World Health Organization
Western Pacific Region

WPSAR
Western Pacific Surveillance and Response Journal

Volume 14, Number 4, 2023, Pages 1–48
p-ISSN: 2094-7321 e-ISSN: 2094-7313

wpsar@who.int | https://ojs.wpro.who.int/

IN THIS ISSUE

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Western Pacific Surveillance and Response

WHO Western Pacific Surveillance and Response (WPSAR) is an open access journal dedicated to the surveillance of and response to public health events. The goal of the journal is to create a platform for timely information sharing within our region and globally to enhance surveillance and response activities. WPSAR is a publication managed by the World Health Organization Regional Office for the Western Pacific.

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p-ISSN: 2094-7321
e-ISSN: 2094-7313

WPSAR after 14 volumes: achievements and future directions

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Since 2010, the *Western Pacific Surveillance and Response* (WPSAR) journal has served as a platform for timely information-sharing on the surveillance of and response to public health events and emergencies in the Western Pacific Region. WPSAR publishes a broad range of articles not limited to conventional research articles and, unlike many other scientific journals, builds capacity in communicating epidemiological and operational findings by providing pre-submission assistance to first-time authors in the Region, particularly those who are fellows or recent graduates of field epidemiology training programmes (FETPs).

WPSAR is the official journal of the World Health Organization (WHO) Regional Office for the Western Pacific and the scientific communication component of the Region's efforts against health security threats. The journal welcomes contributions from field epidemiologists, staff of Ministries and Departments of Health and other government officials, those working in health security and global health, other front-line professionals responding to public health events and emergencies in the Region, and specialists from other disciplines and settings such as academia and clinical practice.

One of the most widely debated journal metrics is impact factor. The impact factor of a journal, as calculated by Clarivate, is a measure of the average number of citations that articles published in the two prior years received in the current year.[1] In June 2023, WPSAR received its first impact factor of 1.0. This means that every article published in WPSAR in 2020 and 2021 was cited by another scientific article an average of 1.0 time in 2022. This is an exciting milestone in the journal's history, as it serves as recognition of the editorial team's efforts to consistently publish timely, high-quality articles. In this editorial, we mark this achievement with a summary of the journal's work over the course of 14 volumes and a look at future directions for WPSAR.

Over the last 14 years, WPSAR has consistently published four quarterly issues per year, plus special editions on timely topics. These special editions have covered the response to Typhoon Haiyan in the Philippines (2015),[2] the centennial of the 1918 influenza pandemic (2018),[3] COVID-19 clinical management and health-care pathways (2023)[4] and the establishment of emergency medical teams in the Pacific (2023).[5] Additionally, while COVID-19 was declared a public health emergency of international concern by WHO (January 2020 to May 2023),[6] each quarterly issue featured a section dedicated to COVID-19 articles.

As of December 2023, WPSAR has cumulatively published 465 articles, 179 (38.5%) of them in the last 5 years. The most frequently published article type is Original Research, followed by Outbreak Investigation Report, Brief Report and Surveillance Report (**Table 1**). By country and area, the highest number of articles cover Region-wide topics (n = 72), followed by those from Australia and the Philippines (n = 63 each), Japan (n = 50), Viet Nam (n = 30), Papua New Guinea (n = 23) and China (n = 22, excluding Hong Kong SAR, China) (**Fig. 1**). The acceptance rate of articles that met the scope of the journal was 87% (47/54) in 2021 and 83% (45/54) in 2022. While showing a slight decrease, this figure is high due to the policy of accepting all submissions that meet the scope of the journal and offering pre-submission assistance to authors to ensure their articles meet publication standards, in line with the

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Published: 31 December 2023
doi: 10.5365/wpsar.2023.14.4.1136

Table 1. **Published articles in WPSAR by article type (*N* = 465)**

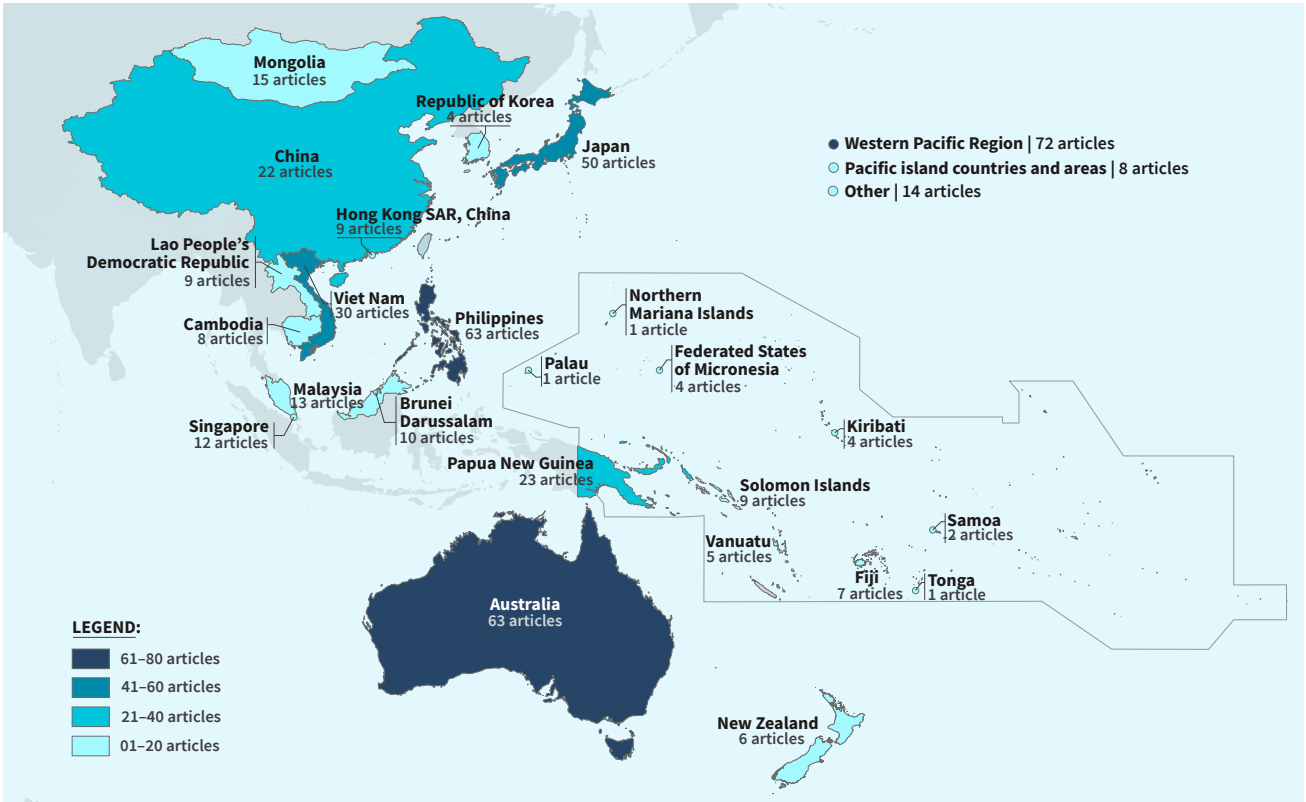
Article type	*n* (%)
Original Research	137 (29.5)
Outbreak Investigation Report	54 (11.6)
Brief Report	48 (10.3)
Surveillance Report	46 (9.9)
Lessons from the Field	41 (8.8)
Perspective	38 (8.2)
Regional Analysis	26 (5.6)
Field Investigation	19 (4.1)
Editorial	15 (3.2)
Surveillance System Implementation / Evaluation	13 (2.8)
Case Report / Case Series	11 (2.4)
Letter to the Editor	8 (1.7)
Risk Assessment	7 (1.5)
News, Meeting and Conference Report	1 (0.2)
Miscellaneous	1 (0.2)

objective of building scientific writing capacity in the Region.

In recent years, WPSAR has expanded its global team of associate editors to offer a wider diversity of expertise during article review. Several initiatives are also underway to reduce the time from article submission to publication, such as expanding the pool of external independent peer reviewers and implementing technology and process improvements. The Executive Editor and the editorial team may select certain manuscripts that are of urgent public health importance for expedited early publication.

In October 2023, the draft *Asia Pacific Health Security Action Framework* was submitted to the 74th session of the WHO Regional Committee Meeting for the Western Pacific, where it was endorsed by Member States.[7] This Framework is the successor to the *Asia Pacific Strategy for Emerging Diseases and*

Fig. 1. **Published articles in WPSAR by country and area (*N* = 465)**



SAR: Special Administrative Region.

Public Health Emergencies (APSED III)[8] and will be implemented by Member States beginning in 2024. Building on the experiences from its previous iterations, the Framework identifies six multisectoral domains that interconnect to form a comprehensive health security system that can be implemented flexibly at subnational, national and regional levels.[9]

In support of the new Framework, the WPSAR editorial team announces the expansion of the journal's scope to include all aspects of health security in response to public health events and emergencies. WPSAR will especially aim to address all activities related to the prevention, preparedness, readiness, response and recovery to public health events and emergencies, prioritizing topics that are of relevance to the Western Pacific Region. Public health events may be acute or ongoing, and topics to be explored can fall under any of the following areas: communicable diseases, emerging infectious diseases, natural disasters, food safety, bioterrorism, and chemical and radiological events. Other events and topics may also be considered as the journal seeks to disseminate important insights that can lead to improved protection of people's health before, during and after outbreaks, epidemics, pandemics, disasters and other public health emergencies.

The WPSAR editorial team would like to thank our authors, anonymous reviewers and associate editors for their outstanding contributions to our success over the last 14 years. We look forward to continuing to work with you. We also look forward to welcoming articles within the expanded scope of the journal and continuing to support and promote the work of all those involved in health security across the Region.

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Population compliance with COVID-19 directions in December 2021, Queensland, Australia

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To contain the spread of coronavirus disease (COVID-19), most countries introduced travel-related control measures such as restricted entry, quarantine of travellers and screening requirements.[1] The Australian response to the COVID-19 pandemic included the closure of the international border and restricted movement between Australian states and territories. In the state of Queensland, *Border Restrictions Direction (No. 56)* came into effect on 13 December 2021. The direction, enacted by the state's Chief Health Officer, stipulated that a person entering Queensland from a declared national COVID-19 hotspot must meet the following conditions: not be an international arrival, be fully vaccinated (≥2 doses), have received a negative COVID-19 polymerase chain reaction (PCR) test result within 72 hours before arrival, and undertake a COVID-19 PCR test on day 5, or as close to day 5 as practical, after arrival.[2] People entering Queensland were required to complete an electronic border pass application within 72 hours before their arrival, declaring their vaccination status and willingness to comply with the order. There are limited data in the public domain reporting compliance with public health directions during the COVID-19 pandemic in Australia. This report summarizes the findings of an audit activity to determine compliance with the Queensland directive that came into force in mid-December 2021 and to assess whether the process could be scaled up for continued compliance monitoring.

Queensland border pass applications lodged between midnight on 12 December 2021 and 21:48 on 13 December 2021 were analysed (data extraction: 16 December 2021). Eligibility required the applicant to be a returning or new Queensland resident with a Queensland residential address recorded. Automatic data linkage methods were used to connect extracted border pass application data, COVID-19 vaccination status in the Australian Immunisation Register (AIR), and evidence of a COVID-19 test from the Queensland Notifiable Conditions System (NoCS). To evaluate process completeness, manual linkage checks were performed for unmatched records. This analysis was conducted as a public health audit activity in accordance with the Queensland *Public Health Act 2005*.[3] Data were extracted and stored on password-protected organizational devices with auditable, individual-user monitoring capabilities. Raw data were available only to staff directly involved in the data linkage. Data were de-identified for analysis and then aggregated for reporting.

From the eligible sample of new and returning Queensland residents (n = 297), 173 (58%) were matched to a COVID-19 test in NoCS in the 9-day period after 13 December 2021 (**Fig. 1**). Of these, 26 (9%) NoCS records were identified via manual searching. The automatic linkage process with the AIR successfully matched 163 (55%) records, while the remaining 134 (45%) were manually searched. Of the 265 residents whose vaccination status could be viewed in the AIR and were eligible for vaccination, 237 (89%) were identified as fully vaccinated.

Policy responses to the COVID-19 pandemic have been dynamic, and public health directions have

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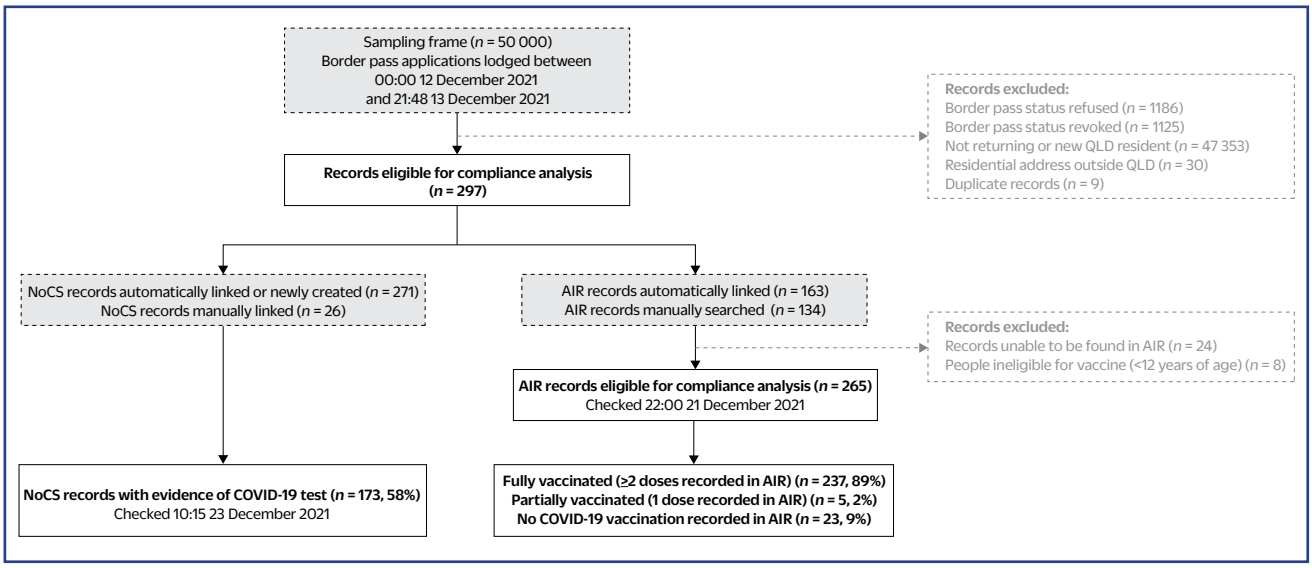
Published: 29 November 2023
doi: 10.5365/wpsar.2023.14.4.1018

Fig. 1. **Summary of compliance analysis process and results**



AIR: Australian Immunisation Register; NoCS: Notifiable Conditions System; QLD: Queensland.

changed frequently in line with emerging evidence.[4] In Australia, information on population compliance with these directions has been limited, more commonly measured through the identification of individual breaches. Our analysis provides a cross-sectional estimate of vaccination and testing compliance among new and returning Queensland residents in December 2021. The high vaccination compliance (89%) reflected broader community vaccination coverage. However, compliance with post-arrival PCR testing was lower, possibly because of the burden on the health system at the time, which resulted in long testing wait times and delayed results.

One limitation of our analysis was the completeness and availability of the data from the border pass applications system. The supplied data did not list date of entry to Queensland. People were required to lodge their applications within 72 hours of entry, resulting in a broad compliance indication instead of a true "day 5" testing representation. The process could match 58% of people to a test recorded in NoCS in the 9-day period after 13 December 2021. Having accurate entry dates could have provided a more accurate population sample and resulting day 5 compliance value. Another limitation was the role of residential address in automated COVID-19 test reporting. Due to the processing of test results based on residential address, testing compliance through NoCS could only be reliably assessed for people with Queensland residential addresses. This resulted in an incomplete sample and limited our understanding of compliance by all entrants to the state, at a time when border restrictions were being eased and many visitors were entering the state.

Although we could estimate compliance for those with Queensland residential addresses, we could not include people entering Queensland without a Queensland residential address. Also, manual input was required to assess vaccination status, with 45% of vaccination records needing to be manually matched. These issues would create barriers to population-level scale-up of this audit activity. Thus, further consideration is required to improve connectivity and integration of public health information management systems. In future, it will be important to consider system capacity to monitor compliance with public health directions during health emergencies, and to improve communication and engagement mechanisms when non-compliance occurs. Ideally, future work could include an extended period of analysis to strengthen our understanding of compliance over time. Although monitoring compliance is a valuable element of an emergency public health response, it is not always feasible within existing infrastructure or resources of the health system. Communication and engagement mechanisms before an emergency

response or before implementation of public health measures could strengthen compliance and reduce the need for monitoring.

Acknowledgements

The authors are grateful to staff within the Queensland COVID-19 Public Health Response Division and the Statistical Analysis and Linkage Team at Queensland Health for their contribution to this work.

Conflicts of interest

EF is an associate editor of the Western Pacific Surveillance and Response journal. She was not involved in the editorial decision to publish this article. The other authors have no conflicts of interest to declare.

Ethics statement

This analysis was conducted as a public health audit activity in accordance with authority under the Queensland *Public Health Act 2005*.

Funding

MD was supported by a Master of Philosophy in Applied Epidemiology scholarship funded by the Department of Health, Queensland Health, and administered by the Australian National University.

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Use of a catch-up programme to improve routine immunization in 13 provinces of Papua New Guinea, 2020–2022

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Objective: Routine immunization coverage in Papua New Guinea has decreased in the past 5 years. This persistently low routine immunization coverage has resulted in low population immunity and frequent outbreaks of vaccine-preventable disease across the country. We describe the use of a catch-up programme to improve routine immunization during the coronavirus disease pandemic in Papua New Guinea during 2020–2022.

Methods: In June 2020, 13 provinces of Papua New Guinea were selected to undergo a vaccination catch-up programme, with technical support from the World Health Organization (WHO) and the United Nations Children's Fund. Twelve provinces received financial and logistic support through the Accelerated Immunization and Health Systems Strengthening programme, and one received support from WHO. All stakeholders were involved in planning and implementing the catch-up programme.

Results: Between July 2020 and June 2022, about 340 health facilities conducted catch-up activities. The highest number of children aged under 1 year were vaccinated in 2022 (n = 33 652 for third dose of pentavalent vaccine). The national coverage of routine immunization (including the catch-up vaccinations) increased between 2019 and 2020 – by 5% for the third dose of pentavalent vaccine, 11% for the measles-rubella vaccine and 16% for the inactivated poliovirus vaccine. The coverage declined slightly in 2021 before increasing again in 2022.

Discussion: The catch-up programme was an instrumental tool to improve routine immunization coverage between 2020 and 2022 and during the pandemic in Papua New Guinea. With appropriate technical and logistic support, including financial and human resources, catch-up programmes can strengthen routine immunization coverage across the country.

Immunization is a cost-effective public health programme and a key contributor to improving health.[1] Globally, in 2021, more than 25 million infants were reported to have never been vaccinated or to have been underimmunized. Most of these children tend to live in communities in low- and middle-income countries that have never received routine immunization services, including Papua New Guinea. These communities lack access to vaccination services, resulting in an increased risk of outbreaks of vaccine-preventable disease. This risk has been exacerbated by disruptions associated with the coronavirus disease (COVID-19) pandemic.[2]

The Papua New Guinea National Immunization Strategy 2021–2025 described a "catastrophic" situation with immunization; for example, national coverage of the third dose of pentavalent vaccine decreased from 70% in the 2000s to less than 45% during 2016–2020.[3] This persistently low routine immunization coverage led to low population immunity, and was the underlying cause of several outbreaks of vaccine-preventable disease across the country. For example, a measles outbreak was reported in 2013–2014; it affected all 22 provinces and resulted in 2299 laboratory-confirmed cases, and continued

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Published: 19 December 2023
doi: 10.5365/wpsar.2023.14.4.1055

with local and small-scale measles outbreaks reported in several provinces.[4] A study conducted in East Sepik province of Papua New Guinea in 2020 found that the prevalence rates of anti-measles and rubella IgG were 63% and 82%, respectively.[5] An outbreak of circulating vaccine-derived type 1 poliovirus occurred in 2018, with 26 cases confirmed in nine of the 22 provinces.[6] In March 2020, the country confirmed the first imported COVID-19 case; by 21 February 2023, there were 46 792 confirmed cases including 670 deaths reported.[7]

In a cross-sectional study conducted in East New Britain province, contributing factors for low immunization coverage included a lack of local planning based on locations of child populations, limited intensification of outreach services, incomplete local information and lack of trained human resources.[8] Another study found that there were several barriers to vaccine delivery, including lack of access to health-care services, natural disasters and intertribal conflicts.[9] In 2020, immunization service delivery was negatively affected by the COVID-19 pandemic because the government issued strict movement restrictions that resulted in reduced health clinic attendance and outreach visits by health-care workers. In 2021, the introduction of the COVID-19 vaccine also negatively affected routine immunization services because the limited health-care workforce and fragile health system were overwhelmed with COVID-19 vaccination activities. This report describes the use of a catch-up programme to improve routine immunization during the COVID-19 pandemic in Papua New Guinea in 2020–2022.

METHODS

Study area

Papua New Guinea has 22 provinces, 89 districts and 349 local-level governments, with over 750 health facilities delivering routine immunization services across the country and 533 health facilities in 13 provinces. According to the 2011 census, the projected population for 2022 was 9 593 926. The target number of children for vaccination aged under 1 year is 314 667, with 70% of these children residing in 13 provinces (**Map 1**).

Design of the catch-up programme

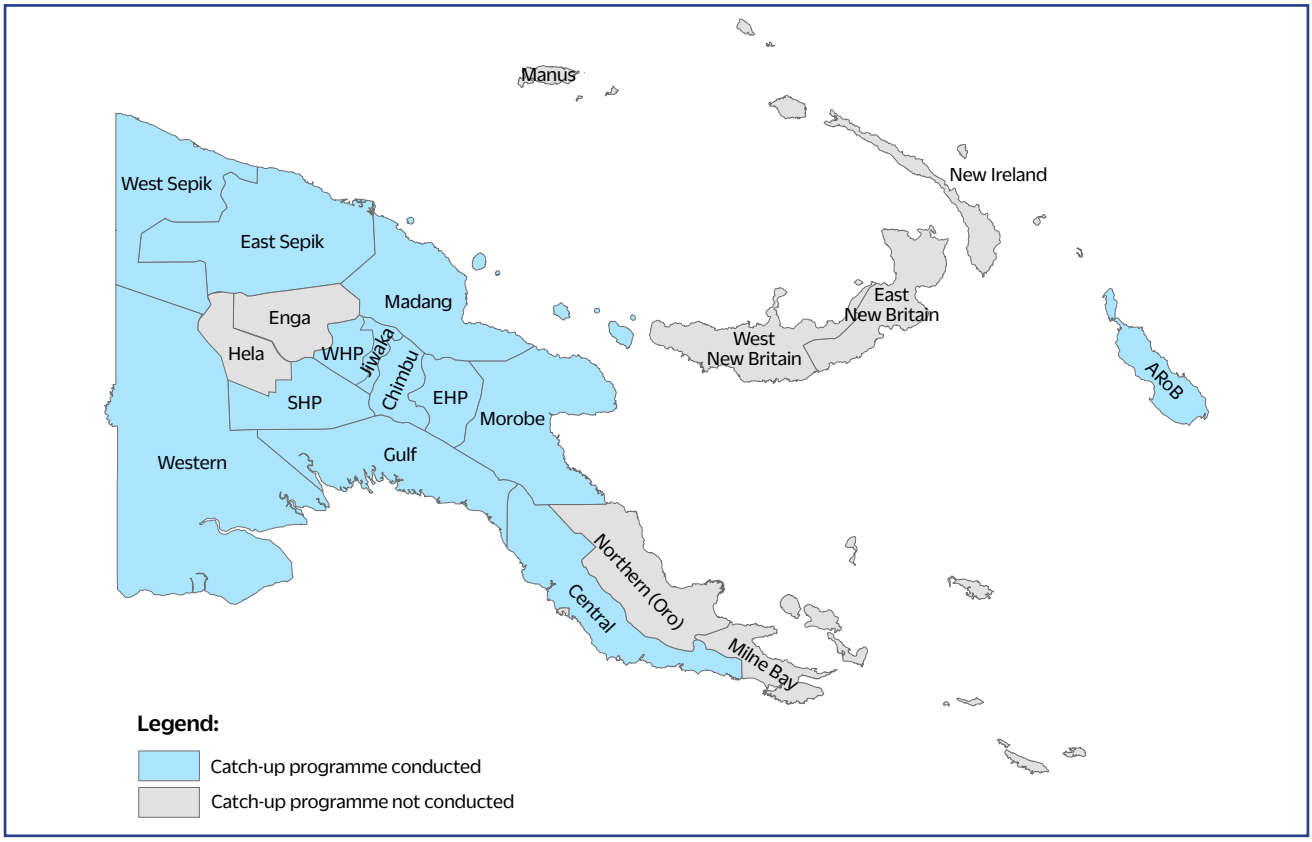
The catch-up programme was designed to provide an additional three rounds of mobile and outreach vaccination activities over 2 weeks of each year in each province. Outreach involved the vaccination team staying overnight for 3–5 days in remote villages; in contrast, mobile teams returned on the same day. Vaccinations were provided to children who had received no doses and underimmunized children aged under 2 years. All available vaccines, in accordance with the national immunization schedule,[10] were offered during the catch-up programme except for the hepatitis B birth dose.

The catch-up programme was led by the Papua New Guinea National Department of Health (NDOH), with technical support from the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF). Financial and logistic support was provided to 12 provinces through the Accelerated Immunization and Health Systems Strengthening Programme, which was donated by GAVI, the Vaccine Alliance, and by the governments of Australia and New Zealand; WHO provided technical support to all 13 provinces and financial support to one province. All stakeholders were involved in planning and implementing the catch-up programme. The NDOH conducted the immunization catch-up programme in 13 provinces from July 2020 to June 2022. In July 2020, the first virtual meeting was conducted, attended by all stakeholders, and the objectives and planning of the catch-up programme were discussed. Meetings continued monthly to review the performance of the catch-up programme.

Data collection and analysis

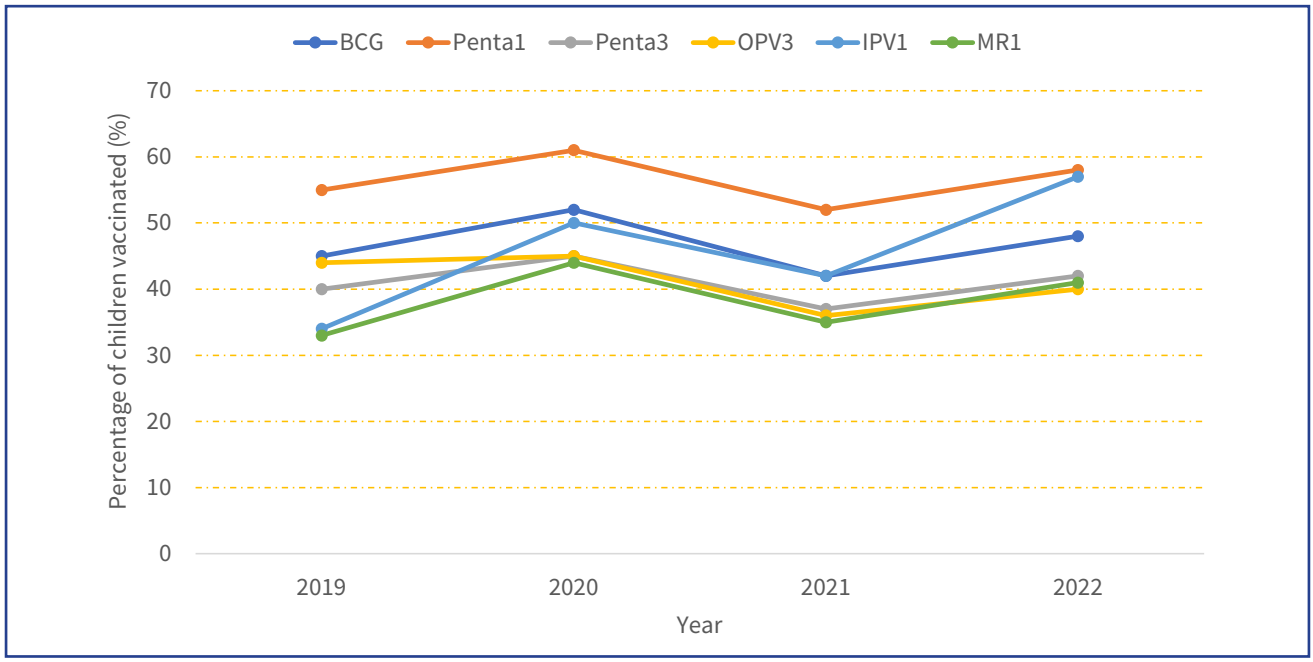
The country's existing electronic national health information system (eNHIS) was used to collect immunization data. The data were submitted to the WHO/UNICEF Estimates of National Immunization Coverage (WUENIC) database annually. Unlike the eNHIS data, the WUENIC data are publicly available online and thus could be referenced for the coverage in this manuscript. A simple Microsoft Excel database was created to monitor the catch-up programme vaccinations in the field. The data were analysed for children aged under 1 year only

Map 1. **The 13 provinces of Papua New Guinea in which the immunization catch-up programme was conducted, 2020–2022**



AROB: Autonomous Region of Bougainville; EHP: Eastern Highlands province; SHP: Southern Highlands province; WHP: Western Highlands province.

Fig. 1. **National routine immunization coverage of children aged under 1 year, Papua New Guinea, 2019–2022**



BCG: bacille Calmette–Guérin (vaccine); IPV1: first dose of inactivated poliovirus vaccine; MR1: first dose of measles-rubella vaccine; OPV3: third dose of oral poliovirus vaccine; Penta1: first dose of pentavalent vaccine; Penta3: second dose of pentavalent vaccine.

Source: Papua New Guinea: WHO and UNICEF estimates of national immunization coverage: 2022 revision. Geneva: World Health Organization; 2023. Available from: https://www.who.int/publications/m/item/immunization-papua-new-guinea-2023-country-profile, accessed 22 July 2023.

(even though the catch-up programme was for children aged under 2 years), because complete data were only available for those aged under 1 year. Vaccines included in the analysis were bacille Calmette–Guérin (BCG), first and third doses of pentavalent vaccine (Penta1 and Penta3), first dose of measles-rubella vaccine (MR1), oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV). The three doses of pentavalent vaccine offer protection against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenza* type B.

RESULTS

About 340 health facilities in the 13 provinces conducted at least three rounds of catch-up programme activities in 2020, two rounds in 2021 and four rounds in 2022.

The highest number of children aged under 1 year vaccinated during the catch-up programme was in 2022, with 40 897 vaccinated with Penta1, 33 652 with Penta3 and 37 099 with MR1 (**Table 1**). This is likely because there were four rounds of catch-up programme activities in 2022, and these started in February.

The performance of catch-up programme activities varied across the provinces. In 2020–2021, East Sepik province vaccinated the highest number of children for Penta3 and MR1, whereas in 2020, Madang province vaccinated the highest number of children for MR1. West Sepik demonstrated the highest number of children vaccinated for Penta3 and MR1 in 2022. Gulf province vaccinated the lowest number of children through catch-up programme activities during the 2 years (**Table 1**).

MR1 and first dose of IPV (IPV1) accounted for the highest number of doses administered during the catch-up programme compared with other vaccines. BCG had the lowest number of doses administered during the catch-up programme (**Supplementary Fig. 1**).

Table 1. **Total target children and number of children aged under 1 year vaccinated during the catch-up programme activities in 13 provinces of Papua New Guinea, 2020–2022**

Province	2020				2021				2022			
	Target <1 year	Penta1	Penta2	MR1	Target <1 year	Penta1	Penta3	MR1	Target <1 year	Penta1	Penta3	MR1
ARoB	10 830	1480	1186	1687	11 164	1156	288	401	11 508	1089	694	639
Madang	26 606	5747	2842	4499	27 471	385	865	1275	28 364	1507	679	1416
East Sepik	23 263	3970	3150	3523	23 959	439	2359	2287	24 675	1720	1499	1514
West Sepik	11 224	2442	2037	2450	11 505	686	1129	1589	11 792	6808	6285	7451
Simbu	10 432	170	181	358	10 609	257	784	996	10 790	4077	3746	3786
Jiwaka	11 334	728	661	674	11 666	2723	864	870	12 008	3296	3711	2556
Southern Highlands	21 691	2839	2920	4043	22 299	1123	891	1341	22 923	4249	3911	5003
Western Highlands	13 806	1173	1070	406	14 166	2125	785	563	14 536	2303	1783	1268
Eastern Highlands	21 654	2475	2634	2911	22 165	856	729	773	22 688	5961	4170	4905
Central	10 177	0	0	0	10 439	261	675	724	10 707	3880	3201	3838
Gulf	7211	195	164	165	7407	0	0	0	7608	686	387	476
Western	11 303	0	0	0	11 665	853	82	318	12 038	864	736	752
Morobe	29 377	1870	1278	2512	30 123	1230	311	390	30 888	4457	2850	3495
Total	**208 909**	**23 089**	**18 123**	**23 228**	**214 637**	**12 094**	**9762**	**11 527**	**220 526**	**40 897**	**33 652**	**37 099**

ARoB: Autonomous Region of Bougainville; MR1: first dose of measles-rubella vaccine; Penta1: first dose of pentavalent vaccine; Penta2: second dose of pentavalent vaccine; Penta3: third dose of pentavalent vaccine.

The national immunization coverage of Penta3, MR1 and IPV1 increased from 40%, 33% and 34% in 2019 to 45%, 44% and 50% in 2020, respectively. The increases ranged from 5% (14 927 additional children aged under 1 year completed Penta3) to 11% (32 839 children aged under 1 year received MR1) and 16% (47 765 children aged under 1 year received IPV1). This improvement was probably due to the catch-up programme activities in the 13 provinces. In 2021, the coverage was slightly lower than in 2019, 2020 and 2022 for some vaccines (**Fig. 1**). The coverage of Penta3, MR1 and IPV1 increased from 37%, 35% and 42% in 2021 to 42%, 41% and 57% in 2022, respectively (**Fig. 1**). The dropout rate from Penta1 to Penta3 was over 10%.

DISCUSSION

National routine immunization coverage improved in Papua New Guinea between 2019 and 2020, slightly declined in 2021 and increased again in 2022. These changes were probably due to the implementation of the catch-up programme in 13 provinces. The decline in coverage in 2021 was likely due to the introduction of COVID-19 vaccination at a point when only two rounds of catch-up programme activities had been conducted. The COVID-19 pandemic had a negative effect on routine immunization in many countries, especially in the initial pandemic phases. This highlights the importance of maintaining and recovering routine immunization through periodic catch-up programmes during and after a pandemic.[11]

Several key field observations were made during the implementation of the catch-up programme. Lessons identified about what is essential for the success of catch-up programme activities included making adequate logistic and financial preparations (e.g. through effective coordination among partners) before starting implementation of activities, including obtaining the average estimated cost per round per province of US$ 10 000; active engagement from district health managers and officers in charge during the planning and implementation stages of the catch-up programme activities; technical support and close monitoring from WHO subnational consultants, to ensure the implementation of a quality microplan; human resources, financial support and timely disbursement of funds at the health facility level (critical for improving the immunization coverage); and distribution and availability of vaccines at the health facility level. A similar study revealed that logistic availability, adequate staffing and reallocation of resources during the COVID-19 pandemic are key elements for the success of a routine immunization catch-up programme.[12]

There were several limitations to conducting the catch-up vaccination programme, including a shortage of health-care workers and a lack of resources such as laptops and computers, electricity supply and Internet connection, particularly in remote areas. This limited the data collection to those aged under 1 year because the full dataset was not available for those aged under 2 years.

During the pandemic, the dropout rate in Papua New Guinea from Penta1 to Penta3 was higher than the recommended 10%. Intensive efforts need to be made to ensure effective communication during the first immunization visit, as this is vital for ensuring timely administration of the second dose and completion of the recommended dose schedule.

The catch-up programme was instrumental in improving routine immunization coverage within a short period of time in Papua New Guinea. It is recommended that similar catch-up programmes be part of the country's national immunization programme, with four rounds implemented each year and funding of US$ 10 000 allocated per round per province. With appropriate technical and logistic support, including finances and human resources, the catch-up programme can contribute to the effort to strengthen routine immunization coverage across Papua New Guinea.

Acknowledgements

The authors acknowledge the Provincial Health Authorities in the Autonomous Region of Bougainville, Western Highlands, Eastern Highlands, Southern Highlands, Jiwaka, Simbu, Morobe, Madang, East Sepik, West Sepik, Gulf, Central and Western provinces for their valuable support. Additionally, the authors extend their gratitude to all Stop Transmission of Poliomyelitis (STOP) team members and WHO consultants for their technical support to provinces during the catch-up programme activities.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This article describes public health actions undertaken as part of routine immunization services under the National Department of Health of Papua New Guinea that did not require ethics approval.

Funding

None

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Circulation of human respiratory syncytial virus and new ON1 genotype in northern Viet Nam, 2017–2020

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Objective: Human respiratory syncytial virus (RSV) is a primary cause of paediatric severe acute respiratory infection (SARI) worldwide, especially in developing countries. We investigated the genetic characteristics of RSV in northern Viet Nam to determine the prevalence and distribution of subtypes as well as the diversity and transmission patterns of genotypes.

Methods: In two facilities, from January 2017 to December 2020, 1563 clinical specimens were collected from paediatric patients hospitalized with SARI and tested for RSV. Selected positive samples underwent sequencing analysis targeting the second hypervariable region of the *G* gene using next-generation sequencing.

Results: The RSV positivity rate was 28.02% (438/1563 samples), and prevalence was highest in children aged <1 year (43.84%; 192/438). Subtype RSV-A accounted for 53.42% (234/438) of cases, RSV-B for 45.89% (201/438), and there was coinfection in 0.68% (3/438). Both subtypes cocirculated and peaked during August–September in each year of the study. Phylogenetic analysis showed that RSV-A samples belonged to the ON1 genotype, which has three subgenotypes: ON1.1, ON1.2 and ON1.3. However, we did not find the 72-nucleotide duplication in the second hypervariable region of the *G* gene, a characteristic of genotype ON1, in any RSV-A samples. RSV-B samples belonged to genotype BA9.

Discussion: Our results provide additional molecular characterization of RSV infections in Viet Nam. Specially, our study is the first to report the absence of the 72-nucleotide duplication in the *G* gene of RSV-A genotype ON1 in Viet Nam, which may help in understanding the genetic evolution of RSV and be useful for vaccine development in the future.

Human respiratory syncytial virus (RSV) is one of the most common causes of severe acute respiratory infection (SARI) among children worldwide. Most children have at least one episode of RSV infection by the age of 2 years, and 5% of these cases require hospitalization.[1] RSV belongs to the recently defined family *Pneumoviridae*, genus *Orthopneumovirus*, and consists of a single-stranded, negative-sense RNA genome packaged in a lipid envelope. It has about 15.2 kb and contains 10 genes encoding 11 viral proteins. The external glycoproteins F and G are the two primary antigens for viral attachment and make a syncytial form.[2] The G protein, especially in the second hypervariable region (HVR), is highly genetically diverse and under selection pressure, and thus is used for the molecular characterization of RSV strains.[3]

RSV is classified into two subgroups – RSV-A and RSV-B – based on the difference in the second HVR of the *G* gene. Currently, RSV-A is divided into 12 genotypes (GA1–7, SAA1, NA1–2, ON1–2), and RSV-B is divided into 32 genotypes (GB1–5, BA1–14, SAB1–4, URU1–2, NZB1–2, BA-CCA, BA-CCB, BA-C, CBB, CB1).[4] In many countries, the predominant genotypes are RSV-A ON1, with a 72-nucleotide duplication in the HVR of the *G* gene, and RSV-B BA, with a 60-nucleotide duplication in the HVR of the *G* gene.[5]

RSV infections range in severity from common cold symptoms to severe, acute symptoms, including pneumonia or bronchiolitis requiring hospitalization. It has been estimated that 2.8–4.3 million children with RSV infection are admitted to hospital each year worldwide,

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Published: 16 October 2023
doi: 10.5365/wpsar.2023.14.4.990

and approximately 66 000–199 000 children aged <5 years die, particularly in developing countries.[6] Human RSV has a seasonal epidemic pattern similar to that of influenza. In Europe, northern Asia and North America, the seasonal RSV epidemic occurs in the winter and early spring months.[7] By contrast, in tropical countries, RSV cases are seen year-round and peak during the rainy season or in the months with the lowest temperatures and highest rainfall.[8]

Research on RSV in Viet Nam has been limited, mostly completed before 2016 and focused on coinfections with other respiratory pathogens. Surveillance data show that RSV usually occurs in the winter, when the temperature in the northern region is lowest.[9] However, that research spanned only 1–2 years, and the majority of research was conducted in central and southern Viet Nam. The objective of this study was to analyse the circulation of RSV in northern Viet Nam during 2017–2020 and to investigate the genetic variability of the second HVR of the *G* gene to characterize the evolution of RSV in Viet Nam.

METHODS

Sample collection

The study was conducted from January 2017 to December 2020 in a paediatric hospital in Hanoi and a general hospital in Quang Ninh province. Children aged <16 years who were admitted with SARI were enrolled. The definition of SARI followed World Health Organization guidelines: fever of ≥38 °C, cough, onset of symptoms within the past 10 days and illness requiring hospitalization.[9] Written consent for study enrolment was obtained from children's parents or legal guardians. Demographic data were recorded on a surveillance questionnaire.

Specimens of nasopharyngeal aspirate and nose–throat swabs were collected from children with SARI 1 day after hospital admission. A maximum of 10 new children were selected weekly for specimen collection in each hospital. Specimens were stored in a viral transport medium at −20 °C until they could be transferred to the National Institute of Hygiene and Epidemiology for testing. All samples were collected for routine surveillance of respiratory viruses under Decision No. 4608/QD-BYT of the Ministry of Health, Viet Nam, which governs ethical conduct during research, among other areas.

Screening and subtyping

Viral RNA was extracted directly from the specimens using the QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany), according to the manufacturer's instructions. All samples were screened for RSV using real-time reverse transcription–polymerase chain reaction (RT-PCR), with primer and probe sequences following the protocol of the United States Centers for Disease Control and Prevention.[10] Subtyping of the RSV strains was achieved using publicly available primers and probes based on the highly conserved genomic regions on the *N* gene for the subgroups RSV-A and RSV-B.[11] SuperScript III Platinum One-Step qRT-PCR reagent (Invitrogen, ThermoFisher Scientific, Waltham, MA, USA) was used with a thermocycler appropriate to each protocol.

Sequencing the second highly variable region of the *G* gene

Specimens that were positive for RSV were selected for sequencing by subtype, age, sex, collection year and hospital. Viral RNA for screening and subtyping was transcribed to copy DNA using the SuperScript IV First-Strand synthesis system (Invitrogen). Conventional PCR targeting of the second HVR was performed using Platinum SuperFi II Green PCR Master Mix (Invitrogen) and primers as described by Hibino et al.[12]

PCR products were purified with ExoSAP-IT PCR Product Cleanup Reagent (ThermoFisher Scientific) and diluted to 0.2 ng/μL. The library used for sequencing followed the protocol of the Nextera XT DNA Library Preparation Kit (Illumina, San Diego, CA, USA). The final concentration of the library was 60 pM for elution into the cartridge of the Illumina iSeq 100 System.

Phylogenetic tree and genotyping analyses

Sequencing data were primarily analysed using CLC Genomics WorkBench v. 11.0 (QIAGEN). First, the FASTQ file was quality controlled, and then the low-quality sequences and the noise in the 3′ and 5′ terminals were trimmed. After trimming, all reads were mapped with representative subtype references to

create final consensus. The nucleotide and amino acid substitutions of the second HVR of all RSV-A and RSV-B strains in this study were compared with, respectively, those of the prototype lineage ON1 (GenBank accession number JN257693) and BA9 (GenBank accession number AY333364).

Phylogenetic trees of the *G* gene's second HVR were generated using maximum likelihood estimation with MEGA (Molecular Evolutionary Genetics Analysis) v. 10 software (https://www.megasoftware.net/). Bootstrap probabilities were calculated with 1000 replications to evaluate confidence estimates. Genotypes were assigned with a 72-nucleotide duplication in RSV-A and 60-nucleotide duplication in RSV-B in the second HVR, as in ON1 and BA, respectively. Known genotype sequences from other countries were used as references for more accuracy. Subgenotypes for RSV-A and genotypes for RSV-B were identified using reference sequences from, respectively, Myanmar and Taiwan (China).[5,6] All Vietnamese RSV sequences were submitted to the Global Initiative on Sharing All Influenza Data (GISAID) database (accession numbers EPI_ISL_16051837 to EPI_ISL_16051941).

Statistical analyses

Patients' information and test results were imported into Filemaker Pro software (Claris, Apple, Cupertino, CA, USA). These data were stored and analysed by the National Institute of Hygiene and Epidemiology. Stata v. 14 (StataCorp, College Station, TX, USA) and Microsoft Excel software (Microsoft, Redmond, WA, USA) were used for testing epidemiological characteristics and graphing RSV surveillance data. *P* values <0.05 were considered statistically significant.

RESULTS

Circulation of RSV

During the study period (2017–2020), 1563 specimens were collected and 438 (28.02%) tested positive for RSV. The number of samples in each year was not similar, with the highest number in 2017 (512) and the lowest in 2020 (263). The RSV positivity rate in 2017 was much higher than the rate in other years, at 36.13% (**Table 1**). The difference in the rate of RSV screening each year was statistically significant (*P* <0.05).

The highest numbers of positive cases occurred in children aged <1 year and those aged 1 to <2 years. The rate of RSV positivity in the youngest age group was about four times higher than that in the group aged >5 years (*P* <0.05). Although RSV positivity in males was higher than in females, this difference was not significant (**Table 1**).

Prevalence of RSV subtypes and genotypes

Both RSV subtypes cocirculated between 2017 and 2020. During 2017 and 2018, there were similar proportions of each subtype, at around 50%. Conversely, during 2019 and 2020, RSV-A and RSV-B circulated alternately, with RSV-B predominant in 2019 and RSV-A in 2020. In 2017, 3/185 patients (1.62%) were coinfected with both subtypes (**Table 1**). During the study period, there was no significant difference in the rate of infection with RSV-A or RSV-B.

The frequency of RSV infection increased beginning every July (month 7), peaking at approximately 40% of tested samples in August–September (months 8 and 9), then falling for the rest of the year (**Fig. 1**). In 2017 and 2018, there was cocirculation of both subtypes of RSV, with peaks in August of both years. A similar time trend was seen in 2019, although RSV-B predominantly circulated. In contrast, in 2020, infection with RSV-A accounted for the highest proportion of cases, while the rate of infection with RSV-B was almost unchanged during the peak period.

Altogether, 105 sequences of the second HVR of the *G* gene were obtained. Phylogenetic analysis revealed that all Vietnamese RSV-A strains (n = 55) belonged to the ON1 genotype (**Fig. 2a**) and clustered with RSV sequences from Italy, Myanmar, Taiwan (China) and Thailand. ON1 samples identified in Viet Nam during the 2017–2020 seasons were located in three lineages: ON1.1, ON1.2 and ON1.3. Although the phylogenetic tree characterized Vietnamese RSV-A as belonging to genotype ON1, these sequences did not have the 72-nucleotide duplication between amino acids 284 and 307 (GQEETLHSTTSEGYLSPSQVYTTS) (**Fig. 3a**).

Most of the Vietnamese sequences had the amino acid substitution N255D (24/55) or E262K (10/55), both of which are characteristic of strains belonging to subgenotype ON1.2. Moreover, the specimens in

Table 1. **Number of samples tested for respiratory syncytial virus (RSV), positivity rate, subtype prevalence and distribution of RSV-positive cases by age group and sex in paediatric cases of severe acute respiratory infection, two sentinel sites in northern Viet Nam, 2017–2020**

Characteristic	Year[a]				
	2017	2018	2019	2020	2017–2020
No. of samples tested					
Total	512/1563 (32.76)	420/1563 (26.87)	368/1563 (23.54)	263/1563 (16.83)	1563/1563 (100)
RSV+	185/512 (36.13)	109/420 (25.95)	77/368 (20.92)	66/263 (25.10)	438/1563 (28.02)
RSV−	327/512 (63.87)	311/420 (74.05)	291/368 (79.08)	197/263 (74.90)	1125/1563 (71.98)
Subtype					
No. of subtyped samples	185/185 (100)	109/109 (100)	77/77 (100)	66/66 (100)	438/438 (100)
RSV-A	99/185 (53.51)	59/109 (54.13)	30/77 (38.96)	45/66 (68.18)	234/438 (53.42)
RSV-B	83/185 (44.86)	50/109 (45.87)	47/77 (60.26)	21/66 (31.82)	201/438 (45.89)
RSV-A and RSV-B	3/185 (1.62)	0/109 (0)	0/77 (0)	0/66 (0)	3/438 (0.68)
Age (years) of RSV+ cases					
<1	118/185 (63.78)	54/109 (49.54)	9/77 (11.54)	11/66 (16.67)	192/438 (43.84)
1 to <2	44/185 (23.78)	40/109 (36.70)	13/77 (16.67)	23/66 (34.85)	120/438 (27.40)
2 to <5	16/185 (8.65)	13/109 (11.93)	26/77 (33.33)	25/66 (37.88)	80/438 (18.26)
≥5	7/185 (3.78)	2/109 (1.83)	29/77 (37.66)	7/66 (10.61)	46/438 (10.50)
Sex of RSV+ cases					
Male	117/185 (63.24)	64/109 (58.72)	40/77 (51.28)	36/66 (54.55)	257/438 (58.67)
Female	68/185 (36.76)	45/109 (41.28)	37/77 (48.05)	30/66 (45.45)	181/438 (41.32)

RSV: respiratory syncytial virus.

[a] Values are numbers (%).

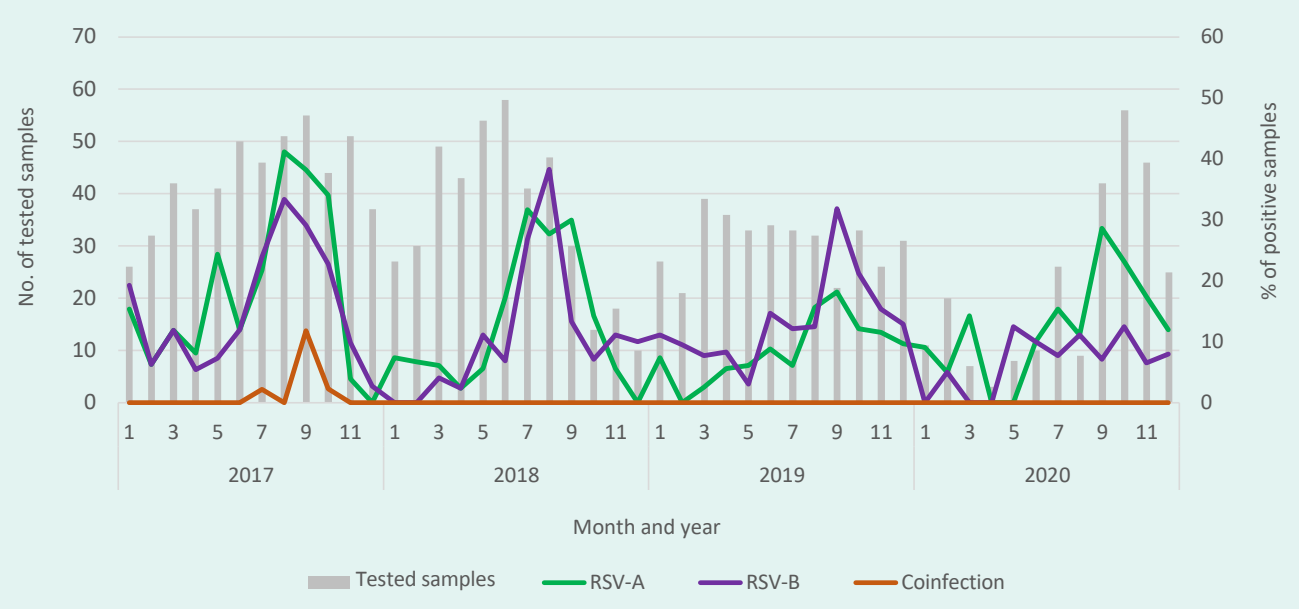
subgenotype ON1.1 shared the same substitutions: H258Q and H266L. Only one substitution, Y304H, was seen in several strains in both the ON1.1 and ON1.2 lineages. All RSV-A specimens in subgroup ON1.3 had one major amino acid substitution: L274P.

The results of the phylogenetic tree for the 50 RSV-B samples showed that they belonged to the BA9 genotype (**Fig. 2b**). All Vietnamese sequences had the insertion of a 60-nucleotide duplication, which means that 20 amino acids (TERDTSTSQSTVLDTTTSKH) were inserted in positions 260–279 (**Fig. 3b**). The Vietnamese BA9 viruses had two different G protein lengths, of 312 and 319 amino acids. All Vietnamese RSV-B sequences were in the same group as sequences from Argentina, England, Mongolia and Taiwan (China) and shared six substitutions (L223P, S247P, T254I, T2701, V271A, I281T).

DISCUSSION

In this study, we investigated the circulation of RSV and its genotypic variations in the second HVR during 2017–2020 in northern Viet Nam. The RSV prevalence in children with SARI was 28.02% during these 4 years.

Fig. 1. **Number of samples tested and proportion positive for respiratory syncytial virus (RSV) subtypes A and B and coinfection with RSV-A and RSV-B in paediatric cases of severe acute respiratory infection, two sentinel sites in northern Viet Nam, 2017–2020**



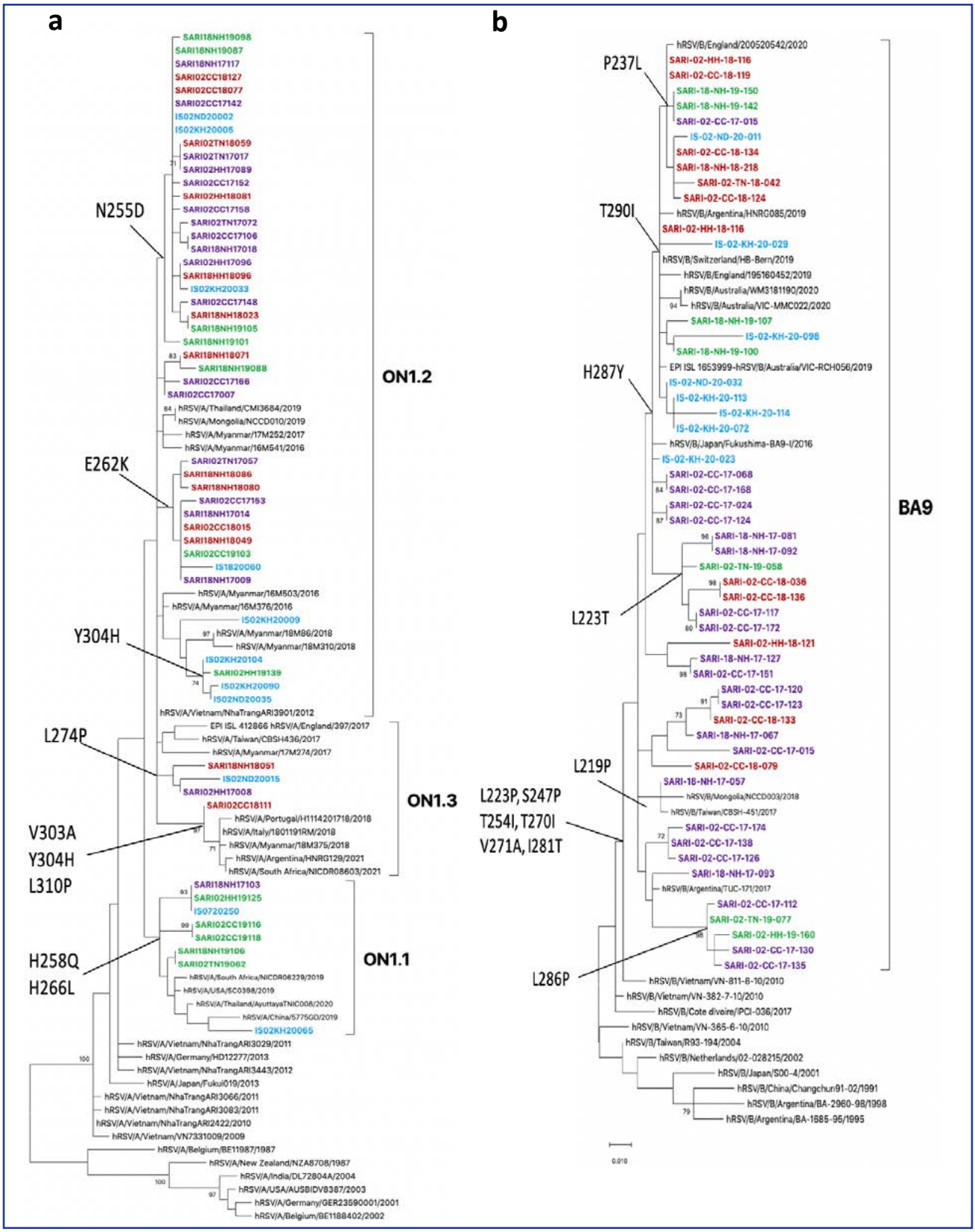
This rate was similar to that in Myanmar (24.5%),[6] but higher than that in China (16%)[13] and Thailand (13.2%),[14] and lower than in Brazil (56%).[1] The rate of RSV infection in children in central Viet Nam during 2007–2012 was 26.8%,[15] whereas SARI specimens from five representative locations in Viet Nam during 2012–2016 showed that the rate of RSV positivity was 22.8%.[16] The RSV positivity rate among paediatric patients in Viet Nam seemed to fluctuate at around 20–30%, depending on the study location and time of sample collection.

These studies showed diversity in the rate of RSV positivity by age. In our study, the difference in RSV positivity was statistically significant between children <2 years and those >5 years. This means that children <2 years have a higher risk of infection than those >5 years (P <0.05). This trend was also seen in other research, where the strongest risk factor for RSV infection was age.[13]

Some previous studies have found no correlation between subtypes and circulation or disease severity, whereas others have shown that RSV-A was more common and virulent than RSV-B.[1] In Viet Nam, there has not been much reporting on the surveillance of RSV subtypes. During our study, RSV-A and RSV-B circulated in parallel during 2017–2020, and cocirculated during the first 2 years. In one analysis of the Netherlands, New Zealand, Portugal and South Africa, out of 24 seasons during 2010–2019 with RSV subtype data available, RSV-A showed at least 60% dominance in 10 seasons and RSV-B in eight seasons, while neither reached 60% in the remaining six seasons.[17] In 2017, RSV-A predominated in Argentina (91% of samples) and the United Kingdom of Great Britain and Northern Ireland (62.5%), while RSV-B predominated in Australia (75%), India (98%), South Africa (64.4%) and Thailand (57%).[8] These results show no clear patterns in dominant subtype by season or geography, and highlight the need for more countries to collect data on subtypes to better understand their global circulation.

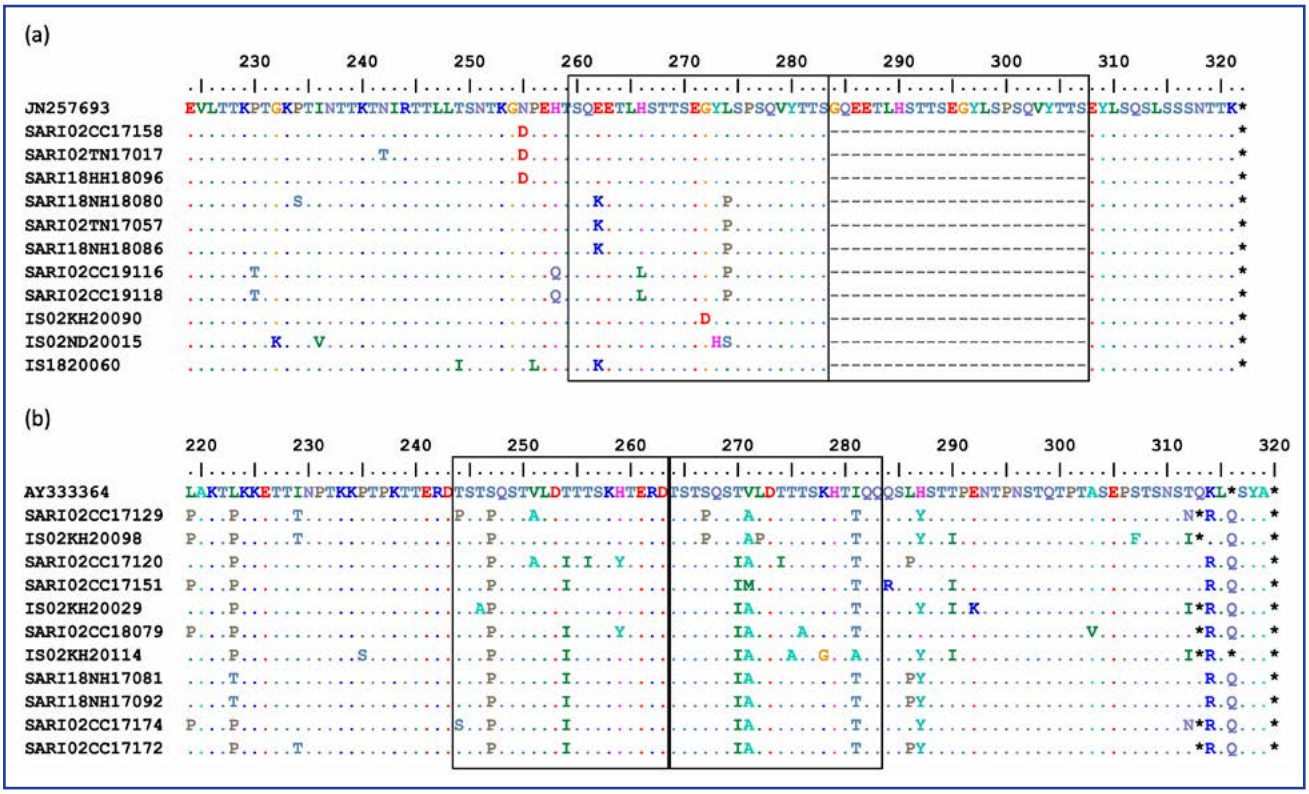
The coronavirus disease (COVID-19) pandemic not only led to a worldwide health crisis but also had a great impact on the circulation of other respiratory viruses, including RSV. According to a report from New Zealand, the number of paediatric hospitalizations for SARI and the number of single RSV or influenza infections decreased significantly during the pandemic.[18] In Thailand, the seasonal RSV peak was delayed by 2 months in 2020,[19] and in the Republic of Korea, the rates of RSV and influenza positivity were close to zero in the first half of the 2020–2021 season, their seasonal peak.[20] However, in the 2020 season in Viet Nam, the rate of RSV positivity was 25.1%, with RSV-A predominant and peaking in September. By comparison, morbidity

Fig. 2. **Phylogenetic analysis of the second hypervariable region of the *G* gene in Vietnamese respiratory syncytial virus (RSV) subtypes (a) A and (b) B from paediatric cases of severe acute respiratory infection, two sentinel sites in northern Viet Nam, 2017–2020**[a]



[a] Reference sequences of known genotypes of RSV detected during the 2017, 2018, 2019 and 2020 seasons are indicated in, respectively, purple, brown, green and blue.

Fig. 3. **Alignment of deduced amino acids of representative samples of Vietnamese respiratory syncytial virus (RSV) (a) subtype A genotype ON1 compared with prototype lineage JN257693 (GenBank accession number) and (b) RSV-B genotype BA9 compared with prototype lineage AY333364 from paediatric cases of severe acute respiratory infection, two sentinel sites in northern Viet Nam, 2017–2020**[a]



[a] Identical amino acids are indicated by dots. The stop codon is indicated by an asterisk. The boxed areas indicate the duplication regions.

from RSV-B was stable at around 10%. In 2020, the prevalence of RSV did not change much despite the COVID-19 pandemic. The Government of Viet Nam had implemented strict border control measures to limit the spread of COVID-19, resulting in only 1551 confirmed cases and 35 deaths reported nationally by late January 2021, most of them in southern Viet Nam.[21] Business operations, manufacturing, travel and study were not greatly affected. Children attended school on-site for the entire academic year, except for 2 weeks of lockdown in April 2020. Although the number of samples tested for RSV was low during the first half of 2020 due to the public's avoidance of hospitals caring for COVID-19 patients, the percentage of positive samples was largely unchanged throughout the year (**Fig. 1**), suggesting that the COVID-19 pandemic may have only weakly affected RSV prevalence in northern Viet Nam. However, our study period included only the first year of the pandemic; RSV data from subsequent years of the pandemic should be analysed as well.

The molecular epidemiological testing conducted in this study showed that the predominant RSV-A subtype was associated with the ON1 genotype, which was classified based on the phylogenetic tree. The ON1 genotype was first identified in Canada in 2010, with a 72-nucleotide insertion in the second HVR of the *G* gene.[6] This genotype subsequently spread rapidly across the world. However, in this study, the strains that lost the 72-nucleotide duplication in the second HVR of the *G* gene were still classified as RSV-A ON1. These results differ from most previous research,[3,4] which found that the ON1 strain had a duplication region in the second HVR of the *G* gene.

Analysis of worldwide nucleotide sequences of the second HVR and the complete *G* gene have suggested a high similarity between the ON1 and NA1 genotypes (p-distance = 0.029).[22] Therefore, phylogenetic tree analysis indicated that ON1 does not constitute a separate genotype from NA1. ON1 was within the NA1 genotype

despite showing distinct genetic characteristics, including the 72-nucleotide duplication. The lost duplication region in our RSV sequences was identified as belonging to the ON1 genotype, suggesting that genotype designation should be based on a systematic analysis of the phylogenetic tree regardless of the presence of a duplication insertion.

Compared with Vietnamese RSV sequences in the past, the ON1 genotype had a duplication region in strains in 2012[23] and 2013–2015.[16] These sequences were also referenced in our phylogenetic tree. Moreover, RSV strains in 2013–2015 were collected from five facilities representing the three regions of Viet Nam, while our sequences were only from northern Viet Nam. This suggests that ON1 strains in northern Viet Nam during 2017–2020 differed from those circulating during 2013–2015 in terms of the 72-nucleotide duplication. Tabatabai et al. mentioned the deletion of the 72-nucleotide duplication in genotype ON1 in their research on patients with haematological disease,[24] suggesting that ON1 strains without the duplication were not Vietnamese domestic strains of RSV, but rather they might be the consequence of imported infections.

The RSV-B BA genotype was defined by the 60-nucleotide duplication region in the second HVR of the *G* gene. RSV-B BA was first reported in 1999, and since 2015, BA9 has been the predominant genotype worldwide.[3] Research in Viet Nam from 2010 to 2020 has shown that BA9 circulates more commonly than other subgenotypes.[16,25] Additionally, the Vietnamese BA9 viruses had two different G protein lengths of 312 and 319 amino acids. During 2010–2011, this was reported not only in Viet Nam but also in other countries.[25,26]

This study has several limitations. First, virus samples were collected from children who were hospitalized with SARI. The prevalence of RSV in patients in the community was not analysed. Therefore, the results may not be representative of all RSV circulating in Viet Nam. In addition, we surveyed two sentinel hospitals that belong to Viet Nam's national influenza surveillance system, under the direction of the Ministry of Health. Although the number of specimens collected was enough for calculations, the two hospitals may not fully represent northern Viet Nam. Last, we primarily sequenced the second HVR of the *G* gene in RSV genomes. Several significant results were identified in the classification of the RSV-A subtype and in amino acid substitutions in RSV-B. Therefore, an extension of genomic sequencing is necessary to further analyse the molecular characteristics of RSV in northern Viet Nam.

The 28.02% RSV positivity rate among paediatric SARI cases in the present study was similar to rates found in Viet Nam previously. Children <1 year had the highest positivity rate. RSV circulated year-round and reached a peak of nearly 40% sample positivity during August–September every year. Both RSV-A and RSV-B were seen during 2017–2020, with RSV-B predominant in 2019 and RSV-A predominant in 2020. RSV-A sequences belonged to genotype ON1 in three lineages (ON1.1, ON1.2, ON1.3), and RSV-B sequences belonged to genotype BA9. Although all Vietnamese RSV-A samples in this study were genotype ON1, they did not have the 72-nucleotide duplication in the second HVR of the *G* gene, which differentiates them from findings in previous research in Viet Nam. This is the first report of the new ON1 genotype without the duplication in Viet Nam.

Acknowledgements

The authors thank all participants from the sentinel hospitals in Hanoi and Quang Ninh province for supporting the collection of specimens.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

Ethical approval for this study was given by the National Surveillance Programme of the Ministry of Health, Viet Nam (decision number: 4608/QD-BYT).

Funding

None.

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Epidemiology of latent tuberculosis infection in Japan-born and foreign-born children in Japan

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Objective: This study aims to compare the epidemiology of notifications of latent tuberculosis infection (LTBI) among Japan-born and foreign-born children in Japan between 2010 and 2020, and to assess the language used during LTBI case interviews with parents or caregivers of foreign-born children with LTBI during 2019.

Methods: Our study consisted of two parts: (1) an analysis of national data from the Japan Tuberculosis Surveillance (JTBS) system on the epidemiology of LTBI among Japan-born and foreign-born children in Japan, and (2) a survey of staff at public health centres that had registered at least one foreign-born child aged ≤14 years with LTBI. Data were extracted from the JTBS system for all children aged ≤14 years who were newly notified as having LTBI between 2010 and 2020, and analysed to determine trends, characteristics and treatment outcomes. Staff at relevant public health centres completed a self-administered survey.

Results: A total of 7160 Japan-born and 320 foreign-born children were notified as having LTBI between 2010 and 2020. Compared with Japan-born children, foreign-born children notified as having LTBI were more likely to be older, have their mother or sibling as their source of infection and have LTBI detected via a routine school health check. At case interviews, the use of language interpretation services was limited, even when both parents were non-Japanese. No interview was directly conducted with children themselves, not even with school-aged children.

Discussion: Foreign-born children and their parents may be unfamiliar with the system of testing for TB infection and the diagnosis of LTBI in Japan in school settings. Public health centres are required to provide education to patients and their families and care that takes into account cultural and linguistic differences. However, the provision of language support during case interviews may need strengthening.

Japan has a low burden of tuberculosis (TB), with 11 519 cases newly notified in 2021, for a rate of 9.2/100 000 population.[1] Although both the number of and the notification rate for TB cases have been steadily declining, the burden of TB among foreign-born persons has been increasing.[1] In 2021, the proportion of foreign-born persons among total TB cases was 11.8%; however, this proportion was 68.4% among those aged 15–24 years and 67.1% among those aged 25–34 years. Approximately 80% of cases of TB among foreign-born people in Japan occur in people from six Asian countries: China, Indonesia, Myanmar, Nepal, the Philippines and Viet Nam. Slightly more than one third are notified as having TB within 2 years of entering Japan.[1]

Latent tuberculosis infection (LTBI) is also notifiable in Japan, and as with active TB, once notified, its treatment is publicly funded and patients receive adherence support from public health centres (PHCs), which are responsible for registering and managing treatment support for persons diagnosed with TB and LTBI. The epidemiology of LTBI follows that of active TB, whereby the proportion of foreign-born persons notified with LTBI has continued to increase.[2] As most cases of LTBI among foreign-born persons are diagnosed among those aged 15–34 years, more attention has been paid to providing care and treatment for adults.[3,4] However, a consistent number of LTBI cases have been diagnosed among foreign-born children in Japan. Patient-centred care and treatment for children with LTBI involve not only

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Published: 23 November 2023
doi: 10.5365/wpsar.2023.14.4.1008

children themselves but also their parents or caregivers. However, little is known about the treatment or support provided to foreign-born children with LTBI in Japan.

The objectives of our study were to compare the epidemiology of LTBI notifications among foreign-born and Japan-born children in Japan between 2010 and 2020, and to assess the language used during LTBI case interviews with parents or caregivers of foreign-born children with LTBI during 2019.

METHODS

Our study consisted of two parts: (1) an analysis of national data from the Japan Tuberculosis Surveillance (JTBS) system about the epidemiology of LTBI among Japan-born and foreign-born children in Japan, and (2) a survey of staff at PHCs in Japan that had registered at least one foreign-born child aged ≤14 years with LTBI.

Analysis of notification data

LTBI has been notifiable in Japan since 2007. In 2017, the JTBS system underwent several major revisions, one of which enabled cohort analysis for all types of TB and LTBI, which was previously possible only for pulmonary TB.

Data were extracted from the JTBS system for all children aged ≤14 years who were newly notified with LTBI between 2010 and 2020. Treatment outcomes were extracted for those notified between 2016 and 2019. The period 2016–2019 was chosen for cohort analysis since treatment outcomes for LTBI became available only from 2016. Trends and characteristics were summarized descriptively using numbers and proportions. Treatment outcomes included "treatment success", "died", "treatment failed", "lost to follow up", "transferred out", "still in treatment" and "unknown". Appropriate variables were compared between foreign-born children and Japan-born children using the χ^2 test with Bonferroni corrections.

Survey of public health centres

All PHCs that had registered at least one foreign-born child aged ≤14 years with LTBI during 2019 were identified from the JTBS system. A self-administered survey was sent by email to TB personnel at each of these PHCs. The survey consisted of questions about the basic demographics of the child (or children), parents or caregivers, and the language used during the case interview with the parents or caregivers. Numerical and categorical variables were entered into Excel spreadsheets and analysed descriptively. R version 4.2.1 (R Core Team, Vienna, Austria) was used for all statistical analyses.

RESULTS

Analysis of notification data

Age and sex

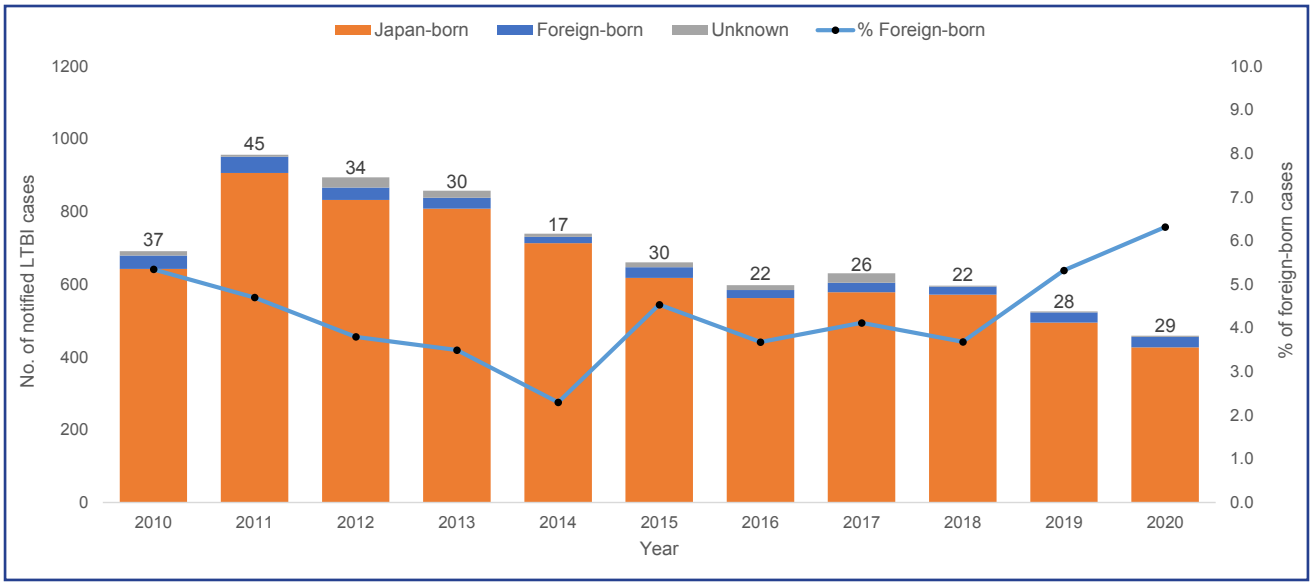
There were 7160 Japan-born and 320 foreign-born children notified with LTBI in Japan between 2010 and 2020. During this time, the annual number of case notifications in Japan declined, while the proportion of foreign-born children among all notified cases in children declined until 2014 and then increased (**Fig. 1**). In 2020, 29 cases of LTBI were notified among foreign-born children, which was 6.3% of all LTBI cases in children.

For Japan-born children, 37.1% (2663/7160) of notifications were among those aged <1 year, with the number per year declining with age (data not shown). For foreign-born children, 70% (224/320) of the notifications were for children aged 5–14 years (**Fig. 2**). The average age of foreign-born children notified with LTBI was 7.3 years (standard deviation [SD]: ± 4.4 years), while for Japan-born children it was 3.8 years (SD: ± 4.4 years) (data not shown).

Country of birth and year of entry to Japan for foreign-born children

The distribution of foreign-born children notified with LTBI by country of birth was 44.1% (141/320) from the Philippines, 12.2% (n = 39) from China and 6.0% (n = 19) from Viet Nam. The year of entry into Japan was recorded for 157 of the 320 foreign-born children notified with LTBI, and of these children, 25.5% (n = 40) were diagnosed in the same year as their arrival, 26.8% (n = 42) were diagnosed 1 year after arrival, 28.0% (n = 44) were diagnosed 2–4 years after arrival and 19.8% (n = 31) were diagnosed 5 years after arrival (data not shown).

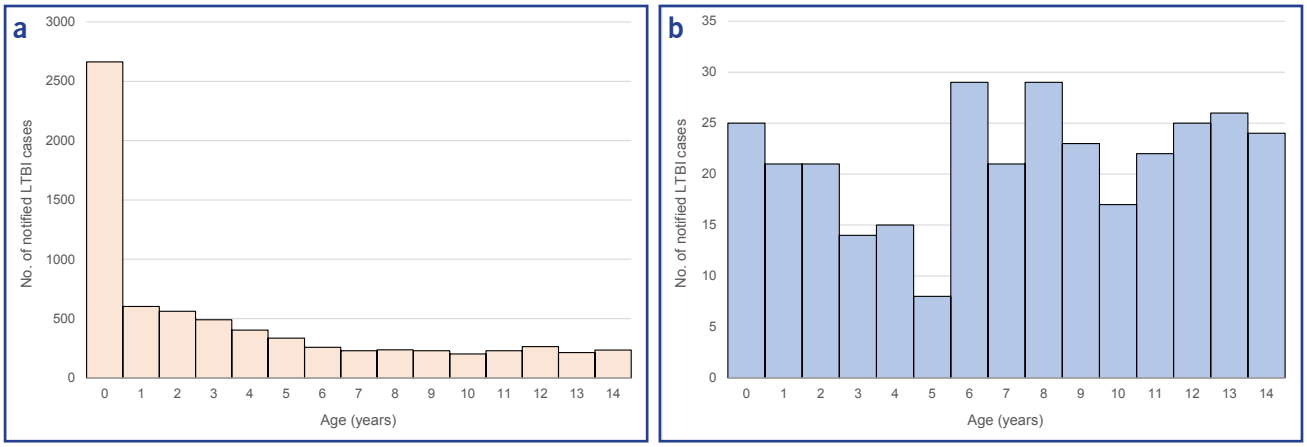
Fig. 1. **Number of new notifications of latent tuberculosis infection in children, by status as Japan-born or foreign-born and year, Japan, 2010–2020**



LTBI: latent tuberculosis infection.

Numbers above the columns indicate the number of newly notified LTBI cases among foreign-born children (dark blue).

Fig. 2. **Age distribution of children notified with latent tuberculosis infection among (a) Japan-born children (n = 7160) and (b) foreign-born children (n = 320), Japan, 2010–2020**



LTBI: latent tuberculosis infection.

Mode of detection and source of infection

The difference in distribution by mode of detection was statistically significant between Japan-born and foreign-born children notified with LTBI (**Table 1**; $P < 0.001$). For both Japan-born and foreign-born children, the majority of LTBI cases notified were contacts of patients with active TB in the same household. A higher proportion of foreign-born cases notified with LTBI were detected through routine school health check-ups compared with Japan-born case notifications (20.3% vs 0.5%, $P < 0.001$), and there were higher proportions of Japan-born cases diagnosed during other contact investigations and in clinical settings compared with foreign-born cases notified (19.4% vs 10.9%, $P = 0.002$ for other contact investigations; 14.0% vs 8.1%, $P = 0.004$ for clinical settings) (**Table 1**).

The reported source of infection was available for 40.6% (2909/7160) of Japan-born and 34.1%

(109/320) of foreign-born LTBI notifications in children, and the difference in distribution by source of infection between the two groups was statistically significant (**Table 1**; $P < 0.001$). The proportion of notifications with grandparents as the source of infection was higher for Japan-born patients (12.2% vs 5.3%, $P = 0.002$), while the proportions of notifications with mothers or siblings as the source of infection were higher for foreign-born patients (14.7% vs 9.4%, $P < 0.001$ for mothers; 3.4% vs 0.4%, $P < 0.001$ for siblings) (**Table 1**).

Treatment outcomes

Data on treatment outcomes between 2016 and 2019 were available for 2187 Japan-born and 99 foreign-born cases. Of these, 2162 Japan-born and 98 foreign-born cases had started LTBI treatment. The difference in treatment outcomes between the Japan-born and foreign-born cases was not statistically significant ($P = 0.979$), with 91.6% (1980/2162) of Japan-born and 89.8% (88/98) of foreign-born cases completing their treatment (**Table 2**).

Survey of public health centre staff

In 2019, 27 foreign-born children were notified with LTBI from 21 PHCs. A questionnaire survey was sent to these PHCs, of which 16 responded about 23 children. For all notifications, face-to-face case interviews were conducted upon registration by public health nurses with parents or caregivers; none of the interviews were conducted with the children themselves.

Table 3 summarizes the nationalities of parents or caregivers (as a foreign national or Japanese national) and the language used for the interview. Among the 10 children who had one foreign-born parent, the interview was conducted with the Japanese parent for four cases, with the non-Japanese parent for four cases and with Japanese-speaking relatives for two cases. Interviews with foreign-born parents were conducted in Japanese without an interpretation service for three cases and in Tagalog for one case (**Table 3**).

Among the 12 children whose parents were both foreign nationals, the interview was conducted in Japanese for seven cases. No interpretation assistance was provided, except for one case in which the public health nurse used a mobile translation application. An informational leaflet was used during the interview for one case, and the leaflet was in Japanese (**Table 3**). For three children, the interview was conducted in the parents' native language with the assistance of a friend or acquaintance, none of whom were professional medical interpreters. No translation apps or other tools were used. For the remaining two children, the language of the interview was not reported.

The final case had two Japanese parents and their interview was conducted in Japanese.

DISCUSSION

Our study is the first to explore the characteristics of foreign-born children notified with LTBI in Japan. Compared with Japan-born children, foreign-born children notified as having LTBI were more likely to be older, have their mother or sibling as their source of infection and have LTBI detected via a routine school health check. That the source of infection was a first-degree relative may be due to visa regulations, as foreign-born persons working in Japan are often permitted to bring only their spouse and child (or children) and, therefore, usually live in a nuclear family. The detection of LTBI in foreign-born children during school health checks is likely due to health workers following the manual on TB prevention in schools,[5] which recommends tuberculin skin testing (TST) or interferon-γ release assay (IGRA) testing for children from countries with a high TB burden upon entry to primary school and LTBI treatment for those who test positive.

In the majority of countries where these children were born (i.e. countries with a high TB burden), routine LTBI screening is not conducted. Rather, LTBI treatment is usually offered only to children aged ≤5 years who are household contacts of active TB cases, after active TB has been ruled out, but neither TST nor IGRA are usually conducted as part of household contact investigations.[6–8] Therefore, it is expected that many foreign-born children and their parents in Japan are unfamiliar with the experience of being tested for and diagnosed with LTBI, and even less familiar with this in school settings. Thus, PHCs are required to provide education to patients and families and care that accounts for these differences.

Furthermore, previous studies have shown that children may face different barriers to initiating and

Table 1. **Mode of detection and possible source of infection for notifications of latent tuberculosis infection in Japan-born and foreign-born children, Japan, 2010–2020**

Characteristic	No. (%) of children				*P*
	Japan-born		Foreign-born		
Total	7160	(100.0)	320	(100.0)	
Mode of detection					< 0.001
Household contact investigation	3718	(51.9)	156	(48.8)	
Other contact investigation	1390	(19.4)	35	(10.9)	
School health check-up	33	(0.5)	65	(20.3)	
Other mass health check-up	125	(1.7)	4	(1.3)	
Clinical setting	1001	(14.0)	26	(8.1)	
Other or unknown	893	(12.5)	34	(10.6)	
Source of infection					< 0.001
Mother	671	(9.4)	47	(14.7)	
Father	516	(7.2)	18	(5.6)	
Grandparent	875	(12.2)	17	(5.3)	
Sibling	32	(0.4)	11	(3.4)	
School	212	(3.0)	3	(0.9)	
Friends (outside school)	34	(0.5)	1	(0.3)	
Hospital	81	(1.1)	0	(0.0)	
Other	488	(6.8)	12	(3.8)	
Unknown	4251	(59.4)	211	(65.9)	

Table 2. **Treatment outcomes for notifications of latent tuberculosis infection in Japan-born and foreign-born children who had started treatment, Japan, 2016–2019**

Treatment outcome	No. (%) of children		*P*
	Japan-born	Foreign-born	
Total[a]	2162 (100.0)	98 (100.0)	0.979
Completed	1980 (91.6)	88 (89.8)	
Died	1 (0.0)	0 (0.0)	
Failed	3 (0.1)	0 (0.0)	
Lost to follow-up	58 (2.7)	3 (3.1)	
Transferred out	47 (2.2)	3 (3.1)	
Still on treatment	67 (3.1)	4 (4.1)	
Unknown	6 (0.3)	0 (0.0)	

[a] A total of 25 Japan-born children and one foreign-born child had not started treatment at the time of analysis; they are not included in the analysis of treatment outcomes.

completing LTBI care compared with adults.[9–11] Some barriers are patient-related factors, such as knowledge, concerns about side-effects and the school environment, which may be important to older children.[12,13] However, especially with younger children, treatment decisions are made by parents or caregivers, and their knowledge and perceptions regarding TB infection,[9] the adverse effects of medication[14,15] and medical contraindications to treatment,[16,17] personal health beliefs[13,18,19] and relationship with their children[20] have been shown to play important roles in treatment completion. In studies from lower-income countries, socioeconomic factors have also been identified as barriers to treatment completion, such as low monthly income,[9] high cost of transport[9] and conflicts with work schedules,[13] which all place burdens on parents or caregivers.

Our results showed that the case interviews at PHCs were largely conducted in Japanese, with limited use of language interpretation services, either in person or via an app, even when neither of the parents were Japanese nationals. Previous studies have repeatedly shown there is limited availability of medical interpretation services for foreign-born patients with[21,22] and without TB[23,24] in Japan and that language is a major barrier to accessing health care for foreign-born persons in Japan.

Table 3. **Language spoken during case interview for notifications of latent tuberculosis infection in foreign-born children, by nationality of their parents, Japan, 2019**

Nationality of parents	No.	Language of the interview		Translation app used
		Japanese	Other	
One parent is a foreign national	10	9	1	0
Both parents are foreign nationals[a]	12	7	3	1
Both parents are Japanese nationals	1	1	0	0
Total	23	17	6	1

[a] No information was provided about the language used during the interview for two of the cases.

Our study is not without limitations, and the most significant is that the study was limited to children notified with LTBI to the JTBS system. Therefore, it was unable to capture those children who, although eligible for LTBI treatment, were not notified and thus had not started treatment. The JTBS system also did not capture the total number of children tested for LTBI nor those who tested negative. A scoping review on care cascades for paediatric LTBI has identified several stages during which dropout from the cascade could occur.[24] In Japan, too, it is quite possible that some foreign-born children who are eligible never begin LTBI treatment. A comprehensive study to capture the care cascade for foreign-born children diagnosed with LTBI, both before travelling to and after entering Japan, is needed. Second, our survey specifically focused on the language spoken during the case interview and did not explore other issues, such as knowledge and attitudes towards and practices around LTBI between Japan-born and foreign-born children and their parents. Further studies are needed to explore these differences.

Our study indicated that foreign-born children notified with LTBI tended to be older, have their mother or sibling identified as the source of infection, and be detected via a routine school health check. The use of language interpretation services by health-care providers and the parents or caregivers of children diagnosed with LTBI in 2019 was limited. This may lead to poorer communication, knowledge and understanding about TB infection and the necessity for preventive treatment, as well as a lack of trust. Action is needed to address long-standing issues around language barriers for foreign-born persons, both children and adults, in Japan.

Acknowledgements

The authors acknowledge all public health centre staff who kindly gave their time to participate in the survey.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This study was approved by the Institutional Review Board of the Research Institute of Tuberculosis, Japan (reference no. RIT/IRB 2020-18).

Funding

This research was partially supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant no. 20K10491).

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Pathogens detected from patients with acute respiratory infections negative for SARS-CoV-2, Saitama, Japan, 2020

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Objective: During the coronavirus disease pandemic in Japan, all patients with respiratory symptoms were initially tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study describes the respiratory pathogens detected from patients who tested negative for SARS-CoV-2 at the Saitama Institute of Public Health from January to December 2020.

Methods: We performed pathogen retrieval using multiplex real-time polymerase chain reaction on samples from patients with acute respiratory diseases who tested negative for SARS-CoV-2 in Saitama in 2020 and analysed the results by age and symptoms.

Results: There were 1530 patients aged 0–104 years (1727 samples), with 14 pathogens detected from 213 patients (245 samples). Most pathogens were human metapneumovirus (25.4%, 54 cases), rhinovirus (16.4%, 35 cases) and *Mycoplasma pneumoniae* (13.1%, 23 cases). Human metapneumovirus, human coronavirus (but not NL63) and *M. pneumoniae* were detected in almost all age groups without any significant bias. Seasonal human coronaviruses, human metapneumovirus, *M. pneumoniae* and several other pathogens were detected until April 2020.

Discussion: Multiple respiratory pathogens were circulating during 2020 in Saitama, including SARS-CoV-2 and influenza viruses. We suggest introducing a system that can comprehensively monitor the regional prevalence of all viruses that cause acute respiratory infections.

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in a cluster of pneumonia cases in Wuhan, China,[1] with the illness later termed coronavirus disease (COVID-19). The number of cases rapidly increased worldwide, and there were repeated waves of the epidemic.[2,3] The first case in Japan was diagnosed on 15 January 2020.[4] In Saitama Prefecture, the first case was reported on 1 February 2020.

Respiratory viral infections mainly follow a seasonal pattern, with an annual increase and cessation of the epidemic in response to changes in temperature and humidity. However, the prevalence of seasonal respiratory viral infections significantly decreased during the COVID-19 pandemic, although the infections did not completely disappear.[5–8] Factors that caused this decrease in Japan included the implementation of personal protective measures – such as wearing masks, encouraging handwashing and avoiding crowds and confined spaces – and the change in attitudes of patients towards receiving medical care and the responses of medical institutions.[9–11] Unlike other countries, Japan did not mandate lockdowns of the population; instead, residents were encouraged to cooperate with the recommended countermeasures.

Saitama Prefecture is part of the Kanto region in eastern Japan. It is located north of Tokyo, covering an area of 3797 km^2. As of 1 January 2020, its population was 7 344 765, of whom 858 384 were aged <15 years and 1 934 994 were aged ≥65 years.[12]

In Japan, during the initial period of the COVID-19 pandemic, the clinical priority for patients with respiratory symptoms or fever was to test for SARS-CoV-2 to ensure patients received appropriate care and to prevent further transmission. Therefore, little is known about pathogens other than SARS-CoV-2 that caused respiratory tract infections during this period. In this study, we report on

[a] Saitama Institute of Public Health, Saitama, Japan.
Published: 15 December 2023
doi: 10.5365/wpsar.2023.14.4.1057

the detection of various respiratory pathogens in samples from patients who tested negative for SARS-CoV-2 at the Saitama Institute of Public Health from January to December 2020.

METHODS

Sample selection

Samples sent to the Saitama Institute of Public Health from 30 January to 31 December 2020 that tested negative for SARS-CoV-2 were included in the study. These comprised nasal, pharyngeal and nasopharyngeal swabs; nasal discharge; tracheal aspirate; alveolar lavage fluid; and sputum from people suspected to have COVID-19. As suspected influenza cases are usually confirmed via antigen testing at the clinical site and only positive samples are sent to public health reference laboratories, such specimens were assumed to contain influenza viruses and were excluded.[13]

The cases' symptoms and age and the date of sample collection were recorded on the laboratory forms collected with the samples. Samples from cases among children aged <15 years were included if they had at least one symptom of fever, upper respiratory tract infection or lower respiratory tract infection (LRTI) reported on the laboratory form; samples from cases aged ≥15 years were included if they had at least one symptom of LRTI reported on the laboratory form.

The number of pathogens detected was tabulated by sample collection date. Cases were divided into three age groups for evaluation, namely paediatric (<15 years), intermediate (≥15 years to <65 years), and elderly people (≥65 years), and the presence of LRTI was assessed in each group.

Pathogen detection procedures

RNA was extracted from specimens using an automated nucleic acid extraction system (EZ1 Advanced XL; QIAGEN, Venlo, Netherlands). Influenza A and B viruses, rhinovirus, adenovirus, enterovirus, human *Parechovirus*, human metapneumovirus, seasonal human coronaviruses (OC43, 229E, HKU1 and NL63), parainfluenza virus types 1–4, human respiratory syncytial virus (RSV), human bocavirus and *Mycoplasma pneumoniae* were detected using a multiplex real-time reverse transcription–polymerase chain reaction (rRT-PCR) kit (FTD Respiratory Pathogens 21 assay; Siemens Healthcare, Erlangen, Germany). If the samples were positive for influenza virus or RSV, the type or lineage was determined by rRT-PCR. If samples were positive for adenovirus, enterovirus or human *Parechovirus*, genotyping was performed using Sanger sequencing.

RESULTS

Detected pathogens

There were 1727 samples from 1530 cases tested during the study period. From these, 14 different pathogens were detected in 245 samples from 213 cases (13.9% of all eligible cases) (**Fig. 1**). Human metapneumovirus was the most frequently detected pathogen, detected in 67 samples from 54 cases (25.4% of 213 positive cases). Rhinovirus and *M. pneumoniae* were detected in, respectively, 38 samples from 35 cases (16.4% of 213) and 34 samples from 28 cases (13.1% of 213). These three pathogens accounted for more than half of the detected pathogens (54.9%, 117 cases). Seasonal human coronaviruses were detected in 58 samples from 50 cases (23.4% of 213 positive cases), and included OC43 detected in 24 samples from 22 cases (10.3%), 229E detected in 21 samples from 18 cases (8.4%), HKU1 detected in 11 samples from 8 cases (3.7%) and NL63 in 2 samples from 2 cases (0.9%).

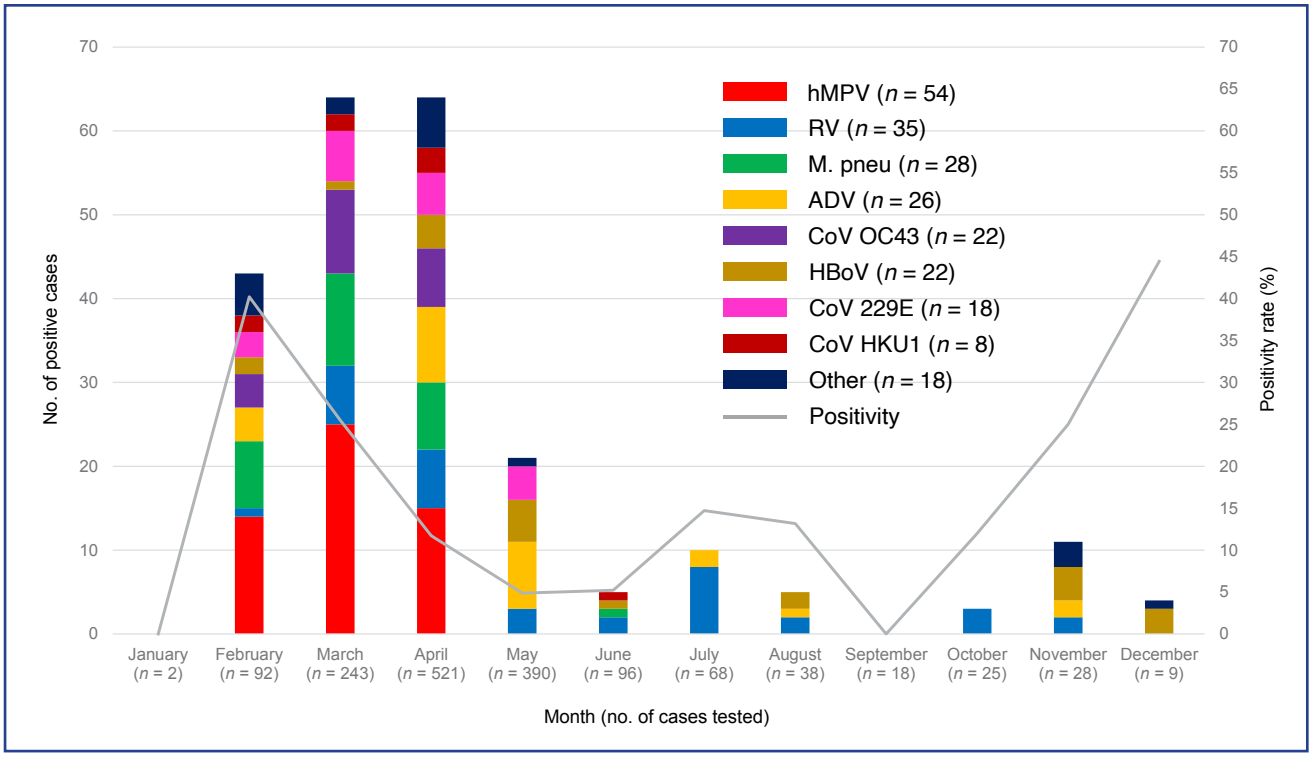
Seasonal differences

Testing was most frequently performed between February and May, with 81.4% of cases (1246/1530) tested during this period (**Fig. 1**). The highest positivity rate was observed in December (44.4%, 4/9 cases), followed by February (40.2%, 37/92 cases), March (25.5%, 62/243 cases) and November (25.0%, 7/28 cases). Human metapneumovirus, RSV, seasonal human coronaviruses and *M. pneumoniae* were detected most frequently between February and May (**Fig. 1**).

Detection of multiple pathogens

Two different pathogens were detected in 16 cases and three different pathogens were detected in one case (**Table 1**).

Fig. 1. **Number of individual respiratory pathogens detected and positivity rate in samples that tested negative for SARS-CoV-2, by month, Saitama, Japan, 2020[a]**



ADV: adenovirus; CoV: human coronavirus; HBoV: human bocavirus; hMPV: human metapneumovirus; M. pneu: *Mycoplasma pneumoniae*; RV: rhinovirus.

[a] The total number includes cases in which multiple pathogens were detected from the same person. The category Other includes respiratory syncytial virus, parainfluenza virus type 4, enterovirus, human coronavirus NL63, human *Parechovirus* and influenza virus.

Virus typing results

Adenoviruses were detected in 26 cases (12.1% of 213 positive cases). These included adenovirus type 1 (7 cases), followed by adenovirus type 2 (3 cases), adenovirus types 3 and 4 (2 cases each) and adenovirus type 6 (1 case); 11 cases could not be typed.

RSV was detected in seven cases (3.3% of 213): RSV-A in four cases (1.9%), RSV-B in two cases (0.9%), and one case could not be typed. Parainfluenza viruses were detected in four cases (1.9%), all type 4. Enterovirus was detected in two cases (0.9%), and coxsackievirus group A type 4 and coxsackievirus group B type 3 were detected in one case each (0.5% each). Human *Parechovirus* was detected in two cases (0.9%), both of which could not be typed. Influenza virus (B/Victoria lineage) was detected in one case (0.5%).

Detection results by age group

Patients' ages ranged from 0 to 104 years, with a median age of 69 years (interquartile range, 39–82 years); 904 patients were male (59.1%), 618 were female (40.4%) and the sex of eight patients was unknown (0.5%). The highest number of samples tested was from patients aged 80–89 years (22.5%, 343/1530), although the positivity rate was only 8.7% (30/343 cases) (**Table 2**).

Children aged 0–9 years had the highest positivity rate, with pathogens detected in 40.5% (77/190) of cases. This was followed by those aged 40–49 years (20.9%, 23/110 cases), 10–19 years (20.4%, 11/54 cases) and 30–39 years (18.8%, 18/96 cases).

Among those aged 0–9 years, the most frequently detected pathogens were rhinovirus (68.5%, 24/35 cases), adenovirus (65.4%, 17/26 cases), human bocavirus (95.5%, 21/22 cases) and RSV (42.9%, 3/7 cases), and enterovirus and human *Parechovirus* (2 cases each) and influenza B virus (1 case) were detected only in this age group.

M. pneumoniae was most frequently detected among those aged 30–39 years (32.1%, 9/28 cases), and human metapneumovirus was most frequently detected

Table 1. **Cases with multiple respiratory pathogens detected in samples that tested negative for SARS-CoV-2, Saitama, Japan, 2020**

Case no.	Respiratory pathogens detected and type	Patient age group (years)	LRTI symptoms	Collection month
1	Human bocavirus Human *Parechovirus*, nt Adenovirus, nt	0–9	–	November
2	Human bocavirus Coxsackievirus A4	0–9	–	May
3	Human bocavirus Coronavirus 229E	0–9	+	November
4	Human bocavirus Adenovirus type 1	0–9	+	May
5	Human bocavirus Human *Parechovirus*, nt	0–9	–	November
6	Human bocavirus Human metapneumovirus	0–9	+	March
7	Human bocavirus Rhinovirus	0–9	+	April
8	Adenovirus type 3 Human metapneumovirus	0–9	+	April
9	Adenovirus, nt Respiratory syncytial virus type B	0–9	–	March
10	Adenovirus type 3 Influenza virus B Victoria	0–9	–	April
11	Coronavirus OC43 *Mycoplasma pneumoniae*	0–9	+	March
12	Adenovirus, nt *Mycoplasma pneumoniae*	0–9	+	February
13	Coronavirus HKU1 Parainfluenza virus type 4	20–29	+	February
14	Coronavirus OC43 *Mycoplasma pneumoniae*	30–39	+	February
15	Adenovirus, nt Human metapneumovirus	40–49	+	February
16	Coronavirus OC43 Human metapneumovirus	40–49	+	March
17	Coronavirus 229E Respiratory syncytial virus type B	80–89	+	March

LRTI: lower respiratory tract infection; nt: not typed.

among those aged 40–49 years (24.0%, 13/54 cases). Seasonal human coronaviruses (OC43, 229E, HKU1 and NL63) were most frequently detected among those aged 80–89 years (32.0%, 16/50 cases). Parainfluenza virus was most frequently detected among those aged ≥90 years (50.0%, 2/4 cases) (**Table 3**).

Classification by age group and symptoms

Based on classifications by age group and the presence of LRTI, the positivity rate observed in the paediatric group with LRTI was 52.0% (39/75 cases); that in the paediatric group without LRTI was 28.6% (46/161 cases); that in patients with LRTI in the intermediate group was 15.9% (69/433 cases) and that in elderly people was 6.9% (59/861 cases).

Human metapneumovirus and three seasonal human coronaviruses (OC43, HKU1 and NL63) were detected only in patients with LRTI, whereas rhinovirus, adenovirus and human bocavirus were more frequently detected in patients without LRTI (**Table 4**). *M. pneumoniae* was more

Table 2. **Number of cases, number of samples and positivity rate for respiratory pathogens among cases that tested negative for SARS-CoV-2, by age group, Saitama, Japan, 2020**

Patient age group (years)	No. of cases	No. of samples	Proportion of total cases (%)	No. of positive cases	Positivity rate (%)
0–9	190	192	12.4	77	40.5
10–19	54	55	3.5	11	20.4
20–29	52	62	3.4	9	17.3
30–39	96	116	6.3	18	18.8
40–49	110	132	7.2	23	20.9
50–59	113	136	7.4	10	8.8
60–69	162	185	10.6	14	8.6
70–79	294	339	19.2	14	4.8
80–89	343	389	22.5	30	8.7
≥90	116	121	7.6	7	6.0
Total	1530	1727	100	213	13.9

Table 3. **Number of positive cases and number of samples of respiratory pathogens from cases that tested negative for SARS-CoV-2, by age group and pathogen, Saitama, Japan, 2020**

Patient age group (years)	No. of positive cases (no. of samples) by pathogen														
	hMPV	RV	ADV	CoV OC43	HBoV	CoV 229E	CoV HKU1	RSV	PIV4	EV	HPeV	CoV NL63	Influenza virus	*M. pneumoniae*	Negative
0–9	9 (9)	24 (24)	17 (18)	1 (1)	21 (21)	3 (3)	1 (1)	3 (3)	1 (1)	2 (2)	2 (2)	1 (1)	1 (1)	4 (5)	113 (113)
10–19	1 (2)	2 (2)	0	0	0	0	0	0	0	0	0	0	0	8 (8)	43 (43)
20–29	3 (4)	1 (1)	1 (1)	1 (1)	0	1 (1)	1 (2)	0	1 (1)	0	0	0	0	1 (2)	43 (50)
30–39	3 (4)	2 (3)	0	2 (3)	0	1 (1)	1 (1)	0	0	0	0	1 (1)	0	9 (12)	78 (92)
40–49	13 (17)	1 (1)	1 (1)	3 (3)	0	2 (3)	1 (2)	0	0	0	0	0	0	4 (5)	87 (102)
50–59	7 (8)	0	1 (1)	0	0	1 (2)	0	0	0	0	0	0	0	1 (1)	103 (124)
60–69	5 (7)	1 (1)	1 (1)	4 (4)	0	2 (2)	0	1 (2)	0	0	0	0	0	0	148 (168)
70–79	2 (3)	3 (5)	3 (3)	2 (2)	0	0	2 (3)	1 (1)	0	0	0	0	0	1 (1)	281 (321)
80–89	9 (10)	1 (1)	2 (2)	8 (9)	1 (1)	6 (7)	2 (2)	2 (2)	0	0	0	0	0	0	313 (356)
≥90	2 (3)	0	0	1 (1)	0	2 (2)	0	0	2 (2)	0	0	0	0	0	108 (113)
Total[a]	54 (67)	35 (38)	26 (27)	22 (24)	22 (22)	18 (21)	8 (11)	7 (8)	4 (4)	2 (2)	2 (2)	2 (2)	1 (1)	28 (34)	1317 (1482)

ADV: adenovirus; CoV: human coronavirus; EV: enterovirus; HBoV: human bocavirus; hMPV: human metapneumovirus; HPeV: human *Parechovirus; M. pneumoniae: Mycoplasma pneumoniae;* PIV4: parainfluenza virus type 4; RSV: respiratory syncytial virus; RV: rhinovirus.

[a] Columns do not add up to the total as multiple pathogens were detected in some cases and samples.

Table 4. **Number of cases, number of samples and positivity rate for respiratory pathogens among people who tested negative for SARS-CoV-2, by age group and presence of lower respiratory tract infection, Saitama, Japan, 2020**

Age group	LRTI symptoms	No. of cases tested (no. of samples)	No. of positive cases (no. of samples)	Positivity rate (%)	No. of positive cases (no. of positive samples) by pathogen														
					hMPV	RV	ADV	CoV OC43	HBoV	CoV 229E	CoV HKU1	RSV	PIV	EV	HPeV	CoV NL63	Influenza virus type B	*M. pneumoniae*	Negative
0–14	+	75 (77)	39 (41)	52.0	9 (9)	9 (9)	6 (7)	1 (1)	7 (7)	2 (2)	1 (1)	2 (2)	0	0	0	1 (1)	0	8 (9)	36 (36)
	–	161 (161)	46 (46)	28.6	0	17 (17)	11 (11)	0	14 (14)	1 (1)	0	1 (1)	1 (1)	2 (2)	2 (2)	0	1 (1)	2 (2)	115 (115)
Total[a]		236 (238)	85 (87)	36.0	9 (9)	26 (26)	17 (18)	1 (1)	21 (21)	3 (3)	1 (1)	3 (3)	1 (1)	2 (2)	2 (2)	1 (1)	1 (1)	10 (11)	151 (151)
15–64	+	433 (513)	69 (89)	15.9	28 (36)	4 (5)	4 (4)	9 (10)	0	5 (7)	3 (5)	1 (2)	1 (1)	0	0	1 (1)	0	17 (22)	364 (424)
≥65	+	861 (976)	59 (69)	6.9	17 (22)	5 (7)	5 (5)	12 (13)	1 (1)	11 (11)	4 (5)	3 (3)	2 (2)	0	0	0	0	1 (1)	802 (907)
Total[a]		1294 (1489)	128 (158)	9.9	45 (58)	9 (12)	9 (9)	21 (23)	1 (1)	15 (18)	7 (10)	4 (5)	3 (3)	0	0	1 (1)	0	18 (24)	1166 (1331)

ADV: adenovirus; CoV: human coronavirus; EV: enterovirus; HBoV: human bocavirus; hMPV: human metapneumovirus; HPeV: human *Parechovirus*; LRTI: lower respiratory tract infection; *M. pneumoniae*: *Mycoplasma pneumoniae*; PIV: parainfluenza virus; RSV: respiratory syncytial virus; RV: rhinovirus.

[a] Totals do not include multiple pathogens detected from the same case and sample.

common in children with LRTI and in the intermediate age group. Although a degree of difference was observed in the positivity rate between the elderly and intermediate age groups, there was no marked difference in the pathogens detected, except *M. pneumoniae*.

DISCUSSION

We detected a variety of pathogens in samples from patients who had acute respiratory symptoms but had tested negative for SARS-CoV-2 in 2020 in Saitama, Japan. Public health and social measures implemented to prevent SARS-CoV-2 transmission might have changed the circulation of seasonal infectious diseases in various regions,[5–8] and the COVID-19 pandemic itself might have suppressed the spread of other respiratory viruses.[14]

The detection of non-SARS-CoV-2 respiratory pathogens in children suggests that other viruses – such as rhinovirus, adenovirus and human bocavirus – should also be considered in the differential diagnosis of upper respiratory tract infections in children. Differences in viral stability between non-enveloped and enveloped viruses, such as seasonal human coronaviruses and human metapneumovirus, may affect differences in detection.[15] Additionally, non-enveloped viruses have been detected in paediatric

patients and are believed to circulate in immunologically susceptible age groups, raising concerns about outbreaks in the future when nonmedical interventions, such as mask-wearing, are lifted.[5–8] Seasonal human coronaviruses have been reported as being more prevalent during winter and early spring;[16] however, in this study, they were not detected during winter in the second half of 2020.

Although weekly reports of the viruses isolated and the detection of cases of upper and lower respiratory inflammation in Japan indicated that respiratory infections spread throughout 2019,[17,18] the decrease in the number of pathogens detected after June 2020 can be partly attributed to the decline in samples received at the public health laboratory. The Ministry of Health, Labour and Welfare issued a notice on 2 June 2020 allowing PCR testing of saliva samples for SARS-CoV-2,[19] after which the number of respiratory tract samples sent to our laboratory drastically decreased.

During the study period, testing for SARS-CoV-2 was limited and controlled by legislation or institute-specific rules.[20,21] In addition, when a patient suspected of having COVID-19 tested negative for SARS-CoV-2, the need for further pathogen testing was determined by the examining doctor. Not knowing about the circulation of respiratory pathogens other than SARS-CoV-2 during this period is problematic for respiratory pathogen surveillance in Japan.[11,22]

By testing patients with suspected COVID-19 for other viruses that cause acute respiratory infections, we have provided a summary of infections caused by other viruses with similar symptoms. Critical surveillance gaps may be filled by having a more systematic process through which public research institutions such as ours can test samples from cases with influenza-like illness and acute respiratory infections to provide information about prevalence, contagiousness and severity of the disease.[23] We propose there is a need to introduce a system that can comprehensively monitor the regional prevalence of all viruses that cause acute respiratory infections, and we hope that the results of this study will be used as a resource to improve surveillance.

Acknowledgments

The authors express their deepest gratitude to Dr Kiyosu Taniguchi for his insightful advice and careful guidance throughout the preparation of this paper. The views expressed are those of the authors and are not necessarily those of the staff at the Saitama Institute of Public Health. The authors also thank Enago (www.enago.jp) for English-language review.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

This study was approved by the ethical review committee of the Saitama Institute of Public Health.

Funding

None.

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COVID-19 clusters in Malaysia: characteristics, detection methods and modes of early transmission

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Objective: Effective prevention and control measures are essential to contain outbreaks of infectious diseases, such as coronavirus disease (COVID-19). Understanding the characteristics of case clusters can contribute to determining which prevention and control measures are needed. This study describes the characteristics of COVID-19 case clusters in Malaysia, the method used to detect a cluster's index case and the mode of early transmission, using the seven cluster categories applied in Malaysia.

Methods: This cross-sectional study collected publicly available data on COVID-19 clusters occurring in Malaysia from 1 March 2020 to 31 May 2021. The characteristics of cases were described by category, and their associations with several outcomes were analysed. Descriptive analyses were performed to explore the method used to detect the index case and the mode of early transmission, according to cluster category.

Results: A total of 2188 clusters were identified. The workplace cluster category had the largest proportion of clusters (51.5%, 1126/2188 clusters), while the custodial settings category had the largest median cluster size (178 cases per cluster) and longest median duration of cluster (51 days). The high-risk groups category had the highest mortality. There were significant differences in cluster size, duration and rate of detection across the categories. Targeted screening was most commonly used to detect index cases, especially in custodial settings, and in imported and workplace clusters. Household–social and social–workplace contacts were the most common modes of early transmission across most categories.

Discussion: Targeted screening might effectively reduce the size and duration of COVID-19 clusters. Measures to prevent and control COVID-19 outbreaks should be continually adjusted based on ongoing assessments of the unique context of each cluster.

Coronavirus disease (COVID-19) was first detected in Malaysia on 25 January 2020, with the first COVID-19 cluster recorded approximately 1 month later, on 1 March 2020.[1,2] The Malaysian Ministry of Health defined a COVID-19 cluster as "a concentration of infections in the same area at the same time".[3]

Identifying case clusters early in an outbreak is crucial because it allows health authorities to link cases to the same source, trace close contacts and isolate all identified cases (i.e. the clusters of cases stage).[4–6] When cases become widespread in a community and are not clearly linked to a source of infection (i.e. during community transmission) and when an increasing number of severe cases require hospitalization, the health-care system can become overburdened, and so its capacity to follow up on new clusters may be limited.[6] Thus, identifying clusters early and implementing containment measures to stop further transmission can limit the spread of an outbreak.

Categorizing clusters of COVID-19 cases and analysing their characteristics allows policy-makers to design targeted public health measures to control outbreaks in key areas and populations.[7] Each country has a different classification system for case clusters. For instance, a study from China classified clusters into combinations of the following categories: family, social, travel, work, community or vehicle.[8] In Malaysia, COVID-19 clusters are divided into seven categories: community, custodial settings, educational institutions, high-risk groups, imported, religious organizations and workplace, based on either the profile or the locality of the index case when the cluster was detected.[3,5]

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Published: 29 November 2023
doi: 10.5365/wpsar.2023.14.4.1058

Clusters in different categories behave distinctively due to differences in context, setting and demographics and, therefore, different categories require different containment approaches.[7]

Several local studies in Malaysia[4,9,10] described the transmission and management of selected clusters of COVID-19 cases, but none has summarized the characteristics of all of the clusters. Understanding the characteristics of the different categories is critical to ensuring that policy-makers can tailor preventive measures – such as vaccination programmes, targeted screening, and health promotion and education programmes – to contain the clusters of cases stage.[6,11] Knowing the origin of a cluster and how the infection was transmitted facilitates the selection of mitigation measures. It also serves as a learning point to strengthen the health system to respond to future outbreaks.

Hence, this study aims to describe the characteristics, detection methods and modes of early transmission of COVID-19 cases using Malaysia's seven categories of clusters. To our knowledge, this is the first study of COVID-19 clusters in Malaysia that attempts to summarize the methods used to detect the index case and modes of early transmission for different categories of clusters and explore the relationships between the characteristics of the clusters.

METHODS

Sources of data

This cross-sectional study included clusters of COVID-19 cases in Malaysia that were publicly reported from 1 March 2020 to 31 May 2021. Detailed information during the earliest stages of the pandemic was published up until 31 May 2021, and this included the method used to detect the index case and the modes of early transmission. Subsequently, the public reporting format was changed as the number of cases increased. Data were collected from the following publicly available sources: COVID-19 data on GitHub,[1] the Ministry of Health COVID-19 website[12] and the Ministry's social media accounts (e.g. Facebook and Twitter), other government agencies and their official websites, and local news portals (**Box 1**).

For every COVID-19 index case identified, the Ministry would perform contact tracing and epidemiological investigations before officially reporting the cluster to the public.[4] Clusters were declared to have ended after no new cases were detected[9] or the last person detected within the cluster had been asymptomatic for 28 consecutive days (i.e. double the incubation period of COVID-19).[13] If this information was unavailable, the authors deemed the cluster end date to be 28 days after the date of onset of the last symptom, as per the definition above.

The data collected included cluster size, duration, number of deaths, number of COVID-19 diagnostic tests

Box 1. **Sources of data on COVID-19 clusters reported in Malaysia, 1 March 2020–31 May 2021**

Official social media accounts and websites of the Ministry of Health and other governmental agencies

- https://github.com/MoH-Malaysia/covid19-public
- https://covid-19.moh.gov.my/
- https://www.facebook.com/kementeriankesihatanmalaysia
- https://twitter.com/kkmputrajaya
- https://kpkesihatan.com/
- https://www.moh.gov.my/
- https://t.me/s/cprckkm

News portals and other websites

- https://www.thestar.com.my/
- https://www.nst.com.my/
- https://www.astroawani.com
- https://www.bharian.com.my/
- https://www.hmetro.com.my/
- https://www.malaysiakini.com/
- https://www.theedgemarkets.com/
- https://www.sinarharian.com.my/
- https://hpupm.upm.edu.my/

performed, detection method and mode of transmission. The case–fatality rate and test positivity rate were then calculated. The test positivity rate was defined as a proportion: the total number of cases who tested positive for COVID-19 in a particular cluster divided by the total number of individuals screened for the particular cluster. Clusters were put into one of the seven categories described above. The four categories used to assess the detection method were: targeted screening, symptomatic screening, self-screening (i.e. screening voluntarily undertaken by individuals and organizations) and not reported (**Table 1**).

The mode of early transmission for a cluster was defined as the reported transmission mode for the index case or for earlier generations of cases that infected other cases within the cluster, beginning from the date the index case was detected until the official start date of the cluster. The category assigned by the research team was based on descriptions and illustrations of clusters provided by the Ministry of Health. The mode of early transmission could be a single mode or a combination of modes. For example, the household–social category indicated that cases were spread through household and social contacts.

Analyses

The characteristics of each cluster were assessed and the cluster was assigned to one of the seven categories. Whether the data fit a normal distribution was explored using histograms and acceptable skewness and kurtosis values of between -2 and +2.[14] The characteristics were summarized using frequencies and the percentage of occurrence for categorical data, and using medians and interquartile ranges (IQRs) for continuous data. We also described the detection methods and modes of early transmission among COVID-19 clusters using the categories.

The differences between the seven categories (i.e. total cases/cluster size, duration and test positivity rate) were analysed using the Kruskal–Wallis test and, subsequently, Dunn's test because the continuous data were not normally distributed. The level of significance was $P < 0.05$. All analyses were performed using R software (version 4.2.1, R Core Team, Vienna, Austria) and Microsoft Excel (2019).

RESULTS

Description of COVID-19 clusters

From 1 March 2020 until 31 May 2021, there were 2188 COVID-19 clusters reported in Malaysia, comprising 243 377 cases. About half of the clusters (n = 1126, 51.5%), comprising 145 018 cases, originated in a workplace, and one quarter (n = 548, 25.0%), comprising 37 105 cases, occurred in the community (**Table 2**).

The clusters with the largest median size were those in custodial settings (median: 178 cases; IQR: 410 cases), despite these comprising only 2.8% (62/2188) of the reported clusters. Cluster size was associated with cluster category ($P < 0.001$), with statistically significant differences in the median cluster size between all pairs of categories, except for community–educational institution, community–high-risk group, high-risk group–imported and religious organization–workplace (**Table 3**). Thus, clusters in custodial settings and religious organizations were significantly larger than those in the other categories, while clusters from imported cases were significantly smaller than in other categories.

Clusters in custodial settings had the longest median duration (median: 51 days; IQR: 45.5 days), while imported clusters had the shortest duration (median: 33 days; IQR: 13 days) (**Table 2**). The duration of clusters was significantly different between categories ($P < 0.001$), with the duration of clusters in custodial settings being significantly longer than in all other categories in the paired analysis. In contrast, the duration of imported clusters was significantly shorter than that in all other categories (**Table 2**).

The test positivity rate was highest for clusters in custodial settings (median: 30.3%; IQR: 33.3%), while the lowest test positivity rates were in imported clusters (median: 17.1%; IQR: 25.5%) and clusters in educational institutions (median: 17.3%; IQR: 22.8%). The test positivity rate was significantly different between categories ($P < 0.001$), with statistically significant differences in median test positivity rates for the following pairs: custodial setting–community, custodial setting–educational institution, custodial setting–imported,

Table 1. **Definitions of categories, detection methods and modes of transmission used for clusters of COVID-19 cases, Malaysia, 1 March 2020–31 May 2021**

Variable	Definition
Cluster category[3]	Community: clusters originating from activities in the community, including at home, at large communal dwellings (i.e. longhouses), and during festivals, funerals, receptions and weddings
	Custodial setting: clusters originating in any custodial setting, including prisons, lock-ups and immigration detention depots
	Educational institution: clusters originating in Ministry of Education institutions, higher education institutions and educational institutions not affiliated with the Ministry of Education
	High-risk group: clusters originating among high-risk groups in aged-care facilities, government and private hospitals, nurseries, dialysis centres and welfare centres
	Imported: clusters in which the index case contracted COVID-19 in another country
	Religious organizations: clusters originating from religious activities
	Workplace: clusters originating in places of employment
Total no. of cases (i.e. cluster size)	The total number of people testing positive for COVID-19 who were linked to a particular cluster when it was reported to have ended
Duration	The number of days between the date on which a particular cluster was officially reported by the Ministry of Health and the date on which it was declared to have ended
Case–fatality rate (%)	The proportion of cases in a cluster who died from COVID-19 divided by the total number of COVID-19 cases in the cluster
Detection method	The method used to detect the index case for each cluster
	Targeted screening: refers to planned screening at points of entry; for contacts of cases; individuals applying for interstate or interdistrict travel permits within Malaysia when Movement Control Orders were in effect; workers at wet markets; health-care workers; patients prior to surgery and admission to hospital; during postmortem examinations; for individuals with influenza-like illness or severe acute respiratory infection; people in areas under an Enhanced Movement Control Order; staff and residents at aged-care facilities; staff and inmates in custodial facilities, including prisons, immigration detention centres, drug rehabilitation centres and other custodial settings; workers at construction sites; security guards; individuals in communities at risk of COVID-19, including those in close contact with COVID-19 cases; workers and staff at factories; staff and students at educational facilities; staff and customers at shopping malls and supermarkets; and employees at workplaces that did not fall under any other workplace screening mechanism in this list
	Symptomatic testing: refers to testing of individuals who have symptoms of COVID-19
	Self-screening: refers to testing voluntarily performed by individuals or organizations
	Not reported: the detection method was not made publicly available
Mode of early transmission	Custodial setting: includes clusters spread within or from prisons, immigration detention centres, drug rehabilitation centres and other custodial settings; includes transmission among inmates and staff
	Educational institution: includes clusters spread within or from all educational institutions, such as primary, second and tertiary schools, preschools and nurseries; includes transmission among staff and students
	Household: refers to spread through household contacts who live under the same roof, including in workers' accommodation, dormitories and hostels; this category excludes aged-care homes
	Social: includes transmission through gatherings at social, festive and cultural events, and through other types of community and residential areas, such as contacts among neighbours
	Workplace (general): includes transmission among local workers, foreign workers and in the place of employment
	Others: refers to modes of transmission that are not covered by the categories described above
	Not reported: refers to modes of early transmission that were not announced or not specified, such as a close contact

Table 2. **Characteristics of clusters of COVID-19 cases, Malaysia, 1 March 2020–31 May 2021 (*N* = 2188)**

Cluster category	No. (%) of clusters	Total no. (%) of COVID-19 cases	Total no. (%) of deaths	Median no. (IQR) of cases per cluster[a]	Median no. (IQR) of days duration[b]	Median % (IQR) test positivity rate[c]
Workplace	1126 (51.5)	145 018 (59.6)	121 (0.08)	44 (78)	39 (17)	25.0 (28.2)
Community	548 (25.0)	37 105 (15.2)	213 (0.6)	33 (48)	39 (14)	19.9 (28.6)
Educational institution	184 (8.4)	12 722 (5.2)	17 (0.13)	35.5 (55.3)	39 (13.3)	17.3 (22.8)
Religious organization	136 (6.2)	15 342 (6.3)	146 (0.95)	54 (92)	41 (16)	24.5 (27.2)
High-risk group	103 (4.7)	3858 (1.6)	108 (2.8)	26 (26.5)	37 (15)	21.8 (40.0)
Custodial setting	62 (2.8)	27 232 (11.2)	23 (0.08)	178 (410)	51 (45.5)	30.3 (33.3)
Imported	29 (1.3)	2100 (0.9)	13 (0.6)	8 (42)	33 (13)	17.1 (25.5)
Total no. of clusters	2188 (100)	243 377 (100)	641 (0.3)	39 (68)	39 (16)	23.0 (29.1)

IQR: interquartile range.

[a] *H* statistic for cluster size = 116.85, df = 6, *P* <0.001.

[b] *H* statistic for cluster duration = 38.71, df = 6, *P* <0.001.

[c] *H* statistic for positivity rate = 51.08, df = 6, *P* <0.001.

educational institution–religious organization, educational institution–workplace, community–workplace and imported–workplace (**Table 3**).

There were 641 deaths, with an average case–fatality rate per cluster of 0.26% (**Table 2**). High-risk groups had the highest case–fatality rate (2.8%), but the majority of clusters (*n* = 1881, 86%) had no deaths.

Detection methods

Targeted screening detected 40.7% (*n* = 890) of all clusters, and it detected 79.0% (49/62) of clusters in custodial settings, 89.7% (26/29) of clusters among imported cases and 51.9% (585/1126) in workplaces. In contrast, more than half of clusters in educational institutions, the community and high-risk groups were detected through screening of individuals who were symptomatic (**Fig. 1a**).

Among the clusters in custodial settings, the largest median number of cases was 368, identified through symptomatic screening, which was threefold higher than for targeted screening (124 cases) (**Fig. 1b**). The median numbers of cases in other categories were similar across the different detection methods. Similarly, clusters in custodial settings, where the index case was detected through symptomatic screening, had a median duration of 72 days, 57% longer than for clusters detected using targeted screening (46 days). The duration for other categories was similar (approximately 40 days) (**Fig. 1c**).

Mode of transmission

The most frequent modes of transmission were through household–social, workplace and social contacts, contributing to approximately two thirds of all COVID-19 clusters in Malaysia (**Table 4**). The transmission mode for most clusters in custodial settings was within the setting (59.7%, 37/62), with 20.9% (13/62) of cases transmitted through social interactions. About 45.1% (508/1126) of workplace clusters were transmitted within workplaces, with another 15.4% (173/1126) and 16.7% (188/1126) transmitted through household–social and social contacts, respectively. Furthermore, between 32% and 75% of clusters in the community, educational institutions, high-risk groups, religious organizations and the workplace were transmitted through household–social and social contacts (**Table 4**).

DISCUSSION

In this study of COVID-19 in Malaysia reported from 1 March 2020 to 31 May 2021, the largest number of clusters occurred in the workplace, while custodial settings had the largest median cluster size and longest median

Table 3. **Results from the post-hoc analysis using Dunn's test for comparisons between cluster category and size, duration and positivity rate, Malaysia, 1 March 2020–31 May 2021**

Cluster category pair	Cluster size vs cluster category		Cluster duration vs cluster category		Positivity rate vs cluster category	
	Z	Adjusted *P*	*Z*	Adjusted *P*	*Z*	Adjusted *P*
Community–custodial setting	-7.608	<0.001	-4.996	0.000	-3.478	0.003
Community–educational institution	-1.448	0.155	-0.174	0.862	1.446	0.194
Community–high-risk group	1.961	0.058	1.161	0.304	-0.897	0.431
Community–imported	3.106	0.003	2.551	0.025	1.153	0.308
Community–religious organization	-4.315	<0.001	-1.774	0.133	-2.012	0.093
Community–workplace	-5.691	<0.001	-0.557	0.638	-5.045	<0.001
Custodial–educational institution	6.102	<0.001	4.458	<0.001	4.013	<0.001
Custodial setting–high- risk group	7.652	<0.001	4.940	<0.001	2.300	0.056
Custodial setting–imported	7.162	<0.001	5.136	<0.001	3.048	0.010
Custodial setting–religious organization	3.955	<0.001	3.259	0.004	1.783	0.130
Custodial setting–workplace	5.542	<0.001	4.909	<0.001	1.559	0.179
Educational institution–high-risk group	2.714	0.009	1.133	0.300	-1.784	0.142
Educational institution–imported	3.580	0.001	2.507	0.026	0.483	0.629
Educational institution–religious organization	-2.565	0.014	-1.372	0.223	-2.795	0.018
Educational institution–workplace	-2.176	0.036	-0.179	0.901	-4.854	<0.001
High-risk group–imported	1.813	0.077	1.719	0.138	1.503	0.186
High-risk group–religious organization	-4.778	<0.001	-2.256	0.046	-0.739	0.483
High-risk group–workplace	-4.926	<0.001	-1.493	0.190	-1.617	0.171
Imported–religious organization	-4.915	<0.001	-3.207	0.004	-2.017	0.102
Imported–workplace	-4.723	<0.001	-2.739	0.016	-2.565	0.031
Religious organization–workplace	1.288	0.198	1.553	0.181	-0.771	0.487

duration. The highest mortality rate was in the high-risk groups. Targeted screening was the most frequently used detection method for clusters, especially for custodial settings, among imported cases and for workplace clusters. The most common modes of early transmission across all categories were through household–social, social and workplace contacts, except for the custodial setting category, where transmission primarily occurred through contact among prisoners.

Workplace clusters contributed the largest number of cluster cases in Malaysia, accounting for 51.5% of these cases. This suggests that ensuring physical distancing and well-ventilated workplaces are essential to prevent transmission in this setting.[15] In Malaysia, overcrowded living and working environments for foreign workers were reported to be one contributor to high transmission in the workplace at the beginning of the pandemic.[9,16,17] To mitigate the situation, the Malaysia Workers' Minimum Standards of Housing and Amenities Act 1990 was amended in 2020 to improve the living conditions of workers, and employers and those who provide their accommodation can face maximum fines of 50 000 Malaysian ringgit (US$ 11 331) for not meeting the criteria.[2,18] For other workplaces, strict standard operating procedures were enforced to prevent transmission at work, and these required physical distancing, sanitizing the premises and restricting the maximum number of clients and workers within an office.[19]

The clusters in Malaysia had a higher median number of cases compared with clusters in the Republic of Korea (39 cases versus 27 cases, respectively).[8,17] This could be due to the use of different definitions of clusters: the Republic of Korea defined a COVID-19 cluster as a group of more than five cases that had the same point of contact, such as a location or an event, and excluded cases with secondary epidemiological links, such as transmission

Fig. 1. **(a) Proportion of clusters of COVID-19, by method used to detect the index case and category; (b) median number of COVID-19 cases per cluster (cluster size), by detection method for the index case and category; (c) median duration of cluster, by detection method for the index case and category**

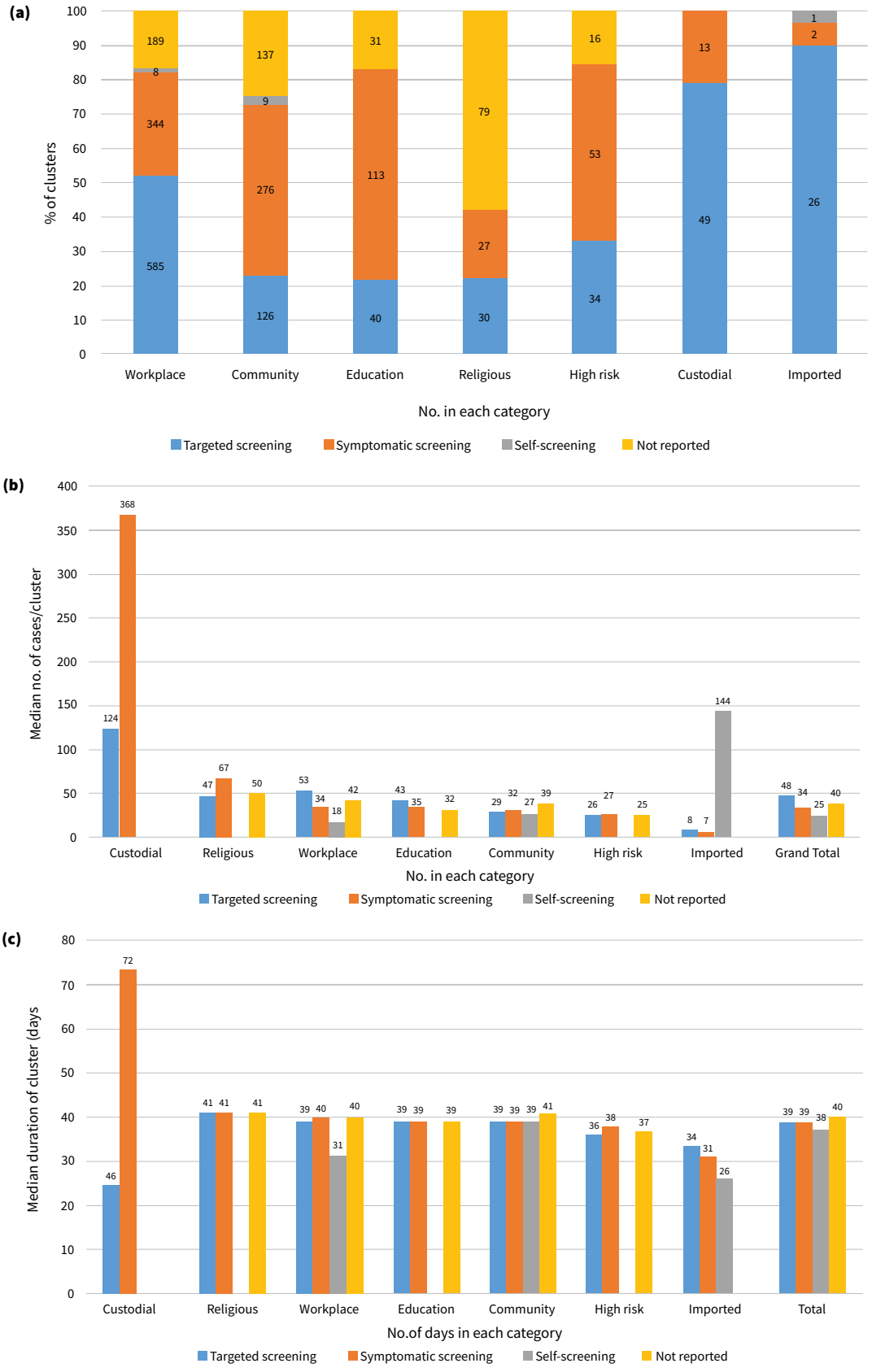

Table 4. **Number and proportion of COVID-19 clusters, by category and mode of transmission, Malaysia, 1 March 2020–31 May 2021**

Cluster category	No. (%) of clusters by mode of transmission[a]									
	Household–social	Workplace	Social	Workplace–household–social	Educational institution–household–social	Household–workplace	Custodial	Other	Not reported	Total
Workplace	173 (15.4)	508 (45.1)	188 (16.7)	60 (5.3)	0	42 (3.7)	1 (0.1)	14 (1.2)	140 (12.4)	1126 (100)
Community	321 (58.6)	2 (0.4)	90 (16.4)	7 (1.3)	2 (0.4)	3 (0.5)	0	5 (0.9)	118 (21.5)	548 (100)
Educational institution	42 (22.8)	2 (1.1)	46 (25.0)	2 (1.1)	72 (39.1)	2 (1.1)	0	4 (2.2)	14 (7.6)	184 (100)
Religious organization	50 (36.8)	1 (0.7)	14 (10.3)	4 (2.9)	1 (0.7)	0	0	11 (8.1)	55 (40.4)	136 (100)
High-risk group	33 (32.0)	0	39 (37.9)	0	0	3 (2.9)	0	17 (16.5)	11 (10.7)	103 (100)
Custodial setting	2 (3.2)	0	13 (21.0)	0	0	0	37 (59.7)	5 (8.1)	5 (8.1)	62 (100)
Imported	1 (3.4)	7 (24.1)	2 (6.9)	2 (6.9)	0	2 (6.9)	1 (3.4)	9 (31.0)	5 (17.2)	29 (100)
Total	622 (28.4)	520 (23.8)	392 (17.9)	75 (3.4)	75 (3.4)	52 (2.4)	39 (1.8)	65 (3.0)	348 (15.9)	2188 (100)

[a] All transmission modes assigned to a cluster were mutually exclusive and independent of any other mode.

occurring within the same household;[8] Malaysia defined a cluster as a concentration of infections occurring in the same area at the same time.[3,10] Moreover, in Malaysia, COVID-19 cases within each cluster, particularly those beyond first-generation transmission, were not limited to occurring in the same setting as the index case, which could explain the larger size of clusters in Malaysia.

Although not many clusters occurred in custodial settings, these settings had the highest median number of cases per cluster and the longest duration. This may be due to the living conditions in custodial settings, such as prisons and detention centres, where the implementation of public health interventions – including physical distancing, mask-wearing and disinfection – was limited.[11] Additionally, Malaysian prisons are 13–36% over their designated capacity,[3,20,21] and local studies have shown that COVID-19 spreads easily in densely populated and confined spaces.[22,23] Yet the restricted movement of inmates in custodial settings eased contact tracing and screening efforts for suspected cases, so fewer resources were required to complete these tasks compared with other settings. Since the source of infection for most inmates could be identified, and clusters of inmates who tested positive had relatively more people and a longer duration of spread, clusters in custodial settings were the largest and had the longest duration compared with other cluster categories. The isolated conditions in custodial settings may also explain the relatively higher test positivity rate among clusters in these settings, as all suspected cases within the settings were screened.[11] Malaysia implemented several mitigation measures to reduce and contain the spread of COVID-19 within custodial settings, including setting up temporary detention centres, treatment centres in prisons and makeshift hospitals.[24] All new inmates were screened and isolated, if necessary, before being transferred to a permanent cell.[25]

Clusters in high-risk groups – which included those in health-care facilities, long-term care facilities and early childhood education and care settings[3] – had the highest case–fatality rate, at 2.8%. Other studies have shown that mortality was higher for residents in long-term care facilities[26,27] and for hospitalized patients[28] compared with other populations in the community. This is because comorbidities increase the risk of complications and death.[11]

The analysis of detection methods showed that targeted screening was the most common detection method for custodial settings, and imported and workplace clusters. Symptomatic screening was the predominant method used for detecting cases in the community, in educational institutions and among high-risk groups. This suggests that a targeted screening method could be more effective when public health authorities have more information about individuals' identities and movements. However, the situation differed for clusters among high-risk groups, which had higher case–fatality rates, with more than half (52%) of index cases detected through symptomatic rather than targeted screening (33% detected). In addition to causing excess deaths in long-term care and health-care facilities, COVID-19 outbreaks in early childhood education and care settings have disrupted children's learning and development, as well as carers' routines.[29] Therefore, high-risk groups need both targeted and symptomatic screening to limit the spread of COVID-19 and reduce mortality.[30]

Our results indicate that early transmission in the community occurs mostly through household and social contacts, in educational institutions, among high-risk groups, through religious organizations and in workplace settings. These observations are supported by a meta-analysis by Lei et al.[31] that found the risk of household secondary attack rate for COVID-19 (i.e. the risk of transmission from an index case to an exposed contact) is approximately 10 times greater than the risk from other contacts. This is because strategies such as physical distancing, quarantine and mask-wearing, which are effective in normal settings, might not work well within a household due to crowded living spaces and behavioural factors.[32] Similarly, two local online surveys in Malaysia in April and July 2020 about health and social behaviours showed that approximately 50–60% of respondents were still meeting in person and socializing with friends and relatives during the Movement Control Order, which was put in place to slow the spread of COVID-19.[33,34] Findings from these studies might explain why household–social and social transmission were the primary modes of early transmission in the community, educational institutions, religious organizations, workplace settings and among high-risk groups.

Our study also found that about 45% of the transmission that occurred among work colleagues was limited to the workplace. To address this, Malaysia implemented several regulations to control outbreaks in the workplace during the pandemic.[35,36] Indeed, a literature review by Lynch et al.[37] found that preventive measures effectively lowered the transmission rate of COVID-19 in workplaces. Nevertheless, as workers interact with other individuals within their household and community,[37] COVID-19 could be spread. This explains how 41% of workplace clusters spread through household and social contacts during the early stage of the cluster.

This study analysed all case clusters in Malaysia during the period for which data were publicly available. Although the study included a large amount of aggregated data from multiple platforms, it has some limitations. The data did not include all details about each individual case in each cluster, such as information about vaccination status or variants of severe acute respiratory syndrome coronavirus 2. Therefore, the study was unable to evaluate the dominant variants in the community or the effect of vaccination on the transmission of cases within clusters. The Malaysian vaccination programme was initiated in February 2021, and the vaccination rate was 3.35% as of 31 May 2021.[1] Moreover, due to the cross-sectional nature of the study, the transmission dynamics of COVID-19 were not captured, and this may have affected the results. Future studies using more complete data are required to explore these areas.

Although each mode of early transmission assigned to a cluster was mutually exclusive and independent of the others, when an individual was exposed to multiple clusters concurrently, they had multiple possibilities for their source of infection, making contact tracing challenging. As such, the decision about the mode of early transmission and assignment to a cluster by case investigators was based on the most likely source of infection for individuals. Lastly, due to the large number of clusters (n = 2188), slight differences in inferential tests may contribute to statistically significant differences. Therefore, our findings should be interpreted with caution.[38]

In conclusion, the different categories of COVID-19 clusters reported in Malaysia from 1 March 2020 to 31 May 2021 had different characteristics and these were related to the context and setting of each category. Therefore, tailored strategies are needed to contain the spread of cases and depend on the category. Targeted

screening might effectively reduce the size and duration of clusters. Prevention and control measures used against COVID-19 should be continually adjusted based on ongoing assessments of the unique context of each cluster category.

Acknowledgements

The authors thank the Director-General of Health Malaysia for his permission to publish this article. The authors also express their gratitude to Ms Tay Kai Ching, Dr Lim Kwok Hoe, Ms Tan Choo Leey, Mr Nornaim Asraf bin Nor Rohaizan and Ms Clairen Foo Jia Ern for their support throughout the process.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethics statement

The study was registered with the National Medical Research Register of Malaysia (Research ID: 54409; NMRR ID: NMRR-20-603-54409) and approval was provided by the Medical Research and Ethics Committee, Ministry of Health, Malaysia (KKM/NIHSEC/P20-738 [7]). No consent to participate was needed as no personal identifying information was collected.

Funding

This project was funded under a research grant from the National Institutes of Health, Ministry of Health, Malaysia. The funding body had no role in designing the study, collecting and interpreting the data, or writing the manuscript.

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