have acquired the infection at Hospital 3, whereas the remainder had either worked at or had also been admitted to Hospital 1. The single case from the residential aged-care facility acquired COVID-19 from a HCW who had previously worked at both Hospitals 1 and 2.

ACTION

A description of the management of the outbreak has been published elsewhere,[5] and key elements are summarized here. Following the initial notifications, emergency response teams were established at Hospital 1 to identify and quarantine close contacts of cases and manage the outbreak consequences in the hospital. Concurrently, the Public Health Emergency Operations Centre (PHEOC) increased its workforce of contact-tracing personnel, public health nursing and medical staff, and epidemiologists, to manage the escalating numbers of cases and contacts requiring investigation. Staff were sourced through government interoperability arrangements and secondment agreements with the University of Tasmania.

Initial interventions at the hospitals included enhanced environmental cleaning, use of surgical face masks by all HCWs in the medical and surgical wards in Hospital 1, and prohibition of visitors to Hospitals 1 and 2. Interventions escalated rapidly as case numbers continued to increase. On 7 April 2020, admission of new patients to the medical and surgical wards of Hospital 1 ceased, and external specialist support was increased, including an infectious disease physician and a mobile PHEOC team comprising a public health physician, an epidemiologist and a clinical nurse consultant. On 10 April, all remaining HCWs from the medical and surgical wards, who had not already been identified as close contacts, were placed in quarantine.

By 12 April, cases had been identified across most clinical areas of Hospital 1 (including medical, surgical and mental health wards, and operating theatres), Hospital 2, and in the pathology service and outpatient clinics co-located with these facilities. On 13 April, Hospitals 1 and 2 and related campus medical services were closed, with patients transferred to other facilities, including Hospital 3. All HCWs who had worked in Hospitals 1 and 2 and co-located facilities from 27 March (approximately 1300 people) and their household members (an estimated additional 3000–4000 people) were placed in quarantine at home for 14 days. This was the first example of the quarantining of secondary close contacts for outbreak management in Australia.

Community restrictions were also implemented on 12 April to reduce social mixing in the affected region. This included a 14-day closure of all non-essential retail

businesses, the strictest restrictions in Australia at the time.[5] The Australian Defence Force provided temporary emergency department services while Hospital 1 was cleaned, recommissioned and reopened.

These control measures were followed by a reduction in the number of new cases over the following days. The outbreak was declared over on 6 June, after two incubation periods (i.e. 28 days) had passed with no new cases.

LESSONS LEARNT

We identified several factors that contributed to and amplified the spread of COVID-19 through the health-care settings.

Physical distancing

The nature of clinical work in a hospital makes it difficult to maintain physical distancing between staff, and between patients and staff. Studies have found no difference in seroprevalence rates between frontline and non-frontline staff, highlighting transmission routes outside of direct patient care, such as from staff to staff.[6,7] These factors were illustrated in this outbreak by the clustering of cases among attendees of recurring events such as nursing handovers and discharge planning meetings.[5] The higher attack rates in doctors at Hospital 1 might be attributable to the sharing of offices, daily visits to most hospital wards, ward rounds in small groups that huddle around a computer screen and attendance at meetings. Hospital meeting places are often small, and cumulative time of close physical contact increases the risk of transmission.[8,9] Several measures, including limits on the number of people in rooms, were introduced after the outbreak to address physical distancing, although space constraints mean that assigning individual office space is often not possible.

Presenteeism

Almost 20% of infected HCWs worked while symptomatic, with more unknowingly working during the presymptomatic stage of illness, an important infectious stage of COVID-19.[9] Some, especially those with pre-existing chronic respiratory conditions, attributed mild symptoms to other causes and were unable to differentiate such symptoms from the onset of COVID-19. It is also possible that some had asymptomatic COVID-19 infection. However, at this stage of the pandemic, the importance of asymptomatic infection and transmission had not been recognized; hence, testing of asymptomatic contacts was not standard practice.[4,10]

Changing work practices relating to presenteeism (i.e. attending work when unwell) requires a cultural shift in long-standing attitudes and perceptions that increase the likelihood of this behaviour. Reasons for individuals continuing to work include workplace culture and expectations, a desire to support their colleagues, especially when there are staff shortages, and to maintain income, a particularly important consideration for casual workers.[11,12] Interventions were subsequently introduced to support this cultural change, including screening staff for acute respiratory symptoms before each shift, requiring COVID-19 testing for staff who develop acute respiratory infection, and developing operational frameworks to support staff absences due to symptomatic respiratory infections and while awaiting test results.

Contact identification and testing

There were many challenges with the timely identification of close contacts from the three hospitals. One challenge was locating multiple electronic and paper-based information systems to identify staff and patient movements during the outbreak, often by outbreak investigation team members unfamiliar with the local setting. COVID-19 response guidelines and the definition of a close contact were frequently updated throughout the investigation and, as the outbreak escalated, contact tracing became overwhelming for the number of contact tracers available.[5] These logistical difficulties made quarantining close contacts challenging.[9,12]

The outbreak occurred early in the pandemic when national guidelines limited COVID-19 testing to symptomatic individuals and access to rapid testing was limited.[4] Consequently, not all contacts were tested. This hindered the rapid identification of new cases and may have resulted in asymptomatic cases going undetected, potentially adding to transmission. Outbreak management principles, including the testing of asymptomatic contacts, were later added to the Australian series of national guidelines for COVID-19 on 28 May 2020.[4]

Staff and patient mobility

Many infectious staff were highly mobile within the health-care facilities or worked in more than one health-care setting. Given the small regional hospital workforce in this location, the mobility between health- care and aged-care facilities was unavoidable. Several patients who were transferred between hospitals were infectious but had not yet been diagnosed with COVID-19; this contributed to transmission from Hospital 1 to Hospitals 2 and 3 early in the outbreak.

Infection prevention and control practices

Independent transmission from the two index cases with COVID-19 to HCWs was confirmed by genomic analysis,[13] and a later instance of transmission from a COVID-19 patient to a HCW at Hospital 3 was identified through epidemiological investigation.[5] Although no specific breaches of infection control protocols were recalled by the HCWs concerned, strengthening of infection control practices for all HCWs through increased resourcing and staff education, training and support was rapidly implemented following the outbreak.[12]

DISCUSSION

Despite no ongoing community transmission in the region, the Tasmanian outbreak was characterized by rapid transmission in health-care settings, with staff-to-staff transmission as the most significant contributor to the escalation of cases. The investigation identified a range of existing HCW practices that facilitate disease transmission in hospital settings, including challenges in achieving physical distancing, a culture of presenteeism and a high level of mobility of staff and patients across multiple health-care settings. The rapid closure of two hospitals highlighted the difficulties of maintaining a workforce in rural settings, because increases in demand coincided with a diminishing workforce due to the escalating isolation and quarantine requirements.[14]

The requirement that all HCWs from Hospitals 1 and 2 and their household contacts quarantine for 14 days, regardless of whether they met existing definitions of a close or casual contact, was associated with achieving rapid control of the outbreak. The definitions of close, casual and secondary contacts have since been refined, and criteria for quarantine of people in these groups form part of the current series of national guidelines for COVID-19.[4]

A limitation of the study is the lack of information about asymptomatic cases. At the time of the outbreak, the availability of rapid testing was limited, and testing of asymptomatic contacts was not routinely conducted. Although seven (5%) of the known 138 cases were found to be asymptomatic, this could be an underestimate. It has been estimated that up to 24% of transmission could be associated with asymptomatic disease.[15]

The learnings from this first large Australian outbreak in a health-care setting have contributed to ongoing interventions and pandemic responses throughout Tasmania and other states and territories of Australia.

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Conflict of interest

As an editor of WPSAR is an author, another editor on the editorial team managed this publication.

Ethics statement

The investigation was conducted under the Tasmanian Public Health Act and did not require ethical review.

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