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Factors contributing to a measles outbreak in a hard-to-reach rural village in Xaisomboun Province, Lao People's Democratic Republic

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Objective: An increase in measles cases was reported in the northwest of the Lao People's Democratic Republic beginning in January 2019, with outbreaks quickly spreading throughout the country. Following identification of two laboratory-confirmed cases in Xaisomboun Province, we conducted an outbreak investigation to identify factors contributing to the measles outbreak in hard-to-reach Village X.

Methods: Active case-finding was undertaken at the provincial hospital and primary health care centre via a retrospective search through admission logbooks and house-to-house surveys in Village X and surrounding villages. Clinical samples were collected from suspected cases, and data were collected using a standard case investigation form. Vaccine coverage data were reviewed.

Results: Of the 40 suspected measles cases with rash onset during 12 February–27 April 2019, 83% (33/40) resided in Village X and 98% (39/40) were of Hmong–Lu Mien ethnicity. Ages ranged from 22 days to 5 years, with 70% (28) aged <24 months. Almost half of cases aged 9 to <18 months (5/11) and 67% (8/12) of cases aged ≥24 months had received a measles-containing vaccine (MCV). Reported MCV coverage in Xaisomboun for children aged <1 year in 2017–2018 was <50%. In 55% (22/40) of cases, case notification was delayed by ≥6 days. The final case classification comprised 10% laboratory-confirmed, 20% clinically compatible, 60% epidemiologically linked and 10% non-cases.

Discussion: This measles outbreak was likely associated with low immunization coverage, compounded by delays in reporting. Effective strategies are needed to address beliefs about and health literacy barriers to immunization and measles awareness. Such strategies may improve MCV coverage and early diagnosis, enabling timely public health interventions and reducing mortality and morbidity.

Measles has been resurgent throughout the World Health Organization's (WHO's) Western Pacific Region in recent years.[1] In 2019, outbreaks occurred nationwide in the Lao People's Democratic Republic (Lao PDR), with the first laboratory-confirmed case reported in January 2019 in the northwest. Subsequent cases were identified 1 month later in the central region, with cases quickly spreading throughout the country. Xaisomboun was the 11th province to experience a measles outbreak during the first half of 2019.

Xaisomboun is a mountainous province centrally located in Lao PDR (**Fig. 1**). Established in 2013, it is the smallest province in terms of area (8550 km^2), population (92 682 people) and population density (10.82 people/km^2). There are three main ethnic groups (43% are Hmong–Lu Mien, 18% are Mon–Khmer and 31% are Lao–Tai in Xaisomboun compared with national proportions of 8%, 21% and 67%, respectively), each with its own unique language and traditional beliefs.[2] During 2012–2017, the under-5 mortality rate in Xaisomboun was 51/1000 live births compared with 46/1000 na-

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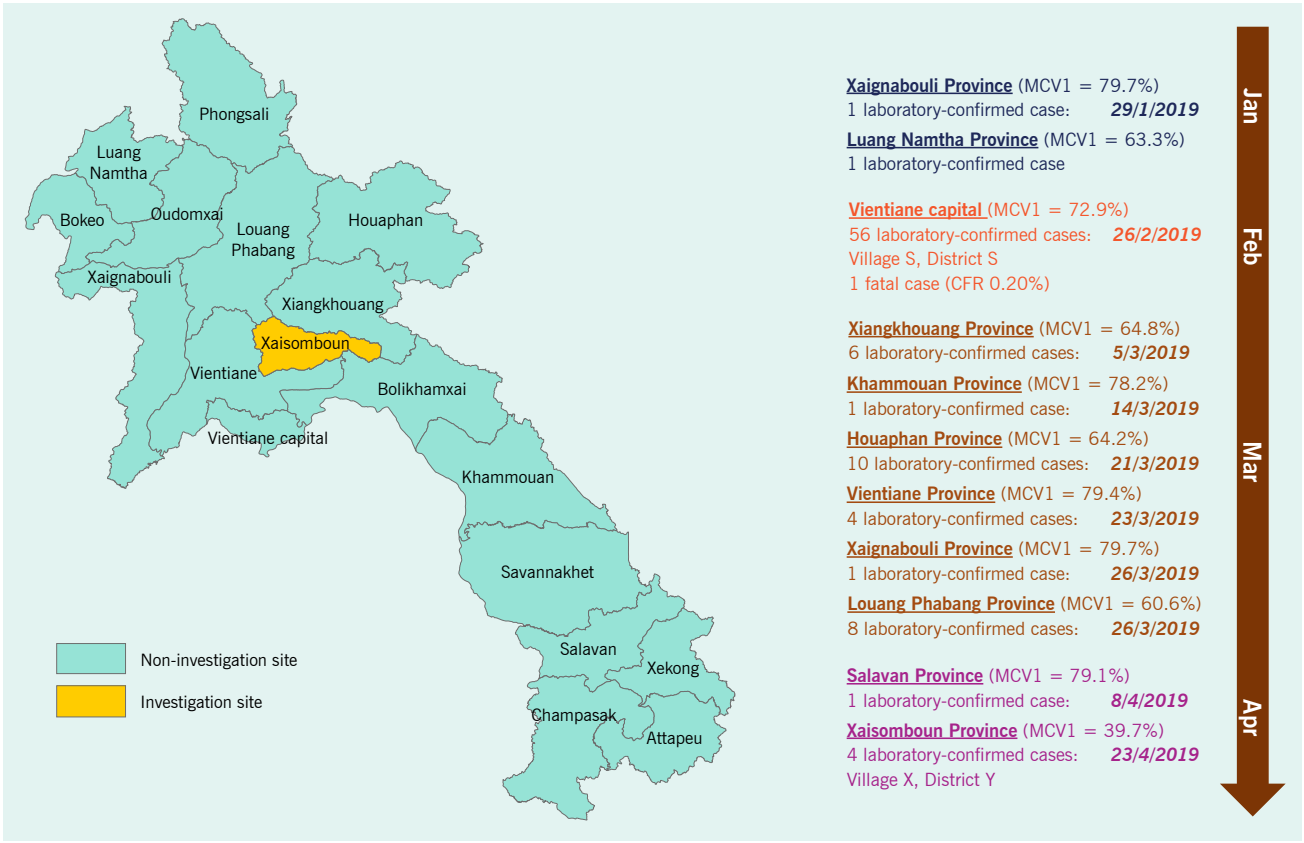
Fig. 1. **Number of cases of measles and coverage of the first dose of measles-containing vaccine (MCV1), by province, with Xaisomboun Province highlighted, Lao People's Democratic Republic, 2019**



tionally.[3] The Lao Social Indicator Survey reported that 54.7% of household members surveyed (*N* = 1606) in Xaisomboun were in the two poorest quintiles, had an average of 3.7 persons/sleeping room, and 66.2% and 17.5% had only basic sanitation services and handwashing facilities, respectively.[3]

Village X* in Xaisomboun had a population of 2821 people in 2018, 97.1% (*N*=2739) Hmong–Lu Mien, 2.2% (62) Mon–Khmer and 0.7% (20) Lao–Tai; the population density was 18.2 people/km^2 and approximately five people slept in one room.[2] The village has access to the provincial hospital (a 30-bed secondary care hospital) about 25 km away, and there is one primary health care centre in the middle of the village.[2] Traditionally, there is a lot of population movement in and out of the region and between homes during the Hmong–Lu Mien traditional New Year celebrations and for other family events.

Since establishing surveillance for acute fever and rash (AFR) in the province in 2013, no measles outbreaks have been reported. Nine measles/rubella test-negative AFR cases were reported in 2018 and only one in 2019 prior to the outbreak.[4] Additionally, one clinically compatible measles case (test negative) was reported with rash onset on 9 April 2019.

This paper describes the outbreak investigation undertaken after two laboratory-confirmed cases were reported in Village X, Xaisomboun Province, on 23 April 2019.

METHODS

Definitions

For case-finding, a suspected case was defined as a person who lived in Village X or a nearby area (Villages Y and Z*) who had symptom onset of fever and generalized maculopapular rash between 1 February and 30 April 2019. After suspected cases were identified and investigations completed, standard WHO definitions were

* For confidentiality, the names of the relevant villages were replaced by X, Y and Z.

applied to determine final case classifications (laboratory-confirmed, epidemiologically linked, clinically compatible and non-measles cases).[5] Delayed case notification was defined as ≥6 days to notification after rash onset.[6]

Case-finding

The 11-person outbreak investigation team included six local public health staff and five central public health and government laboratory staff who travelled from the capital to Xaisomboun by road. The field investigation was carried out from 23 to 30 April 2019. We undertook active case-finding at the provincial hospital and primary health care centre via a retrospective search of admission logbooks and house-to-house surveys in Village X and surrounding villages to identify people fulfilling the definition of a suspected case.

Data collection and analysis

Face-to-face interviews with caregivers of suspected cases from the three villages were undertaken, guided by the national standard case investigation form. The form is used to collect information about demographics, history of immunization with measles-containing vaccine (MCV), clinical symptoms, complications, hospitalization and treatment outcomes, as well as contacts, travel and participation at gatherings. Vaccination status was identified from the interview or a vaccination card, or both. These descriptive data were analysed using Microsoft Excel (2010).

Laboratory investigations

Throat swabs and blood samples were collected from suspected cases during their hospital visit or the house-to-house surveys in the three villages. Specimens were transported to the WHO-accredited laboratory at the National Center for Laboratory and Epidemiology (NCLE) and tested for measles and rubella using the Euroimmun anti-measles virus nucleoprotein enzyme-linked immunosorbent assay (ELISA) (immunoglobulin M [IgM]) and the anti-rubella virus glycoprotein ELISA (IgM) (Euroimmun, Lubeck, Germany). Detection of measles virus RNA by reverse transcription–polymerase chain reaction was conducted as described in WHO's Surveillance standards for vaccine-preventable diseases.[5] About 10% of suspected cases were sampled due to the remote location of the village, as per the NCLE's unpublished standard protocol for measles outbreak investigations.

RESULTS

Cases

Forty suspected measles cases with rash onset between 12 February and 27 April were identified: 10 from the primary health care centre logbook, 24 from the house-to-house survey and six via notifications from hospital clinicians. Four of the 40 initial suspected cases were ultimately classified as non-cases; there were 24 epidemiologically linked cases, eight clinically compatible and four laboratory-confirmed (**Fig. 2**, **Table 1**). The majority of suspected cases resided in Village X (83%; 33) and were of Hmong–Lu Mien ethnicity (98%; 39). All were aged between 22 days and 5 years, with 70% (28) aged <24 months. There were twice as many males (27) as females (13). The median time from rash onset to notification was 19 days (minimum = 0; maximum = 73; Quartile 1 = 6, Quartile 3 = 31). Altogether, 55% (22) of suspected cases had delayed notification, but all cases had investigation initiated within 48 hours of notification, thus meeting WHO's surveillance standards.[5] There were no reported deaths, but 15% (6/40) of cases were hospitalized at the provincial hospital (**Table 1**).

Laboratory results

Of the 40 cases identified through the investigation, specimens were collected from 28% (11; eight from Village X, two from Village Y and one from Village Z). The time from rash onset to serum sample collection for 8 cases and to throat swab for 11 cases ranged from 0 to 4 days (**Table 1**), meeting criteria for specimen collection adequacy as per WHO's standards.[5] All samples were delivered to the NCLE laboratory within 4 days of collection, and the results were reported within 2 days of specimen receipt, also meeting WHO's performance indicators.[5]

Of the four laboratory-confirmed cases, all resided in Village X, and three swabs from these cases and all their serum specimens were positive for measles. One laboratory-confirmed case had specimens collected 1 day after rash onset, and the other three had specimens collected on day 3 after rash onset (**Table 1**). All 11 specimens tested negative for rubella.

Vaccination history

Of those aged 9 to <18 months, 46% (5/11) had received an MCV through routine immunization, as had

Fig. 2. **Epidemic curve of the measles outbreak in Xaisomboun Province, Lao People's Democratic Republic, 1 February–30 April 2019 (*N* = 40)**

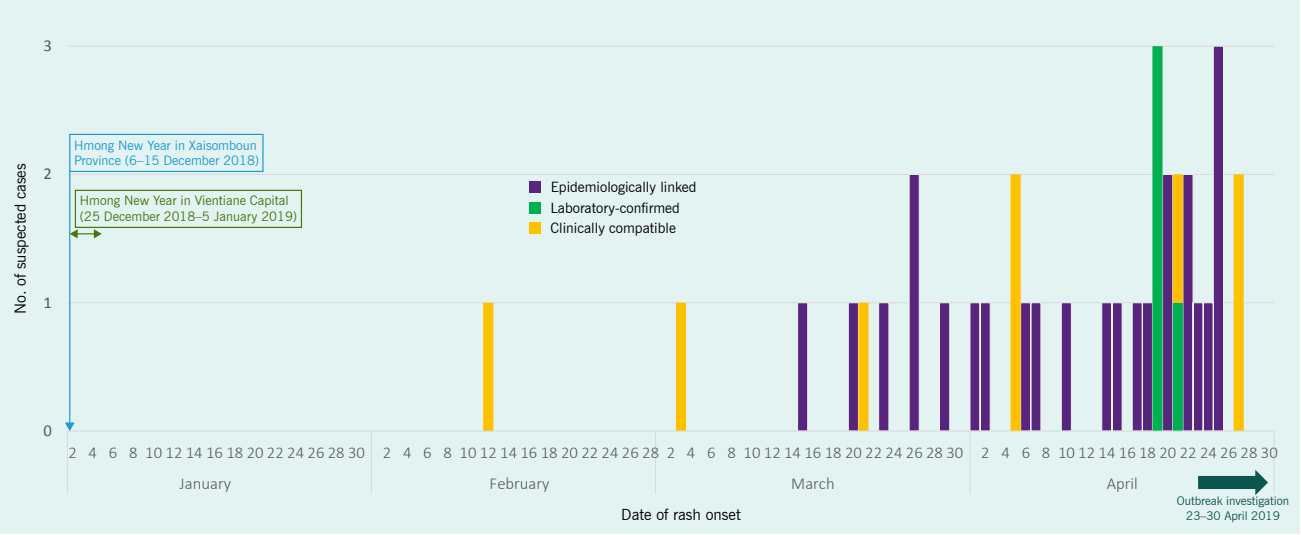


Table 1. **Characteristics and risk factors by final case classification for 40 suspected measles cases in Xaisomboun Province, Lao People's Democratic Republic, 1 February–30 April 2019**

Characteristic	Laboratory-confirmed[a]	Epidemiologically linked	Clinically compatible	Discarded (non-cases)	Total
Sex					
Female	2 (15.4)	7 (53.8)	2 (15.4)	2 (15.4)	13 (100)
Male	2 (7.4)	17 (63.0)	6 (22.2)	2 (7.4)	27 (100)
Age (months)					
<9	1 (5.9)	9 (52.9)	5 (29.4)	2 (11.8)	17 (100)
9 to <18	1 (9.1)	8 (72.7)	1 (9.1)	1 (9.1)	11 (100)
18 to <24	0	0	0	0	0
≥24	2 (16.7)	7 (58.3)	2 (16.7)	1 (8.3)	12 (100)
Identification					
Provincial hospital	3 (50.0)	1(16.7)	1 (16.7)	1 (16.7)	6 (100)
Primary health care centre	1 (10.0)	4 (40.0)	4 (40.0)	1 (10.0)	10 (100)
House-to-house survey	0	19 (79.2)	3 (12.5)	2 (8.3)	24 (100)
Immunization status					
Measles-containing vaccine: 1 dose	1 (7.1)	11 (78.6)	1 (7.1)	1 (7.1)	14 (100)
Measles-containing vaccine: 2 doses	1 (100)	0	0	0	1 (100)
None	2 (9.5)	11 (52.4)	5 (23.8)	3 (14.3)	21 (100)
Unknown	0	2 (50.0)	2 (50.0)	0	4 (100)
Ethnicity					
Lao–Tai	0	0	0	1 (100)	1 (100)
Hmong–Lu Mien	4 (10.3)	24 (61.5)	8 (20.5)	3 (7.7)	39 (100)
Mon–Khmer	0	0	0	0	0
Village					
X	4 (12.1)	24 (72.7)	3 (9.1)	2 (6.1)	33 (100)
Y	0	0	5 (58.3)	1 (16.7)	6 (100)
Z	0	0	0	1 (100)	1 (100)

Characteristic	Laboratory-confirmed[a]	Epidemiologically linked	Clinically compatible	Discarded (non-cases)	Total
Contact with people with fever and rash 7–21 days prior to rash onset					
Yes	0	12 (70.6)	2 (11.8)	3 (17.6)	17 (100)
No	2 (11.1)	9 (50.0)	6 (33.3)	1 (5.6)	18 (100)
Unknown	2 (40.0)	3 (60.0)	0	0	5 (100)
Travel during 3 weeks prior to rash onset					
Yes	0	1 (25.0)	1 (25.0)	2 (50.0)	4 (100)
No	1 (3.0)	23 (69.7)	7 (21.2)	2 (6.0)	33 (100)
Unknown	3 (100)	0	0	0	3 (100)
Participation in social events or gatherings					
Yes	0	3 (50.0)	2 (33.3)	1 (16.7)	6 (100)
No	0	18 (69.2)	6 (23.1)	2 (7.7)	26 (100)
Unknown	4 (50.0)	3 (37.5)	0	1 (12.5)	8 (100)
Time to notification					
≤5 days	4 (22.2)	7 (38.9)	3 (16.7)	4 (22.2)	18 (100)
≥6 days	0	17 (77.3)	5 (22.7)	0	22 (100)
Throat swab collected					
Yes	4 (36.4)	0	3 (27.3)	4 (36.4)	11 (100)
No	0	24 (82.8)	5 (17.2)	0	29 (100)
Serum sample collected					
Yes	4 (50.0)	0	1 (12.5)	3 (37.5)	8 (100)
No	0	24 (75.0)	7 (21.9)	1 (3.1)	32 (100)
Hospitalization					
Yes	3 (50.0)	1 (16.7)	1 (16.7)	1 (16.7)	6 (100)
No	1 (2.9)	23 (67.6)	7 (20.6)	3 (8.8)	34 (100)
Days from rash onset to throat swab					
0	0	0	2 (100)	0	2 (100)
1	1 (50.0)	0	0	1 (50.0)	2 (100)
3	3 (50.0)	0	1 (16.7)	2 (33.3)	6 (100)
4	0	0	0	1 (100)	1 (100)
Days from rash onset to serum collection					
0	0	0	1 (100)	0	1 (100)
1	1 (50.0)	0	0	1 (50.0)	2 (100)
3	3 (75.0)	0	0	1 (25.0)	4 (100)
4	0	0	0	1 (100)	1 (100)

[a] Values are number (%).

67% (8/12) of those aged ≥24 months. Only one child aged ≥24 months had received the second dose of MCV. Immunization status could not be determined for four cases (**Table 1**).

Contact, travel and mass gatherings

Altogether, 43% (17) of suspected cases had a history of exposure to a case with fever and rash during the 7–21 days prior to their rash onset (**Table 1**). Ten percent (4) had travelled during the 3 weeks prior to rash onset: two had travelled to Xiengkhouang Province, one living in Village X travelled to an unknown village and one living in Village Y visited Village X (**Table 1**). Fifteen percent (6) of cases had participated in social events or gatherings. There was no report of international travel.

Population risk factors

In Xaisomboun, MCV coverage rates among those aged <1 year were <50% in both 2017 and 2018 compared with 80% nationally.[7] Surveyed coverage of one dose

of MCV in those aged 12–23 months in Xaisomboun in 2017 was 40%, the lowest of all provinces, compared with 66% nationally.[3] Vaccination coverage data were not available for minority groups in this province. However, nationally surveyed coverage rates for measles–rubella vaccine in 2017 for children aged 12–23 months varied according to the ethnolinguistic group of the head of household: coverage was highest among families with a Lao–Tai (74%) head of household and lowest among those with a Hmong–Lu Mien (45%) head of household.[3]

The traditional Hmong–Lu Mien New Year celebration was during 6–15 December 2018 in Xaisomboun Province and 25 December 2018–5 January 2019 in Vientiane Capital. This event is locally and nationally recognized as a feast that brings together family members who often live in different regions across the country to renew ties and social bonds, and it is also a time to remember ancestors, to pay repect to family spirits, and to reflect on the passing years and prepare for the new year.[8]

Public health interventions

We assisted local teams in notifying health facilities in the area to trigger a risk assessment and immunization response to enhance the current, local surveillance systems for acute fever and rash and clinical case management strategies and to initiate community engagement, awareness and risk communication activities. We provided health education to parents about home care strategies, sanitation, isolation and when to seek medical attention; initiated vitamin A prophylaxis for the cases; and advised health-care workers (HCWs) to undertake regular home visits and to follow up. Subsequently, the Ministry of Health conducted a mass vaccination campaign in the province beginning in early May 2019.

DISCUSSION

The outbreak investigation identified 40 suspected measles cases, of whom almost all resided in Village X and were of Hmong–Lu Mien ethnicity. All were children, predominantly aged <24 months. Among those aged 9 to <18 months, MCV coverage was <50%. Notification was delayed for most cases. The source of this outbreak was not determined. Travel and gatherings related to the traditional New Year festival may have been contributing factors, although these occurred well before the 7–21-day incubation period for the first suspected case. It is possible that earlier cases related to festival attendance were undetected or, more likely, there was importation from travellers visiting or returning to Xaisomboun from provinces experiencing outbreaks in January and February 2019, such as in Xiengkhouang.

Low MCV coverage likely contributed to the outbreak. We verified that the province had not achieved the recommended MCV coverage of 95%. Contributing factors to low vaccination coverage, all of which are relevant to Xaisomboun, include financial barriers to vaccination,[9] being a member of an ethnic minority group with linguistic and cultural barriers,[10] lack of knowledge or a low level of education,[9] difficulty accessing vaccination centres[9] and socioeconomic inequalities.[11] Reported factors affecting vaccine compliance in Lao PDR may also relate to vaccine provision and include problems with the supply of vaccines and diluents, the cold chain, lack of availability of HCWs, and capacity issues affecting coordination between relevant organizations to assess needs and make appropriate decisions.[9] Vaccine failure[5] and vaccine quality are other possible contributing factors. A reduction in immunogenicity related to suboptimal vaccine handling and poor immune response during the national measles campaign in 2011 have previously been proposed and may also be contributory.[12]

Additional likely contributing factors to the outbreak include delayed reporting and a lack of case recognition and infection prevention and control measures, as well as hesitancy to seek health care. Delayed reporting as a contributing factor is supported by the number of clinically and epidemiologically linked cases identified during the investigation and the atypical progressive-source epidemiological curve. Two barriers recognized to hinder the provision of high-quality care by HCWs, namely lack of provider education and necessary equipment, may have contributed to the lack of case recognition.[13] Inadequate infection prevention and control measures in the health-care setting can contribute to increased measles transmission and spread; however, we did not formally review these measures. Furthermore, poor health-seeking behaviour is associated with low income[14] and poor health insurance coverage.[15] Evidence indicates that in Lao PDR there is limited coverage of the health equity fund, which creates challenges to accessing health services for those in the poorest quintiles.[10] Evidence also suggests that the use of health-care services in Lao PDR often results

in financial hardship for patients and their relatives.[14] Uninsured people frequently use traditional medicine and self-medication due to perceptions of high prices and poor quality associated with public health services.[14] Although there is a relatively robust network of public health services, access can be hindered by the mountainous terrain and lack of year-round roads.[10] Overcrowded environments and inadequate sanitation in Xaisomboun, as identified by the Lao Social Indicator Survey,[3] also facilitate measles virus transmission.[16] The survey[3] also suggests that the community in Xaisomboun is hesitant to seek health care, as it reported that for children aged 0–59 months, advice or treatment was not sought for 48.4% of children with diarrhoea and 72% of those with fever compared with national rates of, respectively, 51% and 42%.[3] The unique languages and traditional beliefs of the Xaisomboun community may also play an important part in their health-seeking behaviour.

This study highlights issues similar to those identified in other measles outbreaks in the Asia–Pacific region. The 2013–2014 measles outbreak in northern Viet Nam reportedly started among ethnic minorities in mountainous areas that had limited access to vaccination.[17] A measles outbreak investigation in a remote area of the Solomon Islands in 2014 suggested that reasons for delayed hospital visits included the long distances between home and hospital, complex sociocultural issues and families first consulting traditional healers.[18]

This study had limitations. The retrospective nature of the study, relying on voluntarily self-reported information from participants, means that recall bias and an underestimation of reported cases are likely. Also, additional suspected cases may not have been identified if they were absent from their village during the investigation. We encountered linguistic and cultural barriers and had limited access to professionally trained interpreters; therefore, the accuracy of the data could be affected. However, our results are supported by collaborative evidence and field observations.

This outbreak investigation in a rural, mountainous village in Lao PDR highlights many important considerations. Likely contributors to this outbreak include population movement, low immunization coverage, delayed notification, and a lack of case recognition and health-seeking behaviour, as well as socioeconomic factors. The isolated nature of mountainous communities that have limited access to health care, education and other public services[19] increases this population's susceptibility to outbreaks. Effective strategies are needed to enable local health authorities and communities to work together to understand and address barriers to immunization and to raise awareness about measles. These strategies need to include further exploration of the cultural beliefs, health literacy rates and socioeconomic status specific to the province. Understanding and addressing these issues may help to improve MCV coverage and early diagnosis, enabling timely public health interventions to control outbreaks and reduce mortality and morbidity. Additionally, delivering training modules for HCWs that specifically address measles detection and surveillance with review of feedback from participants and serial nationwide measurements of performance by the Ministry of Health could contribute to increasing the standard of primary health care, thereby improving the health of the population of Lao PDR.[13]

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Conflicts of interest

None.

Ethics statement

This study was conducted as part of an outbreak response under the Lao PDR law for outbreak investigations. The Australian National University ethics committee approved the study (protocol no. 2017/909).

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Epidemiological survey to establish thresholds for influenza among children in satellite cities of Tokyo, Japan, 2014–2018

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Objective: We described the characteristics of children reported as having influenza across five consecutive influenza seasons and investigated the usefulness of setting influenza thresholds in two satellite cities of Tokyo, Japan.

Methods: An annual survey was conducted among parents of children at preschools (kindergartens and nursery schools), elementary schools and junior high schools in Toda and Warabi cities, Saitama prefecture, at the end of the 2014–2018 influenza seasons. Using the World Health Organization method, we established seasonal, high and alert thresholds.

Results: There were 64 586 children included in the analysis. Over the five seasons, between 19.1% and 22% of children annually were reported as having tested positive for influenza. Influenza type A was reported as the dominant type, although type B was also reported in more than 40% of cases in the 2015 and 2017 seasons. The median period of the seasonal peak was 3 weeks in mid-January, regardless of school level. Of the five surveyed seasons, the high threshold was reached in 2014 and 2018, with no season exceeding the alert threshold.

Discussion: This study provides insights into the circulation of influenza in children in the study areas of Toda and Warabi, Japan, from 2014 to 2018. Although we were able to utilize these annual surveys to calculate influenza thresholds from five consecutive seasons, the prospective usefulness of these thresholds is limited as the survey is conducted at the end of the influenza season.

The World Health Organization (WHO) estimates that annual epidemics of influenza cause 3–5 million cases of severe illness worldwide.[1] The epidemiology of influenza changes markedly each year and varies in different locations.[2] In general, approximately 80% of influenza cases are caused by influenza type A, whereas influenza type B accounts for approximately 20% of total global cases.[3]

Schoolchildren are the primary vulnerable population for influenza because they have the highest rates of influenza transmission and infection among infected populations.[4] In the Asia-Pacific region, influenza type B appeared to cause more illness in children between the ages of 1–10 years than in other age groups.[5] Although influenza surveillance data have been reported in various forms for populations across Japan,[6–8] few studies have investigated seasonal influenza among schoolchildren in and around Tokyo, the capital city of Japan and the most populous metropolitan area of the country.

Owing to the various thresholds for influenza epidemics,[9–12] WHO has proposed global standards for the collection, reporting and analysis of seasonal influenza epidemiological surveillance data.[9] The WHO further recommends obtaining average epidemic curves plus seasonal and alert thresholds as established tools to help control annual influenza epidemics.[9] The thresholds using the WHO methods are simple to implement and can be adapted easily for any influenza surveillance system with adequate historical data.[13] In some countries, the WHO method is used to inform key decision-makers for influenza outbreak management and public health action.[14–16]

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We conducted a survey of children (from preschool to junior high school) during five consecutive influenza seasons in two satellite cities of Tokyo, Japan. Using these data, we described the characteristics of circulating influenza and investigated the usefulness of establishing thresholds for the influenza epidemic with the WHO method. To our knowledge, this is one of the first documented assessments using the WHO method to set thresholds for children in cities near Tokyo, Japan, based on survey data.

METHODS

Study area

The study area comprised two cities, Toda and Warabi, which are located in Saitama prefecture to the north of Tokyo. The study region was 23.3 km^2 (Toda: 18.2 km^2; Warabi: 5.1 km^2) and had a population of 208 410 (Toda: 136 150; Warabi: 72 260), including a population of 28 056 aged 0–14 years (Toda: 20 252; Warabi: 7804) according to the 2015 census.[17]

Study procedure

Throughout five consecutive influenza seasons, from 2014 to 2018 (ending March 2019), an annual survey was conducted among parents of children who were attending preschool (kindergarten or nursery school, 0–6 years old), elementary school (7–12 years old) or junior high school (13–15 years old) in the Toda and Warabi regions. A questionnaire was mailed to parents asking for the following information regarding their children: school level, sex, siblings, underlying medical condition, vaccination status, and incidence of influenza infection, influenza type and date of illness (**Supplementary Table 1**). In clinical practice in Japan, the influenza type (type A or B) is typically diagnosed by the children's local physician or an emergency outpatient health-care provider, who administers an influenza antigen rapid test covered by health insurance. The survey was conducted every June, and the responses pertained to the preceding season. Completed questionnaires were collected by schoolteachers.

Statistical analysis

We determined the number of children, percentage of influenza cases by type and week for each influenza season, and the seasonal, high and alert thresholds for influenza. The data were also analysed by school level (preschool, elementary school and junior high school; in Japan, there is no system for these schoolchildren to repeat the school year). Comparisons between those with and without reported influenza infection were compared using the chi-squared test.

Each influenza season was defined as beginning in October and ending in March of the following year; for example, the 2014 season began in October 2014 and ended in March 2015. The epidemic peak was defined for each influenza type as the week with the highest number of reported influenza cases.

Data were extracted from the pooled survey responses of the five consecutive influenza seasons. In accordance with the WHO protocol,[9] we calculated the average and upper limit of the 90% confidence interval (CI) curves and the seasonal, high, and alert thresholds based on the number of children reported as having influenza each week throughout the five seasons. The average curves denoted the peak weekly mean, and the 90% upper curve was for the upper limits of the 90% CI of the peak weekly mean.[9,13] For these curves, the WHO protocol suggests using the normal distribution to assign thresholds based on the mean and standard deviation of the aligned data for weekly counts.[9] The seasonal threshold was defined as the annual median amplitude of the number of children reported with influenza per week throughout the study period. Therefore, half of the study weeks are necessarily above the seasonal threshold, and these correspond to the seasonality in the influenza epidemic (e.g. from week 40 of 2014 to week 13 of 2015).

The high threshold was defined as the number of children with influenza higher than the average peak for each of the five seasons, that is, the peak number of children with influenza of the average epidemic curves.[15] Theoretically, we can expect that seasonal peaks can be higher than the high threshold in two or three of the five seasons, whereas the seasonal peaks will be lower in other seasons. Finally, we defined the alert threshold as being higher than the upper limits of the 90% CI of the high threshold as defined earlier.[9,13,15] The data for the total number of children studied and for each school level from week 40 of 2014 to week 13 of 2019 were plotted against the calculated seasonal, high and alert thresholds. We analysed the data using Stata version 16.0 (Stata Corp., College Station, TX, United States of America).

RESULTS

A total of 76 753 responses (response rate 70.8%) were collected from the 108 362 surveys sent to parents of children attending preschool, elementary school or junior high school during the 2014–2018 seasons. We excluded responses that did not include basic information (n = 4445) and those that reported influenza vaccination before 30 September or influenza infection after 1 April for each season (n = 7722).[18] This analysis, therefore, consisted of 64 586 responses (**Fig. 1**).

Of the included children, 49.6% were male, 78.6% had siblings and 8.3% had an underlying medical condition (**Table 1**). Among preschool children, having siblings and the presence of underlying medical conditions were associated with influenza infection ($P < 0.001$). In elementary school children, sex and having siblings were associated with influenza infection ($P < 0.001$ and = 0.026, respectively). Conversely, sex, having siblings and the presence of underlying medical conditions were not associated with influenza infection in junior high school children (P = 0.103, 0.713 and 0.405, respectively) (**Table 1**).

Children with influenza and their distribution by influenza type

The total number of children who were reported to have been infected with influenza was 13 754 (21.3% of analysed responses). With respect to the dominant influenza type in each season, type A dominated in 2014, 2016 and 2018, while type B dominated in 2017 and the two were nearly equal in 2015. These patterns mostly held when divided by school level (**Table 2**).

Week of epidemic peak by influenza type

The epidemic peaks occurred earlier in 2014 and 2016 (week 51) than in 2015 (week 6), 2017 (week 3) and 2019 (week 3) (**Table 2**). The epidemic peaks of influenza type B occurred later than type A in 2015, 2016 and 2017. By school level, the epidemic peaks in preschool occurred later than the other levels in 2014, 2016 and 2017 (**Table 2**).

Curves and thresholds by the WHO method

The start of the influenza season was between weeks 43 and 1 (late October and early January), and the end of the season was between weeks 8 and 13 (late February and late March). The median peak in the number of children with influenza was similar to the corresponding mean peak (**Table 3**). The median week of the peak was week 3 (mid-January; **Table 3**). The plotted curve of the number of children with influenza crossed the seasonal threshold multiple times over the five seasons. The peak in seasonal influenza activity in 2015, 2016 and 2017 did not reach the high threshold (**Fig. 2A**).

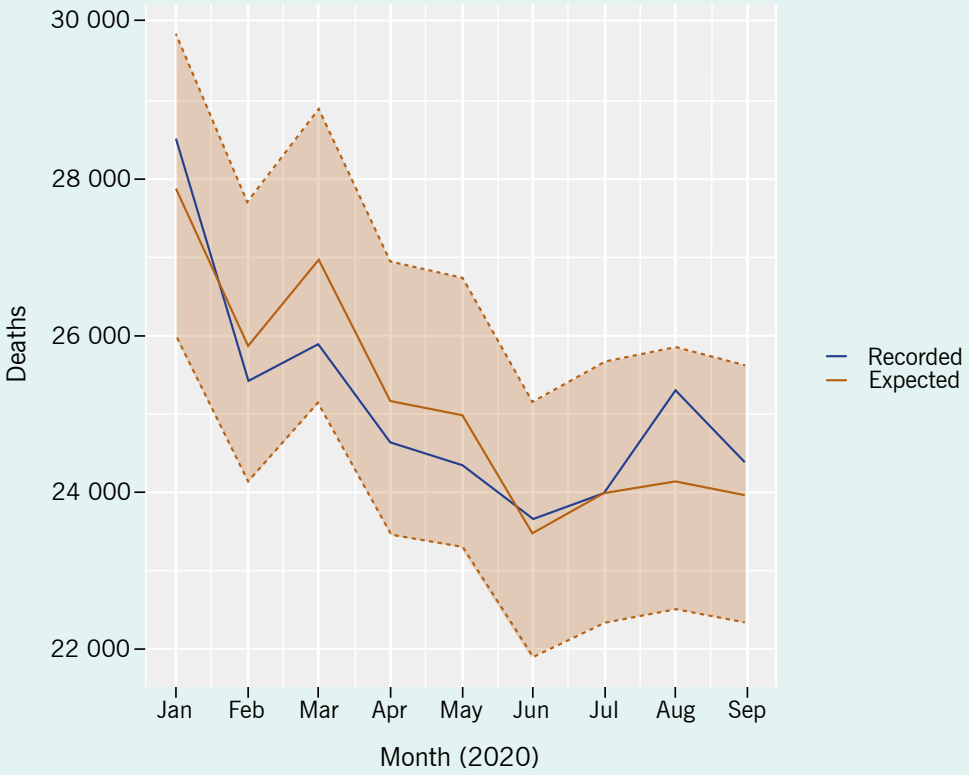
The peak in seasonal influenza activity varied when the children with influenza were stratified by school level (**Fig. 2B–D**). In none of the five seasons did the plotted curve of the prevalence of children with influenza cross the alert threshold. The results were almost confirmatory when classified by school level, except for junior high school during the 2014 season, where the number of children with influenza was close to the alert threshold (**Fig. 2D**).

DISCUSSION

We present data on the circulation of influenza in children who were attending preschool, elementary school or junior high school in Toda and Warabi, Japan, during five consecutive influenza seasons from 2014 to 2018. Over the five seasons, between 19.1% and 22% of children annually were reported as having tested positive for influenza. Over the whole period, there was a higher proportion of elementary school children reporting influenza infection (23.4%) compared to preschool and junior high school children (18.9% and 18.7%, respectively). Having siblings was associated with reported cases of influenza in preschool and elementary school children. Moreover, we successfully established seasonal, high and alert thresholds based on survey data from five consecutive seasons of influenza using the WHO method.

In Japan, the Ministry of Health, Labour and Welfare, in collaboration with the National Institute of Infectious Diseases (NIID), provides a weekly influenza outbreak report.[19] This report is based on a school survey in which the absence of children and temporary closure of schools are recorded. The total number of temporary school closures was highest in 2017, which supports our finding that the highest number of reported influenza cases also occurred in 2017. Our survey differed from this national report[19] for junior high school children, as the highest number of influenza cases was reported in 2016 for this group.

Fig. 1. **Selection of the study population for consecutive annual surveys of schoolchildren in Toda and Warabi, Japan, during the 2014–2018 influenza seasons**



In our survey, approximately 40% of influenza cases in 2015 and 2017 were type B. These results are similar to those reported in NIID's influenza outbreak summaries for each season,[19] although their proportion of type B reported among children in junior high school was higher, at >50% in 2015. Characteristics of outbreaks can differ by region, even within a single country, warranting local-level surveys.

In the national report,[19] the peak week for temporary school closures occurred in weeks 4, 7, 4, 5 and 4 in the 2014, 2015, 2016, 2017 and 2018 seasons, respectively. The week of the influenza epidemic peak in our survey occurred consistently earlier than that in the national report, although the overall tendency was similar. This may be because the national report used the dates of school absence due to influenza,[19] whereas our survey showed the week with the highest number of detected influenza cases which is likely to precede the week of temporary school closures. There may also be regional characteristics that contribute to differences in the national patterns.

The increase in reported influenza type B cases in the national data occurred later than type A in our survey. The epidemic order is in accordance with that observed in other influenza seasons in the northern hemisphere.[20] Understanding the geographical and temporal patterns of seasonal influenza could help strengthen influenza surveillance for the early detection of epidemics.[21] As Mosnier et al. reported,[22] timely data on the circulation of influenza collected by influenza surveillance systems are essential for optimizing influenza prevention and control strategies.[21,22]

In accordance with the WHO method, we developed three thresholds (seasonal, high and alert thresholds) for children at each school level in two satellite cities of

Table 1. **Comparison of characteristics of schoolchildren included in consecutive annual influenza surveys in Toda and Warabi, Japan, during the 2014–2018 influenza seasons**

Characteristic	Total	Influenza infection reported, n (%)		*P*[a]
		Yes	No	
	n = 64 586	n = 13 754	n = 50 832	
School				
Preschool (0–6 years)	17 260	3262 (18.9)	13 998 (81.1)	
Elementary school (7–12 years)	34 966	8186 (23.4)	26 780 (76.6)	< 0.001
Junior high school (13–15 years)	12 360	2306 (18.7)	10 054 (81.3)	
Sex				
Male	32 039	7037 (51.2)	25 002 (49.2)	< 0.001
Female	32 547	6717 (48.8)	25 830 (50.8)	
Siblings (yes)	50 756	10 888 (79.2)	39 868 (78.4)	0.064
Underlying medical condition (yes)	5347	1220 (8.9)	4127 (8.1)	0.005
Preschool children (0–6 years)				
Sex (male)	8611	1663 (51.0)	6948 (49.6)	0.166
Siblings (yes)	12 020	2386 (73.2)	9634 (68.8)	< 0.001
Underlying medical condition (yes)	1397	319 (9.8)	1078 (7.7)	< 0.001
Elementary school children (7–12 years)				
Sex (male)	17 378	4210 (51.4)	13 168 (49.2)	< 0.001
Siblings (yes)	28 392	6578 (80.4)	21 814 (81.5)	0.026
Underlying medical condition (yes)	2987	731 (8.9)	2256 (8.4)	0.152
Junior high school children (13–15 years)				
Sex (male)	6050	1164 (50.5)	4886 (48.6)	0.103
Siblings (yes)	10 344	1924 (83.4)	8420 (83.8)	0.713
Underlying medical condition (yes)	963	170 (7.4)	793 (7.9)	0.405

[a] Data from influenza infection (Yes) and influenza infection (No) were compared using the chi-squared test.

Tokyo, based on survey data from the same region. The WHO method is a simple protocol to establish influenza thresholds. Epidemic peaks for each season occurred at week 51 or later, particularly at week 2 or later among preschool children. Two of the five seasons, 2014 and 2018, reached the high threshold; none of the seasons reached the alert threshold.

The data used in this study were not collected in a near real-time manner and are not surveillance data for which the threshold calculations are best suited. Therefore, the calculated thresholds cannot be used to establish an outbreak warning system; they can only be used to assess an influenza season after its completion. This is in contrast to the influenza surveillance system in Japan which provides alerts throughout the influenza season when the reported number of cases exceeds the threshold in any given week.[23] However, the annual survey is cost-effective and feasible and can provide a retrospective assessment of an influenza season in a subgroup of the population. Furthermore, the established thresholds can be used to guide public health decision-making and risk communication for children, for example by planning national and municipal budgets and long-term staffing as well as preparing for periods and intensive education for children when epidemics are expected. The thresholds can also be helpful in establishing an early warning system for influenza epidemics customized to each region when a near real-time report such as the aforementioned NIID report in Japan[19] is feasible and can facilitate collaboration.

Our study has several limitations. First, preschool-aged children who were not attending kindergarten or nursery school, and children who were attending school out of town, were excluded from the analysis.

Table 2. **Number of children reported with influenza and week of the epidemic peak in consecutive annual surveys of schoolchildren in Toda and Warabi, Japan, during the 2014–2018 influenza seasons**

Season	Cases (%) / total no. of children	Influenza type reported (%)			Week of epidemic peaks		
		Type A	Type B	Unknown	All	Type A	Type B
All children							
2014	2793 (20.0) / 13 961	80.2	11.6	8.2	51	51	51
2015	2594 (21.6) / 12 020	45.7	43.7	10.6	6	5	9
2016	2770 (22.0) / 12 616	71.6	17.9	10.5	51	51	12
2017	3070 (24.0) / 12 783	28.7	45.9	25.4	3	3	5
2018	2527 (19.1) / 13 206	84.3	6.6	9.1	3	3	3
Total	13 754 (21.3) / 64 586	61.2	25.7	13.1	N/A	N/A	N/A
Preschool (0–6 years)							
2014	659 (17.3) / 3809	79.2	11.1	9.7	2	2	7
2015	614 (18.5) / 3321	48.4	41.0	10.6	5	5	7
2016	688 (20.5) / 3348	70.8	17.3	11.9	3	5	12
2017	701 (20.2) / 3472	37.8	42.9	19.3	5	2	5
2018	600 (18.1) / 3310	85.3	7.0	7.7	2	2	3
Subtotal	3262 (18.9) / 17 260	63.9	24.1	12.0	N/A	N/A	N/A
Elementary school (7–12 years)							
2014	1567 (21.6) / 7269	80.6	11.5	7.9	51	51	51
2015	1672 (25.9) / 6445	45.9	42.6	11.5	6	6	9
2016	1503 (22.1) / 6793	71.1	19.0	9.8	3	51	12
2017	1905 (28.0) / 6807	28.7	49.0	22.3	3	51	5
2018	1539 (20.1) / 7652	83.6	6.4	10.0	3	3	3
Subtotal	8186 (23.4) / 34 966	60.2	27.0	12.8	N/A	N/A	N/A
Junior high school (13–15 years)							
2014	567 (19.7) / 2883	80.4	12.5	7.1	51	51	51
2015	308 (13.7) / 2254	39.3	55.2	5.5	7	5	10
2016	579 (23.4) / 2475	73.6	15.7	10.7	51	51	12
2017	464 (18.5) / 2504	15.1	37.5	47.4	3	51	52
2018	388 (17.3) / 2244	85.6	6.7	7.7	3	3	3
Subtotal	2306 (18.7) / 12 360	60.9	23.1	16.0	N/A	N/A	N/A

N/A: not available.

The influenza season begins in October and ends in March of the following year; for example, the 2014 season was from October 2014 to March 2015.

In the study area (Toda and Warabi), the total number of children aged ≤15 years was 27 562 according to the 2015 census. As only 60% of mailed surveys were returned and qualified for analysis, we cannot guarantee that the present findings accurately represent the epidemiology of children in the general population. Second, as the questionnaires were answered by the parents of the targeted children, influenza diagnosis was based on self-reporting. Detailed medical information was not requested, so the proportion reported with influenza might not be accurate. Third, not all participants completed all five surveys that were conducted for this report. As the last survey was completed in March 2019, the data were not affected by the COVID-19 pandemic and related confounding circumstances. Whether the current estimates regarding the influenza epidemic will be applicable after the COVID-19 pandemic has subsided remains unknown; this is the same issue for the epidemiology of most infectious diseases.

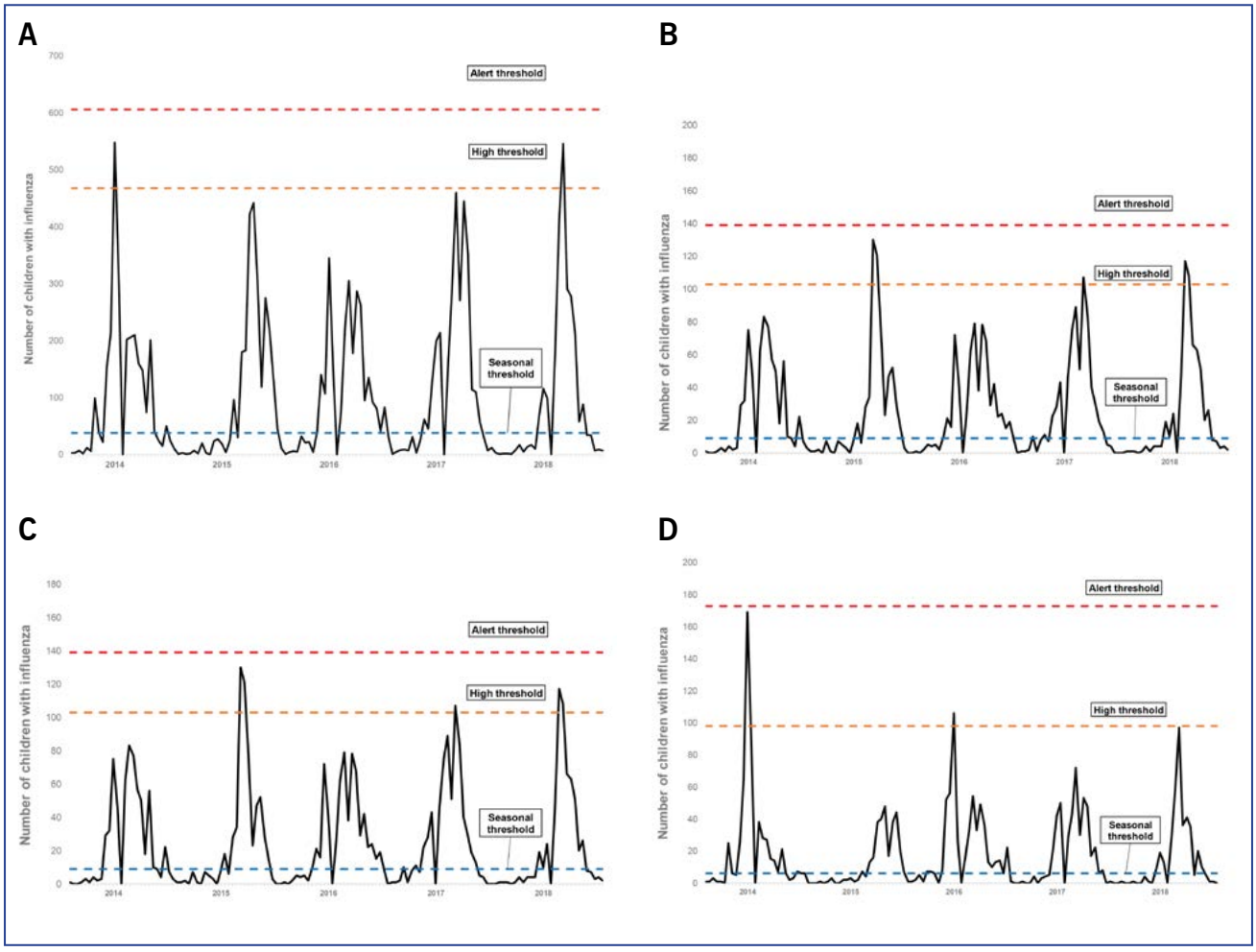
This study provides insights into the circulation of influenza in children in the study areas of Toda and Warabi. The calculated thresholds provide some assessment of the influenza seasons from 2014 to 2018 in

Table 3. **Epidemic curve characteristics and thresholds in consecutive annual surveys of schoolchildren in Toda and Warabi, Japan, during the 2014–2018 influenza seasons**

	Total	School level		
		Preschool	Elementary school	Junior high school
Median week of peak	3	3	3	3
Median peak in influenza cases	460	107	299	97
Mean peak in influenza cases	468.2	103.2	279.4	98.4
Standard deviation	84.2	21.9	63.9	45.5
Upper 90% confidence interval	606.7	139.2	384.5	173.2
Upper 95% confidence interval	633.2	146.1	404.6	187.6
Threshold level	–	–	–	–
Seasonal threshold	38	9	21	6
High threshold	468	103	279	98
Alert threshold	606	139	384	173

The influenza season begins in October and ends in March of the following year; for example, the 2014 season was from October 2014 to March 2015.

Fig. 2. **Number of reported influenza cases from consecutive annual surveys of schoolchildren in Toda and Warabi, Japan, during the 2014–2018 influenza seasons plotted against the calculated WHO thresholds (A) overall, and for (B) preschool, (C) elementary and (D) junior high school children**



this group and the epidemic curve information may help prepare for the health care of children as the influenza season starts. If this survey data could be collected routinely during the influenza season, then the thresholds may contribute to an early warning system; currently, they can only be used to assess influenza seasons after they have occurred. Our findings based on an influenza survey of children are useful for general practitioners, health policy-makers and disease control planners who are concerned with the prevention and control of influenza in this local area.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Ethical approval for this study was obtained from the institutional review board of Todachuo General Hospital (No. 0436). Informed consent was obtained from the participating parents and/or legal guardians of children in Toda and Warabi schools, and their information was anonymized for use in the present study. All methods were performed in accordance with relevant guidelines and regulations and were approved by the institutional review board of Todachuo General Hospital.

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Use of Epidemic Intelligence from Open Sources for global event-based surveillance of infectious diseases for the Tokyo 2020 Olympic and Paralympic Games

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The establishment of enhanced surveillance systems for mass gatherings to detect infectious diseases that may be imported during an event is recommended. The World Health Organization Regional Office for the Western Pacific contributed to enhanced event-based surveillance for the Tokyo 2020 Olympic and Paralympic Games (the Games) by using Epidemic Intelligence from Open Sources (EIOS) to detect potential imported diseases and report them to the National Institute of Infectious Diseases (NIID), Japan. Daily screening of media articles on global infectious diseases was conducted using EIOS, which were systematically assessed to determine the likelihood of disease importation, spread and significant impact to Japan during the Games. Over 81 days of surveillance, 103 830 articles were screened by EIOS, of which 5441 (5.2%) met the selection criteria for initial assessment, with 587 (0.6%) assessed as signals and reported to NIID. None of the signals were considered to pose a significant risk to the Games based on three risk assessment criteria. While EIOS successfully captured media articles on infectious diseases with a likelihood of importation to and spread in Japan, a significant manual effort was required to assess the articles for duplicates and against the risk assessment criteria. Continued improvement of artificial intelligence is recommended to reduce this effort.

The Tokyo 2020 Olympic and Paralympic Games (the Games) were postponed for a year due to the coronavirus disease (COVID-19) pandemic. They were finally held from late July to early September 2021. Approximately 83 000 athletes, staff, press and sponsors from over 200 countries and areas attended the event and were hosted across Japan's 47 prefectures.

Mass gatherings can pose a risk of public health emergencies, and event-based surveillance (EBS) for these events is highly recommended.[1] EBS is the organized collection and triage of public health signals that are systematically verified and assessed based on their risk to public health.[2] It is used to detect public health signals in countries where mass gatherings occur, as well as public health threats from participating countries.[1] During the London 2012 Olympic and Paralympic Games, the Health Protection Agency (currently Public Health England) implemented EBS to provide timely and reliable national epidemic intelligence. EBS sourced events by screening local health authority reports and electronic applications.[3]

Public health and social measures were in place to respond to COVID-19 during the Games. However, the threat of importation of non-COVID-19 infectious diseases and their subsequent spread in the community remained. Early detection of acute public health events occurring outside of Japan could have triggered the early response and mitigation of these public health incidents occurring during the Games.

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The Japanese National Institute of Infectious Diseases (NIID) conducted enhanced EBS to capture infectious diseases occurring overseas during the Games,[1] which comprised their pre-existing EBS system plus external systems. The Epidemic Intelligence from Open Sources (EIOS) system, operated by the World Health Organization (WHO) Regional Office for the Western Pacific, was one of the external systems used. EIOS was built to assist in the early detection, verification, assessment and communication of public health signals and events[4] by capturing and aggregating publicly available information, categorizing the information with keywords and providing the results in a secure dashboard. EIOS enables users to monitor media articles of interest on the dashboard by filtering pre-identified keywords, such as the names of countries and diseases.[5] EIOS was the main surveillance tool used for the Games to capture articles on infectious diseases and other public health threats occurring outside of Japan.

We describe the experiences and lessons learned from using EIOS for enhanced EBS and risk assessment during the Games. We focused on the screened and assessed media articles on infectious diseases, the continued improvement of artificial intelligence in advancing the use of EIOS as a surveillance tool in mass-gathering events, and collaboration and information sharing between NIID and the WHO Regional Office.

METHODS

Design and planning

The planning of routine and ad hoc surveillance activities, as well as the information-sharing mechanisms included in the enhanced EBS using EIOS (**Fig. 1**), were jointly determined by NIID and the WHO Regional Office before the start of EBS operations. Enhanced EBS and risk assessment for the Games was conducted from 1 July to 19 September 2021, covering the period prior to and after both the Olympic and Paralympic Games, which were held from 23 July to 8 August 2021 and from 24 August to 5 September 2021, respectively.

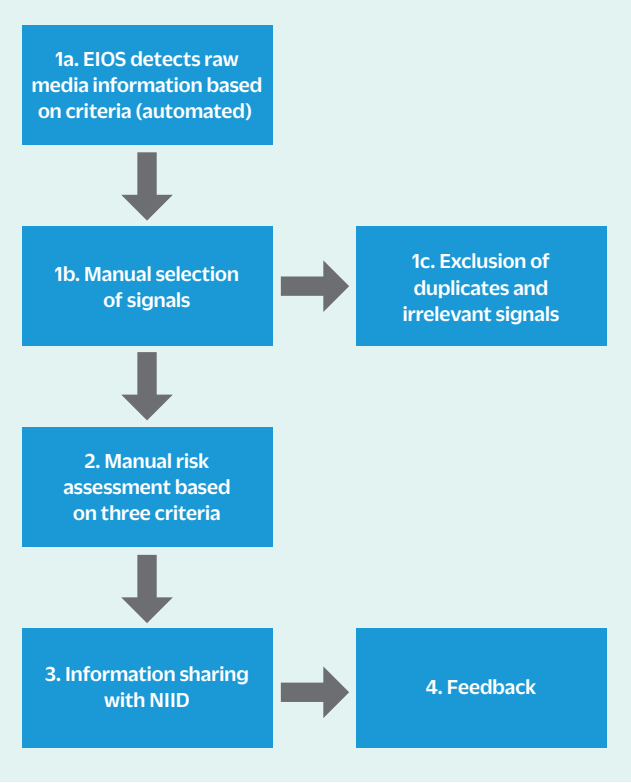
Data collection using Epidemic Intelligence from Open Sources

EIOS was identified as a suitable tool to use for screening publicly available online media articles and sources for unverified reports referencing infectious diseases. With support from the Information Systems and Data Management Team at WHO headquarters, the Tokyo 2020 EIOS dashboard was developed by late June 2021 using the agreed sets of countries, infectious diseases and other public health threats to be screened using EIOS (**Fig. 2**). The selection of 69 countries and areas (**Box 1**) from Africa, the Americas, Asia, Europe and Oceania was made based on the number of participants and delegations to the two previously held Games.[1] Further, the selection of infectious diseases of interest (**Box 2**) was determined by the prevalence of these diseases among the selected countries. Signals about the risk of bioterrorism and outbreaks of unknown origin were also captured.

Data collection process

An automated exclusion process was conducted by EIOS to filter out the diseases and countries not included in the pre-identified categories of countries and infectious diseases. During manual screening by a WHO Regional Office staff member, duplicates and irrelevant articles were discarded. For screened media articles requiring further verification, epidemiological data on the infectious disease of interest were collected manually from the reporting country. Media articles that were considered to indicate public health risks were regarded as signals and were then compiled in a daily media screening report. This report includes the category of the disease of interest in each media signal, a summary of the available information on the situation, and the continent and country where the signal was reported. When available, details on the action and response taken by the local health authorities were included to support the risk assessment.

Fig 1. **Flow chart of EIOS use during the Tokyo 2020 Olympic and Paralympic Games for event-based surveillance and risk assessment**



EIOS: Epidemic Intelligence from Open Sources; NIID: National Institute of Infectious Diseases, Tokyo, Japan.

Risk assessment

Each selected media signal was assessed using the following criteria:

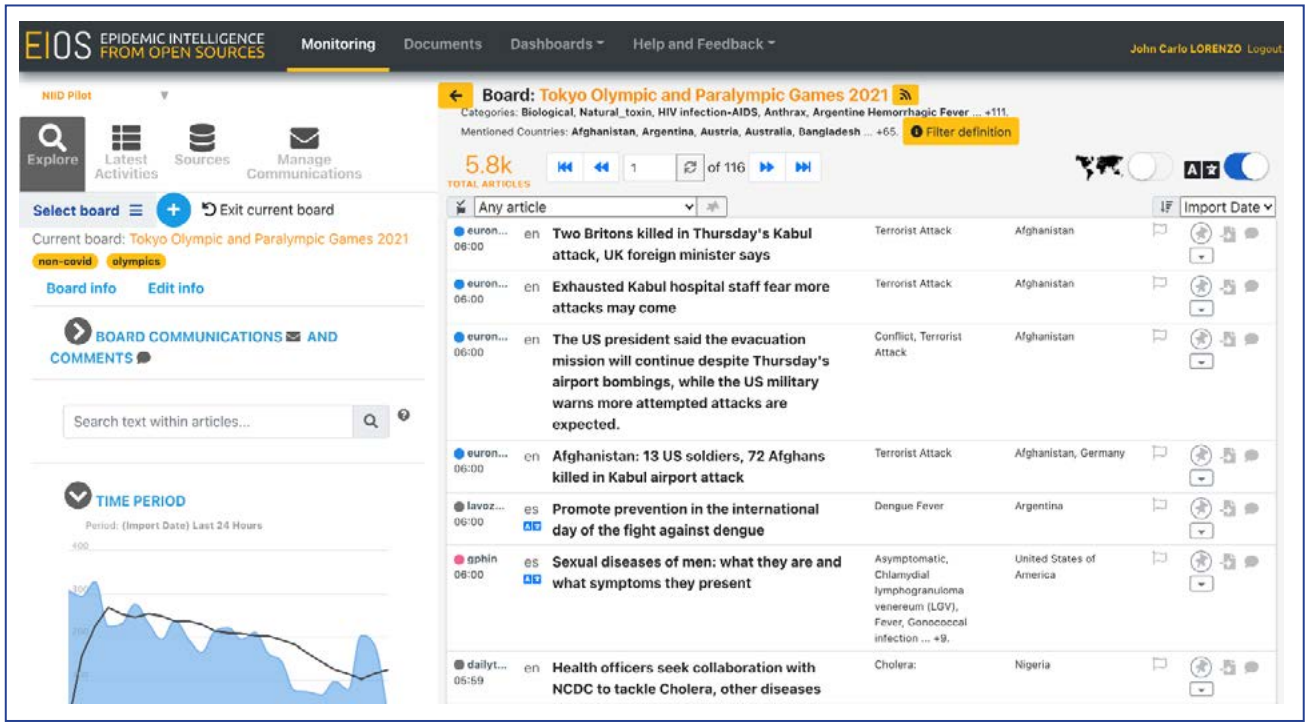
- Criterion 1: Does the condition have the likelihood of importation of infectious disease? (Yes/No)
- Criterion 2: Does the condition have the likelihood of transmission among Games personnel and the community? (Yes/No)
- Criterion 3: Does the condition have the likelihood of having a significant impact on society? (Yes/No)

If criterion 1 was marked "No", criteria 2 and 3 were not assessed. Criterion 3 focused on bioterrorism signals as they can have a significant impact on society. Additional information on the disease, including seasonality, trends, recent outbreaks and other epidemiological data, were collected and shared with NIID to increase confidence in the assessment for each criterion.

Information sharing and feedback

The assessed signals compiled in the daily media screening reports by the WHO Regional Office were shared

Fig. 2. **Example of how the EIOS dashboard was used for the Tokyo 2020 Olympic and Paralympic Games**



EIOS: Epidemic Intelligence from Open Sources.

Source: EIOS [online database]. Berlin: WHO Hub for Pandemic and Epidemic Intelligence; 2021.

Box 1. **Initial EIOS criteria for screening targeted countries and areas during the Tokyo 2020 Olympic and Paralympic Games**

i. Africa: Egypt, Kenya, Morocco, Nigeria, South Africa, Tunisia.
ii. Americas: Argentina, Brazil, Canada, Colombia, Cuba, Jamaica, Mexico, Peru, United States of America, Venezuela.
iii. Asia: Afghanistan, Bangladesh, Cambodia, China, Hong Kong SAR (China), India, Indonesia, Islamic Republic of Iran, Kazakhstan, Malaysia, Mongolia, Myanmar, Nepal, Pakistan, Philippines, Republic of Korea, Singapore, Sri Lanka, Taiwan (China), Thailand, Uzbekistan, Viet Nam.
iv. Europe: Austria, Belarus, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom of Great Britain and Northern Ireland.
v. Oceania: Australia, New Zealand.

Source: EIOS [online database]. Berlin: WHO Hub for Pandemic and Epidemic Intelligence; 2021.

Box 2. **Initial EIOS criteria for screening targeted infectious diseases and events during the Tokyo 2020 Olympic and Paralympic Games**

i. Human-to-human: acute gastroenteritis, bacterial meningitis, diphtheria, hepatitis B, influenza, measles, meningococcal infection, Middle East respiratory syndrome, mumps, pertussis, polio, rubella, sexually transmitted infections (chlamydia infection, gonococcal infection, HIV, syphilis), tuberculosis, varicella.
ii. Foodborne: amoebiasis, botulism, cholera, cryptosporidiosis, enterohaemorrhagic *Escherichia coli*, giardiasis, hepatitis A, hepatitis E, listeriosis, shigellosis, typhoid/paratyphoid.
iii. Soil/waterborne: coccidiosis, *Cryptococcus gattii* infection, histoplasmosis legionellosis, leptospirosis, melioidosis, strongyloidiasis, tetanus.
iv. Zoonosis: anthrax, avian influenza, brucellosis, hantavirus infection, Hendra virus infection, Lassa fever, monkeypox, Q fever, rabies, Rift Valley fever, Rissa virus infection, South American haemorrhagic fever, tularaemia.
v. Mosquito-borne: Barmah Forest virus infection, chikungunya, dengue, East equine encephalitis, Japanese encephalitis, La Crosse encephalitis, malaria, Oropouche fever, Ross River virus infection, Saint Louis encephalitis, West equine encephalitis, West Nile fever, yellow fever, Zika virus disease.
vi. Tick-borne: African spotted fever, anaplasmosis, Crimean-Congo haemorrhagic fever, Colorado tick fever, ehrlichiosis, Kyasanur Forest fever, Lyme disease, Omsk haemorrhagic fever, Powassan encephalitis, Queensland tick typhus, recurrent fever, severe fever with thrombocytopenia syndrome, spotted fever (Mediterranean spotted fever, Rocky Mountain spotted fever and other spotted fever groups), tick-borne encephalitis.
vii. Other arthropod-borne: Chagas disease, leishmaniasis, plague, scrub typhus.
viii. Potential risk of bioterrorism: white powder, attack.
ix. Disease outbreaks with unknown etiology: symptoms (coma, respiratory, diarrhoea, haemorrhage, fever).

Source: EIOS [online database]. Berlin: WHO Hub for Pandemic and Epidemic Intelligence; 2021.

with NIID on a daily basis for their assessment against the Playbooks, which were a set of guidelines prepared by the Tokyo Organizing Committee of the Olympic and Paralympic Games that outlined the responsibilities and rules of all the Games participants and Games-related personnel. They were also compiled by NIID in the daily situational report, together with data on priority notifiable infectious diseases in Japan and COVID-19 information relevant to the Games. The daily situational report was disseminated to Japan's local health authorities and to WHO through the International Health Regulations (IHR) communication mechanism.

RESULTS

Between 1 July and 19 September 2021, a total of 103 830 media articles appeared on the Tokyo 2020 EIOS dashboard. Of these, 5441 (5.2%) were deemed relevant to public health threats and manually screened, out of which 587 (0.6%) were regarded as signals and were reported to NIID (**Table 1**).

Among the 587 signals, 211 (35.9%) had "Yes" for both criteria 1 and 2, emphasizing the likelihood of their importation into Japan through the Games and spread to the local community. About 82% (173 of 211 with "Yes" for criteria 1 and 2) were mosquito-borne diseases such as dengue, chikungunya and Zika virus disease. Of these 173 mosquito-borne disease signals, dengue accounted for 139 (80.3%). The WHO South-East Asia Region and the WHO Region of the Americas reported the most dengue signals with 78 (56.1%) and 39 (28.1%) signals, respectively.

Sexually transmitted infections were the next most common at 13.7% (29/211), and diseases with unspecified causative agents accounted for the remaining 2.8% (6/211) of signals. Of all reported signals, 0.3% (2/587) had "Yes" for criterion 3, implicating the likelihood of having a significant impact on society.

None of the signals detected were assessed as having the likelihood of a significant impact on the Games.

Table 1. **Number and proportion of signals detected through the EIOS dashboard for the Tokyo 2020 Olympic and Paralympic Games, assessment outcomes and reported diseases that met criteria 1 and 2, 1 July to 19 September 2021**

Signals	Number of articles (%)
Detected through EIOS (*N*=103 830)	
Not screened (did not meet selection criteria)	98 389 (94.7)
Screened and discarded	4854 (4.7)
Screened and reported as signals	587 (0.6)
Assessment of signals (*n*=587)	
"No" for criterion 1[a]	329 (56.0)
"Yes" for criterion 1	258 (44.0)
"Yes" for criteria 1 and 2[b]	211 (35.9)
"Yes" for criterion 3[c]	2 (0.3)
Reported diseases of signals that met criteria 1 and 2 (*n*=211)	
Mosquito-borne diseases	173 (82.0)
Sexually transmitted infections	29 (13.8)
Unknown diseases	6 (2.8)
Others	3 (1.4)

EIOS: Epidemic Intelligence from Open Sources.

[a] Criterion 1: Does the condition have the likelihood of importation of infectious disease?

[b] Criterion 2: Does the condition have the likelihood of transmission among Tokyo 2020 personnel and the community?

[c] Criterion 3: Does the condition have the likelihood of having a significant impact on society?

Further, none of the signals required the activation of the IHR communication mechanism.

DISCUSSION

EIOS provided an enhanced surveillance system with quality-assured risk assessment for the Games. None of the 587 signals reported had a potentially significant impact on the Games. One of the possible reasons may be the significant decrease in infectious disease activity due to public health and social measures for COVID-19 globally. Population mobility restrictions, international and domestic travel measures, and school closures resulted in the decline of several infectious diseases, especially vaccine-preventable diseases.[6–8] Decreases were also observed for respiratory infectious diseases globally, during and after the implementation of community control strategies for COVID-19.[9–11] However, some decrease in cases of infectious diseases might be caused by potential under-detection due to less opportunity for testing and/or delays in final diagnosis as a consequence of overwhelmed health-care systems and the fear of being treated as a suspected COVID-19 case.[12,13] Even though none of the detected signals were considered significant, the detection, monitoring and information-sharing processes pertaining to acute public health events occurring outside Japan were valuable.

As EIOS displays publicly available articles from multiple sources tagged by pre-identified categories, it was considered a good tool to capture information on infectious diseases occurring globally. However, EIOS displays multiple replicated articles, revealing duplication of effort in conducting EBS screening activities. Due to its sensitivity, EIOS also displays irrelevant articles which significantly increases the number of articles tagged for events with high media attention.

So as to improve the use of EIOS as a mass gathering surveillance tool, continued use and improvement of artificial intelligence that selects and clusters articles with duplicate content before being displayed on the EIOS dashboard should be considered. Clustering similar media signals would lessen the time spent manually screening the results as duplicated content would only appear once. It would also show if a signal has high media attention without omitting valuable information from other media articles. Moreover, inclusion and exclusion features of a specific category based on international political and social conditions would be effective in reducing irrelevant articles and minimizing the clamour from incidents with high international media attention. An additional function able to search articles from an official information source may also contribute to increasing specificity and reducing the time spent manually screening EIOS articles.

The major advantage of using EIOS during the Games was the timely and consistent identification of global epidemiological information, which complemented NIID's other EBS activities and supported the conduct of appropriate risk assessment.[1] This timely detection and quality-assured risk assessment enabled the Japanese Ministry of Health, Labour and Welfare (MHLW) and the WHO Regional Office to consider whether facilitating IHR communication for further verification was necessary. Through collaboration and information sharing, and having EIOS managed externally, MHLW and NIID were able to receive relevant information on potential public health events that could have resulted in imported disease during the Games. EIOS was a successful component of the enhanced surveillance system for infectious diseases and public health threats that could have impacted the Games.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval

Ethics approval was not required. Information collected using EIOS regarding infectious disease outbreaks and situations in different countries was collected from open sources that are readily available to the public through their respective websites.

Funding

None.

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A rare presentation of *Mycobacterium africanum* after two decades: a case report from Brunei Darussalam

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Mycobacterium africanum is endemic to West Africa and is rare outside this region. Most of the people infected with *M. africanum* outside Africa are migrants from affected parts of Africa. We report a rare case of pulmonary tuberculosis (TB) secondary to *M. africanum* in a man in Brunei Darussalam who had lived and worked in Guinea, West Africa for 6 years more than 20 years ago. He had been well until December 2020, when he presented with a chronic cough and was diagnosed with coinfections of *Klebsiella pneumoniae* and *M. africanum*, and newly diagnosed diabetes mellitus. This case highlights an interesting manifestation of pulmonary TB secondary to *M. africanum* in a patient whose last exposure was 20 years ago, contributed to by development of diabetes mellitus.

Tuberculosis (TB) remains endemic in many parts of the world and pulmonary TB (PTB) is the most common manifestation. TB is usually caused by *Mycobacterium tuberculosis*.[1] However, in some parts of the world, variants predominate; for example, in West and Central Africa, *M. africanum* predominates, accounting for over 50% of PTB cases.[2,3] *M. africanum* comprises two phylogenetically distinct lineages within the *M. tuberculosis* complex (MTBC): *M. africanum* West African 1 and *M. africanum* West African 2.[2,3] Cases of *M. africanum* outside Africa are rare and often occur in people who originate from affected regions.[4]

Cases have been reported in England, France, Germany, Spain and the United States of America (USA),[2] and local transmission outside endemic regions has also been reported. A study from Norway reported a cluster of six cases of *M. africanum* originating from a single imported case.[5] Three patients were from countries in West Africa, and the other three were from south Asia and the Caribbean, where *M. africanum* is not known to be present. Four of the six patients had lived in Norway for more than 10 years, and the other two for 3–9 years. The six cases were diagnosed over a 3-year period (2016–2018).[5] Prior to this report, no cases of *M. africanum* have been reported in the Western Pacific Region.

THE CASE

Case identification

A 52-year-old Malaysian man living in Brunei Darussalam who had been previously well presented with a chronic cough that had recently become productive with greenish-yellow sputum. He also reported weight loss of 3 kg in recent months. Several courses of antibiotics prescribed by a private doctor had been ineffective. A chest X-ray (CXR) showed pleural parenchymal lesions with fibrosis in the right upper zone with cavitation. His past medical history was insignificant, apart from a CXR (February 2018) done as part of occupational health screening, which showed pulmonary fibrosis in the right upper zone. CXR done before this in 2014 was normal (**Fig. 1**). He was referred for evaluation but cancelled his appointment because he was well. He is a smoker of 24 pack-years and does not consume alcohol. He reported no past history, family history or

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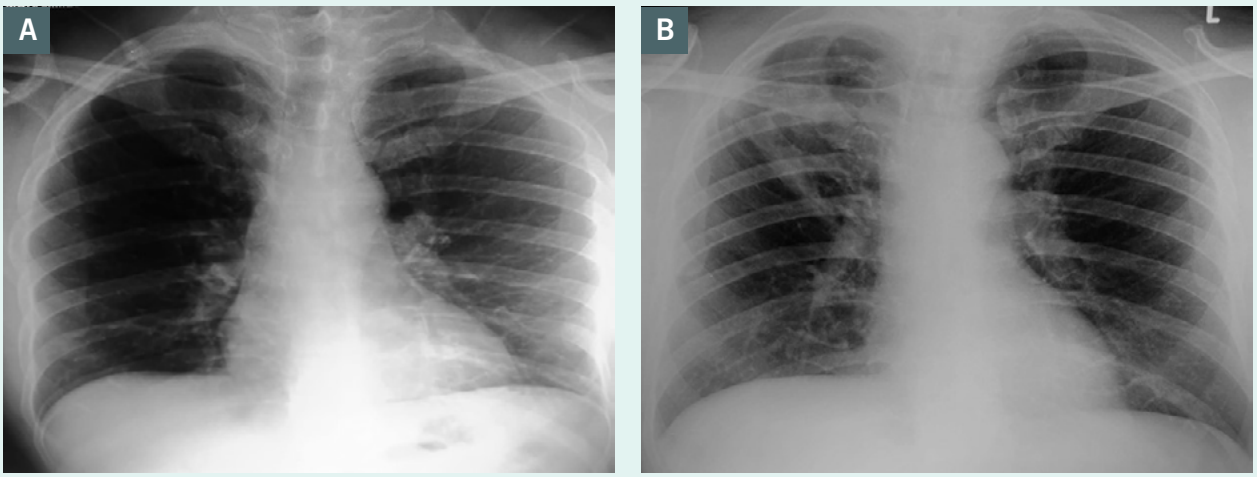
Fig. 1. **A) Chest X-ray from 2014 with normal findings, and B) from presentation in December 2020, showing fibrosis with cavitation in the upper zone on the right**



contact with anyone with TB. He was referred to the hospital for evaluation for PTB based on his history of chronic cough and CXR findings.

Clinical examination revealed minimal coarse crepitations in the right upper lung. Blood investigation showed elevated white cell count, elevated inflammatory markers, hyperlipidaemia and hyperglycaemia.

Laboratory investigations

Three consecutive morning sputum specimens were sent to the National Mycobacteria Reference Laboratory, Department of Laboratory Services, Brunei Darussalam. In brief, the specimens were decontaminated and inoculated in both liquid (Mycobacterium growth indicator tube, Becton Dickinson, NJ, USA) and Lowenstein-Jensen slant (Becton Dickinson). Simultaneously, an aliquot of concentrated specimen was prepared for Auramine O Fluorescent Stain Kit M (Becton Dickinson). Smear-positive samples were screened for the presence of MTBC DNA and drug (rifampicin and isoniazid) resistance genes using GenoType MTBDRplus version 2.0 (Hain Lifescience GmbH, Germany), performed according to the manufacturer's instructions. Further species differentiation within MTBC was identified using GenoType MTBC version 1 (Hain Lifescience GmbH). After reverse hybridization, the final step was a line-probe assay (LPA), which involved fixing the test strips on a designated sheet and interpretation according to the specific species or mutation band profile provided by the manufacturer.

Sputum culture isolated *Klebsiella pneumoniae* and sensitivity testing showed it to be sensitive to all antibiotics apart from ampicillin. All three morning sputum smears also came back positive for acid fast bacilli (AFB), confirming the diagnosis of PTB and *K. pneumoniae* coinfection. Serum glycosylated haemoglobin came back as 9.3% (reference: <6.5%), confirming a new diagnosis of diabetes mellitus. AFB culture identification (LPA, GenoType MTBC) came back as *M. africanum*. HIV screening was negative.

Treatment

The patient was started on a course of antibiotics while waiting for PTB investigations, after which he was started on anti-diabetes treatment (metformin 1000 mg twice daily and linagliptin 5 mg once daily); also, glucose control improved, with a glucose range of 5–10 mmol/L.

The patient was started on standard anti-tubercular treatment (ATT) as per World Health Organization guidelines, with 2 months of intensive treatment with isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. His treatment while waiting for three consecutive negative sputum AFB tests was only complicated by mild anti-TB side-effects. On

day 17 of ATT, he developed an urticarial reaction that resolved with regular antihistamines. On day 26, he developed deranged liver function tests (LFT). Hepatotoxic drugs were withheld and the patient was treated with ethambutol and second-line levofloxacin in the interim period. Once LFT normalized, ATT re-challenge with the sequential introduction of main-line ATT was achieved.

The patient completed the extended intensive-phase therapy followed by the continuation phase without any further adverse events. CXR after completion of treatment, 9 months after diagnosis, showed resolution of cavities, leaving only fibrotic changes in the right upper zone. His glycaemic control initially improved to 9.3% but later deteriorated as he had stopped his diabetes treatment due to financial issues that were compounded by the coronavirus disease (COVID-19) pandemic.

Case history

We revisited the patient's history, which revealed that he had lived in a small village in Guinea, West Africa from 1995 to 2000. He could not recall having contact with anyone who had chronic cough or symptoms of TB. Apart from the occasional bout of influenza, he had been well during his 6 years of living there. He then returned to his home country of Malaysia and subsequently moved to Brunei Darussalam in 2011. His family reside in Malaysia and are all well. He reported no history of contact with his former African colleagues and had not returned to Africa.

DISCUSSION

Humans are the only natural reservoir for *M. africanum*, which is usually transmitted by inhalation of infected droplets. However, cases of *M. africanum* infection in animals such as monkeys and cows have been reported.[2,6] A study from Bangladesh reported *M. africanum* type I identified through spoligotyping in autopsied lung tissue homogenate samples of four cows, probably infected through a farm caretaker.[2]

Clinical manifestations of *M. africanum* are similar to *M. tuberculosis* but have a more indolent course and less severe symptoms.[7] The infection may have host specificity, be influenced by factors such as age, and have less severe cough symptoms and slow progression to disease, showing the lower virulence of *M. africanum* compared with *M. tuberculosis*. A study from endemic parts of Africa has shown that patients with *M. africanum* had shorter duration of symptoms but more severe changes on chest imaging.[7] Those of older age and with conditions that affect the immune system (e.g. HIV and diabetes mellitus) are at higher risk. A recent study from Brunei Darussalam reported that a third of TB patients have underlying diabetes at or within 6 months of diagnosis of TB, highlighting the importance of diabetes as a risk factor in patients with TB.[8]

Smoking has also been shown to contribute to the risk of poor outcomes from TB. A large study of patients from 32 high TB burden countries reported an estimated 17.6% (95% confidence interval [CI]: 8.4–21.4) of TB cases and 15.2% (95% CI: 1.8–31.9) of TB mortality were attributable to smoking.[9] In our case, smoking is likely also a contributing factor in addition to diabetes mellitus. TB remains endemic in Brunei Darussalam, with an average of 227 cases recorded every year, for a rate of 54 per 100 000 population per year.[8] This case represents the first case of *M. africanum* recorded in Brunei Darussalam. In fact, literature searches failed to locate any report of *M. africanum* in South-East Asia.

This case is interesting from several aspects. First, our patient is from South-East Asia and his only exposure was during a period of residence in Guinea. There was no history of other possible exposures after returning from Guinea. Second, PTB manifested more than 20 years after exposure. In the interim period, he had been well, apart from CXR findings during an occupational health screening. He probably manifested the disease after he developed diabetes mellitus, which was diagnosed simultaneously with PTB. Apart from diabetes mellitus, there was no evidence of other conditions that can cause immune suppression. An HIV test was negative and there was no clinical evidence of underlying malignancy. Furthermore, his condition improved after starting treatment for PTB and diabetes mellitus.

TB remains an important public health problem, causing more than a million deaths each year, especially in developing countries.[10] With effective

and timely treatment, TB is curable. Therefore, enhanced surveillance and reporting remain an integral component and should be continuously monitored and improved, especially in areas where TB remains endemic, including the Western Pacific Region. This is especially true as pandemic-related travel restrictions are eased, resulting in increasing population movement, which can lead to the appearance of TB strains in non-endemic regions.

CONCLUSION

This case represents the first case of *M. africanum* recorded in Brunei Darussalam. Our patient's only risk factor was having lived in Africa 20 years ago and this unusual manifestation probably resulted from development of underlying diabetes mellitus. Clinicians need to consider the possibility of *M. africanum* in any person with a history of travel to an endemic region, even after such a long interval. In addition, our case highlights that TB can manifest at any time, especially with the presence of underlying risk factors such as diabetes mellitus and heavy smoking.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

The patient provided verbal consent for publication of this report. No identifying images are used in this report.

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Occurrence of the Omicron variant of SARS-CoV-2 in northern Viet Nam in early 2022

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The Omicron variant caused a surge of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Viet Nam in early 2022, signalling community transmission. We report on active whole-genome sequencing surveillance of positive SARS-CoV-2 samples collected at that time in northern Viet Nam from international arrivals and community clusters. We used an amplicon protocol developed with 14 polymerase chain reaction products and the Illumina iSeq 100 platform. Overall, 213 nasopharyngeal or throat swabs were analysed, of which 172 samples were identified with the Omicron variant. Of these, 80 samples were collected from community cases in February 2022, among which 59 samples were sublineage BA.2 and one sample was the recombinant XE variant. Our results indicated that Omicron had replaced Delta as the dominant variant in a very short period of time and that continuously conducting active whole-genome sequencing surveillance is necessary in monitoring the evolution and genomic diversity of SARS-CoV-2 in Viet Nam.

During the coronavirus disease (COVID-19) pandemic, Viet Nam changed its policy from "zero COVID" to "safe and flexible adaptation and effective control of the COVID-19 pandemic" (Resolution No. 128/NQ-CP, dated 11 October 2021). This was in an attempt to achieve a new normal by the end of September 2021, when the surge of the Delta (B.1.617.2) variant had decreased and was under control in southern Viet Nam. However, a surge of the Omicron (B.1.1.529) variant in early 2022 caused the highest peak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the country compared to previous waves.

The Omicron variant of SARS-CoV-2 was first identified in South Africa in mid-November 2021.[1] The first case of the Omicron variant in Viet Nam was confirmed in a person who returned to Hanoi from the United Kingdom of Great Britain and Northern Ireland on 27 December 2021.[2] The first community cluster of the Omicron variant (three cases) was documented in Ho Chi Minh City on 18 January 2022. Since then, a large number of cases have been detected among people arriving from overseas. As of 2 January 2022, approximately 79.2% of the population of Viet Nam had received one dose of COVID-19 vaccine and 70.1% had received two doses. However, the Omicron variant's greater transmissibility and ability to evade immunity meant the surge of SARS-CoV-2 infections and the ensuing community transmission was expected.[3,4]

Since early 2020, the National Institute of Hygiene and Epidemiology (NIHE) has conducted active virological surveillance using whole-genome sequencing on samples positive for SARS-CoV-2. Until 15 March 2022, these samples were collected from international arrivals at quarantine centres and new community cluster infections in order to monitor the genomic epidemiology of SARS-CoV-2 virus circulation in northern Viet Nam. Here

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we report the results of complete genome sequences of SARS-CoV-2 from samples collected from 1 January to 28 February 2022 in northern Viet Nam.

METHODS

We sequenced 213 nasopharyngeal or throat swab samples that were sent to NIHE from 22 of the 28 Provincial Centers for Disease Control and Prevention in northern Viet Nam. All samples were positive for SARS-CoV-2 with a Ct value of <30 by real-time reverse transcription polymerase chain reaction (RT-PCR). Of the 213 specimens, 80 were collected from community outbreaks during February 2022, and the remaining 133 were from international arrivals at quarantine centres during January and February 2022 (**Fig. 1**, **Table 1**).

We used the amplicon protocol developed with 14 PCR products – primers designed for sequential amplified fragments with a size band of about 2.5 kb based on the SARS-CoV-2 reference genome (ID: MN 908947-Wuhan-Hu-1). Firstly, RNA was converted into cDNA using SuperScript™ IV VILO™ (Thermo Fisher Scientific, Waltham, MA, United States of America), then 14 amplicons were amplified from the cDNA using Platinum™ SuperFi II Green PCR Master Mix (Thermo Fisher Scientific). Following amplification, PCR products were checked by electrophoresis using a 1% agarose gel. PCR fragments were pooled and purified by Applied Biosystems ExoSAP-IT™ (Thermo Fisher Scientific). Library preparation was performed following protocol using the Nextera XT Library Preparation Kit (Illumina, San Diego, CA, United States of America) and sequencing was performed on the Illumina iSeq 100 System (Illumina). Data analysis was performed using CLC Genomics Workbench 11.0 for consensus assembly and variant detection. The sublineages were assigned using Nextclade V1.14.0 and Pangolin (lineage version 2022-02-28).[5,6] These sequences were uploaded to GISAID (IDs: EPI_ISL_11775985 to EPI_ISL_11776195).

RESULTS

Sample source

Among the 213 samples in this study, 97 were collected in January 2022 (45.5%), all of which were from foreigners or returning Vietnamese citizens who were staying in quarantine centres in northern Viet Nam in accordance with immigration requirements (**Fig. 1**).

After the Vietnamese Lunar New Year (Tet holiday from 31 January to 4 February 2022), increases in SARS-CoV-2 infections in many cities and provinces in Viet Nam were reported, and samples collected from community outbreaks were sent to NIHE. We analysed a total of 116 samples in February, 80 of which came from community outbreaks in 18 cities and provinces in northern Viet Nam. Most of these (58/80; 72.5%) were collected during week 8 of 2022 (20 February). The other 36 samples were collected from quarantine centres (**Table 1**).

Two variants of concern were detected in this study. The Delta variant was at its most dominant (81.3%; 13/16) in week 1 of 2022, then decreased to 6.8% (5/74) by the last week of February. Conversely, the Omicron variant was detected in week 1 in 18.8% (3/16) of samples, then increased to 85.7% (12/14) by the last week of January (**Fig. 1**). Among the samples analysed in February 2022, the Omicron variant comprised 90.5% (105/116) overall and reached its highest rate of 93.2% (69/74) in week 8 (**Fig. 1**).

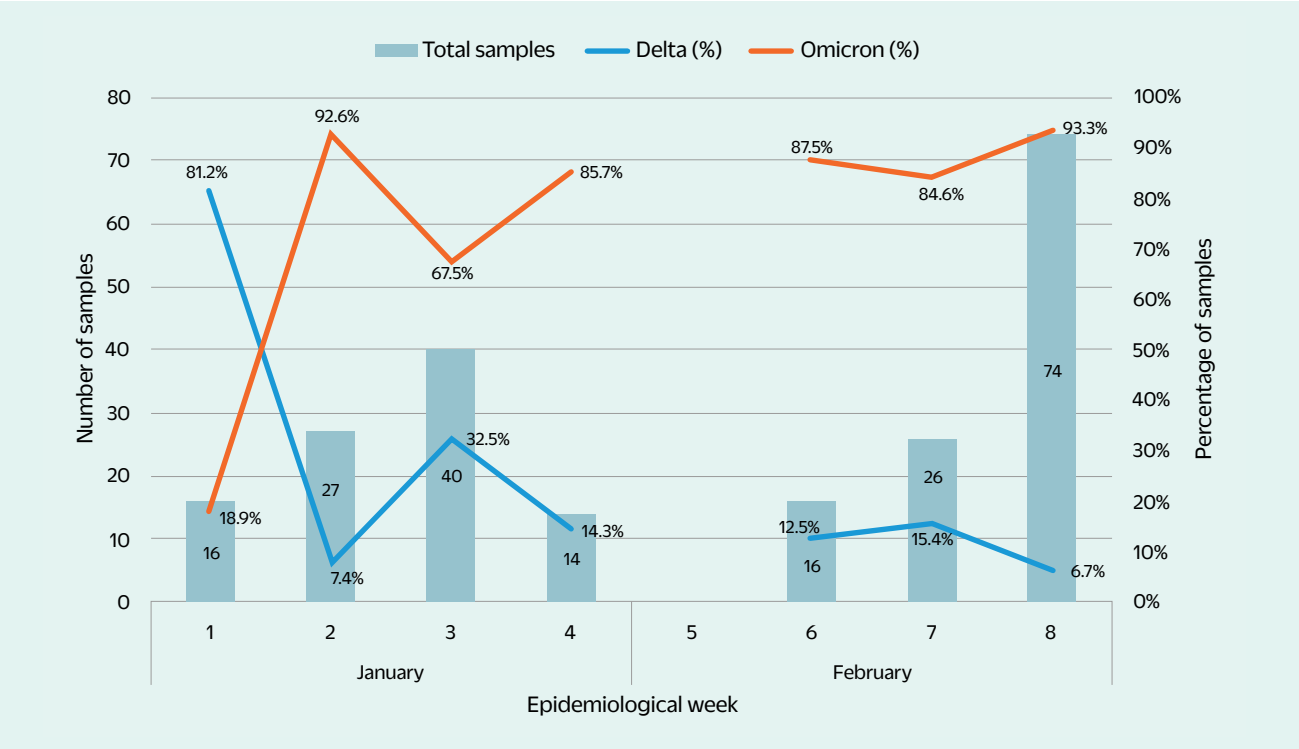
Sublineages of SARS-CoV-2 variants detected in northern Viet Nam in early 2022

Of the 213 positive samples, 41 (19.2%) were the Delta variant. Most of these (75.6%; 31/41) were imported: 30 in January and one in early February. The other 10 Delta samples were detected in the community throughout February. The remaining 172 positive samples were the Omicron variant. We detected four Omicron sublineages: 21.5% BA.1 (37/172), 22.1% BA.1.1 (38/172), 55.8% BA.2 (96/172) and one sample (0.58%) was determined to be recombinant Omicron XE (**Table 1**). The XE variant was first detected in week 8 (on 26 February) from a community outbreak in the capital of Hanoi (GISAID ID: EPI_ISL_11776032).

Time course of the Omicron variant in community outbreaks

Our results show that the Omicron variant was first detected in the community in week 7 of 2022 and accounted for the majority of cases in weeks 7 and 8. BA.2 was the predominant sublineage comprising most of the new COVID-19 cases in northern Viet Nam after the Tet

Fig 1. **Distribution of samples sent for whole-genome sequencing by SARS-CoV-2 variant in northern Viet Nam, January and February 2022**



Samples were not collected during week 5 due to the Tet holiday.

Table 1. **Circulation of SARS-CoV-2 variants in samples sent for whole-genome sequencing in northern Viet Nam, January and February 2022**

Variant	January (week)					February (week)				
	1	2	3	4	Total	5[a]	6	7	8	Total
Imported cases										
Delta	13	2	13	2	30	Tet holiday	1	0	0	1
Omicron BA.1	3	9	15	2	29		3	0	1	4
Omicron BA.1.1	0	14	10	3	27		5	0	0	5
Omicron BA.2	0	2	2	7	11		6	5	15	26
Community cases										
Delta	0	0	0	0	0	Tet holiday	1	4	5	10
Omicron BA.1	0	0	0	0	0		0	1	3	4
Omicron BA.1.1	0	0	0	0	0		0	3	3	6
Omicron BA.2	0	0	0	0	0		0	13	46	59
Omicron XE	0	0	0	0	0		0	0	1	1

[a] Samples were not collected during week 5 due to the Tet holiday.

holiday.[2] Co-circulating with BA.2 were the BA.1 and BA.1.1 sublineages, both of which outnumbered BA.2 among cases in January but accounted for only a small number of cases in February (**Table 1**). From week 7 to week 8, the number of BA.2 cases in the community jumped from 13 to 46, far outpacing the growth rate of other sublineages (**Table 1**).

DISCUSSION

As of writing, the Omicron variant is the predominant variant circulating globally.[6–8] Our findings revealed the rapid replacement of Delta by the Omicron variant in Viet Nam in January 2022, during which all positive samples were collected from people arriving in Viet Nam from abroad. Our results showed the proportion of the Omicron variant increased over time and accounted for 69.9% of infections among international arrivals in January 2022. These results corresponded to the epidemiological situation in other parts of Asia such as Hong Kong Special Administrative Region (China), Japan, the Republic of Korea and Singapore at that time.[7–10]

Among the Omicron sublineages, BA.2 was the main cause of community outbreaks. This sublineage accounted for 73.8% of analysed samples that underwent genetic sequencing and increased quickly among samples from the community (0 in week 6, 13 in week 7 and 46 in week 8), which shows the Omicron BA.2 sublineage to be a more contagious strain.

This report is the first to identify the Omicron XE variant in the community in Viet Nam. Because all imported cases were sequenced and the XE variant was not found among international arrivals, this case had no known link to the XE variant circulating in the United Kingdom at the time and may have developed independently.[11]

Our study has some limitations. It was conducted during the first 8 weeks of 2022 and was paused during week 5 due to the Tet holiday, so the data are not consecutive. The results were only collected in northern Viet Nam and were not representative of the entire country at the time. Additionally, this study focused on virological data, thus epidemiological data were not included. As specimens sent for whole-genome sequencing are from international arrivals and community clusters, not all notified cases are included in virological surveillance. For example, during the week of 14–20 February 2022, there were 276 633 new COVID-19 cases reported in Viet Nam, suggesting that those included in this study are a small fraction of total cases.[12]

Our results provide additional information about the spread of the Omicron BA.2 sublineage in Viet Nam, which may help plan for and manage infections in the near future. Active surveillance of SARS-CoV-2 variants based on whole-genome sequencing is one source of information along with other sources of surveillance that contribute to risk assessment for adjusting public health measures and assessing vaccine effectiveness.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics approval

The analyses conducted in this study were conducted as part of the regular activities of the National Institute of Hygiene and Epidemiology. Patient data are anonymized and no ethical approval was required for this study.

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Clinical and demographic characteristics of COVID-19 cases in Brunei Darussalam: comparison between the first and second waves, 2020 and 2021

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Objective: Differences in clinical manifestations between strains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been reported. This retrospective descriptive study compares the clinical and demographic characteristics of all confirmed coronavirus disease (COVID-19) cases admitted to the National Isolation Centre (NIC) in the first wave and at the beginning of the second wave of the pandemic in Brunei Darussalam.

Methods: All COVID-19 cases admitted to the NIC between 9 March and 6 May 2020 (first wave) and 7–17 August 2021 (second wave) were included. Data were obtained from NIC databases and case characteristics compared using Student's t-tests and chi-squared tests, as appropriate.

Results: Cases from the first wave were significantly older than those from the second wave (mean 37.2 vs 29.7 years, $P<0.001$), and a higher proportion reported comorbidities (30.5% vs 20.3%, $P=0.019$). Cases from the second wave were more likely to be symptomatic at admission (77.7% vs 63.1%, $P<0.001$), with a higher proportion reporting cough, anosmia, sore throat and ageusia/dysgeusia; however, myalgia and nausea/vomiting were more common among symptomatic first wave cases (all $P<0.05$). There was no difference in the mean number of reported symptoms (2.6 vs 2.4, $P=0.890$).

Discussion: Our study showed clear differences in the profile of COVID-19 cases in Brunei Darussalam between the first and second waves, reflecting a shift in the predominating SARS-CoV-2 strain. Awareness of changes in COVID-19 disease manifestation can help guide adjustments to management policies such as duration of isolation, testing strategies, and criteria for admission and treatment.

The emergence and rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal pathogen of the coronavirus disease (COVID-19) pandemic, has presented health services with major challenges and has disrupted social and economic activities worldwide. As of 15 August 2022, the World Health Organization (WHO) had recorded over 587 million confirmed cases and over 6.4 million deaths due to COVID-19 worldwide.[1] In Brunei Darussalam, the first wave of the COVID-19 pandemic started on 9 March 2020 and lasted until 6 May 2020, the date of the last documented case of community spread. After approximately 15 months of being at WHO Level 2 transmission (low community incidence or a risk of community transmission beyond clusters),[2] a second wave, confirmed to be due to the Delta strain (SARS-CoV-2 variant B.1.617.2), started on 7 August 2021.

Compared with the original SARS-CoV-2 strain, the Delta variant has a higher reproduction number (R_0) and was the dominant variant circulating in Brunei Darussalam during 2021 when this study was conducted.[3] Differences in the clinical characteristics of cases due to the original and Delta strains of the virus have been widely reported in the literature, although these studies have been restricted to patients needing hospital admission.[4–8] To date, few studies have compared the first and second waves across the full spectrum of COVID-19 disease severity, i.e. by including asymptomatic and

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symptomatic patients as well as those with more severe disease. Understanding differences between the two waves in disease presentation can help improve the management of patients.

During the first wave in Brunei Darussalam, all confirmed COVID-19 patients were admitted to the National Isolation Centre (NIC) for isolation and treatment. During the second wave, community isolation centres (CICs) with minimal medical facilities were used to care for asymptomatic or mild cases (i.e. symptomatic cases that did not need specific treatment). Recovering patients admitted to the NIC were also transferred to CICs until they fulfilled criteria for discharge, and patients admitted to CICs whose condition subsequently deteriorated were transferred to the NIC. Until the CICs were opened on 18 August 2021, the NIC remained the only designated isolation and treatment centre in Brunei Darussalam for all confirmed cases of COVID-19.

The objective of this study was to compare the differences between the first and second waves in the clinical and demographic characteristics of all confirmed COVID-19 cases in Brunei Darussalam, including asymptomatic, mild and severe cases.

METHODS

Study participants

All cases admitted to the NIC between 9 March and 6 May 2020 (the first wave) and between 7 and 17 August 2021 (the second wave) were included in the study. Subjects admitted to the NIC after 18 August were not included in this study, as from this date onwards asymptomatic and mild cases of COVID-19 were instead admitted to CICs. Inclusion of subjects admitted to the NIC after 18 August would have led to a second wave study population that was biased towards more severe cases and thus not representative of the complete spectrum of COVID-19 disease severity.

Data collection

Case finding and contact tracing were conducted by the Department of Public Health, and all confirmed COVID-19 cases were registered and assigned a unique case identification number. Data for all cases were retrieved from prospectively maintained Excel databases, created by the various teams set up by the Ministry of Health's National COVID-19 Committee to help with the management of patients. Data collected included information on patient demographics, comorbidities, reported COVID-19 symptoms, disease progression and outcomes. Each patient was asked to complete a detailed symptom checklist on admission to the NIC, which included questions about symptom onset.

Case definitions

Symptom category

Cases were categorized as (i) asymptomatic (no symptoms experienced during course of illness), (ii) pre-symptomatic (no symptoms at NIC admission but developed symptoms later), (iii) symptomatic (symptoms at NIC admission) and (iv) recovered (symptoms resolved before NIC admission). Patients were assigned to a symptom category according to their status at the time of their admission to the NIC.

Disease category

For the purposes of this study, four categories of disease were defined: (i) asymptomatic/mild (no symptoms or symptomatic without evidence of pneumonia on chest imaging), (ii) moderate (clinical or imaging evidence of pneumonia), (iii) severe (required oxygen supplementation) and (iv) critical (respiratory failure requiring mechanical ventilation with or without other organ failure). Patients' disease categories were assessed daily and reported to the Ministry of Health. Patients were assigned to the highest category reached during the course of their illness.

Data analysis

Patient data were anonymized before analysis. Clinical and demographic characteristics of patients from the two waves were compared; tests for statistical significance of differences between the two cohorts were performed as appropriate (Student's t-test for continuous variables and chi-squared test for categorical variables). *P* values of <0.05 were considered statistically significant. Analyses were conducted using SPSS version 26.0.

RESULTS

During the first wave of the COVID-19 pandemic, a total of 141 cases were admitted to the NIC. During 7–17 August 2021, the period of the second wave included in this

study, 359 cases were admitted. COVID-19 cases from the first wave were significantly older and were more likely to have cardiovascular comorbidities compared with those in the second wave (**Table 1**).

There was no difference in the mean duration of symptoms before admission between first and second wave cases (3.9 ± 3.6 vs 3.6 ± 2.6 days, respectively, P=0.260). However, the mean time between specimen collection and admission to the NIC was shorter in the second wave than in the first (0.2 ± 1.0 vs 2.6 ± 2.0 days, respectively, P<0.05).

A significantly higher proportion of second wave cases reported symptoms at admission compared with the first wave (77.7% vs 63.1%, respectively, P<0.001). Relative to the first wave, patients were significantly more likely to report cough, anosmia, sore throat and ageusia/dysgeusia, but significantly less likely to report myalgia and nausea/vomiting (all P<0.05) (**Fig. 1**). There was no difference in the number of symptoms reported between the first and the second waves (2.6 ± 1.4 vs 2.4 ± 1.2, respectively, P=0.890).

The proportion of asymptomatic patients at admission was higher in the first wave (P<0.001; **Table 1**). However, there was no significant difference between the two waves in terms of the distribution of cases by disease severity (P=0.148; **Table 1**); in both waves, the majority of cases (>80%) were categorized as either asymptomatic or mild.

During the first wave, none of the cases were vaccinated as vaccines against COVID-19 had not yet become available. Of the second wave cases, 13 (3.6%) were fully vaccinated (two doses), 41 (11.4%) were partially vaccinated (one dose) and 305 (85.0%) were unvaccinated. Of the unvaccinated cases, 117 (32.6%) were under the age of 18 years and not eligible for vaccination at the time. Most of the vaccinated cases had asymptomatic or mild disease, and there were more severe cases in the unvaccinated group (**Table 2**).

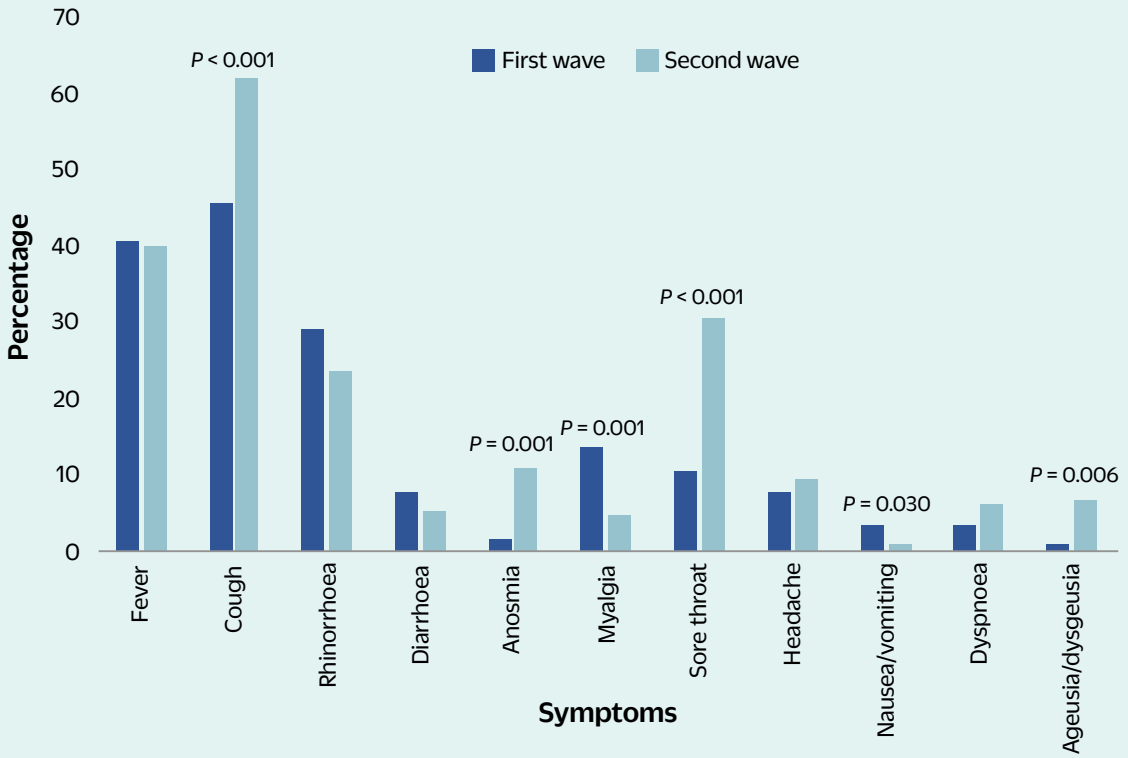
DISCUSSION

Brunei Darussalam experienced a significant increase in the number of COVID-19 cases in its second wave of the pandemic in 2021, with nearly three times as many cases recorded just in the first 11 days than in the whole 2-month period of the first wave. This was not unexpected given that the Delta strain is more contagious than the original and has a higher R_0.[3,9] In this respect, Brunei Darussalam's experience is similar to other countries, with larger second waves widely reported.[10–12] For instance, a study in Thailand reported a seven-fold increase in case numbers between its first and second waves and another seven-fold increase between its second and third waves.[10]

As well as the substantial increase in the number of cases, this study has demonstrated distinct differences in the demographic profile of cases between the two waves. Cases in the second wave were significantly younger, with a lower proportion of cases occurring in people aged more than 50 years. One possible explanation for this shift to younger cases is the increase in case numbers among children following several outbreaks in schools in one of the country's four districts at the start of the second wave. Other countries have also reported proportionally higher case numbers in the younger population in their second or subsequent waves, which some have attributed to acquired immunity as a result of SARS-CoV-2 infection, either diagnosed or undiagnosed during previous waves.[13,14] However, this is less likely to be true in the case of Brunei Darussalam as the first wave was quickly controlled and limited to just 141 confirmed cases when the last case of community spread was reported. While the possibility that undetected cases were circulating in the community cannot be ruled out, the numbers were likely to have been small.

Cases from the second wave were less likely to have comorbidities, which may simply be a reflection of the younger age of the second wave cohort.[4–8] Of the five specific comorbidities investigated, dyslipidaemia, cardiovascular disease, hypertension and respiratory disorders were more common among cases from the first wave, although the differences were only significant for dyslipidaemia and cardiovascular disease. Studies from Brazil, Japan, Spain and the United States of America have also reported similar differences between the first and second wave cases.[4–8] As well as being younger and having fewer comorbidities, second wave cases were less severe – exhibiting lower hospitalization rates, shorter lengths of stay, lower requirement for invasive mechanical ventilation and lower in-hospital mortality.[5]

Fig. 1. **Comparison of symptoms reported at admission among COVID-19 cases in the first wave (n=141) and second wave (n=359), Brunei Darussalam, 2020–2021**



In addition to demographic shifts, we also observed distinct differences in symptom burden. Compared with the first wave, the proportion of cases who reported symptoms at admission was significantly higher in the second wave, despite a shorter duration between symptom onset and NIC admission. However, there was no difference in the number of symptoms reported. Cough, anosmia, sore throat and ageusia/dysgeusia were significantly more common in second wave cases, whereas myalgia and nausea/vomiting were more likely to be reported by first wave cases, albeit in small numbers. It is unlikely that patients would have underreported symptoms such as anosmia and ageusia considering how uncommon and distressing these symptoms can be for patients.

Other studies conducted in the earlier part of the pandemic have reported variable but generally higher rates of symptoms than we found in our study.[15,16] A large meta-analysis which included data for over 60 000 patients reported that 87% of patients (95% confidence interval [CI]: 73–93, $P<0.001$) had at least one COVID-19-related symptom.[16] Cough was reported by 68% of patients (95% CI: 56–74, $P<0.001$); rates for other symptoms were as follows: fatigue, 39%; myalgia, 24%; dyspnoea, 24%; sore throat, 14%; headache, 14%; diarrhoea, 8%; rhinorrhoea, 7%; and nausea/vomiting, 6.5%.[16] However, studies included in this meta-analysis were limited to patients that presented for medical treatment or were hospitalized. In contrast, our study included patients from across the whole spectrum of COVID-19 disease severity, including mild and asymptomatic cases, and thus would be expected to yield a lower symptom rate. The proportion of patients who were asymptomatic accounted for almost a quarter of patients in the first wave and approximately 10% in the second wave. A further 12% had recovered by the time they were diagnosed and admitted for isolation, a proportion that remained largely unchanged between the first and second waves. Despite the differences in symptom burden between the first and second waves, the majority of cases were categorized as asymptomatic or mild, and fortunately, the proportion of critical cases remained low (<5%).

The timing of the roll-out of the vaccination programme in Brunei Darussalam[17] meant that no first wave cases had been vaccinated, and by the end of the study

Table 1. **Demographic and clinical characteristics of COVID-19 cases in the first and second wave, Brunei Darussalam, 2020–2021**

Characteristic	First wave (n = 141)	Second wave (n = 359)	*P*
Age (years; mean ± SD)	37.2 ± 17.4	29.7 ± 16.6	<0.001
Age group (years)			
<13	12 (8.5)	47 (13.1)	<0.001
13–18	9 (6.4)	70 (19.5)	
19–29	28 (19.9)	76 (21.2)	
30–39	30 (21.3)	57 (15.9)	
40–49	20 (14.2)	62 (17.3)	
50–59	25 (17.7)	29 (8.1)	
≥60	17 (12.1)	18 (5.0)	
Sex			
Male	85 (60.3)	190 (52.9)	0.137
Female	56 (39.7)	169 (47.1)	
Pregnant patients	2 (1.4)	8 (2.2)	0.560
Comorbidity (at least one)	43 (30.5)	73 (20.3)	0.015
Diabetes mellitus	8 (5.7)	24 (6.7)	0.678
Dyslipidaemia	22 (15.6)	19 (5.3)	<0.001
Hypertension	22 (15.6)	38 (10.6)	0.120
Respiratory disease	8 (5.7)	17 (4.7)	0.665
Cardiovascular disease	7 (5.0)	5 (1.4)	0.019
Symptom category (at time of NIC admission)			
Asymptomatic	33 (23.4)	34 (9.5)	<0.001
Pre-symptomatic	1 (0.7)	9 (2.5)	
Symptomatic	89 (63.1)	279 (77.7)	
Recovered	18 (12.8)	37 (10.3)	
Disease severity			
Asymptomatic/mild	116 (82.3)	301 (83.8)	0.148
Moderate	17 (12.1)	34 (9.5)	
Severe	3 (2.1)	19 (5.3)	
Critical	5 (3.5)	5 (1.4)	
Outcome			
Survival	138 (97.9)	354 (98.6)	0.556
Death	3 (2.1)	5 (1.4)	

NIC: National Isolation Centre; SD: standard deviation.

Numbers in parentheses are percentages.

period of the second wave, only 13 (3.6%) patients had been fully vaccinated (two doses). Despite the small sample size, our study provides some evidence that two doses of a COVID-19 vaccine conferred a benefit. Among the fully vaccinated group, over 90% of those who contracted COVID-19 had mild disease and there were no cases of severe/critical disease, whereas 23 of the 24 severe/critical cases in the second wave occurred in the unvaccinated group. Cases among children and adolescents, a group that was ineligible for vaccination during the period of our study, were all mild. This is consistent with other studies which also report that children and younger persons are more likely to have mild disease and are at low risk for mortality.[18,19]

Table 2. **COVID-19 cases in the second wave (admitted to the National Isolation Centre during 7–17 August 2021) by vaccination status and disease severity, Brunei Darussalam, 2021[a]**

Vaccination status	All cases (*N* = 359)	Asymptomatic/mild (*n* = 301)	Moderate (*n* = 34)	Severe/critical (*n* = 24)
Vaccinated	13	12 (92.3)	1 (7.7)	0 (0)
Partially vaccinated	41	35 (85.4)	5 (12.2)	1 (2.4)
Unvaccinated	188	137 (72.9)	28 (14.9)	23 (12.2)
Ineligible	117	117 (100)	0 (0)	0 (0)

[a] COVID-19 vaccination was not available during the first wave and therefore data are not presented for this group.
Numbers in parentheses are percentages.

To our knowledge this study is unique in that, due to our management policy which required all confirmed cases, including asymptomatic and mild cases, to be isolated (at least at the start of the second wave), we were able to compare the characteristics of two cohorts of COVID-19 cases, one from the first wave and the other from the second wave, both of which comprised cases across the spectrum of disease severity. Had we included patients admitted to the NIC after 18 August, we would have artificially shifted the profile of our second wave study cohort towards moderate, severe and critical cases. Since more severe cases are typically associated with older age and higher prevalence of comorbidities, as well as a greater frequency of co-infections,[20] this would have invalidated our comparisons. However, only including patients from the start of the second wave can itself be a limitation as any clinical and demographic shifts that occurred as the second wave progressed would not have been captured.

In conclusion, our study showed a distinct shift in the clinical and demographic characteristics of COVID-19 cases in terms of age, comorbidities and symptom burden between the first and second waves in Brunei Darussalam. This is similar to what has been reported in other countries. Knowledge of the changes in disease manifestations can help guide changes in management strategies, such as duration of isolation, testing strategies, and criteria for admission and treatment. Further studies will be required to assess if further shifts have occurred as the pandemic progressed.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This study used anonymized data and was conducted in accordance with the Declaration of Helsinki.

Funding

None.

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Replacement of SARS-CoV-2 strains with variants carrying N501Y and L452R mutations in Japan: an epidemiological surveillance assessment

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Objective: Monitoring the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants is important due to concerns regarding infectivity, transmissibility, immune evasion and disease severity. We evaluated the temporal and regional replacement of previous SARS-CoV-2 variants by the emergent strains, Alpha and Delta.

Methods: We obtained the results of polymerase chain reaction screening tests for variants conducted in multiple commercial laboratories. Assuming that all previous strains would be replaced by one variant, the new variant detection rate was estimated by fitting a logistic growth model. We estimated the transmission advantage of each new variant over the pre-existing virus strains.

Results: The variant with the N501Y mutation was first identified in the Kinki region in early February 2021, and by early May, it had replaced more than 90% of the previous strains. The variant with the L452R mutation was first detected in the Kanto-Koshin region in mid-May, and by early August, it comprised more than 90% of the circulating strains. Compared with pre-existing strains, the variant with the N501Y mutation showed transmission advantages of 48.2% and 40.3% in the Kanto-Koshin and Kinki regions, respectively, while the variant with the L452R mutation showed transmission advantages of 60.1% and 71.9%, respectively.

Discussion: In Japan, Alpha and Delta variants displayed regional differences in the replacement timing and their relative transmission advantages. Our method is efficient in monitoring and estimating changes in the proportion of variant strains in a timely manner in each region.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the coronavirus disease (COVID-19), which has rapidly spread worldwide. Novel variants have been reported, particularly with mutations in the receptor-binding domain (RBD) of the spike protein that may affect infectivity, transmissibility, immune evasion and disease severity. Based on virological characteristics and epidemic status, the World Health Organization (WHO) and other agencies have designated variants of concern (VOC), variants of interest and variants under monitoring.[1,2] By 18 October 2021, the Pango lineage B.1.1.7 and B.1.167.2 (WHO label: Alpha and Delta, respectively) were designated as VOC. B.1.1.7 and B.1.617.2 are characterized by N501Y, D614G and P168H mutations in the RBD and L452R, T487K, D614G and P618R mutations, respectively.

The Alpha variant, first identified in the United Kingdom of Great Britain and Northern Ireland in November 2020, spread rapidly nationally and then globally and was more infectious and transmissible than the earlier strains.[3–5] In Japan, the Alpha variant was first detected at the end of December 2020 among travellers from the United Kingdom and, in January 2021, in a COVID-19 patient without a history of international travel. The Delta variant demonstrated immune evasion with higher infectiv-

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ity and transmissibility than previous strains.[6,7] In Japan, the Delta variant was first identified in April 2021 in a patient without a travel history, and multiple cases were detected earlier in quarantined international travellers.

Whole-genome sequencing (WGS) is used to classify SARS-CoV-2 variants, with WHO developing guidance on surveillance methods using WGS for COVID-19.[8] In Japan, WGS is mainly performed at the National Institute of Infectious Diseases (NIID), as well as at some local public health institutes (PHIs), university laboratories and commercial laboratories. However, testing all COVID-19 specimens by WGS has been challenging; on 27 September 2021, WGS had been conducted for 88 355 specimens, which corresponded to 5.2% of the 1 707 848 reported cases, including duplicate cases.[9,10]

Therefore, in Japan, screening tests for variants are also conducted using the polymerase chain reaction (PCR) methods developed by the NIID and commercial laboratories to detect the N501Y and L452R mutations in the Alpha and Delta variants, respectively. Since the end of March 2021, approximately 40% of patients who tested positive for COVID-19 at PHIs and commercial laboratories have undergone these PCR variant screening tests. WGS is then performed preferentially on those specimens that are positive for each mutation by the PCR variant screening test, which biases the WGS results toward strains with these mutations.[11]

Newly emerging variant strains, as mentioned above, may have different characteristics than pre-existing strains. It is very important to know the local status of these variant strains in the region for appropriate public health and clinical response, such as duration of isolation, estimating vaccine efficacy and selecting appropriate antiviral drugs. As far as we know, this is the first regional comparative study on variant replacement in Japan. We analysed the replacement of previous strains by variants with the N501Y and L452R mutations using region-wide data obtained from PCR screening tests and estimated the transmission advantages of the Alpha and Delta variants over pre-existing strains to describe geographical distribution differences in Japan.

METHODS

We obtained the results of PCR screening tests for variants conducted in multiple commercial laboratories, which were commissioned by the NIID for an active epidemiological investigation based on the provisions of the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. In 2021, data were shared weekly with the NIID from 8 March to 17 May and from 7 June to 20 September for the variant with the N501Y mutation and the variant with the L452R mutation, respectively. Data were obtained on the numbers of specimens with and without mutations, the dates of specimen submission and the prefectures of the testing institutions. The number of commercial laboratories that provided data increased over time. Six and seven laboratories shared data on the variants with the N501Y and L452R mutations, respectively.

A sensitivity analysis was undertaken to compare data between the period when all laboratories were submitting samples and the total period. For the variant with the N501Y mutation, the sensitivity analysis compared the results from the period when data were reported from all six laboratories to those from the entire study period, including weeks when not all data were available. For the variant with the L452R mutation, the sensitivity analysis compared the results from the period when data were reported from all seven laboratories to those from the entire study period.

Assuming that all previous strains would be replaced by one variant, we estimated detection rates by fitting a daily logistic growth model to the mutation detection rates for each region. The denominator was the number of specimens with information regarding the presence of mutation, excluding those that could not be analysed by screening tests. Based on the same data, we estimated the transmission advantage of each variant over the pre-existing virus strains that were available from the genomic surveillance data.[12,13] The serial interval of COVID-19 required for the calculation was set to 4.8 days.[14]

We conducted analyses of the Kanto-Koshin and Kinki regions, which are metropolitan areas that include major urban centres (e.g. Tokyo and Osaka) and tend to be the centres of epidemics, plus the total for Japan. Daily numbers of COVID-19 cases reported from each region were obtained from data published by the Ministry of Health, Labour and Welfare (MHLW).[10] All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). This study was conducted under the provisions of the Act on the

Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases and did not require ethical approval, as no personally identifiable information was collected.

RESULTS

Variant with the N501Y mutation

During 2021, between 8 March (week 10) and 17 May (week 20), PCR screening tests detected the N501Y mutation in 37 823 specimens, which accounted for 15.3% of the 247 962 specimens that were positive for SARS-CoV-2 during the same period, including duplicated samples (**Table 1**). Relative to the number of COVID-19 cases reported, screening was the highest in the Kanto-Koshin region (23.8 per 100 reported cases) and lowest in the Hokuriku region (3.1 per 100 reported cases) (**Table 1**). The highest number of specimens was obtained in the Kanto-Koshin region (19 369, 51.2%), followed by the Kinki region (10 108, 26.7%). Although the data were reported to the NIID each week, the average duration between the time the specimens were submitted to each laboratory and their being reported to the NIID was 9.4 days (standard deviation: 1.0 days).

In the Kinki region, the variant with the N501Y mutation was detected in early February (week 5), and by mid-April (week 15), it had replaced more than 90% of the virus strains previously circulating. In the Kanto-Koshin region, the variant with the N501Y mutation was detected in mid-February (week 6), and by mid-May (week 19), it had replaced more than 90% of the previously prevalent strains. In Japan, more than 90% of the previous virus strains were replaced by the variant with the N501Y mutation by early May (week 18; **Fig. 1A**).

The sensitivity analysis showed that in the periods when specimens were submitted from all laboratories, compared with all study periods, 50% of the variants with the N501Y mutation were replaced by the circulated strain 4 days, 1 day and 20 days earlier in all of Japan, the Kanto-Koshin region and the Kinki region, respectively. However, 90% were replaced by the previous strain 3 and 2 days later in Japan and the Kanto-Koshin region, respectively, and 2 days earlier in the Kinki region. The proportion of samples with the N501Y mutation increased from week 10 in the Kinki region, followed by in western Japan, including the Chugoku and Shikoku regions, and in week 18, it was detected in the majority of samples in all of Japan (**Fig. 2A**).

The increase in transmission advantage of the variant with the N501Y mutation relative to the pre-existing virus strains was 48.2% (95% confidence interval [CI]: 46.5–50.2%) in the Kanto-Koshin region, 40.3% (95% CI: 37.3–43.5%) in the Kinki region and 39.5% (95% CI: 38.4–40.7%) nationwide (**Fig. 3**).

Variant with the L452R mutation

Between 7 June (week 23) and 20 September (week 38), PCR screening tests to detect the variant with the L452R mutation were conducted on 251 783 specimens, which accounted for 23.6% of the 913 109 specimens reported positive for SARS-CoV-2 during the same period. Relative to the number of COVID-19 cases reported, screening was highest in the Kanto-Koshin region (38.4 per 100 reported cases) and lowest in the Shikoku region (5.6 per 100 reported cases) (**Table 1**). The highest number of specimens was obtained from the Kanto-Koshin region (183 315, 72.8%), followed by the Kinki region (29 639, 11.8%). The average interval between the time when the specimens were submitted to each laboratory and their being reported to the NIID was 8.5 days (standard deviation: 0.6 days).

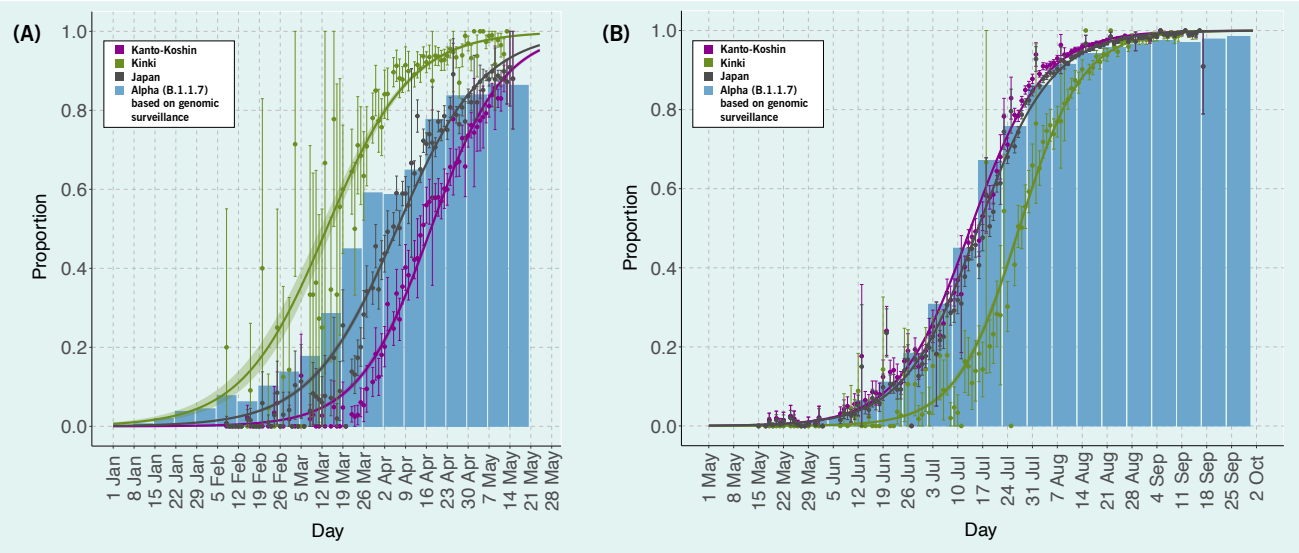
In the Kanto-Koshin region, the variant with the L452R mutation was first detected in mid-May (week 20), and by early August (week 31), it had replaced more than 90% of the virus strains previously prevalent in the region. This same variant was detected in the Kinki region in early June (week 23), and by mid-August (week 33), it had replaced more than 90% of the previous virus strains prevalent in the region. In Japan, more than 90% of the existing virus strains had been replaced by the variant with the L452R mutation in early August (week 31) (**Fig. 1B**).

The sensitivity analysis showed that in the period when specimens were submitted from all laboratories, compared with all study periods, 50% of the variants with the L452R mutation were replaced by the circulated strain on day 0 in Japan, the Kanto-Koshin region and the Kinki region; meanwhile, 90% of the variant with the L452R mutation was replaced by the previous strain 1 day later in Japan, 1 day earlier in the Kanto-Koshin region and on day 0 in the Kinki region.

Table 1. **PCR tests conducted for N501Y and L452R mutation screening and COVID-19 cases reported by region, Japan, March to September 2021**

Region	N501Y			L452R		
	8 March to 17 May 2021			7 June to 20 September 2021		
	A) Number of variant screening tests performed	B) Number of COVID-19 cases reported	A) to B) ratio	A) Number of variant screening tests performed	B) Number of COVID-19 cases reported	A) to B) ratio
Hokkaido	1955	11 302	17.3	6186	20 258	30.5
Tohoku	549	10 428	5.3	1896	19 351	9.8
Kanto-Koshin	19 369	81 471	23.8	183 315	477 227	38.4
Hokuriku	130	4187	3.1	860	13 053	6.6
Tokai	2157	21 987	9.8	14 038	90 442	15.5
Kinki	10 108	80 016	12.6	29 639	165 811	17.9
Chugoku	1023	8708	11.7	3293	22 470	14.7
Shikoku	232	4006	5.8	495	8915	5.6
Kyushu	1606	20 255	7.9	8496	65 259	13.0
Okinawa	694	5602	12.4	3565	30 322	11.8
Japan	37 823	247 962	15.3	251 783	913 108	23.6

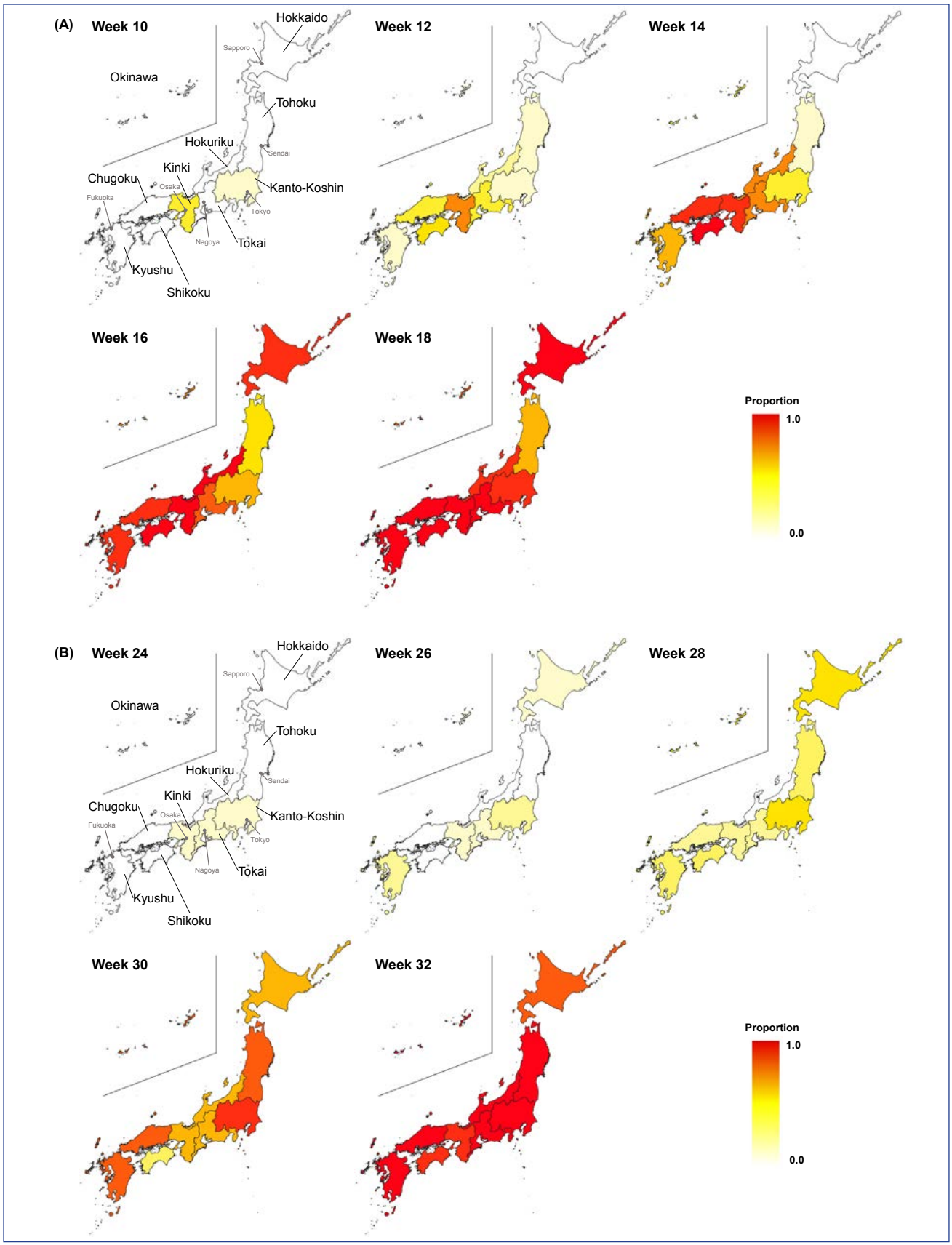
Fig. 1. **Rise in proportions of the (A) N501Y mutation and B.1.1.7 variant, January to May, and (B) L452R mutation and AY.29 (B.1.167.2) variant, May to September, Japan, 2021**



The points represent the proportion of positive results by submission date, and the bars represent the respective 95% confidence intervals. The lines indicate the estimated proportion of positive results based on the logistic growth model for the respective variant. The detection rates of the Alpha (B.1.1.7) and Delta (B.1.167.2 or AY.29) variants in Japan were obtained using genomic surveillance data.[11]

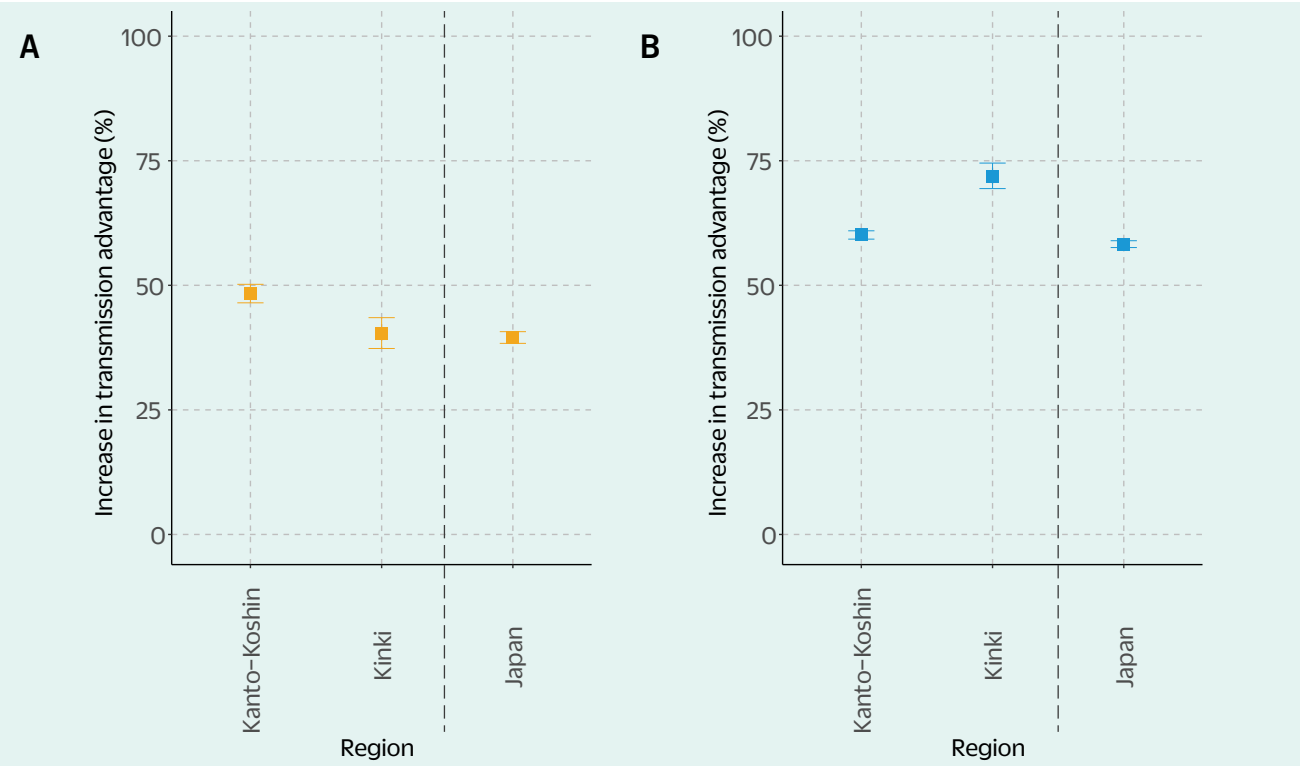
The proportion of specimens with the L452R variant in the Kanto-Koshin region increased from week 24; the Kinki and Kyushu regions followed, and at week 32, the majority of specimens in Japan were positive for this variant (**Fig. 2B**). The transmission advantage of this variant increased by 60.1% (95% CI: 59.3–60.9%) in the Kanto-Koshin region, 71.9% (95% CI: 69.4–74.5%) in the Kinki region and 58.3% (95% CI: 57.6–59.0%) nationwide, compared with the pre-existing virus strains (Alpha variant) (**Fig. 3**).

Fig. 2. **Biweekly geographical distribution of variants with the (A) N501Y (weeks 10–18) and (B) L452R (weeks 24–32) mutations by week and region, Japan, 2021**



Colour range shows proportions positive for the variants with mutation, from low (yellow) to high (red), indicating changes in the proportion of variants in each region.

Fig. 3. **Estimated transmission advantages of the (A) N501Y mutation (March to May) and (B) L452R mutation variant (May to September) in the Kanto-Koshin region, Kinki region and Japan, 2021**



The points represent the proportion of positive results by submission date, and the bars represent the respective 95% confidence intervals.

Summary

The number of COVID-19 cases in Japan increased substantially from March to June 2021 and from July to September 2021, which coincided with increased proportions of variants with the N501Y and L452R mutations assumed to have been the dominant strain in these epidemics, respectively (**Fig. 4**).

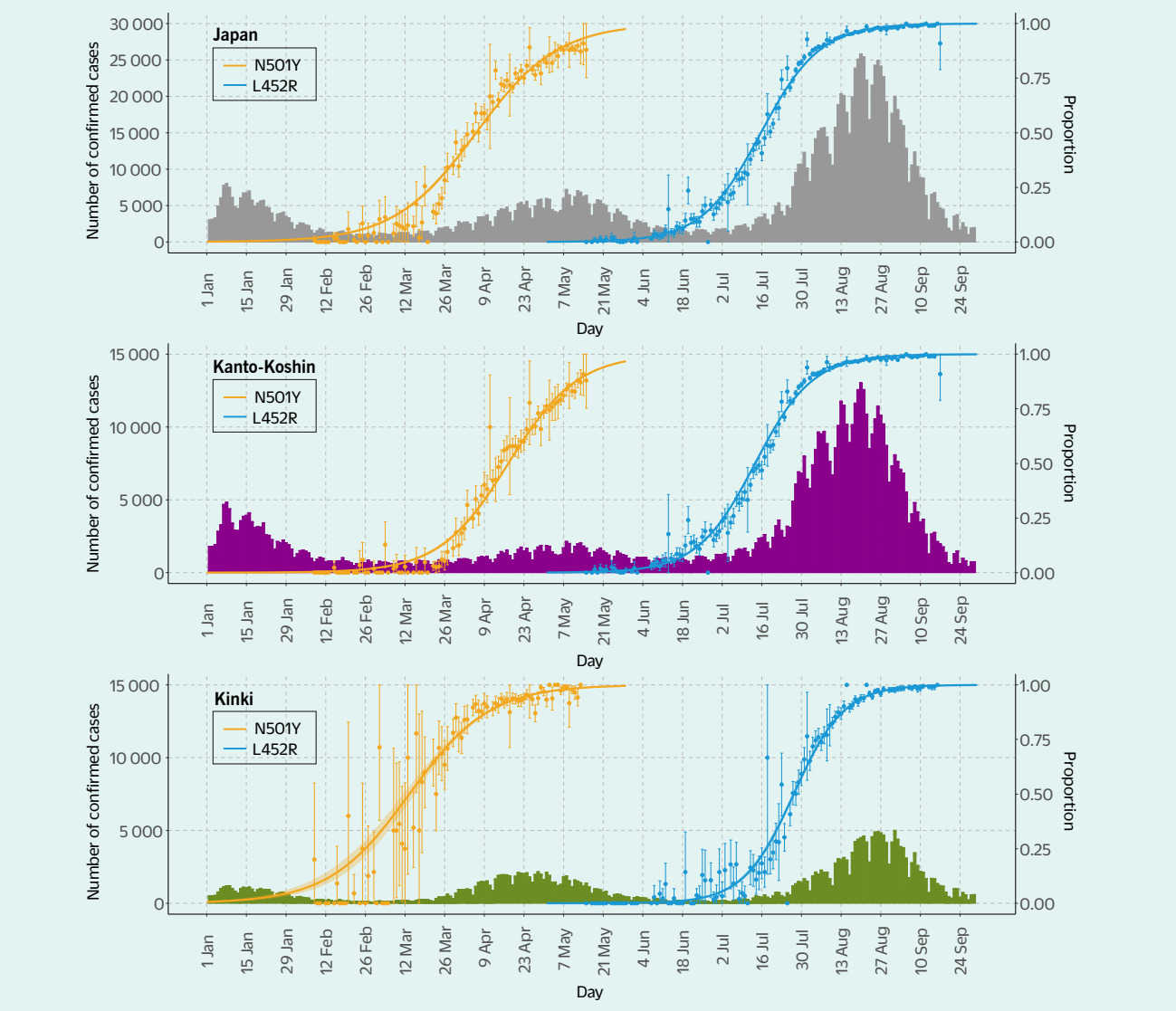
The data and published genomic surveillance results showed that the detection rate was higher for the Alpha variant (genomic surveillance) relative to that of the variant with the N501Y mutation in screening. However, the detection rates of the Delta variant and those of the variant with the L452R mutation were almost identical (**Fig. 1**).[11]

DISCUSSION

This study revealed a rapid replacement of pre-existing virus strains by the variant with the N501Y mutation from mid-February 2021 in the Kinki region and the variant with the L452R mutation from late June in the Kanto-Koshin region, which thereafter spread throughout Japan. Relative to pre-existing virus strains, the transmission advantage of the variant with the N501Y mutation increased by 39.5% and that of the variant with the L452R mutation by 58.3%.

Various SARS-CoV-2 variants have emerged worldwide since the beginning of 2021, some of which spread rapidly and have become dominant in certain countries. In Japan, the proportion of variants with the N501Y and L452R mutations increased in line with the increased number of COVID-19 cases from March to June (fourth wave) and from July to September (fifth wave) 2021, respectively, with the increase in the proportion of these strains probably resulting in the respective epidemics. According to the WGS results, the B.1.214 strain accounted for the majority of cases in Japan from October 2020 to February 2021 (third wave), after which the number of cases with the R.1 strain increased, followed by cases

Fig. 4. **Daily counts of reported COVID-19 cases and rise in the proportions of variants with the N501Y and L452R mutations in Japan (grey), the Kanto-Koshin region (purple) and the Kinki region (green), January to September, 2021**



The points represent the proportion positive by submission date, and the bars represent the respective 95% confidence intervals. The lines indicate the estimated positive proportion based on the logistic growth model for the respective variant.

with the Alpha variant. From March to June 2021 (fourth wave), the Alpha variant accounted for a large proportion of cases, while the number of cases with the R.1 strain decreased around mid-March. From late May onward, the number of cases with the B.1.617.2 variant (Delta variant; mostly reclassified as AY.29) increased, accounting for a large case proportion from July to September (fifth wave).[11] Therefore, it was considered that most of the cases with N501Y mutations in this study were caused by the Alpha variant, and those with L452R mutations were due to the Delta variant.

Genomic surveillance in Japan is performed on 5–10% of the specimens positive for SARS-CoV-2 and has been conducted continuously regardless of changes in the number of patients. In contrast, PCR testing to screen for a specific variant is initiated after the prediction of an epidemic caused by a particular variant strain. Therefore, genomic surveillance is more advantageous for the early detection of variant strains than PCR screening tests. Before their detection using PCR screening tests, the Alpha and Delta variants were first identified in the Kanto-Koshin region (Tokyo) in week 51 of 2020 and

week 18 of 2021, respectively, based on genomic surveillance reports. As earlier genomic surveillance tended to focus on specimens testing positive by PCR screening, the proportion of specimens tested by genomic surveillance for specific mutations (i.e. N501Y and L452R mutations) was expected to be higher, resulting in a bias that overestimated the prevalence of these variant strains. However, the comparison of genomic surveillance data from this study showed no significant difference in the transition of the detection rate of either variant.

This study suggests that the proportion of cases with the N501Y mutation first increased in the Kinki region, while those with the L452R mutation initially increased in the Kanto-Koshin region. Similarly, the number of COVID-19 cases increased earlier in the Kinki region than in the Kanto-Koshin region during the fourth wave of the epidemic caused by the N501Y mutation and vice versa during the fifth wave due to the L452R mutation. Genomic surveillance reports showed that the Alpha variant was first detected in the Kanto-Koshin region. However, the subsequent rise in the percentage of cases occurred earlier in the Kinki region, which concurs with the findings of this study. The period during which Delta variant cases increased across regions corresponded to the concurrent increase in cases with L452R mutations in this study.[11]

The transmission advantage above pre-existing virus strains was compared for each variant. The variant with the N501Y mutation demonstrated a 39.5% rise in transmission compared to the B.1.1.214 and R1 strains, whereas that of the variant with the L452R mutation was 58.3% higher than the Alpha variant. A previous study in Japan that compared the transmission advantages of the B.1.1.7 and B.1.617.2 variants with pre-existing virus strains demonstrated an increase of 44% and 95%, respectively.[15] In contrast, reports from Europe and the United States of America showed that the transmission advantage of the Alpha variant increased by 42–100% compared with that of previous strains, and the Delta variant increased by 55–120% compared with that of the Alpha variant.[13,16–19] These values are based on the Global Initiative on Sharing Avian Influenza Data and surveillance data on the number of patients and genomic surveillance level conducted in each country, and as a result, the estimation methods might differ from those used in this study.[20]

Vaccination status in each country could lead to decreased transmission advantages. In Japan, COVID-19 vaccination programmes began in February 2021 for health-care workers and the older population. Increased vaccination rates might also have influenced the transmission advantage, although this could not be assessed in the present study. A retrospective survey in the Kinki region suggested that regional replacement and transmission advantage may have been due to the introduction of the Alpha variant that was not detected immediately or to a potential regional transmission that occurred earlier than detected by the investigation.[21] Other factors such as the composition of pre-existing strains, the timing of the introduction of each variant and the public health response to COVID-19 may have influenced the difference in transmission advantage in the Kanto-Koshin and Kinki regions. We have not been able to fully evaluate the factors that caused the differences between the regions.

This study has several limitations. First, PCR screening for variants in Japan is conducted not only in commercial laboratories but also at PHIs, some universities and hospitals. The data from commercial laboratories exhibited a regional bias in the number of specimens obtained from medical institutions. Therefore, the number of specimens might not have been sufficient to adequately evaluate the changes in the proportions of variants. In addition, there may be biases in the characteristics of the populations tested by each laboratory, such as those with a high incidence of outbreaks. Second, in the early stages of analysis, the rise in the number of laboratories might have affected the regional bias and influenced the results of regional replacement of the previous variant by that with the N501Y mutation. However, while the number of laboratories changed over time, the sensitivity analysis showed that this had little effect on the 90% replacement time. Third, in addition to the Alpha variant, the B.1.351 (Beta), P.1 (Gamma) and B.1.621 (Mu) variants have the N501Y mutation. Furthermore, with the exception of the Delta variant, B.1.617.1 (formerly Kappa) and other variants also carry the L452R mutation. When multiple variants with the same mutation are prevalent, further analysis may be required to evaluate the replacement of each mutant variant.

In conclusion, based on the PCR test results conducted at commercial laboratories to screen for the Alpha variant carrying the N501Y mutation and the Delta

variant carrying the L452R mutation, we evaluated the replacement and transmissibility of the variant with the N501Y mutation and the variant with the L452R mutation compared to the B.1.1.214 and R1 strains, and Alpha strains, respectively. Our method is a reasonable and simple way to promptly monitor and estimate changes in the proportion of variant strains in each region, even in regions where genomic surveillance is not sufficiently conducted.

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Conflict of interest

The authors have no conflicts of interest to declare.

Ethics approval

This study was conducted under the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases and did not require ethical approval; we did not collect any personally identifiable information.

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Challenges during the second wave of COVID-19 in Brunei Darussalam: National Isolation Centre to National COVID-19 Hospital

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Problem: Soon after the start of the second wave of coronavirus disease 2019 (COVID-19) in Brunei Darussalam, which was confirmed to be due to the more infectious Delta strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it became apparent that the National Isolation Centre (NIC) was not coping.

Context: The NIC was the only isolation and treatment centre for COVID-19 in Brunei Darussalam. During the first wave and the first 11 days of the second wave, all confirmed cases were admitted to the NIC for isolation and treatment in line with the management strategy to isolate all confirmed cases to control the outbreak.

Action: The Ministry of Health opened five community isolation centres and two quarantine centres to divert asymptomatic and mild cases from the NIC. The community isolation centres also functioned as triage centres for the NIC, and the quarantine centres accommodated recovered patients who did not have their own quarantine facilities.

Outcome: The community isolation and quarantine centres diverted cases from the NIC and enabled recovered cases to be transferred to these step-down facilities. This reduced the NIC's occupancy to a safe level and enabled the reorganization of the NIC to function as a treatment centre and a national COVID-19 hospital.

Discussion: During any disease outbreak, health facilities must be prepared to adapt to changing situations. Strong leadership, stakeholder commitments, teamwork and constant communication are important in this process.

PROBLEM

As of 13 June 2022, the coronavirus disease 2019 (COVID-19) pandemic had amounted to more than 532 million cases globally and more than 6.3 million deaths.[1] Brunei Darussalam reported the first case of COVID-19 on 9 March 2020 and implemented measures that successfully contained the first wave, with the last case of community spread reported on 6 May 2020.[2] From then, Brunei Darussalam was at Level 2 out of the four levels of COVID-19 transmission classified by the World Health Organization, with no community spread and only sporadic imported cases.[3] While measures implemented during the first wave had remained in place to monitor the situation, it was not possible to accurately predict the impact of the second wave until it happened. Soon after the second wave started on 7 August 2021, owing to the more infectious Delta strain of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it quickly became apparent that the existing quarantine and isolation measures would not be sufficient. A similar situation was faced by many countries where health-care systems were stretched or had collapsed due to factors such as overwhelming numbers of COVID-19 patients, burnout among health-care providers and the depletion of resources.[4–6]

With the expected increase in the number of COVID-19 cases, it was important to change the role of the National Isolation Centre (NIC) from an isolation centre to a COVID-19 hospital. This report describes the challenges faced by Brunei Darussalam during the second wave of COVID-19, the measures implemented to avoid overwhelming the NIC and its transition to a COVID-19 hospital.

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CONTEXT

Setting

Brunei Darussalam, with an estimated population of 453 600 (2020), is divided into four districts, each served by a government hospital. The NIC is the designated national isolation facility for any infectious disease, located in the Tutong district, consisting of three wards: one intensive care unit (ICU) and two ICU-capable isolation wards with a total bed capacity of 27. Prior to COVID-19, this complex was used for isolation and treatment of pulmonary tuberculosis. It is located adjacent to the district government hospital, which has 135 beds in six wards. These two facilities have a combined bed capacity of 162.

When COVID-19 was discovered in Wuhan, the People's Republic of China, in late December 2019, Brunei Darussalam began closely monitoring the situation, prepared thorough strengthening of surveillance and testing processes, and reviewed and updated infection control and outbreak management protocols. Prior to the first wave, several suspected cases, mainly travellers returning from affected areas, were isolated in the NIC, but all tested negative for SARS-CoV-2. When the first case of COVID-19 was detected, all non-essential services were closed at the NIC, and all inpatients were transferred to other hospitals in anticipation of more cases. The NIC and district hospital were converted into a COVID-19 isolation and treatment centre.

Due to the further increase in cases in the early phase, the Ministry of Health (MoH) decided to build the National Isolation Centre Extension (NICE) adjacent to the NIC. The NICE consisted of 20 bays with six to eight beds per bay, including an ICU-capable bay with six isolation rooms. However, soon after the NICE was completed, the first wave was brought under control. The district hospital eventually reopened for general services, and the original NIC cared for a small number of imported cases of COVID-19 until the second wave began. Altogether, the three complexes, henceforth all referred to as the NIC, increased bed capacity to between 260 (preferred) and 320 (maximum), taking into consideration the available personnel.

Testing and triaging strategy

Over the course of the pandemic, the testing and management protocols used in the NIC were revised several times.[7] The current testing protocol requires testing by reverse transcription polymerase chain reaction (RT-PCR) on day 8 after the first positive RT-PCR (designated as day 0 of COVID-19 infection). If the test is negative, the patient is discharged to a designated quarantine centre. If the test is positive, testing is repeated every 48 hours until it is negative. The case must also be symptom-free or mildly symptomatic with no or resolving abnormalities in the investigations prior to discharge. Post-discharge cases are isolated for another 2 weeks, either at a designated isolation facility or at the case's own accommodation, if suitable.

For risk stratification, cases were initially categorized by disease severity (mild, moderate, severe and critical) based on the clinical, laboratory and imaging parameters used in the first wave.[8] However, on 13 August 2021, during the second wave, an adjustment was introduced to the new categorization system, which was adapted from that used by the MoH Malaysia,[9] and based on clinical assessment supplemented by chest imaging. This system is more specific and facilitated the daily categorization of cases (**Table 1**).

Challenges

By day 7 of the second wave (13 August 2021), the preferred bed capacity of 260 was reached, and it was clear that the NIC would be quickly overwhelmed. The national number of new and cumulative confirmed cases recorded over the first 16 days reached the maximum occupancy threshold of 320 by day 9 (**Fig. 1a**). The number of new daily cases reached a peak of 314 on day 16 (22 August). Due to the cumulative increase, a backlog of patients waiting to be admitted for assessment was expected. Most of the cases admitted to the NIC were asymptomatic or mildly symptomatic (Categories 1 and 2) (**Fig. 1b**).

The situation was compounded by logistical, personnel and supply chain issues as a result of service expansion to cater to the increasing number of cases. Existing personnel had to be reallocated to areas of need, and additional personnel were sought from within the MoH, other ministries and volunteers in order to run the centre. Support services such as transportation, laundry, catering, safety and cleanliness had to be increased. Similarly, maintaining adequate stocks of consumables and medications and ensuring smooth supply chains were crucial.

Table 1. **Clinical categories for adults with COVID-19, Brunei Darussalam**

Staging	Description
Category 1	Asymptomatic
Category 2	Symptomatic without pneumonia[a]
Category 3	Symptomatic with pneumonia
Category 4	Symptomatic with pneumonia requiring supplemental oxygen
Category 5	Critically ill (respiratory failure requiring mechanical ventilation with or without other organ failure)
Category 2 can be further divided into two subcategories: MILD (2A) and MODERATE (2B). This subcategorization is for clinical management team reference only to risk-stratify patients who can be transferred to the community isolation facility.	
Category 2A (Mild)	**Category 2B (Moderate)**
Sore throat or rhinorrhoea with no fever or dyspnoea	Persistent fever (≥2 days) or new onset fever
Cough with no fever or dyspnoea	Exertional dyspnoea
Loss of taste but able to consume food orally	Chest pain
Loss of smell	Unable to consume food orally
Diarrhoea two times or less within 24 hours with normal urine output	Worsening lethargy, e.g. difficulty with usual activities or struggling to get out of bed
Nausea and vomiting with normal urine output	Unable to ambulate without assistance
Mild lethargy but still able to carry out daily activities	Worsening or persistent symptoms, e.g. cough, nausea, vomiting or diarrhoea
Myalgia but still able to carry out daily activities	Reduced consciousness
	Reduced urine output in the last 24 hours

Source: adapted from Ministry of Health Malaysia guidelines.[9]

[a] Determined by either clinical findings or chest imaging.

It was also important to have sufficient numbers and the right mix of doctors and nurses to maintain services and manage cases with different medical conditions. Redeployment from other hospitals was required at short notice, further straining the personnel shortage in source hospitals. With rapidly increasing numbers of patients being admitted and spread out across the three buildings of the NIC, it was challenging to group cases with similar medical needs and levels of care together. In addition, the different social needs of patients needed to be taken into consideration.

ACTION

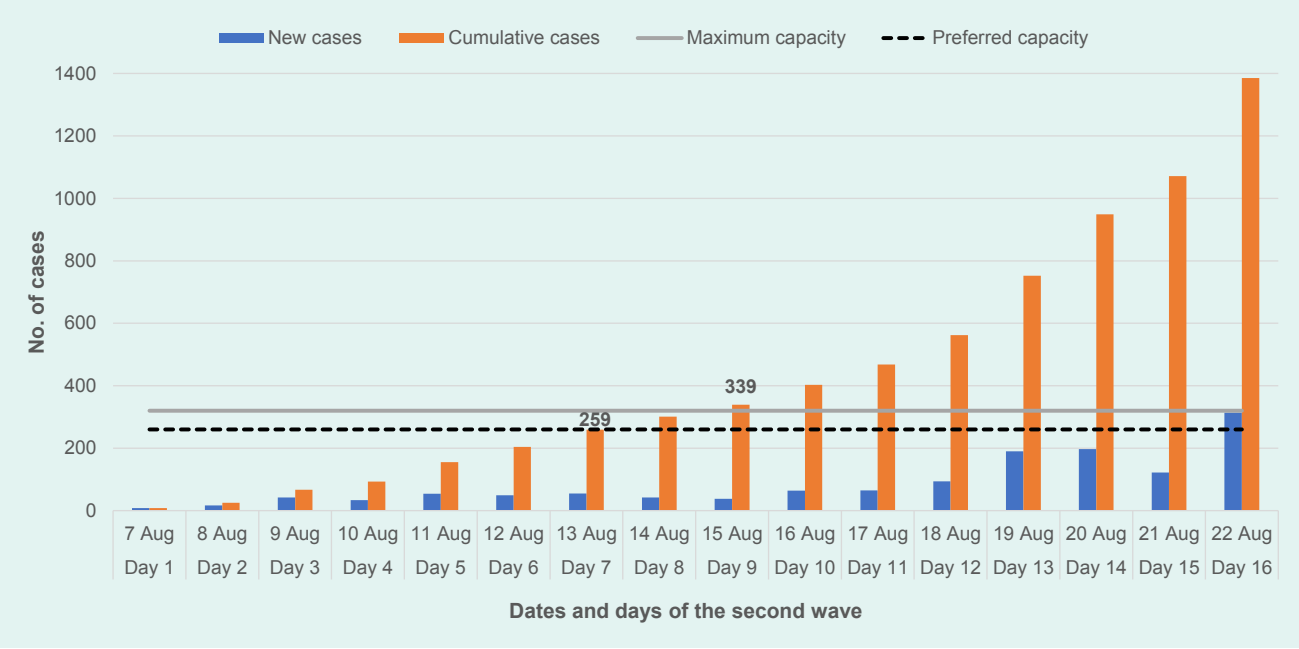
Opening of supporting community isolation and quarantine centres

An important step taken by the MoH was the identification and conversion of existing government facilities into isolation centres, which enabled the diversion of milder cases from the NIC. In total, there were seven centres, all of which were suitable government complexes for isolation, such as schools or training centres. Initially, there were two centres (Centres A and B) that received patients who remained positive for SARS-CoV-2 by RT-PCR (Centre A) on day 8 and patients who had recovered (RT-PCR negative on day 8 or 10) but did not have their own suitable accommodation for isolation (Centre B). Later, most of the centres also served as triage centres and admitted asymptomatic or mild cases for isolation (**Table 2**). The Emergency Medical Ambulance Service initially triaged patients and decided on their destination according to an admission criterion.

National Isolation Centre

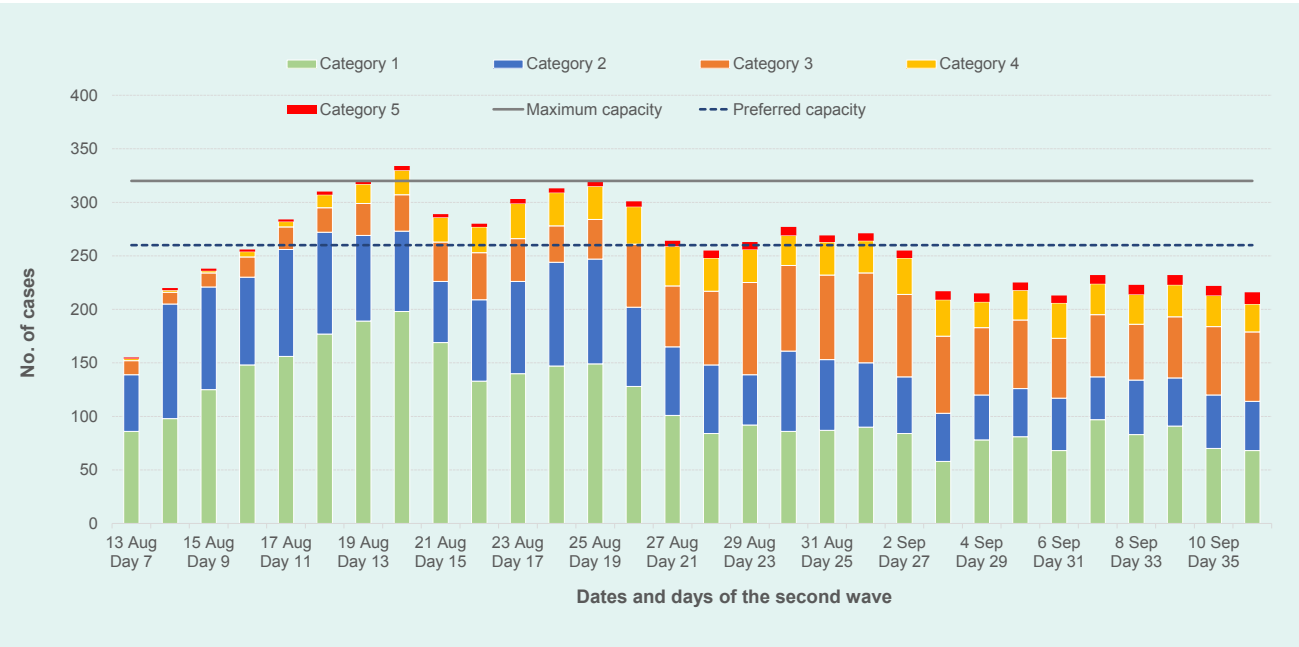
The process of transforming the NIC from an isolation centre to a national COVID-19 hospital required several conditions to be met. The diversion of asymptomatic and mildly symptomatic cases to other isolation centres led to a reduction in total occupancy and allowed for personnel distribution to improve the nurse-to-patient and doctor-to-patient ratios. This also provided the opportunity to restructure and introduce other relevant specialty services to cater to the various medical needs of patients such as pregnant patients, patients with

Fig. 1a. **Recorded number of daily new and cumulative COVID-19 cases for the first 16 days of the second wave, Brunei Darussalam[a]**



[a] The solid line depicts the maximum capacity of the NIC (320 patients), and the dotted line depicts the preferred capacity (260 patients).

Fig. 1b. **Recorded number of COVID-19 cases admitted to the NIC from 13 August (day 7 of second wave) to 11 September 2021 by clinical category, Brunei Darrusalam**



[a] The solid line depicts the maximum capacity of the NIC (320 patients), and the dotted line depicts the preferred capacity (260 patients).

Table 2. **Isolation and quarantine centres by role, category and occupancy as of 18 September 2021, Brunei Darussalam**

Centre	Facility	Role	Categories of cases admitted	Capacity (overall/ usable)	Current occupancy	Staffing personnel
National isolation centre	Isolation centres Hospital	Isolation and treatment centre	All categories	320/320	238	Existing and redeployed staff
Community isolation centre A	Youth national programme centre	Isolation centre	1, 2A	532/532	353	Onsite medical team Military security
Community isolation centre B	Secondary and boarding school	Isolation centre	1, 2A, 2B	789/511	618	Onsite medical team Military security
Community isolation centre C	Army battalion camp	Isolation centre	1	300/200	40	Remote medical team in Centre B Military security
Community isolation centre D	School	Isolation centre	1	320/320	79	Remote medical team based in district hospital Military security
Community isolation centre E	School	Isolation centre	1	222/222	10	Onsite military medical team Military security
Quarantine centre A	School	Post-discharge quarantine	Recovered	150/45	0	Administrative staff
Quarantine centre B	School	Post-discharge quarantine	Recovered	408/222	78	Administrative staff

end-stage renal failure and patients needing intensive care and monitoring.

Home isolation

Due to the increase in the number of patients waiting to be admitted to isolation centres, home quarantine/isolation was attempted. This had to be discontinued due to patients breaking quarantine orders and difficulties with monitoring adherence. Since then, all cases are required to stay in designated isolation centres.

OUTCOMES

With the opening of the community isolation and quarantine centres, the number of cases admitted to the NIC declined with the opening of Centre A (which started accepting patients on 18 August 2021) and declined further from day 20 with the opening of Centre B, evident from day 15 (21 August 2021) (**Fig. 1b**). This also coincided with the increase in Category 3 and 4 patients admitted to the NIC, highlighting the importance of the new centres. With the reduction in occupancy at the NIC, it was possible to carry out the restructuring and adjustment of processes to function as a COVID-19 hospital.

Restructuring of the isolation processes allowed for increasing the capacity of high-dependency units and ICUs, converting existing wards into a dedicated obstetrics and gynaecology (OB/GYN) ward with en-suite labour room, paediatric ICU and neonatal ICU, expanding physiotherapy services particularly chest physiotherapies, increasing dialysis points, and establishing a remote on-call surgical team based in the main tertiary hospital located in the capital that was ready for acute surgical emergencies (**Table 3**). These changes also allowed for grouping of patients with similar medical needs (i.e. obstetric, renal dialysis and paediatric patients), effective allocation and distribution of nurses and doctors according to areas of expertise and improvements in patient care.

Table 3. **List of medical services available before and during the COVID-19 outbreak**

Specialties	Before COVID-19	Changes during COVID-19	Description
Intensive care / High-dependency setting	Services not available 9 capable rooms 18 capable rooms	Increased capacity of ICU and high-dependency bay	27 ICU-capable rooms, 24 high-dependency beds
Nephrology	Services not available 2 capable rooms (2 dialysis points)	Increased dialysis capability	Increased to 16 dialysis points
OB/GYN	Outpatient clinics only Unused OB/GYN ward/labour room	Reopening of the ward with labour room	15 beds
OT	2 ready for use for minor cases 1 unused and ready for use	To operationalize OTs 1: OB/GYN ward 2: For other cases	Operationalization of all OTs
PICU and NICU	Services not available	Initially used NICE isolation rooms as designated PICU and NICU isolation rooms due to their high-dependency readiness Later relocated to be near the OB/GYN ward	Conversion of a ward near the OB/GYN ward
Surgery	Outpatient clinics Day-case surgery	Remote consultant on-call Team ready for acute surgical emergencies Available junior surgeons	Team on-call from another hospital
Physiotherapy service	Visiting services that were stopped during COVID-19	Re-introduction of regular physiotherapy, especially chest physiotherapy	Team of physiotherapists 5 days a week

NICU: neonatal intensive care unit; OB/GYN: obstetrics and gynaecology; OT: operating theatre; PICU: paediatric intensive care unit.

DISCUSSION

In any disease outbreak, it is important that the health-care system is prepared for the unexpected. A key lesson learned from the ongoing COVID-19 pandemic is that preparedness is very important. Even then, it is not always possible to predict whether preparations will be adequate to cope with demand. Our experience highlighted this when the NIC was almost overwhelmed, but this was averted by the opening of community isolation and quarantine centres so that asymptomatic or mild cases could be diverted away from the NIC. This also enabled the NIC to restructure and transition from an isolation centre to a COVID-19 hospital to deal with the increasing numbers of more severe cases.

Our success was dependent on the system's ability to rapidly adapt to changing situations. It also required strong leadership, stakeholder commitment, teamwork, and especially constant and open communication between all stakeholders. Since the start of the second wave, daily online conferences were scheduled between the different centres and the MoH. These conferences were headed by the Minister of Health or executive-level officials, allowing for rapid decision-making. Involvement of the other ministries made it possible for the use and conversion of other facilities into isolation centres, and enabled provision of security by the armed forces. Centres where medical teams monitored patients remotely were under the control of the armed forces. Therefore, good teamwork within and between the MoH and other agencies was essential. Similar to during the first wave, there was considerable goodwill from the public and organizations, with donations in the form of food and daily-use items for the staff and patients.

Our experience highlighted that even during ongoing major disease outbreaks, it is possible to restructure services to cater to the changing situations and needs of cases. The transition of the NIC from an isolation and treatment centre to a COVID-19 hospital was made possible through strong leadership and commitment of relevant stakeholders.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

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Operational challenges of the Philippine Antimicrobial Resistance Surveillance Program during the COVID-19 pandemic

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Problem: Operation of the Philippine Antimicrobial Resistance Surveillance Program (ARSP) has been affected by the coronavirus disease 2019 (COVID-19) pandemic, during which time difficulties in maintaining laboratory functions, staffing levels and participation were reported.

Context: The COVID-19 pandemic has increased pressure on most health systems and programmes in the Philippines, including ARSP. As ARSP is the source of national data on antimicrobial resistance (AMR) trends, there are concerns that the negative effects of the pandemic may have impacted the quality of data produced.

Action: We describe disruptions to laboratory operations, personnel availability and participation in ARSP surveillance, and their impact on reported data for 2020.

Outcome: Surveillance operations were challenged by reallocation of human, infrastructure and financial resources for pandemic response among both the sentinel sites and the coordinating laboratory, the Antimicrobial Resistance Surveillance Reference Laboratory. There was a decrease in the amount of data submitted to the surveillance system, as well as in the number of isolates sent to the reference laboratory for confirmation of bacterial identification and antimicrobial susceptibility testing. Nevertheless, overall performance scores of the sentinel sites for most parameters were comparable to 2019, the year prior to the pandemic.

Discussion: The impact of operational changes to ARSP due to the pandemic needs to be considered when analysing AMR surveillance data from 2020. Automation of data submission, good working relationships between the coordinating laboratory and sentinel sites, and supply chain system strengthening were identified as key to maintaining AMR surveillance during the COVID-19 pandemic.

PROBLEM

By the end of 2020, the coronavirus disease 2019 (COVID-19) pandemic had caused around 3.2 million excess deaths worldwide and continues to pose major challenges globally.[1] In the Philippines, there have been 474 064 confirmed COVID-19 cases and 9244 deaths (as of the end of 2020),[2] raising concerns that the pandemic may accelerate antimicrobial resistance (AMR) in health-care facilities as a consequence of possible antibiotic overuse and misuse.[3,4] The full effect of the COVID-19 pandemic on AMR will only be observed in the upcoming years through continued AMR surveillance at all levels.

During a pandemic, it is likely that routine surveillance for AMR monitoring, if not prioritized, may contain gaps and missing data.[5] This paper describes the challenges posed by the COVID-19 pandemic to the operations of the Antimicrobial Resistance Surveillance Program (ARSP) in the Philippines, from January to December 2020.

CONTEXT

ARSP is a sentinel, laboratory-based surveillance network comprising 24 sentinel sites located in 16 of the Philippines' 17 regions, and a further two sites for gonococcal surveillance. Data from both the regular and gonococcal sentinel sites are presented. The coordinating laboratory – the Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL) – is based at the Research Institute for Tropical Medicine (RITM). Case finding is based on specimens sent to sentinel sites' clinical laboratories for diagnostic purposes.

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RITM has been at the forefront of the Philippine COVID-19 response for both patient care and laboratory testing. From January to June 2020, RITM served as the primary COVID-19 testing centre for the Philippines, responsible for more than 90% of all COVID-19 tests conducted in the country. In March 2020, to accommodate the surge in demand for reverse transcription polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ARSRL, together with RITM's other laboratories, was directed to assist the national testing effort by undertaking some of the procedures required, such as sample inactivation and DNA extraction. This directive resulted in the reassignment of ARSRL laboratory staff to the COVID-19 testing team. Facilities, workspaces, equipment and critical resources (reagents, supplies, consumables and personal protective equipment [PPE]) were also repurposed to meet the demand for COVID-19 testing. Directives were also made to postpone scheduled trainings, monitoring visits and face-to-face meetings – activities usually performed by the reference laboratory – until the end of June 2020. Consequently, the number of laboratory technicians who underwent training for AMR bacteriology procedures decreased from 27 to 6.

By July 2020, sufficient additional staff had been recruited to cover the COVID-19 response tasks, allowing existing reference laboratory staff to return to their routine AMR surveillance work. However, until the end of 2020 about 20% of ARSRL laboratory space remained allocated to the COVID-19 response. The annual ARSP Program Implementation Meeting (ARSP PIM) was held virtually via Zoom instead of the usual face-to-face format and the publication of the ARSP 2019 annual surveillance report was delayed by 5 months.

ACTION

The impacts of the above-mentioned institutional directives on the operations of RITM's ARSRL were reviewed. In addition, the challenges experienced by the surveillance sentinel sites participating in ARSP during the course of 2020 were summarized.

In order to assess the impact of the pandemic, ARSP performance indicators (and corresponding targets for participation and number of isolates reported to the surveillance system) for 2020 were compared to those for 2019 (**Table 1**). The set of indicators and targets had been jointly agreed upon by the sentinel sites and ARSRL during previous annual meetings. Information about how the COVID-19 pandemic had affected sentinel site participation in ARSP was gathered from the site status reports that were presented at the ARSP PIM, in particular, the responses to the following questions that sites had been asked to provide: 1) How has the COVID-19 pandemic affected your laboratory operations? and 2) How has the COVID-19 pandemic affected your participation in ARSP?

OUTCOME

Laboratory operations

All 26 sentinel sites reported experiencing operational challenges, which varied in type and extent. Most (18/26, 69.2%) of the sentinel sites cited delays in the usual schedule of delivery of reagents and supplies due to transportation issues. Another commonly reported supply challenge stemmed from the new requirement to use extra layers of PPE, which resulted in episodes of low or depleted supplies of PPE at nearly two thirds (17/26, 65.4%) of sites. In some areas, suspension of courier services had reportedly delayed the referral of bacterial isolates to RITM for confirmatory testing.

Half (13/26, 50%) of all sentinel sites reported a decrease in the number of specimens requiring routine culture and sensitivity testing. Four reported periodic closure of their outpatient departments. Sites also reported a low influx of patients, and the two nongovernment sentinel sites experienced a reduction in revenue for the laboratory.

Laboratory personnel

The majority (14/26, 53.9%) of sentinel sites reported being designated as COVID-19 referral hospitals during the pandemic and having to establish or expand their molecular biology facilities. Even though this provided opportunities for acquisition of new equipment and increasing laboratory staff capacity for molecular detection of pathogens, it also meant temporary reallocation of space and human resources for RT-PCR testing for COVID-19.

The majority of sentinel sites also reported encountering various challenges relating to laboratory personnel.

Table 1. **Performance scores of the Philippine Antimicrobial Resistance Surveillance Program by sentinel site, 2019 and 2020**

Performance indicator	Description	Target (%)	2019 (%)	2020 (%)
1. On-time submission of regular data	Percentage of data sent on time to ARSRL on a monthly basis	90	68	68
2. Completeness of demographic data	Percentage of data with the minimum demographic data requirements for reporting	95	94	93
3. Referral of isolates	Percentage of isolates referred according to the list agreed upon during the ARSP annual meeting (includes pathogens of public health importance based on CLSI and WHO recommendations)	90	48	52
4. Concordance in identification	Percentage of referred isolates with correct bacterial identification confirmed by the ARSRL (different targets are set for genus and species levels)			
4.1 Genus level	Concordance at the genus level	95	98	98
4.2 Species level	Concordance at the species level	87	96	97
5. Concordance in AST	Percentage of discordant antimicrobial susceptibility results from the sites compared with AST results from ARSRL			
5.1 Critical deviations	AST discordance for resistant and susceptible results only	≤5	3	3
5.2 Total deviations	AST discordance for resistant, susceptible and intermediate results	≤10	7	7
6. Inclusion of working diagnosis	Percentage of data that includes a working diagnosis (disease indicated by physician's examination that prompted the request for culture and sensitivity testing)	60	68	66
7. Completeness of antibiotic panel	Percentage of AMR surveillance data that follows the antibiotic panel agreed upon in the most recent ARSP annual meeting	85	59	61
8. Encoding of negative results	Percentage of negative culture results encoded in WHONET	85	94	94

AMR: antimicrobial resistance; ARSP: Antimicrobial Resistance Surveillance Program; ARSRL: Antimicrobial Resistance Surveillance Reference Laboratory; AST: antimicrobial susceptibility testing; CLSI: Clinical Laboratory Standards Institute.

Seventeen sites (65.4%) experienced a reduction in the number of active-duty staff over several periods due to reassignment to other hospital units for COVID-19 sample processing and testing. Furthermore, around one third (9/26, 34.6%) reported that on several occasions staff work schedules had to be reduced to a skeletal workforce to maintain physical distancing in the laboratory. Staff in high-risk groups were ordered to work from home, further decreasing the number of staff available to work in bacteriology laboratories. Eleven sentinel sites (42.3%) reported that they were provided with additional manpower to help overcome staffing challenges.

The health status of frontline workers at ARSP sites was also affected, with some infected with COVID-19 and some experiencing anxiety because of the requirement to be at work. Laboratory personnel from four sites in the National Capital Region (NCR) reported experiencing difficulties in getting to work due to travel restrictions and suspension of transport services.

Participation in ARSP

Delays in transporting isolates to ARSRL for confirmatory testing, typically because of the lack of courier services, was a common challenge among sentinel sites (9/26, 34.6%). Moreover, the decrease in the number of samples requiring testing at sentinel sites also reduced the demand for confirmatory testing of isolates.

Although automated transmission of data from the sentinel sites to ARSRL had already been established

Table 2. **Number of isolates with antimicrobial susceptibility testing data submitted to the Philippine ARSP by sentinel sites in 2019 and 2020, and percentage change from 2019**

Region/sentinel site	2019	2020	% change
Luzon – National Capital Region			
Site 1	548	0	–100.00
Site 2	4358	0	–100.00
Site 3	2371	1019	–57.02
Site 4	13 895	6818	–50.93
Site 5	507	255	–49.70
Site 6	2722	1419	–47.87
Site 7	4433	2713	–38.80
Site 8	2375	2027	–14.65
Luzon – outside National Capital Region			
Site 9	90	13	–85.56
Site 10	3633	1569	–56.81
Site 11	2521	1176	–53.35
Site 12	5234	2968	–43.29
Site 13	4824	3248	–32.67
Site 14	5668	3782	–33.27
Site 15	4462	3581	–19.74
Visayas			
Site 16	2539	1425	–43.88
Site 17	3957	2624	–33.69
Site 18	10 286	6886	–33.05
Site 19[a]	352	289	–17.90
Site 20	3874	4056	+4.70
Mindanao			
Site 21	12 177	7412	–39.13
Site 22	3181	2076	–34.74
Site 23	1205	1115	–8.07
Site 24	3409	3735	+9.56
Site 25	1644	1192	–27.49
Site 26[a]	69	129	+86.96
TOTAL	**100 334**	**61 527**	**–38.68**

[a] Gonococcal surveillance sites.

prior to the pandemic, many sentinel sites still reported experiencing delays in encoding identification and susceptibility data to WHONET due to decreased staff numbers in their bacteriology sections.

ARSP performance indicators

Of the 10 reported performance indicators, five were unchanged between 2019 and 2020 (**Table 1**). These were: on-time submission of regular data (1), concordance in identification (genus level) (4.1), concordance in antimicrobial susceptibility testing (AST) (critical deviations) (5.1), concordance in AST (total deviations) (5.2), and encoding of negative results (8). There were decreases for completeness of demographic data (2) and inclusion of working diagnosis (6), but increases for referral of isolates (3), concordance in identification (species level) (4.2), and completeness of antibiotic panel (7).

Comparison of ARSP data submission: 2019 versus 2020

Across all sentinel sites, the number of AST data submissions dropped by 38.7%, from a total of 100 334 in 2019 to 61 527 in 2020 (**Table 2**). All sentinel sites in the NCR recorded substantial decreases in reported data, with two sentinel sites unable to submit any AST data at all in 2020. Relative to the NCR, sites in Visayas had smaller decreases in test data submissions, with one site reporting a 5% increase. In Mindanao, a decrease was observed in four out of the six sites (**Table 2**).

Lessons learnt

Sentinel sites that submitted the same or increased volumes of AMR surveillance data in 2020 were asked to explain how they were able to maintain their 2019 levels of performance despite the pandemic. At Site 26, a gonococcal surveillance site, scheduled testing for sex workers continued despite the pandemic, resulting in an increase in submissions, a commendable achievement and one that highlights the importance of retaining AMR surveillance for gonococcal infections. Site 20's increase in submitted data may have been due to the increase in the number of admissions due to COVID-19 infections, which prompted an increase in requests for AST, especially for those admitted for respiratory symptoms. Site 24 reported that they were able to mitigate challenges related to procurement of laboratory reagents and supplies by strengthening communications and coordination with suppliers regarding possible delays, changes and expiration dates of goods for delivery.

Practices that proved useful in overcoming challenges caused by the COVID-19 pandemic included prompt preparation of a procurement plan for reagents and supplies for COVID-19 testing, which helped minimize the risk of depletion of supplies; establishment of a process for sharing laboratory supplies among the reference laboratory and sentinel sites; and use of logistics created for the COVID-19 pandemic to support AMR surveillance (i.e. some sentinel sites were able to send both isolates for AST and samples for COVID-19 testing to RITM simultaneously).

DISCUSSION

The challenges to ARSP laboratory operations, including staffing, experienced during the COVID-19 pandemic did not appear to reduce overall participation of the sentinel sites in ARSP. This could be due, at least in part, to the fact that all sentinel sites, having been involved in ARSP for more than 5 years, have surveillance activities ingrained in their operations such that the disruptions of the COVID-19 pandemic did not result in lessened participation in surveillance activities. However, we recognize the limitation that the activity reports provided by each site may not have included other relevant aspects of laboratory operations. Estimated changes in the performance indicators reported here cannot therefore be conclusively attributed to the actions described by the sentinel sites in their activity reports.

The good working relationships between RITM and sentinel site personnel, formed through partnerships that have been in place since 1988, may have been a contributory factor in maintaining high levels of participation in ARSP. The practice of recognizing and incentivizing sites with top participation scores, which was established in 2012, may have also encouraged continued participation in ARSP during the COVID-19 pandemic.

The process of automated data transfer, whereby WHONET encoded data from the sentinel sites are automatically transmitted to the ARSRL server, facilitated the data submission from sentinel sites throughout 2020. ARSRL, as the coordinating laboratory, adapted to the challenges caused by the pandemic by adjusting staff schedules and activities, holding the annual PIM online and delaying the publication of the annual surveillance report.

There was, however, a reduction in the amount of surveillance data submitted in 2020, a factor that must be considered when interpreting the overall AMR rates reported by ARSP for 2020. It is possible that the decrease in submitted data was due to the shift towards remote outpatient consultations (to lessen the risk of infection at the sentinel sites), a trend which could introduce bias in patient and testing denominators for the 2020 ARSP surveillance data, and which should be considered in the analysis of AMR data.[6,7]

The actions implemented by the participating sentinel sites alleviated much of the negative impact of the pandemic on laboratory operations and logistics. Performance indicators revealed that despite the ongoing health crisis, sentinel sites were able to perform their tasks as the primary contributors to national AMR data collection. It is imperative for ARSRL to disseminate information and encourage other facilities to adopt the good practices observed at these sites. The success and continuity of ARSP is contingent upon the collaborative efforts of the reference laboratory and the sentinel sites. The COVID-19 pandemic has the potential to exacerbate the AMR situation in the Philippines and put stewardship efforts at risk. It is imperative therefore that efforts against the development of AMR should not cease.

Further studies should be conducted to provide more information on the impact of the COVID-19 pandemic on AMR emergence and spread. Moreover, the expanded molecular biology facilities established to meet the needs of the COVID-19 response should be utilized to enhance national AMR surveillance through genomic epidemiology.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethics statement

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