World Health Organization
Western Pacific Region

WPSAR
Western Pacific Surveillance and Response Journal

Volume 16, Number 1, 2025, Pages 1–67
p-ISSN: 2094-7321 e-ISSN: 2094-7313

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

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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.




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

# Focusing field epidemiology training on national health priorities in Papua New Guinea: consultative prioritization, from health workers to policy-makers

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Papua New Guinea (PNG) faces significant public health threats: low immunization coverage; weak primary health-care systems; high maternal mortality; repeated outbreaks of circulating vaccine-derived poliovirus type 1, measles, cholera, dengue and chikungunya; uncontrolled multidrug-resistant tuberculosis; and the emergence of extensively drug-resistant tuberculosis, Zika virus disease and Japanese encephalitis. The generation of high-quality, policy-relevant knowledge is critical to enable evidence-informed decisions that will strengthen PNG's health systems and effectively manage health threats. PNG's 2012 guide to health research policy identified a need for research targeting national health priorities.[1] In 2018, we conducted a prioritization exercise to identify key prioritization areas (KPAs) for operational research projects to be undertaken by fellows completing a new, advanced Field Epidemiology Training Programme in PNG (aFETPNG) during 2019–2021. The aFETPNG programme aimed to build evidence to inform policy and practice, and focus on strengthening health systems in PNG.

## METHODS

The prioritization exercise occurred during October–November 2018. Several health research priority setting methodologies were reviewed to identify a systematic approach suited for adaptation to our needs.[2-6] Our methods synthesized elements of all reviewed approaches, and adapted Viergever et al.'s checklist for health research priority setting.[7] **Fig. 1** illustrates the three-phase approach adopted in this prioritization exercise.

The initial list of health priorities for ranking was drawn from the PNG National Health Plan 2011–2020,[8] the Papua New Guinea–WHO Country Cooperation Strategy 2016–2020,[9] the Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies III[10] and the PNG International Health Regulations Core Capacity Development Plan 2014–2016.[11]

In Phase 1, faculty from the FETPNG met to discuss and agree on key values to underpin the prioritization process; the nominal group technique[12] was used to gain consensus. During the same meeting, the faculty identified and finalized criteria for the prioritization of focus areas for operational research. For this study, we defined operational research as research that examines factors associated with the implementation of programmatic activities. Operational research questions are targeted at identifying and addressing factors that have a direct impact on the quality and effectiveness of the delivery of health services.

During Phase 2 of the prioritization process, 39 stakeholder representatives were identified and engaged

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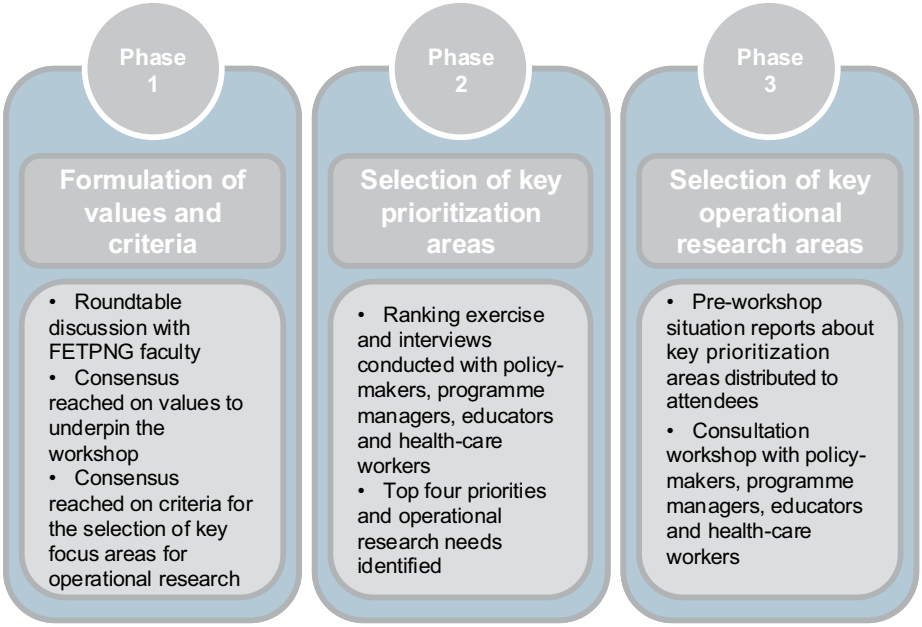
Published: 24 March 2025
doi: 10.5365/wpsar.2025.16.1.1105

Fig. 1. **Process for selecting operational research priorities for the advanced Field Epidemiology Training Program in Papua New Guinea (aFETPNG), 2018**




from various departments and organizations, including the National Department of Health, provincial health authorities, district health authorities, programme management, the health-care workforce, the World Health Organization, the University of Papua New Guinea, church-run health services, the United Nations Population Fund, Pacific Adventist University, the National Agriculture Quarantine and Inspection Authority and FETPNG.

These representatives were given a questionnaire to rank 14 priority areas for operational research based on perceived public health importance, with 1 being the most important and 14 the least.

For each respondent, the four highest ranked priorities were weighted in the following way: areas ranked as priority 1 were given a score of 4; those ranked as priority 2 were given a score of 3; priority 3 was given a score of 2; and priority 4 was given a score of 1.

To explore the reasons why certain areas were prioritized, 18 of the stakeholder representatives were invited to participate in semi-structured interviews. Participants were selected based on efforts to include a diversity of expertise, gender and region, as well as availability. The interviews explored perceptions about the reasons why a KPA was chosen, what was currently working well in that area, operational research needs, potential barriers to conducting operational research, the potential for policy and programmatic changes, and the proposed beneficiaries of research outputs. Interviews were recorded, transcribed and analysed using NVivo software (version 11, Lumivero, Denver, CO, USA). Structural codes of segments of text were created and categorized into broader subcategories, which were then collated by KPA under overarching themes.

Integrated analysis of the data collected during Phases 1 and 2 informed the design of a consultation workshop (Phase 3). A situation report for each KPA was compiled that included information about the burden of disease, current knowledge, recent developments, current policies, future focus and alignment with the National Health Plan.[8] These were circulated to invited workshop participants and were available during the workshop for further review. Invitees included policy-makers, programme managers, educators and health-care workers.

Table 1. **Weighted prioritization of key priority areas for operational research to be conducted by fellows of the advanced Field Epidemiology Training Programme in Papua New Guinea, 2018**[a]

| Key areas for prioritization | Priority weighting | | | | Total |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| Vaccine-preventable diseases and immunization | 40 | 24 | 12 | 2 | 78 |
| Health systems strengthening | 56 | 6 | 6 | 4 | 72 |
| Maternal and reproductive health | 12 | 30 | 12 | 7 | 61 |
| Communicable disease control | 20 | 18 | 12 | 5 | 55 |
| Child health | 12 | 15 | 16 | 3 | 46 |
| Public health emergency preparedness | 4 | 6 | 6 | 7 | 23 |
| Zoonotic diseases | 8 | 3 | 0 | 0 | 11 |
| Laboratory capacity | 0 | 3 | 4 | 2 | 9 |
| Vector-borne diseases | 0 | 0 | 2 | 4 | 6 |
| Healthy lifestyles | 0 | 3 | 0 | 1 | 4 |
| Infection prevention and control | 0 | 0 | 2 | 1 | 3 |
| Noncommunicable diseases | 0 | 0 | 2 | 0 | 2 |
| Access to medical products | 0 | 0 | 0 | 0 | 0 |
| Diarrhoeal disease | 0 | 0 | 0 | 0 | 0 |

[a] Key priority areas were weighted in the following way: those rated as priority 1 were given a score of 4; those rated as priority 2 were given a score of 3; priority 3 was given a score of 2; and priority 4 was given a score of 1.

During the consultation workshop on 24 November 2018, programme managers for the identified KPAs provided a brief overview of the context and key challenges associated with meeting programmatic targets. Participants brainstormed key operational research areas (KORAs) before grouping them into overarching themes: supply, procurement and distribution, governance, workforce, quality of care, service delivery, data management, health-related behaviour and access to services.

The KORAs were used to direct the formulation of operational research questions. Questions were reviewed against previously developed assessment criteria, and those meeting the criteria were ranked using consensus ranking.

The workshop concluded with an overall evaluation of the prioritization process. This evaluation was guided by six questions addressing each workshop activity and participants' perceptions of the overall utility of the exercise.

## RESULTS

In Phase 1, eight FETPNG faculty agreed on four values to underpin the prioritization process: operational research should improve current health systems (8/8), have the potential to reduce mortality and morbidity (7/8), contribute to policy and practice (7/8) and contribute to evidence (4/8).

Consensus was reached on seven criteria for the selection of key focus areas, with three identified as mandatory: the operational research must be ethical, implementable using existing resources, and able to be completed within an 18-month time frame. Consideration of four additional criteria was deemed non-mandatory but important: the magnitude of the health problem (8/8); demonstrated effectiveness, i.e. the potential for the proposed research to address objectives (5/8); the potential for recommendations to be successfully implemented (5/8); and the size of the knowledge gap or lack of adequate implementation (4/8).

All 39 identified stakeholders completed the ranking exercise (100% response rate). **Table 1** provides the results of the prioritization exercise; the top four KPAs identified were: vaccine-preventable diseases and immunization, health systems strengthening, maternal and reproductive health, and communicable disease control.

All 18 individuals invited for interview agreed (100% response rate). Key themes emerging from the interviews encompassed challenges related to governance,

workforce capacity, data collection, management and reporting, as well as logistics, including resourcing, supply, procurement and distribution. Additional themes highlighted issues around access to health services; health-seeking behaviour; knowledge, attitudes and practices; service delivery; and the quality of care.

Twenty-one participants attended the consultation workshop, including clinicians, clinical managers in health facilities, district and provincial health staff, and programme managers from the National Department of Health.

Sixteen operational research questions were developed under KPA1 (vaccine-preventable diseases and immunization), 16 under KPA2 (health systems strengthening) and 19 under KPA3 (maternal and reproductive health). Due to time constraints, questions were not developed for KPA4 (communicable disease control); these were developed later by aFETPNG fellows in consultation with national programme managers. Research questions for each KPA, grouped by the KORA, are available in **Supplementary Table 1**.

All participants completed the post-workshop evaluation. Participants felt that the prioritization exercise provided a transparent and collaborative approach to reaching collective decisions about focus areas for operational research. The involvement of a cross-section of stakeholders from each tier of the health system was viewed as a strength. For example, one participant commented that, "The workshop was transparent. Many people come and say this is what we have developed, but in this process, we were engaged; it is our contribution."

## DISCUSSION

Building on the success of the intermediate FETPNG, the aFETPNG took a more systematic approach to aligning fellows' projects with national health priorities. The prioritization exercise focused on strengthening health systems by building a body of evidence around identified KPAs: vaccine-preventable diseases and immunization, health systems strengthening, maternal and reproductive health, and communicable disease control. Altogether, 17 operational research projects were conducted during 2019–2021 by fellows of aFETPNG with support from the Global Outbreak Alert and Response Network (GOARN), which provided technical and logistical support through the University of Newcastle, Australia. During this period, COVID-19 was added as a fifth KPA.

The methodology described in this report provides a model for aligning field epidemiology fellows' projects, and operational research more generally, with national priority areas. The inclusive and transparent approach fostered ownership of identified priorities by those involved in the process, increasing the likelihood of translational impact. The process also strengthened links among stakeholders across the health sector and fostered greater understanding and appreciation for others' roles, accountabilities and challenges. Key lessons learned were the importance of including national programme managers in formulating KORAs and questions. The national managers provided invaluable context in discussions, highlighting gaps in knowledge and evidence for policy development. The small sample size may have led to biased results; however, the broad representation of stakeholders provided the opportunity to capture diverse views. This approach could be adopted by other GOARN partners and relevant stakeholders, who aim to support research prioritization for operational research, to ensure such research is driven by national priorities.

### *Acknowledgements*

The authors acknowledge the contributions from all involved in this project including the Papua New Guinea National Department of Health, the Field Epidemiology Training Programme of Papua New Guinea, several provincial public health authorities, universities and church health services in Papua New Guinea.

### *Conflicts of interest*

The authors have no conflicts of interest to declare.

### *Ethics statement*

Formal ethics approval was not needed as stakeholders were invited to participate in the study in their official capacity to advise on the direction of a national programme. Survey responses were anonymously submitted, and interview transcriptions were deidentified for coding and reporting.

*Funding*

This work was supported by funding from the Australian Department of Foreign Affairs and Trade's Indo-Pacific Centre for Health Security via the Accelerating the Development of Evidence-based Policy and Practice programme.

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# Whole-genome sequencing of SARS-CoV-2 from residual viral RNA present on positive rapid antigen test kits for genomic surveillance

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COVID-19 is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Since the onset of the COVID-19 pandemic in 2020, SARS-CoV-2 genomic surveillance has been implemented to guide public health responses, initiate early detection and characterization of emerging variants, and understand the impact of emerging mutations on vaccine efficacy. Multiple SARS-CoV-2 variants such as the variants of concern Alpha, Beta, Gamma, Delta and Omicron have emerged.[2,3] Surveillance of circulating SARS-CoV-2 variants is performed through whole-genome sequencing (WGS) of residual viral transport media previously tested positive by real-time reverse transcription-polymerase chain reaction (RT–PCR).[3] However, since the update of the interim guidance by the World Health Organization in October 2021 regarding the use of rapid antigen test kits (RTK-antigen) for the diagnosis of SARS-CoV-2 infection,[4] the majority of COVID-19-positive cases are currently diagnosed by this method. In Malaysia, the Ministry of Health promoted self-testing using RTK-antigen as the country began transitioning to the endemic phase in April 2022.[5] Thus, genomic surveillance has become more challenging, as COVID-19-positive patients may need to undergo PCR retesting solely for the purpose of WGS. Furthermore, opportunities for SARS-CoV-2 genomic surveillance to identify circulating variants are constrained, as WGS laboratories receive fewer residual PCR-positive clinical samples.

RTK-antigen has emerged as the primary diagnostic tool for detecting SARS-CoV-2 infection, especially in low- and middle-income countries.[6] To circumvent the challenges related to a reduction in residual PCR-positive clinical samples, several groups have attempted to recover SARS-CoV-2 ribonucleic acid (RNA) from positive RTK-antigen cassettes for WGS.[6–8] In this study, we adopted an approach to recover SARS-CoV-2 RNA from RTK-antigen cassettes for WGS of SARS-CoV-2.

## METHODS

### Extraction of SARS-CoV-2 RNA from positive RTK-antigen cassettes

In this study, we adopted and modified a method from a previous study to extract SARS-CoV-2 RNA from positive RTK-antigen cassettes.[8] Thirty-three leftover ProDetect™ COVID-19 Antigen Rapid Test cassettes (Mediven, Penang, Malaysia) that tested positive from 27 July to 11 August 2022 were collected from a hospital in Klang district, Malaysia. COVID-19 diagnostic testing was routinely performed as part of clinical care using RTK-antigen assay and nasopharyngeal swabs at this hospital. The cassettes were sealed separately in biohazard specimen bags and transported on ice within 48 hours to the sequencing laboratory, where they were processed immediately upon receipt.

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Published: 31 March 2025
doi: 10.5365/wpsar.2025.16.1.1140

Each cassette was disassembled. The lateral flow strip was transferred to a microcentrifuge tube containing 500 μL of a nucleic acid preservation buffer (Monarch® DNA/RNA Protection Reagent, New England Biolabs, MA, USA), which was diluted to 1:1 from its 2x concentrate (**Fig. 1**).

The microcentrifuge tube, containing both the strip and the nucleic acid preservation buffer, was stored at 2–8 °C before nucleic acid extraction. The period between the collection of samples and nucleic acid extraction in this study was 3–16 days. Before RNA extraction, the strip fragments obtained from the RTK-antigen cassettes were stored in RNA preservation buffer for a maximum of 15 days (**Table 1**).

MagMAX Viral/Pathogen Nucleic Acid Isolation Kit (Thermo Fisher Scientific, MA, USA) was used to extract 400 μL of the nucleic acid preservation buffer contained within the microcentrifuge tube. Nucleic acid extraction was performed according to the manufacturer's instructions on the KingFisher Apex (Thermo Fisher Scientific) automated sample purification system, with a final elution volume of 60 μL.

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

RT–PCR was performed using a real-time fluorescent RT–PCR kit for detecting SARS-CoV-2 (MFG030015; BGI Europe A/S, Copenhagen, Denmark), targeting the ORF1ab and N genes of SARS-CoV-2. Ten microlitres of the extracted nucleic acid were added to the RT–PCR master mix, and CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories Inc., CA, USA) was used for thermal cycling as follows: 50 °C for 20 minutes and 95 °C for 5 minutes, followed by 45 PCR cycles of 95 °C for 15 seconds and 60 °C for 30 seconds. Cycle threshold (Ct) values detected for the N gene were recorded for subsequent analysis.

### SARS-CoV-2 genomic sequencing and bioinformatic analysis

Reverse transcription, amplification and library preparation of the SARS-CoV-2 genome for sequencing were performed using Oxford Nanopore Technologies (Oxford, United Kingdom of Great Britain and Northern Ireland) kits inclusive of the Midnight Expansion Kit with Midnight-ONT/V3 primers (EXP-MRT001.30) and Rapid Barcoding Kit 96 (SQK-RBK110.96), as per the protocol outlined by Oxford Nanopore Technologies.[9] After quantification of the library using the Invitrogen Qubit 1X dsDNA BR Assay Kit (Q33265, Thermo Fisher Scientific), a total of 800 ng of the library was incubated for 5 minutes at room temperature with 1 μL of Rapid Adaptor F and loaded onto an R9.4.1 flow cell (FLO-MIN106D) for sequencing on an Oxford Nanopore Technologies GridION (MinKNOW v22.05.7) for 72 hours with live high-accuracy (minimum q-score of 9) model basecalling (Guppy v6.1.5). Upon completion of sequencing and basecalling, the FASTQ data were automatically analysed to generate a SARS-CoV-2 consensus sequence using wf-artic Nextflow (v.0.3.14), an automated bioinformatic analysis pipeline provided by Oxford Nanopore Technologies. Variant calling was made with a minimum of 20x coverage, and lineage assignment was made using software version pangolin v4.1.1. Genome coverage or completeness was calculated using nextclade v2.5.0 by identifying the number of Ns in relation to the SARS-CoV-2 reference sequence (NCBI Reference Sequence: NC_045512.2). Consensus sequences with genome coverage of 70% and above were uploaded to the GISAID EpiCoV database.

## RESULTS

### Detection of SARS-CoV-2 RNA extracted from positive RTK-antigen cassettes

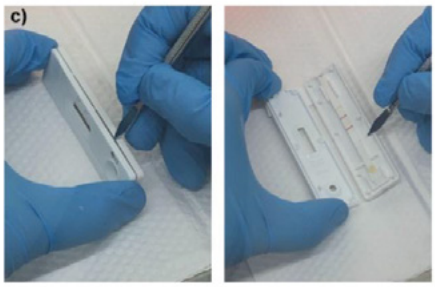
The RNA recovered from 33 RTK-antigen cassettes that showed positive results for SARS-CoV-2 was evaluated using real-time RT–PCR to determine the Ct values of the samples. Of the 33 samples, 30 (90.9%) were positive for SARS-CoV-2 by RT–PCR. The Ct values from these RNAs ranged between 23.47 and 37.62 for the N gene (**Table 1**). Three of the samples (LF0006, LF00025, LF00026) did not yield any Ct values.

A Spearman's rank correlation coefficient ($r_s$) analysis revealed a statistically non-significant and very weak negative correlation between Ct values obtained from real-time RT–PCR and the duration of strip storage in sample RNA preservation buffer ($r_s$ = -0.1349; $P > 0.05$). The three samples that did not yield Ct values were excluded from Spearman's rank correlation coefficient analysis.

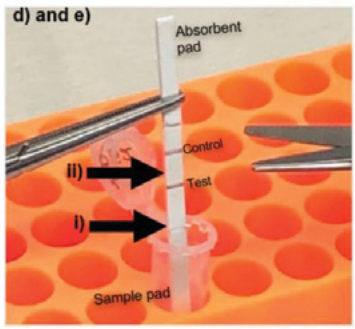
Fig. 1. **Methodological workflow for RTK-antigen cassette processing**


a) Receive and inspect the cassette. Ensure the result is positive (i.e. both control and test lines are visible).


b) Add 500 µL of RNA preservation buffer (Monarch® DNA/RNA Protection Reagent, New England Biolabs, MA, USA) in a 1.5 mL microcentrifuge tube (MCT).

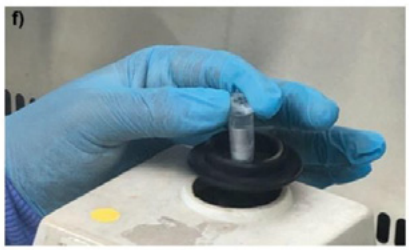



c) Carefully disassemble the housing of the cassette along the sides using an appropriate blunt metal spudger.




d) Using a pair of artery forceps, grasp the absorbent pad above the control line to transfer the test strip from its housing to the 1.5 mL MCT containing buffer.

e) Cut across the test strip **i) just above the sample pad and ii) between the control and test lines** using a pair of surgical scissors. Allow the two cut pieces to drop into the MCT. Discard the remaining absorbent pad end of the strip.




f) Cap the MCT and vortex for 10 seconds. Store at 2–8 °C before nucleic acid extraction.


g) Wipe forceps, scissors and spudgers with 70% alcohol wipes or swabs between processing each cassette.

### Whole-genome sequencing of RNA recovered from positive RTK-antigen cassettes

Eighteen positive samples (60%) were successfully sequenced to a reasonable genome coverage: 13 achieved more than 90% genome coverage, and five achieved 80–90% genome coverage, with depth of coverage of at least 20x (**Table 1**). Lineage assignment was successful for all 18 samples. Quantification of RNA from these samples after PCR amplification during library preparation showed that 10 of the 18 samples had RNA quantities in the range of 2.0–28.0 ng/µL, while the other eight samples exhibited RNA quantities similar to the negative control (~0.9 ng/µL). WGS revealed BA.5.2 to be the dominant Omicron subvariant circulating in Malaysia during the study period, with 13 of the samples assigned to this subvariant. Other detected subvariants included BA.2.38 ($n$ = 1), BA.5.6 ($n$ = 1), BA.5.2.1 ($n$ = 2) and BA.5.3 ($n$ = 1).

All samples with Ct values in the 20–30 range yielded genome coverage of more than 80% (**Table 1**). The genome coverage significantly diminished for the samples with Ct values of more than 31, with only one of 11 samples in this category achieving genome coverage of more than 80% (**Fig. 2**). Inspection of the quality control parameters for the samples with failed lineage assignment showed that they have a low quantity of starting RNA. Of the 15 samples that failed lineage assignment, 12 exhibited very low RNA quantities ranging from 0.8 to 1.3 ng/µL.

## DISCUSSION

With the advent of genome sequencing technologies, the global genomic surveillance of SARS-CoV-2 was performed in a near real-time fashion.[10] For countries that have adopted RTK-antigen as the primary diagnostic tool for COVID-19, we demonstrated that it is feasible to perform genomic surveillance using RNA extracted from SARS-CoV-2 RTK-antigen cassettes. An adequate quantity and reasonable quality of RNA, suitable for targeted sequencing using Oxford Nanopore Technologies, can be obtained from these cassettes.

Ideally, samples should be extracted and sequenced quickly. However, sequencing is typically done in batches to reduce costs, with around 48 to 96 samples

Table 1. **Duration of strip storage in sample RNA preservation buffer, Ct value for N gene, RNA quantity after PCR amplification, depth of coverage, genome coverage and Pango lineage of all study samples (*N* = 33)**

| Sample ID | Duration of strip storage in sample RNA preservation buffer (day) | Ct value for N gene | RNA quantity after amplification (ng/μL) | Genome coverage (%)[a] | Pango lineage |
|---|---|---|---|---|---|
| LF00001 | 1 | 28.09 | 25.0 | 99.04 | BA.2.38 |
| LF00002 | 1 | 27.25 | 28.0 | 99.13 | BA.5.6 |
| LF00003 | 1 | 30.87 | 8.8 | 95.59 | BA.5.2 |
| LF00004 | 1 | 30.4 | 12.0 | 98.42 | BA.5.2 |
| LF00005 | 1 | 35.66 | 3.8 | 53.00 | N/A |
| LF00006 | 2 | N/A | 1.3 | N/A | N/A |
| LF00007 | 2 | 33.38 | 3.1 | 49.58 | N/A |
| LF00008 | 2 | 31.12 | 3.6 | 99.23 | BA.5.2.1 |
| LF00009 | 2 | 34.52 | 4.9 | N/A | N/A |
| LF00010 | 15 | 30.42 | 0.8 | 18.02 | N/A |
| LF00011 | 13 | 23.84 | 0.8 | 82.89 | BA.5.2 |
| LF00012 | 12 | 30.48 | 0.8 | 88.84 | BA.5.2 |
| LF00013 | 12 | 30.24 | 0.8 | 83.38 | BA.5.2 |
| LF00014 | 13 | 32.9 | 1.3 | 24.46 | N/A |
| LF00015 | 12 | 23.47 | 1.0 | 99.19 | BA.5.2 |
| LF00016 | 12 | 32.87 | 0.8 | 3.47 | N/A |
| LF00017 | 9 | 27.96 | 2.2 | 99.25 | BA.5.2 |
| LF00018 | 9 | 24.6 | 3.3 | 99.03 | BA.5.2 |
| LF00019 | 10 | 28.91 | 2.7 | 99.04 | BA.5.2.1 |
| LF00020 | 10 | 31.9 | 0.8 | 7.18 | N/A |
| LF00021 | 9 | 25.75 | 3.4 | 99.05 | BA.5.2 |
| LF00022 | 9 | 30.17 | 0.8 | 95.93 | BA.5.2 |
| LF00023 | 9 | 37.62 | 0.8 | 24.43 | N/A |
| LF00024 | 6 | 32.47 | 0.8 | 39.33 | N/A |
| LF00025 | 5 | N/A | 0.8 | N/A | N/A |
| LF00026 | 5 | N/A | 0.8 | N/A | N/A |
| LF00027 | 5 | 37 | 0.8 | 7.31 | N/A |
| LF00028 | 5 | 30.71 | 0.8 | 82.37 | BA.5.2 |
| LF00029 | 4 | 31.72 | 0.8 | 3.62 | N/A |
| LF00030 | 1 | 29.21 | 0.8 | 89.70 | BA.5.2 |
| LF00031 | 2 | 25.99 | 2.0 | 95.59 | BA.5.3 |
| LF00032 | 1 | 35.1 | 0.8 | 7.02 | N/A |
| LF00033 | 2 | 25.24 | 1.0 | 95.93 | BA.5.2 |
| NC | N/A | N/A | 0.9 | N/A | N/A |

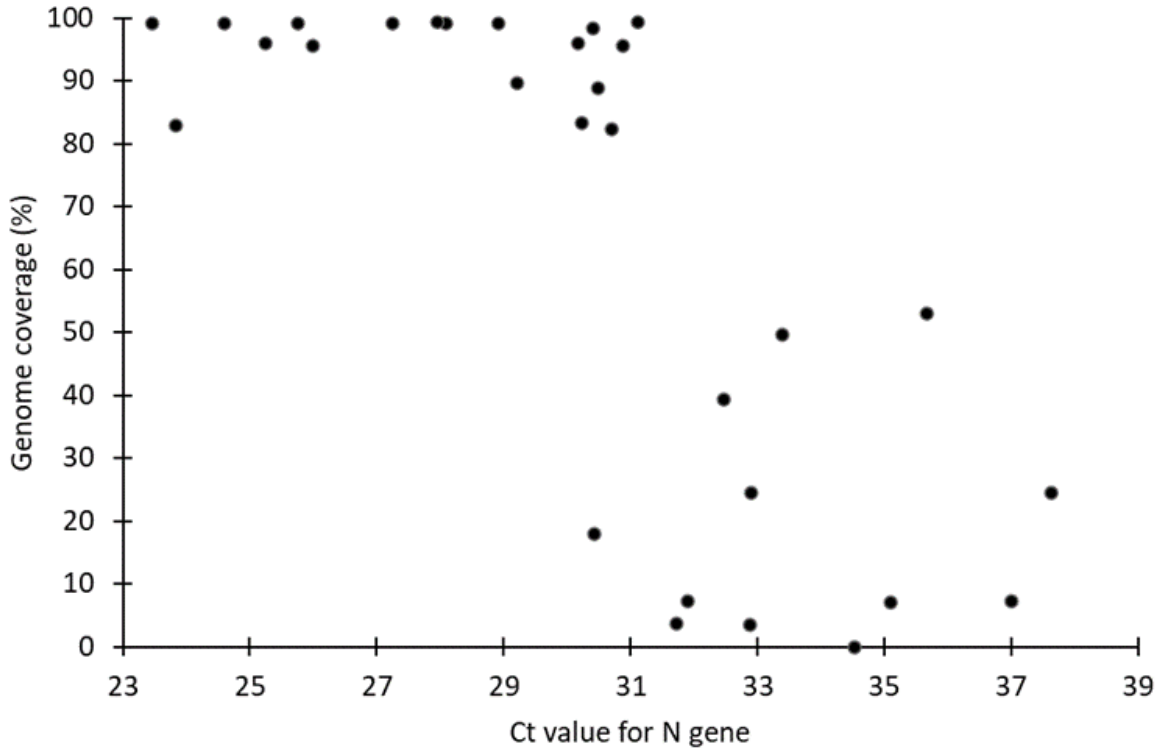
Ct: cycle threshold; ID: identification; N/A: not available; RNA: ribonucleic acid.

[a] Variant filtering during the analysis with wf-artic Nextflow mandates a minimum coverage of at least 20x at variant/genotyping loci for a call to be made.

per run. This means strip fragments may be stored in RNA preservation buffer for an extended period before extraction. While our RT–PCR data did not show a correlation between storage time and Ct values, further assessment is needed to understand any potential decline in sample quality over time in the buffer.

The sample extraction buffer for RTK-antigen typically includes a phosphate-buffered saline solution with blocking agents, surfactant, lysis agent and preservative.[11] The inability to detect SARS-CoV-2 RNA in three samples could be attributed to the absence of an RNase inhibitor in the RTK-antigen buffer. This absence

Fig. 2. **Association between Ct values of SARS-CoV-2-positive samples and genome coverage by whole-genome sequencing ($n$ = 30)**




Ct: cycle threshold.

makes the RNA vulnerable to degradation when exposed to the extraction buffer.

Our data showed that WGS can be performed using RNA extracted from RTK-antigen collected as a part of clinical practice, with real-world storage and transport conditions for tropical countries like Malaysia. Our WGS results correlated with the circulating variant during the period of sample collection in Malaysia. Crucially, this study builds on previous proof-of-principle studies and supports the inclusion of RTK-antigen in genomic surveillance.[6–8]

In resource-limited settings, thoughtful sample selection is critical to ensure a high success rate of SARS-CoV-2 WGS. Thus, evaluating the quality of samples using RT–PCR or Qubit is crucial to avoid wasting resources. Our study suggests that Ct values obtained from RT–PCR can be a good indicator for predicting the success of WGS. Samples with Ct values of <31 are optimal for inclusion in WGS. The limitations of our study include the small sample size, consisting of only 33 samples, and the short period of sample collection (from 27 July to 11 August 2022). Conducting studies with larger sample sizes and over a longer collection period would enable a more comprehensive evaluation of the feasibility of integrating RTK-antigen cassettes into the genomic surveillance of SARS-CoV-2. Another limitation is that our study used RTK-antigen cassettes from a single commercial brand. While we acknowledge the inability to test all available commercial RTK-antigen cassettes, future experiments should include various other brands to ensure their suitability for inclusion in genomic surveillance programmes. Furthermore, Spearman's rank correlation coefficient analysis revealed that the correlation between Ct values and duration of strip storage in RNA preservation buffer was not statistically significant ($P$ > 0.05), indicating that the

observed relationship may be due to random variation. Further studies with larger sample sizes are needed to validate these preliminary findings.

## *Acknowledgements*

The authors thank the Director-General of Health Malaysia for his permission to publish this article.

## *Conflicts of interest*

The authors have no conflicts of interest to declare.

## *Ethics statement*

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-23-02125-WFK).

## *Funding*

This study was funded by a Strategic Research Fund grant from the Ministry of Science, Technology and Innovation (SRF03211046).

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# COVID-19 infection control practices in designated quarantine hotels in Hong Kong SAR (China), 2020–2022: key elements in preparing for the next pandemic

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**Problem:** Despite the widespread use of designated quarantine hotels to minimize the transmission of COVID-19 from imported cases, there is scant literature on the infrastructure and operational requirements of such facilities.

**Context:** Travellers to Hong Kong Special Administrative Region (SAR) (China) were required to undergo quarantine in designated hotels for up to 21 days. Prior to operation, all these hotels were modified and hotel staff received structured training in infection control practices.

**Action:** We conducted retrospective reviews of the procedures and operational protocols that were followed to convert and manage commercial hotels as quarantine hotels during the early part of the pandemic. We also reviewed the training provided and compliance monitoring. Finally, we reviewed intra-hotel outbreak investigations that were conducted between April 2021 and June 2022.

**Outcome:** Designated quarantine hotels received 842 510 quarantined travellers from December 2020 to October 2022. Ten outbreaks were reported, affecting 28 guests (0.003%) and two staff. Prompt epidemiological investigation and action stopped further transmission.

**Discussion:** In Hong Kong SAR (China), designated quarantine hotels successfully minimized COVID-19 transmission from imported cases to the community and should be considered as part of integrated response plans for future pandemics. Based on our COVID-19 pandemic experience, we recommend specifying requirements for quarantine centres and hotels to ensure adequate ventilation inside guest rooms and corridors, functioning drainage systems and the adoption of stringent infection control practices. We also recommend the installation of closed-circuit television cameras in all common areas to support compliance monitoring and outbreak investigation.

## PROBLEM

During rapidly evolving infectious disease epidemics like the recent COVID-19 pandemic, the rapid scaling up of designated quarantine hotels (DQHs) proved crucial in preventing community transmission from imported cases. However, at the time of the pandemic onset, there were no international standards governing the infrastructural or operational requirements of quarantine hotels. While the World Health Organization (WHO) regularly issued guidance on infection control throughout the pandemic period – covering topics such as hygiene practices, the use of masks and waste management – the guidance focused on preventing transmission in health-care facilities and the community and was not specifically tailored to quarantine hotels.[1,2] Post-pandemic, there has also been a notable lack of literature documenting public health practices on the preparation and operation of quarantine hotels. This knowledge gap is concerning, given the critical role played by DQHs in preventing the transmission of COVID-19 in hotels and to the local community. We addressed this gap by reviewing the operation of DQHs in

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Published: 4 March 2025
doi: 10.5365/wpsar.2025.16.1.1167

Table 1. **Quarantine measures in Hong Kong SAR (China), 8 February 2020 to 26 September 2022**

| Date | Quarantine measures |
|---|---|
| 8 February 2020 | Persons returning from China were required to undergo home quarantine for 14 days. |
| 1 March 2020 | Inbound travellers arriving from specific high-risk overseas areas in the previous 14 days were required to stay in quarantine centres. |
| 14 March 2020 | Inbound travellers arriving from specific high-risk overseas areas in the previous 14 days were required to undergo compulsory home quarantine. |
| 11 May 2020 | Inbound travellers arriving from additional high-risk areas were required to stay in quarantine centres for 14 days. |
| 25 July 2020 | Inbound travellers arriving from additional high-risk areas were required to quarantine in hotels for 14 days. |
| 25 December 2020 | All inbound travellers were required to quarantine in DQHs for 21 days. |
| 5 February 2022 | All inbound travellers were required to quarantine in DQHs for 14 days. |
| 1 April 2022 | All inbound travellers were required to quarantine in DQHs for 7 days, if they had been vaccinated twice. |
| 12 August 2022 | Travellers were required to quarantine in DQHs for 3 days, followed by medical surveillance for 4 days. |
| 26 September 2022 | No quarantine was required at DQHs, but travellers had to undergo medical surveillance for 3 days followed by a 4-day self-monitoring period. |

DQH: designated quarantine hotel.

Hong Kong Special Administrative Region (SAR) (China) during the period December 2020 to October 2022. We hope that the lessons identified by this review will inform strategies for improving DQH management in preparation for future pandemics.

## CONTEXT

Following WHO's declaration of COVID-19 as a public health emergency of international concern on 30 January 2020,[3] many countries including Hong Kong SAR (China) used quarantine hotels to delay transmission to the community.[4–7] Their use is a recognized public health containment measure to slow down community transmission from imported cases by identifying and isolating individuals, thereby buying time to implement other response measures and to build up population immunity through vaccination.

In Hong Kong SAR (China), travellers were required to undergo quarantine in designated centres or hotels for up to 21 days during different periods of the pandemic (**Table 1**). Additional measures were introduced to reduce the risk of transmission, including:

- mandatory use of face masks in public areas;
- school suspension;
- teleworking for civil servants;
- restrictions on restaurants' opening hours;
- temporary closure of community facilities such as sports centres, libraries, karaoke lounges, bars and cinemas; and
- physical distancing measures.

COVID-19 vaccination of the population was introduced on 26 February 2021. The pandemic in Hong Kong SAR (China) consisted of five waves, resulting in a total of 1 745 505 cases and 10 116 deaths (**Table 2**; **Fig. 1**).[7]

Notably, most quarantine hotels globally were not purpose-built quarantine facilities, but rather commercial complexes that were adapted for quarantine use. Intra-hotel transmission of SARS-CoV-2 was reported in several countries and areas, including Australia, China, New Zealand, Spain, Taiwan (China) and Thailand.[4,5,8–12] In the case of the facility in New Zealand,[9] detailed investigation revealed that transmission may have occurred due to brief periods of simultaneous door-opening, which may have caused airborne infectious particles to disperse down a concentration gradient, across the corridor and into the confinees' rooms.

## ACTION

As part of a designated team set up by the Government to oversee the management of DQHs, we retrospectively reviewed the protocols and procedures that were followed during the pandemic to (i) select and convert hotels

Table 2. **Number of cases and deaths during COVID-19 waves in Hong Kong SAR (China), 23 January 2020 to 25 September 2022**

| COVID-19 wave | Period | No. of cases | No. of deaths |
|---|---|---|---|
| 1st | 23 January to 14 March 2020 | 142 | 4 |
| 2nd | 15 March to 30 June 2020 | 1064 | 4 |
| 3rd | 1 July to 31 October 2020 | 4118 | 103 |
| 4th | 1 November 2020 to 30 April 2021 | 6451 | 101 |
| Window phase | 1 May to 30 December 2021 | 861 | 1 |
| 5th | 31 December 2021 to 25 September 2022 | 1 732 869 | 10 116 |

*Source*: Wong et al.[7]

to DQHs, (ii) operate the chosen hotels as DQHs and (iii) investigate any intra-hotel outbreaks. We also reviewed available epidemiological information on the number of cases and vaccination coverage from the Centre of Health Protection at the Department of Health.

## Transforming ordinary hotels into designated quarantine hotels

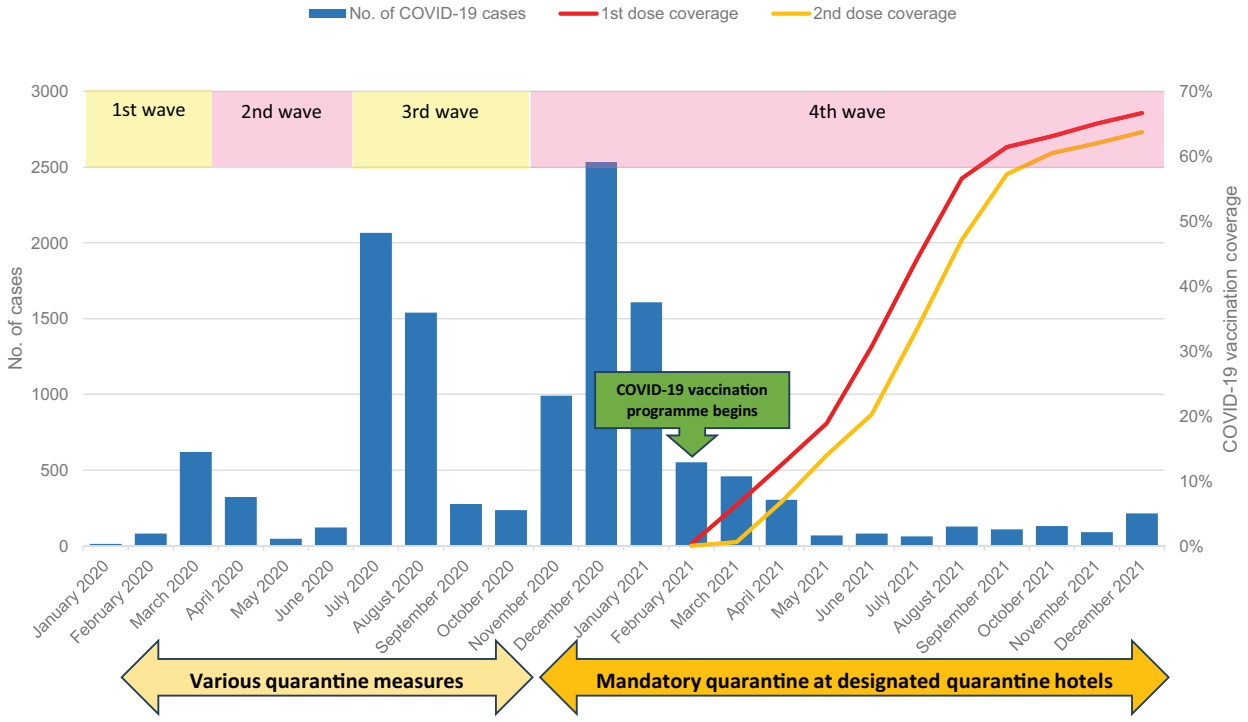
Available WHO guidelines on infection control in the community[1,2] were consulted in drawing up the operational rules and protocols for setting up and operating DQHs. A multidisciplinary team comprising public health physicians, infection control personnel and government engineers inspected all potential hotels, conducting a thorough on-site assessment of the infrastructure, operations and staff composition to ascertain feasibility. The team also advised on the modifications required to prevent intra-hotel transmission. Inspections covered: reception areas; use of designated lifts and routes from the reception area to guest rooms; meal arrangements; linen and waste management; the setup inside guest rooms (for example, simple furniture and bed linen covered with materials for easy disinfection, the provision of disposable water bottles, plastic bags for waste disposal); designated routes for transferring sick or positive cases to hospitals; clean routes for confinees to leave hotels after completion of their quarantine period; and the setup of closed-circuit television (CCTV) cameras in reception areas, guest floors, public areas and back staircases for monitoring compliance. Mini posters were displayed in prominent sites inside guest rooms as a reminder for confinees to wear a face mask before opening doors and to pour 500 mL of water into each drain outlet (U-trap) once a week to prevent vertical transmission through the drainage system. Special attention was paid to the adequacy of the ventilation systems: hotels had to have negative room pressure (to ensure airflow from the corridor to the guest rooms), toilet exhaust fans with a flow rate of >18 L/s and an adequate distance (>7.5 m) from exhaust fans in "dirty" zones to fresh air intake of "clean" zones (to minimize the risk of transmission to nearby residential buildings).

For hotels considered suitable to serve as DQHs, infection control personnel provided training to the hotel staff on the donning and doffing of personal protective equipment (PPE), proper hand hygiene at critical moments, environmental cleaning and disinfection using hypochlorite, and the handling of sick patients and potentially contaminated waste. The PPE required for different staff was fully explained based on risk assessment, including the wearing of respirators for those working in dirty zones.

## Operation

Confinees were required to follow the designated path to their room at the beginning of their quarantine period, which included the use of a designated lift. During the quarantine period, confinees were not allowed to leave their rooms and visitors were not permitted. Infection prevention measures were taken around meal provision, handling of clean and dirty linen and clothing, and waste management. The hotel staff were advised to place meals and other items on a chair or table outside guest room doors, and to clean and disinfect the area regularly. Conversely, confinees were instructed to put their used and soiled items and waste in waterproof plastic bags and leave them outside their doors. A designated trolley was used for transporting the laundry and waste bags in assigned "dirty" lifts to a designated area for temporary storage before being transported outside for further management. Donning

Fig. 1. **COVID-19 cases and vaccination coverage before and during the operation of designated quarantine hotels in Hong Kong SAR (China), January 2020 to December 2021**




and doffing areas for PPE were set up to ensure adequate protection of the staff in the daily handling of meals, linens and waste.

Trained health-care workers took nasopharyngeal swabs from all confinees near the guest room doors for SARS-CoV-2 testing by polymerase chain reaction (PCR). Portable high-efficiency particulate air (HEPA) filters were used to minimize droplet spread during specimen collection. Persons who tested positive were immediately transferred to hospitals for isolation and treatment. Close contacts who were staying in the same room were transferred to purpose-built quarantine facilities (non-DQH quarantine facilities) for the continuation of their quarantine. Approved cleaning companies cleaned and disinfected the affected rooms with real-time monitoring of the whole process through CCTV cameras by the hotel staff or nurses on the compliance team to ensure proper cleaning and disinfection.

The compliance team for infection control comprised a public health physician and over 40 nurses trained in infection control. The team conducted daily on-site inspections of the DQHs to monitor infection control practices. In case of non-compliance of COVID-19 regulations, confinees might be subject to verbal or written warnings or legal liability based on the severity of the infraction. Another team comprising members of the disciplinary services were retired police officers who helped ensure that the confinees stayed in their rooms.

## Outbreak investigation and control

When someone in quarantine became ill or tested positive for COVID-19, they were sent to hospital for treatment. Positive PCR specimens underwent whole-genome sequencing at a public health laboratory. If more than one case at the same DQH had the same or a highly similar genetic sequence, this was interpreted as indicating intra-DQH transmission.

When there was a suspected outbreak of COVID-19 within a DQH, prompt investigation was carried out by a multidisciplinary team comprising epidemiologists, infection control specialists, clinical microbiologists, engineers and technicians for inspection of drainage systems. Epidemiologists interviewed the DQH staff and

reviewed CCTV camera footage to assess for possible interaction between cases or lapses in infection control measures. A smoke test was performed to test the airflow direction between the guest rooms and corridors. Environmental swabs were taken to identify potential fomite contamination in different areas of the hotel to inform possible routes of transmission. Where necessary, prompt action was implemented to minimize the risk of further spread within the DQH.

## OUTCOME

The number of DQHs in operation from December 2020 to October 2022 ranged from 30 to 68. A total of 842 510 inbound travellers underwent mandatory quarantine in DQHs. By ensuring early identification and isolation, the use of DQHs successfully delayed transmission from imported cases to local communities. This important containment measure provided an opportunity to put in place other response measures, and for the community to build up immunity through vaccination. COVID-19 vaccines became available in Hong Kong SAR (China) in February 2021, and the coverage climbed to over 60% for first and second doses by December 2021 (**Fig. 1**).

Significantly, intra-hotel transmission was minimal: a total of 10 clusters were reported, involving 28 guests (0.003% of all guests) and two staff (**Table 3**). The number of cases affected in each cluster ranged from two to six. The reason for these clusters was attributed to either inadequate infrastructure (such as poor ventilation systems in guest rooms or stagnant air in the corridors), improper infection control practices (for example, the use of an inappropriate mask with a valve) or non-compliance with environmental disinfection procedures (**Table 3**).

## DISCUSSION

During their operation, DQHs minimized the spillover from imported cases to the community despite a high level of COVID-19 infection around the world, until Hong Kong SAR (China) was hit by a fifth wave of the highly transmissible Omicron variant in January 2022. Thorough preparation of DQHs, training of staff in infection control practices and prompt intra-hotel outbreak investigation were among the factors that contributed to the effectiveness of DQHs in reducing transmission of SARS-CoV-2 from imported cases.

In terms of preparing DQHs, particular attention was paid to ventilation systems, given that studies conducted in other quarantine facilities, such as in New Zealand and Taiwan (China), had identified inadequate ventilation systems, simultaneous door-opening and interaction between positive cases as risk factors for hotel outbreaks.[5,9,10] Subsequent studies have found that the number of exhaust fans and their distance from occupants, ventilation rates and indoor airflow patterns were critical elements in preventing indoor transmission in quarantine facilities.[13–15] A simulation study in a quarantine hotel demonstrated that SARS-CoV-2 could be transmitted from air inside a guest room to the corridor outside, and then to other rooms on the same floor.[15]

During operation, prompt epidemiological investigation of outbreaks followed by swift action were shown to be effective in minimizing the number of cases affected in intra-hotel outbreaks, with six confinees making up the largest cluster. Moreover, only two hotel staff were infected in the reported clusters. No member of the swabbing team was infected. Outbreak investigation and action was facilitated by regular SARS-CoV-2 testing and genetic analysis of the isolated viruses. Immediate removal of positive cases and close contacts to designated isolation or quarantine facilities stopped further transmission. Remedial actions, including the installation of air purifiers in hotel rooms and corridors, ensuring confinees wore proper masks before opening their door, and proper disinfection of guest rooms and common areas, were implemented after each outbreak to address the possible contributing factors. Continuous review and monitoring of infection control practices by the compliance team also helped to ensure that staff were protected from infection.[16] Lessons learned were shared to prevent the occurrence of similar cases in other DQHs.

The successful preparation and operation of DQHs owed much to the joint efforts of health-care and other workers, including engineers and retired members of the disciplinary forces. As the understanding of the route of transmission and infectivity of SARS-CoV-2 evolved, infection control personnel worked closely with engineers in implementing evidence-based advice on ventilation, for example, the installation of air purifiers at strategic locations in the hotels and modifications to ventilation systems to improve air change.

Table 3. **Factors possibly contributing to intra-hotel transmission of COVID-19 occurring in designated quarantine hotels in Hong Kong SAR (China), 17 April 2021 to 1 June 2022**

| Hotel | Date of detection | No. of persons affected | Likely contributing factors |
|---|---|---|---|
| A | 17 April 2021 | 3 confinees | Improper handling of meal delivery |
| B | 23 April 2021 | 4 confinees | When the guest room window and door were both open, air spread from the index case's room through the corridor to other guest rooms. |
| C | 2 July 2021 | 1 confinee, 1 cleaning staff | Non-compliance with infection control practices by the cleaning staff when disinfecting the index case's guest room |
| D | 17 August 2021 | 3 confinees | When the guest room window and door were both open, air spread from the index case's guest room through the corridor to other guest rooms. |
| E | 11 November 2021 | 2 confinees | Index case engaged in vigorous exercise; no mask wearing when opening the guest room door; inadequate environmental cleaning and disinfection |
| F | 22 November 2021 | 2 confinees | Index case wore a mask with a valve; no mask wearing when opening the guest room door; inadequate negative pressure inside the guest room |
| G | 16 January 2022 | 6 confinees | Inadequate negative pressure inside the guest room; poor ventilation in the corridor leading to the guest room |
| H | 20 May 2022 | 4 confinees | Fire exit door was open when specimens were taken from confinees, which may have led to transmission between two floors. |
| I | 27 May 2022 | 3 confinees | Air spread from the index case's guest room to the corridor; no mask wearing when opening the guest room door |
| J | 10 June 2022 | 1 staff | The ventilation outlet of a dirty area was too close to the inlet of a clean zone (staff area). |

Our findings and lessons learned can be applied to other countries and areas in the Western Pacific Region and other parts of the globe that use hotels for quarantine purposes to prevent the importation of SARS-CoV-2. While hotel facilities may vary, the general principles of infection control can be universally applied. One of the challenges to implementing stringent infection control measures is the recruitment of health-care professionals for compliance monitoring. During the pandemic, there was high demand for health-care staff in various facilities, including not only hospitals but also quarantine centres and vaccination centres. We successfully recruited retired nurses, including those with knowledge and skills in infection control, to meet operational needs. Similarly, we were able to call upon retired members of the disciplinary forces to assist in ensuring that confinees observed the regulations.

Limitations of the current review include the possible underreporting of COVID-19 cases, especially in the later phase of the pandemic when the length of time travellers were required to stay in DQHs was reduced to 7 days. However, confinees were required to report to community centres for testing for a further 14-day period after leaving a DQH. This should have reduced the likelihood of underreporting. Second, some cases of intra-hotel transmission might have been missed. Third, recall bias among cases and hotel staff might have affected the epidemiological investigations; however, such information was verified by hotel records and CCTV camera footage as far as possible.

With the gradual return to normalcy, WHO has urged countries to prepare for "disease X" and form integrated plans for responding to any respiratory pathogen including influenza and coronaviruses.[17] If quarantine hotels are included in containment measures to delay the importation of an emerging infectious pathogen, it is crucial to reflect on the experience gained from their use during the COVID-19 pandemic.[18] Based on our experience, we recommend the adoption of infrastructure requirements for DQHs to ensure that adequate ventilation, air purification and drainage systems are installed before operation. We also recommend the installation of CCTV cameras in all common areas to support the monitoring of compliance with infection control practices (e.g. mask wearing and surface disinfection) and outbreak investigation. These measures will help countries formulate a better plan to tackle the next pandemic.

## *Acknowledgements*

The authors thank the members of the compliance team for their dedicated work in the DQHs. The authors also thank the Electrical and Mechanical Services Department and Buildings Department, Government of Hong Kong SAR (China), for providing professional support for inspection and investigations of the clusters reported.

## *Conflicts of interest*

The authors have no conflicts of interest to declare.

## *Ethics statement*

The operation of a DQH is not human subject research and is part of the public health response and measures to control COVID-19 in Hong Kong SAR (China). Therefore, ethics approval was deemed unnecessary.

## *Funding*

None.

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# Hepatitis A outbreak among men who have sex with men, Shinjuku, Japan, 2018

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**Objective:** In 2018, the Shinjuku City Department of Health detected excess cases of hepatitis A virus (HAV) infection. The objectives of this investigation were to characterize the outbreak, identify transmission routes among inpatient cases and make recommendations to control and prevent HAV infection among men who have sex with men.

**Methods:** Information about cases of HAV infection was collected from the National Epidemiological Surveillance for Infectious Diseases system and inpatient interviews conducted by public health nurses in 2018.

**Results:** There were 131 HAV cases in 2018. Of these, 98% (129/131) were male, of whom 81% (105/129) were men who have sex with men. Hospitalization was required for 40 cases (31%). The age groups with the highest proportion of cases were 30–39 and 40–49 years (each 34%; 44/131). Two cases (2%) had received the second dose of the HAV vaccine, but only 10 days before symptom onset; all others had received no doses. The sequence type subgroup 13, an RIVM-HAV-16–090-like strain, was seen in 51 cases (39%). Of the 40 hospitalized cases, 21 (53%) participated in an interview conducted using a semistructured questionnaire. Altogether, of 21 cases, 12 (57%) had coinfection with HIV, 13 (62%) had casual sexual contact within the preceding 2 months and 10 (48%) had used social networking services (SNS) to find a sexual partner.

**Discussion:** In Shinjuku, this outbreak almost exclusively affected the population of men who have sex with men. The detected outbreak strain has previously been reported in outbreaks among men who have sex with men in Taiwan (China) and Europe. For HAV prevention, the most important measures are raising awareness of the risk of HAV as a sexually transmitted infection via SNS and promoting immunization at the appropriate time.

Hepatitis A virus (HAV) is transmitted person-to-person through the faecal–oral route or by ingestion of contaminated food or water.[1,2] In countries where HAV is not endemic, the onset of illness among adults is usually abrupt, comprising fever, malaise, anorexia, nausea and abdominal discomfort, followed within a few days by jaundice. Since June 2015, outbreaks of HAV infection with particular strains have emerged among men who have sex with men in Taiwan (China) and in European countries.[2–4] Thus, HAV infection is a major re-emerging infectious disease among populations of men who have sex with men in developed countries. The strain mainly implicated among these groups and patients with HIV infection or other sexually transmitted infections (STIs) is TA-15 (RIVM-HAV16–090).[1]

Shinjuku is one of the special wards in Tokyo that has its own public health administration and local public health centre (PHC), as authorized in the Community Health Act.[5] It is host to the Tokyo Metropolitan Government Building and the head offices of many major corporations, and had a population of around 347 000, as of the end of 2018.[6] Shinjuku is known for its gay quarter, Shinjuku 2-chome, with more than 400 commercial recreational facilities that cater to the LGBTQ+ (lesbian, gay, bisexual, transgender, intersex, queer/questioning, asexual and others) community.[7]

HAV infection is classified as a category IV notifiable disease in Japan, in accordance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases.[8] The annual number

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Published: 25 February 2025
doi: 10.5365/wpsar.2025.16.1.1088

of HAV infections nationwide ranged from around 100 to 350 cases in 2004–2014.[9] An excess number of cases of HAV infection was reported in 2018, with 177 cases diagnosed nationwide in the first 15 weeks of the year.[10] As of week 7 of the epidemic (18 February 2018), Shinjuku's PHC had recorded 10 HAV cases, exceeding the threshold for declaring an outbreak, with some severe cases requiring inpatient care. The PHC initiated an outbreak investigation and established control measures. Some reports have described HAV outbreaks since 2018.[7,11–13] However, no study in Japan has investigated the prevention of HAV infection among men who have sex with men and who engage in high-risk sexual behaviours. The objectives of this investigation were to characterize the outbreak, to identify transmission routes among inpatient cases, and to make recommendations for the control and prevention of HAV infection among men who have sex with men.

## METHODS

Two types of data analysis were conducted for this outbreak investigation: the first was a descriptive cross-sectional study that involved analysing cases of HAV infection recorded in the National Epidemiological Surveillance for Infectious Diseases (NESID) system, and the second involved reviewing the interviews conducted with inpatients in 2018. The interview data were descriptively analysed.

Data were extracted from NESID about individuals diagnosed with HAV at medical institutions in Shinjuku from 1 January to 31 December 2018; the characteristics analysed included age, sex, transmission route, molecular analysis of HAV strain, and other recorded data. Descriptive statistics were calculated using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

Molecular typing – including reverse transcription polymerase chain reaction (RT-PCR), sequence analysis and phylogenetic tree analysis – was conducted by the Tokyo Metropolitan Institute of Public Health, as previously reported by Ishii et al.[14]

Interviews were conducted in January–December 2018 with 21 hospitalized patients who had severe HAV infection, with the aim of learning how to prevent transmission and severe complications of infection in the community of men who have sex with men. The interviews were conducted by public health nurses from the Shinjuku PHC using a semistructured questionnaire. The questionnaire had 13 items, with questions about transmission route and infection prevention measures; it included questions about lifestyle factors, types of sexual partners, use of social networking services (SNS) to find sexual partners, whether the respondent visited gay cruising spots, the number of casual sexual contacts, condom use, knowledge of the HAV epidemic, whether the respondent was employed in food handling and the respondent's HAV vaccination status. The interviews were conducted as part of the legal requirements for outbreak prevention and response activities, and informed consent for interviews was obtained from patients and their doctors. The participants had the right to decline to answer any interview item.

## RESULTS

### Surveillance data from Shinjuku

The number of HAV cases in 2018 was 131; males comprised 98% (129/131; **Table 1**). For comparison, Shinjuku reported fewer than 10 cases of HAV infection annually from 2014 to 2017, totalling only 27 cases during that period (**Fig. 1**). Of the 131 cases, 126 (96%) were reported from a hospital designated by the government to provide medical services to people living with HIV (i.e. a designated HIV hospital) and were initially detected during a routine health check. The suspected source of infection was same-sex sexual contact in 81% of male cases (105/129) (**Table 1**) but was oral ingestion in the two female cases. In 2018, the most common age groups infected with HAV were those aged 30–39 years and 40–49 years (each 34%; 44/131; **Table 1**). The most common initial symptoms of HAV infection were malaise (113 cases; 86%), liver dysfunction (109 cases; 83%) and fever (93 cases; 71%). HAV infection was diagnosed based on immunoglobulin testing, IgM (130 cases; 99%), IgG (1; 1%) or RT-PCR (59; 45%), or a combination of these. The high rate of positivity for the IgM test included an asymptomatic case detected by a blood test. Only 2 cases (2%) had received the second dose of the HAV vaccine.

Altogether, 40 cases (31%) were hospitalized with severe illness. The reporting medical institution was a designated HIV hospital for 126 cases (96%; 2 females and 124 males). The 2 female cases were not infected

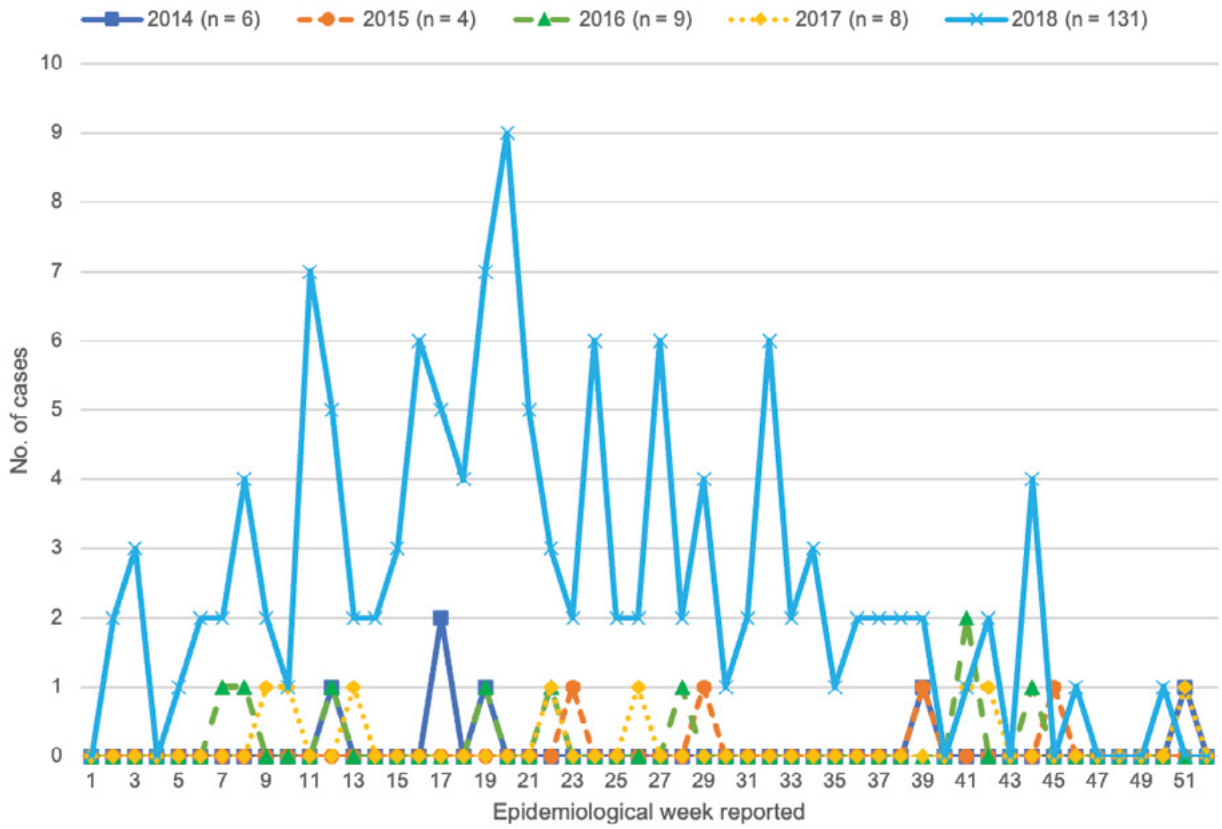
Table 1. **Characteristics of hepatitis A cases by sex, Shinjuku, Japan, 2018 (*N* = 131)**

| Characteristic | Female (*n* = 2)[a] | Male (*n* = 129)[a] | Total (*N* = 131)[a] |
|---|---|---|---|
| Age group (years) | | | |
| 10–19 | 0 (0) | 2 (2) | 2 (2) |
| 20–29 | 0 (0) | 29 (22) | 29 (22) |
| 30–39 | 0 (0) | 44 (34) | 44 (34) |
| 40–49 | 1 (50) | 43 (33) | 44 (34) |
| 50–59 | 1 (50) | 10 (8) | 11 (8) |
| 60–69 | 0 (0) | 1 (1) | 1 (1) |
| Symptom | | | |
| Malaise | 1 (50) | 112 (87) | 113 (86) |
| Fever | 2 (100) | 91 (71) | 93 (71) |
| Lack of appetite | 1 (50) | 79 (61) | 80 (61) |
| Jaundice | 0 (0) | 82 (64) | 82 (63) |
| Hepatomegaly | 0 (0) | 26 (20) | 26 (20) |
| Liver dysfunction | 1 (50) | 108 (84) | 109 (83) |
| Upper abdominal pain | 0 (0) | 1 (1) | 1 (1) |
| Diarrhoea | 0 (0) | 1 (1) | 1 (1) |
| Pale stool | 0 (0) | 1 (1) | 1 (1) |
| Dark urine | 0 (0) | 1 (1) | 1 (1) |
| Joint pain | 0 (0) | 1 (1) | 1 (1) |
| Asymptomatic | 0 (0) | 1 (1) | 1 (1) |
| Method of testing | | | |
| IgM | 2 (100) | 128 (99) | 130 (99) |
| IgG/paired | 0 (0) | 1 (1) | 1 (1) |
| RT-PCR | 2 (100) | 57 (44) | 59 (45) |
| Immunization (at least first dose) | | | |
| Yes | 0 (0) | 2 (2) | 2 (2) |
| No | 1 (50) | 52 (40) | 53 (40) |
| Unknown | 1 (50) | 69 (53) | 70 (53) |
| Not recorded | 0 (0) | 5 (4) | 5 (4) |
| Reported medical institution | | | |
| Designated HIV hospital | 2 (100) | 124 (96) | 126 (96) |
| Other | 0 (0) | 5 (4) | 5 (4) |
| Strain | | | |
| Subgroup A | 1 (50) | 0 (0) | 1 (1) |
| Subgroup B | 1 (50) | 50 (39) | 51 (39) |
| Unknown/not recorded | 0 (0) | 79 (61) | 79 (60) |
| Travelled abroad within 30 days before onset | 0 (0) | 0 (0) | 0 (0) |
| Hospitalized | 0 (0) | 40 (31) | 40 (31) |
| Suspected source of infection | | | |
| Same-sex sexual contact | 0 (0) | 105 (81) | 105 (80) |
| Oral ingestion | 2 (100) | 10 (8) | 12 (9) |
| Oral ingestion and same-sex sexual contact | 0 (0) | 5 (4) | 5 (4) |
| Other | 0 (0) | 9 (7) | 9 (7) |

IgG: immunoglobulin G; IgM: immunoglobulin M; RT-PCR: reverse transcription polymerase chain reaction.

[a] Values are number (%).

Fig. 1. **Number of weekly confirmed cases of acute hepatitis A infection by week and year of diagnosis, Shinjuku, Japan, 2014–2018 (*N* = 158)**




with HIV. Only 52/131 samples (40%) were sequenced for molecular typing. HAV subgenotype IA/subgroup 13 (S13), an RIVM-HAV-16-090-like strain, was identified in 51 samples (98%). The only hospitalized female case also had S13, but the suspected source of infection was food. S13 strains were registered in the GenBank database, with accession numbers shown in **Supplementary Table 1**. No cases had travelled abroad within 30 days before symptom onset.

## Interviews with hospitalized cases

Semistructured interviews were conducted with 22 of the 40 cases hospitalized with severe illness (55%), comprising 21 males and 1 female (**Table 2**). Among the 21 male cases, the most common age group was 30–39 years (7 cases; 33%) followed by 40–49 years (6 cases; 29%).

For the transmission route in the 21 cases, same-sex sexual contact was suspected in 17 cases (81%). The numbers of cases with a specific risk factor were: 13 cases (62%) who had sexual contact with an unspecified number of persons within the preceding 2 months; 12 cases (57%) who were coinfected with HIV; 10 cases (48%) who found sexual partners using SNS; and 8 cases (38%) who had visited gay cruising spots. Two cases (10%) had received the HAV vaccine, 8 cases (38%) were aware of the current HAV epidemic and 4 cases (19%) were employed in food handling. For the 2 vaccinated cases, the HAV vaccine had been administered within 10 days before symptom onset.

Stratified by age group, around 60% among those in their 20s and 30s found sexual partners using SNS. Additionally, 6 of the 8 cases who visited gay cruising spots were in their 40s and 50s.

## Outbreak control measures

After the outbreak was detected, a few gay community voluntary support groups, the Tokyo Metropolitan Government and Shinjuku City Government discussed strategies for preventing HAV infection in the community

Table 2. **Transmission route and risk factors identified in interviews with cases hospitalized with severe hepatitis A infection, by age group, Shinjuku, Japan, 2018 ($N$ = 21)**

| Transmission route or risk factor | Age group[a] | | | | | Total ($N$ = 21)[a] |
|---|---|---|---|---|---|---|
| | 10–19 ($n$ = 1) | 20–29 ($n$ = 5) | 30–39 ($n$ = 7) | 40–49 ($n$ = 6) | 50–59 ($n$ = 2) | |
| Route | | | | | | |
| Oral (food) | 1 (100) | 1 (20) | 1 (14) | 1 (17) | 0 | 4 (19) |
| Same-sex sexual contact | 0 | 4 (80) | 6 (86) | 5 (83) | 2 (100) | 17 (81) |
| HIV coinfection | | | | | | |
| No | 1 (100) | 3 (60) | 3 (43) | 1 (17) | 0 | 8 (38) |
| Yes | 0 | 1 (20) | 4 (57) | 5 (83) | 2 (100) | 12 (57) |
| Not answered | 0 | 1 (20) | 0 | 0 | 0 | 1 (5) |
| Unspecified number of sexual contacts | | | | | | |
| No | 1 (100) | 2 (40) | 2 (29) | 1 (17) | 0 | 6 (29) |
| Yes | 0 | 2 (40) | 5 (71) | 4 (67) | 2 (100) | 13 (62) |
| Not answered | 0 | 1 (20) | 0 | 1 (17) | 0 | 2 (10) |
| Usual partner | | | | | | |
| No | 1 (100) | 1 (20) | 3 (43) | 3 (50) | 0 | 8 (38) |
| Yes | 0 | 3 (60) | 3 (43) | 3 (50) | 2 (100) | 11 (52) |
| Not answered | 0 | 1 (20) | 1 (14) | 0 | 0 | 2 (10) |
| Uses SNS to find sexual contacts | | | | | | |
| No | 1 (100) | 0 | 2 (29) | 2 (33) | 1 (50) | 6 (29) |
| Yes | 0 | 3 (60) | 4 (57) | 2 (33) | 1 (50) | 10 (48) |
| Not answered | 0 | 2 (40) | 1 (14) | 2 (33) | 0 | 5 (24) |
| Gay cruising spot use | | | | | | |
| No | 1 (100) | 3 (60) | 4 (57) | 1 (17) | 0 | 9 (43) |
| Yes | 0 | 0 | 2 (29) | 4 (67) | 2 (100) | 8 (38) |
| Not answered | 0 | 2 (40) | 1 (14) | 1 (17) | 0 | 4 (19) |
| Condom use | | | | | | |
| No | 0 | 2 (40) | 3 (43) | 1 (17) | 1 (50) | 7 (33) |
| Yes | 0 | 2 (40) | 2 (29) | 3 (50) | 1 (50) | 8 (38) |
| Not answered | 1 (100) | 1 (20) | 2 (29) | 2 (33) | 0 | 6 (29) |
| Sexual contact with HAV-positive individual | | | | | | |
| No | 0 | 1 (20) | 0 | 1 (17) | 0 | 2 (10) |
| Yes | 0 | 1 (20) | 2 (29) | 1 (17) | 0 | 4 (19) |
| Not answered | 1 (100) | 3 (60) | 5 (71) | 4 (67) | 2 (100) | 15 (71) |
| Sexual contact with HIV-positive individual | | | | | | |
| No | 0 | 2 (40) | 0 | 0 | 0 | 2 (10) |
| Yes | 0 | 1 (20) | 1 (14) | 2 (33) | 0 | 4 (19) |
| Not answered | 1 (100) | 2 (40) | 6 (86) | 4 (67) | 2 (100) | 15 (71) |
| Immunization | | | | | | |
| No | 0 | 4 (80) | 7 (100) | 4 (67) | 2 (100) | 17 (81) |
| Yes | 0 | 0 | 0 | 2 (33) | 0 | 2 (10) |
| Not answered | 1 (100) | 1 (20) | 0 | 0 | 0 | 2 (10) |
| Aware of epidemic | | | | | | |
| No | 0 | 2 (40) | 5 (71) | 3 (50) | 1 (50) | 11 (52) |

| Transmission route or risk factor | Age group[a] | | | | | Total (*N* = 21)[a] |
|---|---|---|---|---|---|---|
| | 10–19 (*n* = 1) | 20–29 (*n* = 5) | 30–39 (*n* = 7) | 40–49 (*n* = 6) | 50–59 (*n* = 2) | |
| Yes | 0 | 2 (40) | 2 (29) | 3 (50) | 1 (50) | 8 (38) |
| Not answered | 1 (100) | 1 (20) | 0 | 0 | 0 | 2 (10) |
| Food handler | | | | | | |
| No | 1 (100) | 3 (60) | 5 (71) | 6 (100) | 2 (100) | 17 (81) |
| Yes | 0 | 2 (40) | 2 (29) | 0 | 0 | 4 (19) |
| Lives with a housemate | | | | | | |
| No | 0 | 3 (60) | 3 (43) | 3 (50) | 1 (50) | 10 (48) |
| Yes | 1 (100) | 2 (40) | 4 (57) | 3 (50) | 1 (50) | 11 (52) |

HAV: hepatitis A virus; SNS: social networking services.

[a] Values are number (%).

of men who have sex with men. Some physicians at collaborating hospitals that offer treatment for HIV and AIDS in Tokyo recommended HAV vaccination for patients and their partners who were part of the population. Support groups were informed about the HAV epidemic through SNS and disseminated information about HAV infection in collaboration with the Tokyo Metropolitan Government and the PHCs of the 23 special wards of Tokyo, including Shinjuku PHC.

## DISCUSSION

The data analysed indicated that the number of HAV infections rapidly increased in January 2018 in Shinjuku. In comparison with past surveillance data, in 2018 the most common transmission route among male cases was same-sex sexual contact (81%). This was most common among those in their 30s and 40s. Among the 21 male cases hospitalized with severe illness who consented to be interviewed, the most common risk factor for cases in their 30s and 40s was the use of SNS to find sexual partners. Only two of the cases had received any doses of the HAV vaccine. Genetic analysis identified the dominant virus strain as sequence type S13, an RIVM-HAV61-090-like strain.[15,16]

### Main affected population

This 2018 outbreak constituted the highest number of HAV infections recorded in Japan since 2014 (at which time 433 cases were reported nationwide),[9,17] and the outbreak was primarily confined to Shinjuku and the population of men who have sex with men. The rate of transmission via same-sex sexual contact among male cases has gradually been increasing since 2016.[17]

### Risk factors

Our results showed that those infected with HAV tended to have multiple casual partners, and half had coinfection with HIV. About half of the recorded cases found sexual partners using SNS, such as X.com, Facebook and Instagram, and about 60% of those in their 20s and 30s used these sites, which was a higher proportion than in other age groups. These age groups use SNS frequently and have access to more mobile communication tools.[18] The use of SNS to find sexual partners is a high-risk behaviour consistent with a previous HAV outbreak among this population.[3] Using SNS and meeting partners online were also associated with HIV-positive status and having an STI.[19,20] Thus, this population should be aware of the risk of HAV infection associated with these behaviours.

### Preventing HAV infection in this population

Around 60% of cases in this study were HIV-positive, which is consistent with previous reports.[21] HIV positivity among men who have sex with men is associated with a high risk of HAV infection, as is frequent oral–anal sexual contact[22] and having multiple sexual partners.[21] Moreover, according to Nishijima et al.,[23] a hospital offering treatment for HIV and AIDS reported that around 90% of patients with HIV or AIDS in metropolitan areas of Japan were men who have sex with men. In the 2018 outbreak, most cases of HAV infection were reported by these HIV/AIDS hospitals, and cases of HAV infection were initially detected during routine health checks (data not shown) performed at the hospital in Shinjuku. In contrast, about 40% of HAV infections were reported by a non-HIV/AIDS hospital later in the outbreak. After the HAV outbreak was detected,

voluntary support groups and the local government discussed how best to disseminate information about the outbreak and institute measures to control it, and the voluntary support groups subsequently disseminated information about the HAV outbreak among the affected population.[24] Communicating to the affected population that approximately half of the cases were not coinfected with HIV or AIDS might have generally increased awareness of the HAV outbreak in the population. SNS have been reported to be an important tool for communicating about infectious disease prevention measures and increasing the uptake of effective sexual health behaviours to reduce the risk of disease transmission.[25] To improve health behaviours to prevent HAV infection and to promote immunization, health-care providers and voluntary support groups should widely disseminate appropriate information via SNS.

## Outbreak strain

The dominant strain of HAV in this outbreak was sequence type S13, which is an RIVM-HAV16-090-like strain.[15] This sequence type was also identified in outbreaks among men who have sex with men in Taiwan (China) from 2015 to 2017, and in England and Germany in 2016 and 2017.[2–4] The RIVM-HAV16-090-like strain had not been reported in Japan before 2016. The strain has circulated among the population of men who have sex with men worldwide, and therefore the outbreak source was possibly importation of the RIVM-HAV16-090-like strain from epidemics in other countries, with subsequent transmission to the Japanese population of men who have sex with men in Shinjuku. Our data showed that in 2018 in Shinjuku, 81% of cases were men who have sex with men. Among those infected with the RIVM-HAV-16-090-like strain, the proportion of men who have sex with men was the same as in previous reports from European countries. For this population, sexual behaviour might facilitate transmission through close contact with someone who is infected.[26–28] In Japan, the RIVM-HAV-16-090-like strain was first reported in 2016, which also suggests the possibility that the strain was imported from other high-income countries.

## Female cases in the outbreak

Of the two female cases in this outbreak, one was infected with the S13 strain reported in 2018, and she had not had contact with other cases or the population of men who have sex with men. Moreover, according to the NESID data, food consumption was the suspected route of infection for this case. However, we did not find evidence of a foodborne outbreak of HAV infection in 2018. Community acquisition could be suspected for this case, but we could not clearly identify the infection route.

## Importance of vaccination

Around two thirds of inpatient cases had an unspecified number of sexual contacts. A previous outbreak investigation reported that such sexual contact was a high-risk behaviour for STIs.[26] HIV infection was one risk factor strongly associated with severe complications.[27,28] Ndumbi et al.[29] reported that avoiding faecal–oral exposure during sexual activity and safer sex practices (e.g. use of barrier methods) play important parts in preventing HAV infection and other STIs, including preventing enteric transmission. Additionally, HAV vaccination can protect against faecal–oral transmission and foodborne infection, but we estimated that the seroprevalence of anti-HAV antibodies might be <10% among those ≤60 years of age in Japan.[30] Some HAV outbreak investigations have recommended that men who have sex with men should be considered a high-risk population for HAV infection and so should be vaccinated.[22,28,31] Post-exposure prophylaxis is significantly effective in preventing HAV infection.[32] However, in two cases, the second dose of the HAV vaccine was received within 10 days before symptom onset. Following close contact with an HAV-positive person, all previously unvaccinated persons should receive the vaccine as soon as possible, preferably within 2 weeks.[2] Infection may have occurred in these two cases due to an inadequate amount of time elapsing between vaccination and exposure, thus the vaccine may not have provided adequate protection. Moreover, Japan has not yet implemented universal HAV vaccination, so most residents are not aware of the importance of receiving the vaccine. We recommend that HAV vaccination be given at the appropriate time nationwide.

## Vaccination among men who have sex with men

Most cases in this outbreak had not received the HAV vaccine. Our results showed that cases had only a low awareness of the risk of an HAV outbreak among men who have sex with men and of the importance of vaccination. A

past outbreak investigation has described the populations of men who have sex with men as having low rates of HAV vaccination.[33] To improve the immunization coverage rate among this population, health-care providers should be made aware of the importance of vaccination, and the population should also be made aware of the availability of vaccination and the importance of asking for the vaccine when they seek routine health care. The United States Centers for Disease Control and Prevention has reported hesitancy to receive HAV vaccination for fear of contracting the disease.[34] A study in Australia showed that health-care workers were significantly more aware of vaccination than those in other occupations.[35] More frequent contact with health-care providers, especially with a regular physician, could be effective in providing education about HAV infection and promoting timely HAV vaccination among men who have sex with men.[36]

### Limitations

This outbreak investigation has some limitations. Around half of the cases were reported from a designated HIV hospital, so some selection bias may have been introduced into the data. Considering that the population is highly vulnerable, we could collect only limited information when tracing sexual contacts. Only half of the inpatient cases among this vulnerable population participated in the interview from which we derived information about risk factors. We could not collect information about the specific SNS tools used by this vulnerable population, such as Tinder or Grindr, as this is sensitive information. Also, our investigation analysed the collection of qualitative data via semistructured interviews to try to understand risk behaviours, and recall bias might be a potential limitation in terms of retrospective data collection. We could not collect details of the clinical course of the illness.

## CONCLUSIONS

In 2018, the annual number of reported cases of HAV infection was 131 in Shinjuku, Tokyo, Japan. Of these, 98% were male and 81% were men who have sex with men. We recommend that men who have sex with men, as a population at high risk for HAV infection, should be made more aware of the risk of infection with this STI. This population should also receive HAV vaccination. To improve adherence to safer sex practices, various sources, including local governments, health-care providers and voluntary support groups, can be engaged to widely disseminate information via SNS to improve vital knowledge, attitudes, beliefs and practices regarding the necessity of HAV prevention and vaccination.

### *Acknowledgements*

The authors thank the Tokyo Metropolitan Institute of Public Health for its assistance in the laboratory analysis and the Tokyo Metropolitan Government for its assistance with the epidemiological information.

### *Conflict of interest*

The authors have no conflicts of interest to declare.

### *Ethics statement*

This investigation was conducted in accordance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases in Japan, and therefore ethics committee approval was not required under the law.

### *Funding*

None.

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# Monitoring mortality in the setting of COVID-19 pandemic control in Victoria, Australia: a time series analysis of population data

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**Objective:** Mortality surveillance was established in the state of Victoria just before the COVID-19 pandemic. Here, we describe the establishment of this surveillance system, justify the modelling approach selected, and provide examples of how the interpretation of changes in mortality rates during the pandemic was influenced by the model chosen.

**Methods:** Registered deaths occurring in Victoria from 1 January 2015 to 31 December 2020 were sourced from the Victoria Death Index. Observed mortality rates were compared to a raw historical 5-year mean and to predicted means estimated from a seasonal robust regression. Differences between the observed mortality rate and the historical mean (ΔMR) and excess mortality rate from the observed and predicted rates were assessed.

**Results:** There were 20 375 COVID-19 cases notified in Victoria as of 31 December 2020, of whom 748 (3.7%) died. Victorians aged ≥85 years experienced the highest case fatality ratio (34%). Mean observed mortality rates in 2020 (MR: 11.6; 95% confidence interval [CI]: 11.4, 11.9) were slightly reduced when compared with the annual rate expected using the historical mean method (mean MR: 12.2; 95% CI: 12.1, 12.3; ΔMR: -0.57; 95% CI: -0.77, -0.38), but not from the rate expected using the robust regression (estimated MR: 11.7; 95% prediction interval [PI]: 11.5, 11.9; EMR: -0.05; 95% CI: -0.26, 0.16). The two methods yielded opposing interpretations for some causes, including cardiovascular and cancer mortality.

**Discussion:** Interpretation of how pandemic restrictions impacted mortality in Victoria in 2020 is influenced by the method of estimation. Time-series approaches are preferential because they account for population trends in mortality over time.

Mortality surveillance is widely used to understand and forecast trends and patterns of mortality over time, thus guiding the development of policy to reduce the burden of specific causes of disease and death.[1,2] Specific applications include monitoring the health impacts of significant public health events, such as extreme temperatures,[3] bushfires[4,5] and epidemics.[6,7] In 2020, existing surveillance systems proved a useful tool for monitoring the direct and indirect impact of the COVID-19 pandemic on mortality.[8,9] Notably, in countries with limited circulation of SARS-CoV-2, mortality was lower than expected in 2020,[10] while in countries with large epidemics, mortality was in excess.[8]

Different approaches to monitoring mortality have been implemented during the pandemic.[11] One simple method, employed by some countries,[10,12,13] compares mean mortality for some historical period with current-year rates. While easy to implement, this approach does not accommodate time trends in expected mortality, which generally declines over time, consistent with increasing life expectancy. Time-series regression models

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Published: 16 January 2025
doi: 10.5365/wpsar.2025.16.1.1091

overcome this problem by incorporating parameters that predict seasonal mortality patterns and predict the increased mortality typically observed during winter months.[7] Various regression approaches have been adopted by national surveillance systems for estimating excess COVID-19-attributable mortality and mortality rates (MRs).[11,14,15] While there are many regression model options available, comparison of different modelling options for influenza surveillance suggests they yield similar estimates.[7,16,17] Moreover, real-time surveillance data availability may be delayed, making some of these approaches inappropriate.

In 2019, mortality surveillance was newly established in the state of Victoria in anticipation of the seasonal influenza epidemic. This surveillance was rapidly adapted in early 2020 to enable real-time situation assessment of changes in mortality associated with COVID-19 infections and restrictions. Here, we describe mortality surveillance in Victoria, provide a summary of COVID-19 deaths in 2020, and compare two methods for real-time monitoring of mortality for public health decision-making.

## METHODS

### Data sources

All laboratory-confirmed cases of COVID-19 are notifiable to the Victorian Department of Health (the Department) under public health and wellbeing legislation. These data were sourced from the Public Health Event Surveillance System (PHESS), along with demographic, clinical and epidemiological risk information. All notified deaths of people with COVID-19 were recorded in this system when official notifications were made to the Department or during case or outbreak follow up. Since these data capture individuals who died due to COVID-19 as well as other causes, deaths where this distinction was unclear underwent clerical review by a multidisciplinary team of public health and infectious disease medical practitioners and epidemiologists in accordance with the national case definition.[18]

Data for all registered deaths between 2015 and 2020 were sourced from the Victorian Death Index (VDI), maintained by the Registrar of Births, Deaths and Marriages. The data provided consisted of an electronic copy of the medical certificate of cause of death for all deaths registered in Victoria, including coroner-referred deaths. The certificate included free-text fields for direct, antecedent and other causes of death, as well as other information such as age, sex, date of birth, date of death, marital status, parents' details, number of siblings, number and age of children and address of the deceased.

Cause-specific deaths were identified using keyword searches in the free-text causes of death fields in the VDI data using the multiple causes of death methodology (see **Supplementary Information**).[2] The term "multiple causes of death" refers to all conditions listed in the death certificate. If the death certificate included any mention of a condition in any of the text fields of causes of death including the direct cause, antecedent cause or other causes, then that deceased person was categorized as having that specific cause of death as one of their causes of death. Data management was conducted using the Stata® statistical package version 16.

A stringency index, categorized into five levels, was developed based on key restrictions implemented by the state government (see **Supplementary Information**).[2] These included restrictions on mobility, social and religious congregation, school and workplace attendance, health and aged-care facility visitation, and access to dining, retail and services. Restrictions were initially implemented in March–April 2020, relaxed in May 2020 with successful containment of SARS-CoV-2 transmission, and then reimplemented in July–October 2020 when new cases were detected due to transmission to workers in hotel quarantine. The implementation and categorization of these restrictions have been described in detail elsewhere.[19]

Population denominators for the calculation of MRs were derived from mid-year resident population estimates provided by the Australian Bureau of Statistics for 2015–2019[20] and from the Victorian Department of Environment, Land, Water and Planning for 2020.[21]

### Statistical analysis

COVID-19 incidence rates, case fatality ratios (CFR) and MRs were calculated overall and for pre-defined age groups (<65 years, 65–74 years, 75–84 years, ≥85 years). The incidence of COVID-19 for 2020 was calculated as the number of notified COVID-19 cases per 100 000 population. CFRs were calculated as the proportion of notified COVID-19 deaths among all notified COVID-19

Table 1. **COVID-19 confirmed cases, incidence rates, registered deaths, case fatality ratio and mortality rates, Victoria, Australia, 2020**

| Age group (years) | Cases | Distribution (%) | Population | Incidence rate (per 100 000 population) | Deaths | Case fatality ratio (%)[a] | COVID-19 mortality rate (per 100 000 population)[b] |
|---|---|---|---|---|---|---|---|
| **<65** | 17 124 | 84.0 | 5 678 949 | 302 | 26 | 0.2 | 0.5 |
| **65–74** | 970 | 4.8 | 582 720 | 166 | 62 | 6.4 | 11 |
| **75–84** | 945 | 4.6 | 328 475 | 288 | 209 | 22.1 | 64 |
| **≥85** | 1336 | 6.6 | 139 481 | 958 | 451 | 33.8 | 323 |
| **Total** | 20 375 | 100 | 6 729 626 | 302 | 748 | 3.7 | 11 |

[a] The case fatality ratio is calculated as the number of COVID-19 deaths among all notified COVID-19 cases.

[b] The COVID-19 mortality rate is calculated as the number of COVID-19 deaths among the total population.

cases. The COVID-19 MR was calculated as the number of COVID-19 deaths among the total population.

The weekly MR was calculated as the weekly number of deaths divided by the population for each age group and cause of death and converted to a rate per 100 000 population. The specific causes of interest included pneumonia and influenza, respiratory causes, cardiovascular disease, cancer and injuries including accidents.

Two methods for assessing the deviation in MRs were used. In the first, the observed weekly MR was compared with the historical mean weekly MR based on the prior 5 years' data (2015–2019). Differences in the weekly observed and historical mean rates were calculated and averaged to estimate the annual mortality rate difference (ΔMR).

Second, excess mortality was estimated as the difference between the observed weekly MR and the expected weekly MR predicted from a seasonal robust linear regression model fit using the observed weekly MRs in the previous 5 years. Data were fit using the rlm function in the MASS package in R (see **Supplementary Information** for associated R scripts), assuming the following equation:

$$Expected\ death\ rate = \beta_0 + \beta_1 week + \beta_2 \sin\left(\frac{2\pi week}{52.18}\right) + \beta_3 \cos\left(\frac{2\pi week}{52.18}\right)$$

This method is an extension of the well-established Serfling method,[22,23] and incorporates a sinusoidal term to predict the seasonal trend in mortality typically observed in temperate settings. Standard errors were estimated using Tukey's bisquare function, which is robust to outliers.[24] This approach was chosen over other options, such as a Poisson regression, to align with methods used in national surveillance[25] and in other states,[23] and because prior studies using Australian data had reported minimal differences in overall estimates using different approaches.[16]

The excess mortality rate (EMR) was estimated as the weekly observed MR minus the predicted MR from the model. We refer to it as the excess MR, even where the estimates were negative, suggesting lower-than-expected MRs. The epidemic threshold that differentiates extreme mortality events (both epidemics and periods of lower-than-expected mortality) from random variation was set as follows:

$$Threshold = seasonal\ baseline \pm 1.96 \times SE\ (seasonal\ baseline)$$

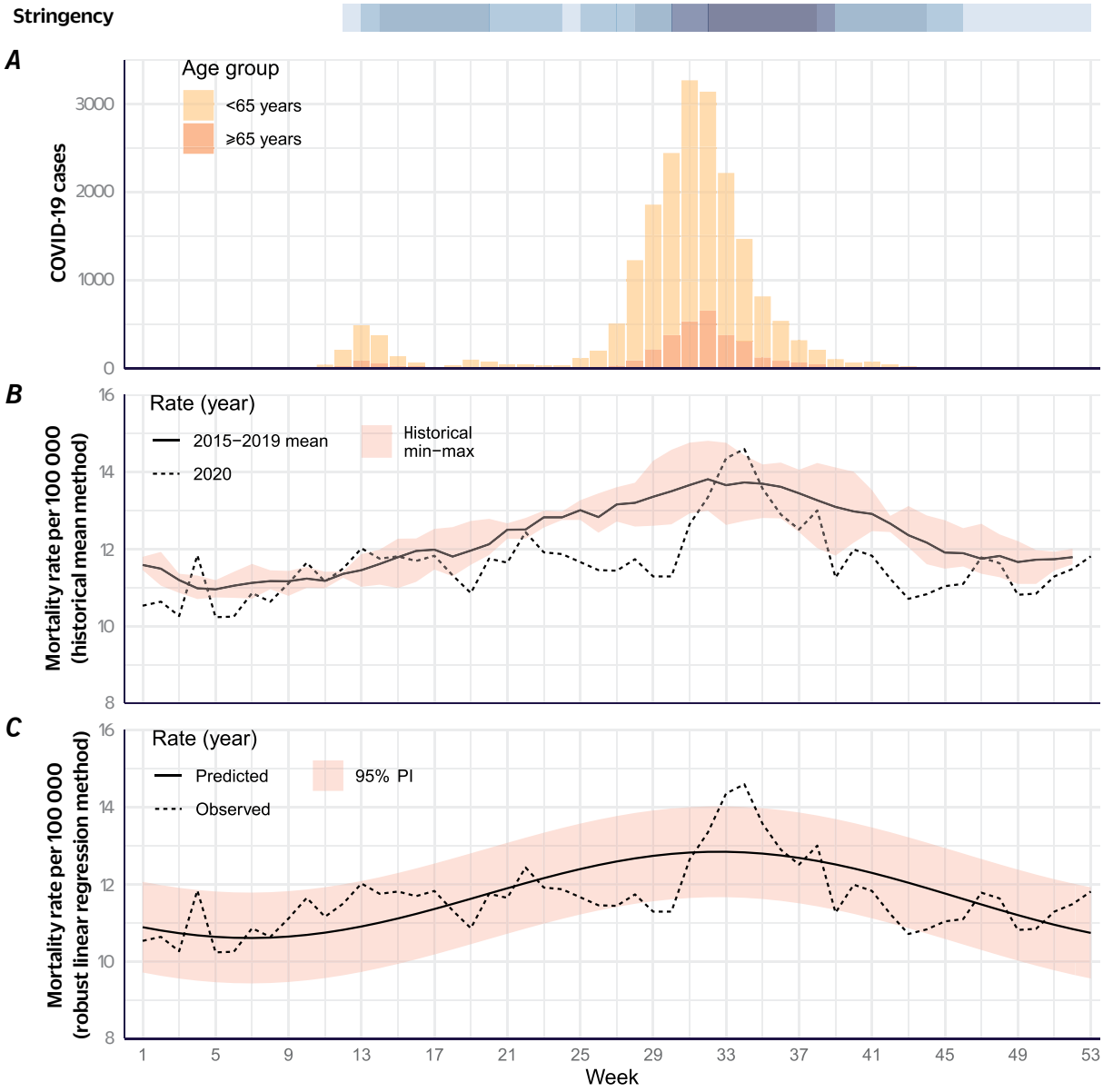
Deviations in observed MRs for 2020 from expected MRs based on either the historical mean or the seasonal robust regression estimates were visually assessed with respect to the stringency of restrictions in place at different times during 2020.

## RESULTS

### COVID-19 deaths

From 27 March to 31 December 2020, there were 20 375 COVID-19 cases in Victoria, Australia. These cases were associated with 748 registered deaths attributed to COVID-19, with another 72 deaths being attributed to other causes. Deaths arising from COVID-19 in Victoria were not evenly distributed across age groups and were positively correlated with age (**Table 1**).

Fig. 1. **Weekly all-cause mortality in Victoria, Australia, considering COVID-19 notifications and pandemic restrictions**




(A) COVID-19 case numbers, shaded by age (above or below 65 years). The stringency band across the top indicates the degree of restrictions, with darker colours indicative of more stringent COVID-19 restrictions (see **Supplementary Information**[19]).

(B) Observed all-cause mortality rate against the 5-year historical mean (2015–2019). Shaded area indicates the range (minimum and maximum) for 2015–2019 and identifies several weeks where mortality in 2020 was below the historical mean and minimum levels.

(C) Observed all-cause mortality rate against the rate expected from the robust regression estimates. Shaded area indicates the 95% prediction interval (PI).

People aged <65 years accounted for 84% of COVID-19 cases, with an incidence rate (IR) of 302 per 100 000 population. However, deaths in this age group were low (CFR: 0.2%; MR: 0.46 per 100 000 population). In contrast, Victorians aged ≥85 years comprised just 6.6% of notified COVID-19 cases but experienced far higher fatality and MR (CFR: 34%, MR: 323 per 100 000 population).

## Mortality and COVID-19 restrictions

Weekly MRs observed in 2020 against COVID-19 cases and pandemic restrictions are shown in **Fig. 1 (B, C)**. Stage 1 restrictions were introduced in mid-March 2020 and were rapidly ramped up to stay-at-home orders (Stage 3) at the end of March (week 14). Mortality rates declined coincident with Stage 3 restrictions and dropped

Table 2. **Summary of mean observed (2020) versus 5-year mean (2015–2019) all-cause mortality rate per 100 000 population, by age group, Victoria, Australia**

| Age group (years) | Observed mortality rate 2020 (95% CI) | Historical mean mortality rate 2015–2019 (95% CI) | Mean rate difference (95% CI) | Predicted mortality rate (95% PI) | Excess mortality rate (95% CI) |
|---|---|---|---|---|---|
| **<65** | 2.28 (2.22, 2.35) | 2.43 (2.40, 2.46) | -0.15 (-0.22, -0.07) | 2.33 (2.32, 2.35) | -0.05 (-0.11, 0.02) |
| **65–74** | 20.5 (19.9, 21.0) | 21.6 (21.3, 21.9) | -1.13 (-1.8, -0.48) | 20.89 (20.60, 21.19) | -0.44 (-1.03, 0.15) |
| **75–84** | 60.7 (59.0, 62.5) | 67.1 (66.2, 68.1) | -6.43 (-7.9, -5.0) | 60.9 (59.73, 62.09) | -0.13 (-1.66, 1.40) |
| **≥85** | 240 (232, 248) | 252 (248, 256) | -11.78 (-17, -6.6) | 240 (233.15, 245.93) | 0.61 (-5.16, 6.38) |

CI: confidence interval; PI: prediction interval.

Week 53 is removed for comparisons. Predicted rates are estimated from the robust linear regression model using weekly mortality data during 2015–2019.

Table 3. **Summary of mean observed (2020) versus 5-year mean (2015–2019) all-cause mortality rate per 100 000 population, by cause of death, Victoria, Australia**

| Cause of death | Observed mortality rate 2020 (95% CI) | Historical mean mortality rate 2015–2019 (95% CI) | Mean rate difference (95% CI) | Predicted mortality rate (95% PI) | Excess mortality rate (95% CI) |
|---|---|---|---|---|---|
| **All causes** | 11.6 (11.4, 11.9) | 12.2 (12.1, 12.3) | -0.57 (-0.77, -0.38) | 11.7 (11.5, 11.9) | -0.05 (-0.26, 0.16) |
| **Pneumonia and influenza** | 1.14 (1.07, 1.20) | 1.60 (1.55, 1.65) | -0.46 (-0.55, -0.37) | 1.28 (1.21, 1.36) | -0.15 (-0.24, -0.07) |
| **Respiratory** | 2.77 (2.65, 2.89) | 3.48 (3.39, 3.56) | -0.71 (-0.83, -0.58) | 2.78 (2.66, 2.91) | -0.02 (-0.15, 0.12) |
| **Cardiovascular** | 5.03 (4.90, 5.15) | 5.61 (5.50, 5.72) | -0.58 (-0.69, -0.48) | 4.45 (4.31, 4.58) | 0.57 (0.47, 0.68) |
| **Cancer** | 3.77 (3.69, 3.84) | 3.92 (3.87, 3.96) | -0.15 (-0.23, -0.07) | 3.56 (3.54, 3.58) | 0.21 (0.13, 0.28) |
| **Injury** | 0.43 (0.40, 0.46) | 0.57 (0.55, 0.58) | -0.14 (-0.17, -0.10) | 0.47 (0.46, 0.47) | -0.03 (-0.06, 0.00) |

CI: confidence interval; PI: prediction interval.

Week 53 was removed for comparisons. Predicted rates are estimated from the robust linear regression model using weekly mortality data during 2015–2019.

by week 19. Rates did not appreciably increase again until week 31, at the height of the second epidemic wave, which was characterized by a series of outbreaks in residential aged-care facilities.[19,26] Mortality rates peaked when restrictions were most stringent, consistent with efforts to limit SARS-CoV-2 transmission and the peak in case fatality among residents in aged-care settings. The control of the SARS-CoV-2 epidemic and relaxation of restrictions were followed by a return to MRs lower than the historical mean and estimated rates.

## Mean mortality rate difference based on the historical mean

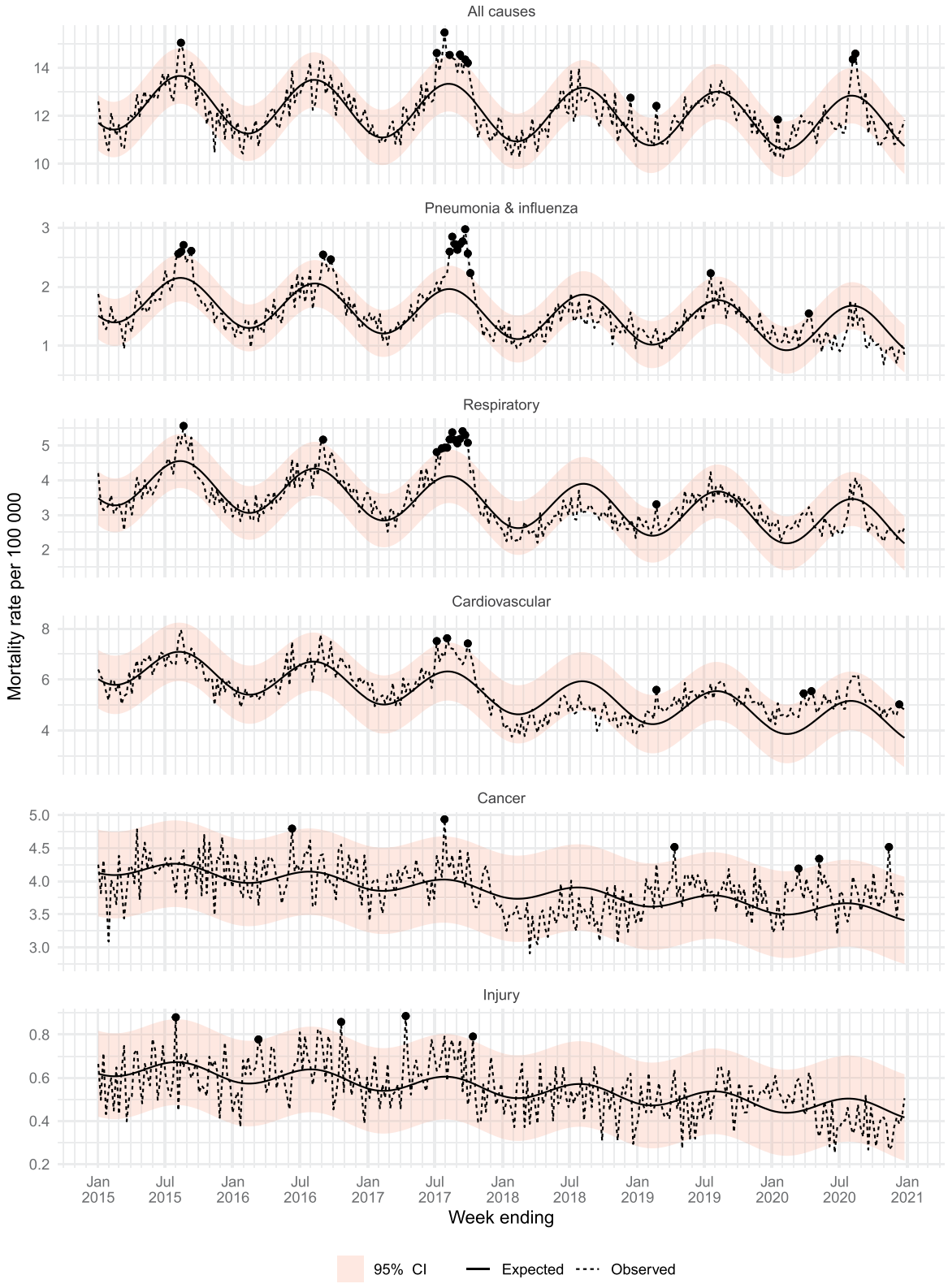
All-cause weekly MRs observed in 2020 compared with the 5-year historical mean are shown in **Fig. 1B**. The all-cause MR in 2020 (MR: 11.6; 95% confidence interval [CI]: 11.4, 11.9) was lower than the historical mean (MR: 12.2; 95% CI: 12.1, 12.3), with a mean difference (ΔMR) of -0.57 (95% CI: -0.77, -0.38), representing a modest decrease. This trend of reduced mortality in 2020 was replicated in all age groups examined (**Table 2**), with the greatest difference observed for those aged ≥85 years (ΔMR: -11.78; 95% CI: -17, -6.6).

A similar trend of lower observed mortality than that expected based on the historical mean was noted for each of the cause-specific MRs (**Table 3**). The observed MR in 2020 was lower than the historical mean for pneumonia and influenza (ΔMR: -0.46; 95% CI: -0.55, -0.37), respiratory (ΔMR: -0.71; 95% CI: -0.83, -0.58) and cardiovascular causes (ΔMR: -0.58; 95% CI: -0.69, -0.48). More modest decreases in mortality were observed for cancer deaths, accidents and injuries (**Table 3**).

## Excess mortality rate estimated from the seasonal robust regression model

As shown in **Fig. 1C**, weekly all-cause MRs observed in 2020 were both higher and lower than the estimated rates predicted by the seasonal robust regression model. However, the all-cause predicted mortality estimate was 11.7 (95% prediction interval [PI]: 11.5, 11.9), which

Fig. 2. **Weekly cause-specific mortality rates estimated from the robust regression model, Victoria, Australia, 2015–2020**




CI: 95% confidence interval.

2020 expected mortality rates are predicted from the seasonal robust regression model using data from 2015–2019. Points are emphasized where observed mortality exceeds the expected rates. Excess all-cause, pneumonia and influenza and respiratory mortality in 2017 are attributed to the severe influenza season experienced that year. Each vertical gridline represents 1 month. Note the different y-axis scales in each facet.

was comparable with the observed rate (PI: 11.6; 95% CI: 11.4, 11.9), and there was thus a negligible net difference across the year with an EMR of -0.05 (95% CI: -0.11, 0.02; **Table 2**). Predicted all-cause mortality over the entire estimation period is shown in **Fig. 2**. Notable weeks of excess mortality can be seen in 2017, during which there was a severe influenza epidemic[27] (**Fig. 2**).

By age, observed MRs were lower than the estimated rates expected from the model for most age groups, except for those aged ≥85 years, for whom the rate was slightly higher, albeit with wide CIs (EMR: 0.61; 95% CI: -5.16, 6.38). Unlike the estimates using the historical mean, the CIs around the age-specific estimates of excess mortality included 0, suggesting the results were compatible with either an increase or decrease in mortality (**Table 2**).

Cause-specific estimates of excess mortality are shown in **Table 3**, and the modelled weekly estimates are shown in **Fig. 2**. Seasonality trends were most apparent for pneumonia and influenza, respiratory and cardiovascular causes (**Fig. 2**). There was a decline in mortality from pneumonia and influenza (EMR: -0.15; 95% CI: -0.24, -0.07), consistent with the analysis using the historical mean. However, unlike the historical mean method, observed mortality in 2020 was estimated to be higher than expected for cardiovascular (EMR: 0.57; 95% CI: 0.47, 0.68) and cancer causes (EMR: 0.21; 95% CI: 0.13, 0.28).

## DISCUSSION

The direct global mortality burden of COVID-19 has without a doubt been substantial.[28] However, the extent to which this may have been offset by pandemic mitigation measures deserves attention. To this end, we explored the impact of COVID-19 and associated containment measures on mortality dynamics in Victoria. Despite the substantial direct mortality burden attributable to COVID-19, there was no overall excess mortality in Victoria during the first year of the COVID-19 pandemic, 2020, highlighting the countervailing impact of containment and mitigation measures.

Although we did not detect higher-than-expected net mortality across 2020, MRs did deviate from their expected values at various times, being both substantially higher and lower than expected at different stages of the pandemic. During the first epidemic wave, a small spike in mortality was observed, followed by a drop when mitigation measures were initially introduced. Observations of reduced mortality during periods of pandemic restrictions have also been reported internationally. In New Zealand, border closures and strict mitigation measures early in the pandemic successfully limited SARS-CoV-2 circulation[29] and were associated with reduced all-cause (notably pneumonia-influenza) mortality.[10] Our findings also accord with an early pandemic study (February–May 2020), which examined all-cause mortality in 21 industrialized countries and showed that Australia was one of the few countries that avoided a detectable rise in all-cause mortality during the first wave of the COVID-19 pandemic, having the seventh-lowest level of excess deaths among the surveyed countries.[28]

As the pandemic progressed, a much larger spike in mortality was observed during Victoria's second epidemic wave, leading to substantial COVID-19 excess mortality, which offset the reductions in mortality seen in earlier months. The CFR in Victoria was high at 3.9%, reaching up to 34% in the oldest age groups, reflecting the large number of outbreaks in residential aged-care facilities. Residents of aged-care facilities comprised 10% of all COVID-19 cases in Victoria in 2020 and 80% of all deaths.[19] Other countries, such as Japan and Singapore, which had comparable COVID-19 incidence rates but far lower CFRs at the time,[30] were successful in preventing outbreaks in residential aged-care facilities.

A key outcome of our study was the discrepancy in estimated excess mortality that was observed when we used different methods to measure the expected weekly mortality rate. We used both a simple historical mean method and a seasonal robust linear regression. The former approach compares a mean mortality rate without adjustment for trend associated with changes in life expectancy.[31] In our study, this method overestimated excess mortality, but in other settings it may underestimate excess mortality.[11] The robust linear regression predicted a lower weekly mortality rate in 2020 because mortality in the years used for estimation (2015–2019) was steadily decreasing, and the model predicted this trend to continue. As a result, differences in observed and expected mortality were less pronounced using the regression approach compared with the 5-year historical mean approach. This has implications for interpretation of national data, and those countries that reported estimated mortality during the pandemic against

the historical mean may have over- or underestimated the true rate.

Within our own data, the difference between these methods could lead to different interpretations of the pandemic's impact on mortality. For example, pneumonia and influenza mortality rates were lower than expected using both methods. This effect was probably quite large in most settings and can be attributed to disruptions to usual seasonal activity of respiratory pathogens, most notably influenza and respiratory syncytial virus, due to containment measures enacted in response to the pandemic, for which there is substantial evidence both locally[32–34] and globally.[35,36] In contrast, the robust linear regression analysis indicated that cardiovascular and cancer mortality rates were higher than expected, while the comparison to the historical mean suggested that rates for these causes were lower than expected.

Reasonable explanations for both an increase and a decrease might be possible. A potential hypothesis for excess mortality due to cardiovascular and cancer causes is that stay-at-home orders may have led to a delay in screening and seeking medical treatment for noncommunicable diseases.[37,38] In contrast, the observation of increased (as opposed to decreased) cardiovascular mortality runs counter to prior observations that have associated excess cardiovascular mortality with influenza infection, and influenza all but disappeared during the study period.[39,40] Further investigation is required to disentangle this paradox. Nevertheless, our assertion is that estimates of excess mortality do need to account for the time trend, in which case, the seasonal robust regression is expected to provide a more reliable estimate of mortality.

One of the major strengths of this mortality surveillance is the utilization of near-real-time death data. To expedite real-time reporting in 2020, we did not code the free-text causes of death into International Classification of Disease 10 (Australian Modification) codes, but instead used keyword search terms, an approach successfully implemented in the neighbouring state of New South Wales for many years.[23] Moreover, we used multiple cause of death methodology, rather than using the principal cause of death. National mortality surveillance conducted by the Australian Bureau of Statistics standardizes the cause of death from data provided by death registries in each Australian state and territory using the World Health Organization *International Classification of Diseases, Tenth Revision (ICD-10)* codes. That surveillance approach is slower because of the need for coding. Moreover, only the underlying cause of death is considered (the disease or injury that initiated the chain of morbid events leading directly to death), which may lead to differences in the number of deaths counted for each cause. This discordance in methodology is a potential limitation of our work in that it makes it challenging to compare our results with other published estimates from Australia.[25] Nevertheless, the use of seasonal robust linear regression and the number of prior years' data used for estimation are similar, and the overall pattern of mortality observed in our study did not substantially deviate from the ICD-coded data analysed by the Australian Bureau of Statistics.[25]

Our study only assessed mortality dynamics during 2020. This allowed us to focus on excess mortality at the time this surveillance system was set up in Victoria and to evaluate two options for conducting that surveillance. Further work could examine in more detail how mortality continued to evolve throughout the pandemic, for example, to explore whether there was any displaced mortality (sometimes referred to as "harvesting") associated with deaths prevented in 2020, or the role of vaccination and public health and social measures. Furthermore, a key purpose of this paper is to show that the measurement of excess mortality is quite a subtle concept and that it is sensitive to the manner in which expected mortality is measured. While this can be construed as a limitation in that it precludes the identification of a single, clear-cut measure of excess mortality, we view this as a methodological contribution of our paper.

This paper provides an overview of COVID-19-associated and excess mortality in Victoria, Australia, during the first year of the COVID-19 pandemic. We observed no excess mortality in 2020; however, our determination of this depended on the method chosen. We have highlighted the limitations of simple methods to estimate excess mortality and the need to consider long-term trends. Regardless of which method is most correct, given the high risk of all-cause, pneumonia and influenza and COVID-19 mortality for those in older age groups, efforts to limit the introduction and spread of disease in communities of older individuals need continued and sustained attention. Above all, this paper

highlights the value of mortality surveillance in providing timely intelligence relating to the impact of major public health events on local populations, which can inform the design and implementation of mitigation and containment measures.

## *Acknowledgements*

The authors thank the Registrar of Births, Deaths and Marriages for providing the VDI data and Anand Bharadwaj (Department of Economics, University of Melbourne) for thoughtful suggestions on statistical methodology and critical review.

## *Conflicts of interest*

At the time this work was undertaken, LS, SGS, DH and SLR were employed at the Victorian Department of Health. SGS has consulted for CSL Seqirus, Pfizer, Moderna and EvoHealth. The other authors have no conflicts of interest to declare.

## *Ethics statement*

Data in this study were collected, used and reported under the Victorian Public Health and Wellbeing Act 2008. Under this act, the Victorian Department of Health has the legal authorization to collect data on certain health-related conditions that are used to inform public heath prevention and control efforts, thereby protecting the health and safety of the Victorian community.

## *Funding*

This work was supported by the Victorian Government Department of Health. The WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health. DM is supported by a National Health and Medical Research Council (NHMRC) Investigator Grant (APP1194109). The contents of the published material are solely the responsibility of the Administering Institution, a Participating Institution or individual authors and do not reflect the views of the NHMRC.

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# Estimating the impact of the COVID-19 pandemic on infectious disease notifications in Klang district, Malaysia, 2020–2022

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**Objective:** The COVID-19 pandemic disrupted disease surveillance systems globally, leading to reduced notifications of other infectious diseases. This study aims to estimate the impact of the COVID-19 pandemic on the infectious disease surveillance system in Klang district, Selangor state, Malaysia.

**Methods:** Data on notifiable diseases from 2014 to 2022 were sourced from the Klang District Health Office. The 11 diseases with more than 100 notifications each were included in the study. For these 11 diseases, a negative binomial regression model was used to explore the effect of the pandemic on case notifications and registrations by year, and a quasi-Poisson regression model was used to explore the changes by week.

**Results:** The results showed a reduction in the number of notifications and registrations for all 11 diseases combined during the pandemic compared with previous years. Changes between expected and observed notifications by week were heterogeneous across the diseases.

**Discussion:** These findings suggest that restrictive public health and social measures in Klang district may have impacted the transmission of other infectious diseases during the COVID-19 pandemic. The differential impact of the pandemic on disease notifications and reporting highlights the large ancillary effects of restrictive public health and social measures and the importance of building resilience into infectious disease surveillance systems.

The COVID-19 pandemic significantly impacted global disease surveillance, leading to disruptions within disease notification systems. The pandemic significantly strained health systems, resulting in reduced capacities for notifications and case detection.[1] However, the restrictions on mobility due to public health and social measures resulted in reduced transmission of infectious diseases within the community.

Malaysia, along with numerous other nations, was severely affected by the COVID-19 pandemic. As of March 2023, Malaysia had reported more than 4 million COVID-19 cases and more than 45 000 deaths.[2] The pandemic prompted the implementation of various public health and social measures, such as movement restrictions, border controls and mask mandates. These interventions were effective in reducing COVID-19 transmission within the community.[3,4] However, public health and social measures have had other well documented, ancillary effects on societies and economies.[5]

A surveillance system in public health refers to the continuous and systematic collection, analysis and interpretation of health-related data that are essential for planning, implementing and evaluating public health practices.[6] These systems play a pivotal role in detecting, monitoring and responding to emerging and endemic diseases to safeguard global health security.[7] Malaysia has an established infectious disease notification system, with all health-care providers mandated by law to report cases to the Ministry of Health.[8] The reduction in human mobility and the strain on the health-care system during the COVID-19 pandemic may have had unintended effects on the notification of other infectious

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Published: 27 January 2025
doi: 10.5365/wpsar.2025.16.1.1097

diseases.[1,9] However, quantifying the effect of acute shocks on a surveillance system can allow for the necessary calibration of a system's capabilities, both in the short-term and for future readiness. The objective of this study was to investigate the impact of the COVID-19 pandemic on the surveillance of infectious diseases in Klang district, Selangor state, Malaysia from 2020 to 2022.

## METHODS

### Study setting, data source and inclusion criteria

The Klang District Health Office serves a population of 1.1 million over a land area of 6 $km^2$, making it one of the most densely populated areas served by a district health office in Selangor.[10] In Malaysia, the Prevention and Control of Infectious Diseases Act 1988 (Act 342) mandates the reporting of 31 diseases by health-care facilities.[8] All diseases included in the Act are notified, verified and registered via an e-notification system except for dengue, measles, tuberculosis (TB) and HIV, which are handled by integrated ancillary systems for case registration and management.

Notification refers to the mandatory reporting of specific infectious diseases by health-care providers to relevant health authorities upon diagnosis, whether suspected or confirmed. Notifications are then verified to determine whether they meet the case definition before a patient is registered as a confirmed case. The verification process conducted by public health inspectors – involving phone checks and source tracing to confirm the authenticity and accuracy of notifications – experienced delays during the COVID-19 pandemic due to resource diversion. Verified notifications meeting the case definition for a disease are registered. Batch processing of registrations – whereby notifications are not registered immediately but might instead be cumulatively registered, for instance, at the end of a week – can lead to discrepancies in the data, showing more registrations than notifications in certain weeks. This does not necessarily indicate a true change in disease patterns but rather reflects the timing of data entry. The case definition and clinical and laboratory criteria are based on Malaysia's case definition guidelines,[11] and these did not undergo any major revision for the diseases studied during the study period.

Data on all notifiable diseases were sourced from the Klang District Health Office between epidemiological week 1 of 2014 (29 December 2013) and epidemiological week 52 of 2022 (31 December 2022). Age, sex, date of notification and date of registration were extracted for each notification. Diseases with fewer than 100 notifications or registrations per year were excluded from the analysis because these small counts are less likely to be accurately modelled (i.e. chikungunya, cholera, leprosy, malaria, rabies, tetanus, typhus, typhoid/paratyphoid, pertussis and viral encephalitis). Notifiable diseases included in the analysis were dengue; leptospirosis; foodborne illness; dysentery; measles; hand, foot and mouth disease (HFMD); TB; HIV; gonorrhoea; syphilis; and viral hepatitis. Additionally, data about policies were obtained from the Oxford COVID-19 Government Response Tracker,[12] specifically the Stringency Index and information about school closures, which quantify the strictness of government measures and the status of educational institutions, respectively.

### Data analysis

Data were collated and aggregated into weekly notification and registration counts for all diseases and for each disease separately. Two analyses were conducted using different dimensions of data and statistical approaches, as previously described.[1,9] The first analysis examined the effect of the COVID-19 pandemic on case notifications and registrations in Klang district.

The between-period rate of change in case notifications and registrations was estimated using a negative binomial regression model. The model estimated the effect of the pandemic on notifications and registrations by comparing baseline (2014–2019) and pandemic years (2020–2022). Exponentiated coefficients from the model represent the multiplicative effect on notifications and registrations, quantifying increases or decreases relative to the baseline. The regression coefficient ($\beta$) used in estimating the percentage change in notifications and registrations (1 – exp ($\beta$) across the different periods is given by the function:

$$\log(E(\text{count})) = \alpha + \beta 1(\text{pandemic})$$

where E(count) is the expected count, $\alpha$ is the intercept and $\beta 1$ is the effect of the pandemic variable on the log count.

The second analysis estimated and was used to visualize the weekly change in the frequency of case notifications and registrations. A quasi-Poisson regression model was trained using observed count data from week 1 of 2014 to week 52 of 2019. The model included terms for trend and seasonality. This model is given by the function:

$$\log(E(\text{count})) = \alpha + \beta1(\text{pandemic}) + \beta2(\text{trend}) + \beta3\left(\sin\left(2\pi*\frac{\text{week}}{52}\right)+\cos\left(2\pi*\frac{\text{week}}{52}\right)\right)$$

where $\alpha$ is the intercept, $\beta1$ is the effect of the pandemic variable on the log count, $\beta2$ is the linear time trend and $\beta3$ is the seasonal variation based on the week of the year.

This baseline model was used to predict the expected counts of notifications and registrations from week 1 of 2020 to week 52 of 2022. The expected counts were then compared with the observed counts, and a weekly rate of change was estimated and visualized. The 95% confidence intervals (95% CIs) were estimated through bootstrapping. Goodness-of-fit of the models was assessed using the Akaike information criterion and log-likelihood values. Data analyses were performed with R software v. 4.3.2 (R Core Team, Vienna, Austria) using the tidyverse and MASS packages.[13]

## RESULTS

Relative to the pre-pandemic period, the total number of notifications and registrations decreased in 2020 and 2021 in Klang district before increasing again from mid-2022 onwards. Throughout the pandemic, variations in the stringency of policies, particularly during periods of increased restrictions and school closures, were observed to correlate with fluctuations in notifications and registrations. Notably, spikes in notifications and registrations often followed the relaxation of these measures (**Fig. 1**). This increase was mostly due to notifications of HFMD and dengue (**Fig. 2**). In late 2022, weekly registrations were lower than the number of notifications for HFMD, dengue, TB, gonorrhoea, syphilis, viral hepatitis and leptospirosis (**Fig. 2**).

In the first analysis, the number of notifications and registrations for all 11 diseases combined in 2020 compared with the reference period of 2014–2019 changed by -38% (95% CI: -46% to -30%) for notifications and -37% (95% CI: -44% to -29%) for registrations. Further declines for both categories were observed in 2021: -69% (95% CI: -73% to -65%) for notifications and -69% (95% CI: -72% to -65%) for registrations. In 2022, notifications were 8% higher (95% CI: -4% to 22%) than during the reference period of 2014–2019, while case registrations were -43% (95% CI: -49% to -36%) (**Table 1**).

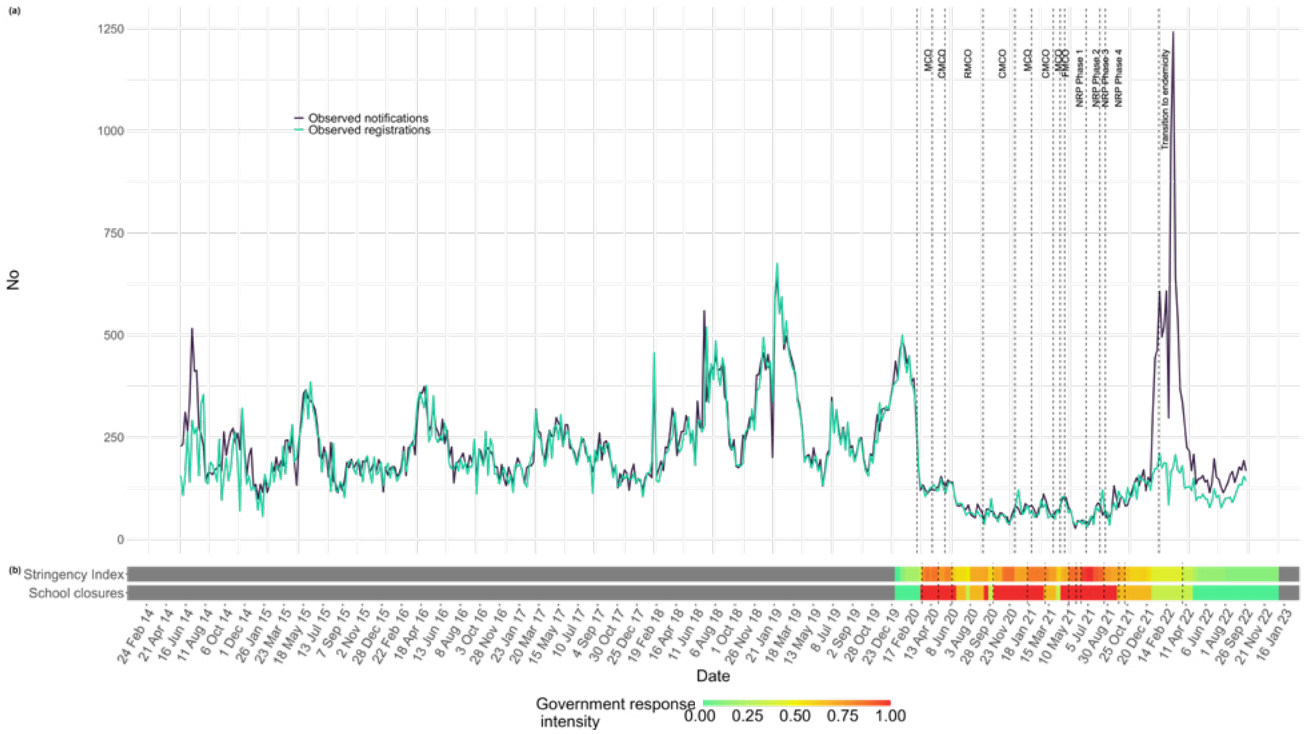
Comparisons of yearly notifications and registrations varied by disease (**Table 1**). Notifications of dengue, foodborne illness, leptospirosis, HFMD and measles decreased during 2020–2022, while those for TB, HIV, gonorrhoea, syphilis and viral hepatitis increased or remained static (**Table 1**).

In the second analysis, comparisons between weekly expected and observed notifications were heterogeneous across the diseases (**Fig. 3**). Dengue, measles and HFMD exhibited clear and consistent reductions in notifications in 2020 and 2021, followed by increases in 2022. However, other diseases, such as foodborne illness and dysentery, showed less consistent reductions.

The exponentiated coefficients for dengue, foodborne illness, dysentery, measles and HFMD indicate there was a decrease in case notifications of 100% or more in 2020 and 2021 when compared with the predicted point estimate, which then moved towards the baseline in week 5 of 2022. In 2022, there was a significant surge in notifications for leptospirosis, dysentery and HFMD, with observed rates substantially exceeding those projected by pre-pandemic trends. During 2020 and 2021, trends for TB, HIV and syphilis were similar to what was expected, with the rates of change for notifications increasing in 2022 in some weeks. Notifications for gonorrhoea and viral hepatitis showed increases of 100% for many weeks during 2020 and 2022, and to a lesser extent during 2021 (**Fig. 3**).

Comparisons between weekly expected and observed registrations were less heterogeneous between diseases. All diseases except TB, HIV, syphilis and viral hepatitis had consistent reductions in the number of registrations between 2020 and 2022 compared with the reference period (**Fig. 4**). However, there

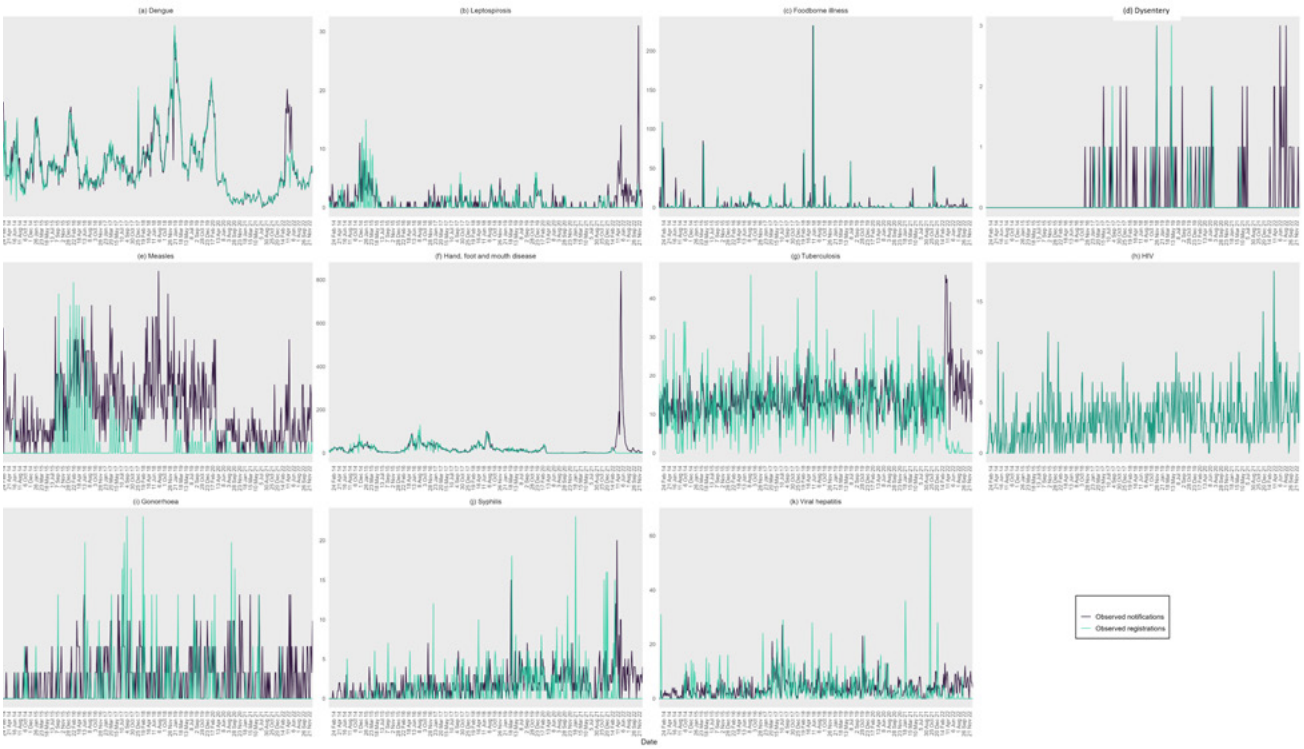
Fig. 1. **(a) All notifications and registrations for the 11 diseases included in the study,[a] Klang district, Malaysia, 2014–2022; (b) COVID-19 government response intensity, Malaysia, 2020–2022**




CMCO: conditional movement control order; FMCO: full movement control order; MCO: movement control order; NRP: national recovery plan; RMCO: recovery movement control order.

[a] Diseases included in this study: dengue; leptospirosis; foodborne illness; dysentery; measles; hand, foot and mouth disease; tuberculosis; HIV; gonorrhoea; syphilis; viral hepatitis.

Fig. 2. **No. of notifications and registrations, by disease, Klang district, Malaysia, 2014–2022[a]**




[a] The numbers of HIV notifications and registrations are the same, thus only one colour is visible.

Table 1. **Differences in notifications and registrations, by year, 2020–2022 compared with 2014–2019, Klang district, Malaysia**

| Disease | Notifications[a] | Registrations[a] |
|---|---|---|
| All diseases | | |
| 2014–2019 | Reference | Reference |
| 2020 | -38 (-46, -30) | -37 (-44, -29) |
| 2021 | -69 (-73, -65) | -69 (-72, -65) |
| 2022 | 8 (-4, 22) | -43 (-49, -36) |
| Dengue | | |
| 2014–2019 | Reference | Reference |
| 2020 | -38 (-46, -29) | -36 (-44, -27) |
| 2021 | -76 (-79, -72) | -75 (-78, -71) |
| 2022 | -20 (-30, -8) | -34 (-42, -24) |
| Leptospirosis | | |
| 2014–2019 | Reference | Reference |
| 2020 | -41 (-64, -5) | -52 (-79, 16) |
| 2021 | -72 (-85, -50) | -70 (-88, -25) |
| 2022 | 194 (105, 330) | -69 (-88, -23) |
| Foodborne illness | | |
| 2014–2019 | Reference | Reference |
| 2020 | -85 (-93, -62) | -92 (-98, -63) |
| 2021 | -24 (-65, 85) | -35 (-82, 205) |
| 2022 | -58 (-80, 0) | -97 (-99, -83) |
| Dysentery | | |
| 2014–2019 | Reference | Reference |
| 2020 | 57 (-28, 218) | 58 (-23, 196) |
| 2021 | 14 (-53, 148) | 15 (-50, 131) |
| 2022 | 273 (108, 565) | 273 (126, 503) |
| Measles | | |
| 2014–2019 | Reference | Reference |
| 2020 | -53 (-63, -40) | -72 (-90, -5) |
| 2021 | -77 (-83, -69) | -92 (-98, -66) |
| 2022 | -53 (-63, -41) | -80 (-94, -33) |

| Disease | Notifications[a] | Registrations[a] |
|---|---|---|
| Hand, foot and mouth disease | | |
| 2014–2019 | Reference | Reference |
| 2020 | -84 (-88, -77) | -84 (-89, -77) |
| 2021 | -96 (-98, -94) | -97 (-98, -95) |
| 2022 | 196 (121, 306) | -93 (-95, -89) |
| Tuberculosis | | |
| 2014–2019 | Reference | Reference |
| 2020 | 6 (-4, 18) | 5 (-16, 31) |
| 2021 | 1 (-9, 12) | 1 (-18, 26) |
| 2022 | 46 (32, 61) | -76 (-81, -69) |
| HIV | | |
| 2014–2019 | Reference | Reference |
| 2020 | 16 (-7, 44) | 16 (-7, 44) |
| 2021 | 29 (4, 59) | 29 (4, 59) |
| 2022 | 71 (40, 109) | 71 (40, 109) |
| Gonorrhoea | | |
| 2014–2019 | Reference | Reference |
| 2020 | 41 (1, 94) | 41 (1, 94) |
| 2021 | -28 (-53, 7) | -28 (-53, 7) |
| 2022 | 14 (-20, 60) | 14 (-20, 60) |
| Syphilis | | |
| 2014–2019 | Reference | Reference |
| 2020 | 87 (45, 142) | 112 (17, 311) |
| 2021 | 45 (10, 91) | 106 (14, 300) |
| 2022 | 172 (114, 246) | -50 (-75, 6) |
| Viral hepatitis | | |
| 2014–2019 | Reference | Reference |
| 2020 | 2 (-20, 32) | -6 (-47, 76) |
| 2021 | -8 (-28, 19) | 26 (-27, 136) |
| 2022 | 37 (8, 75) | -75 (-87, -51) |

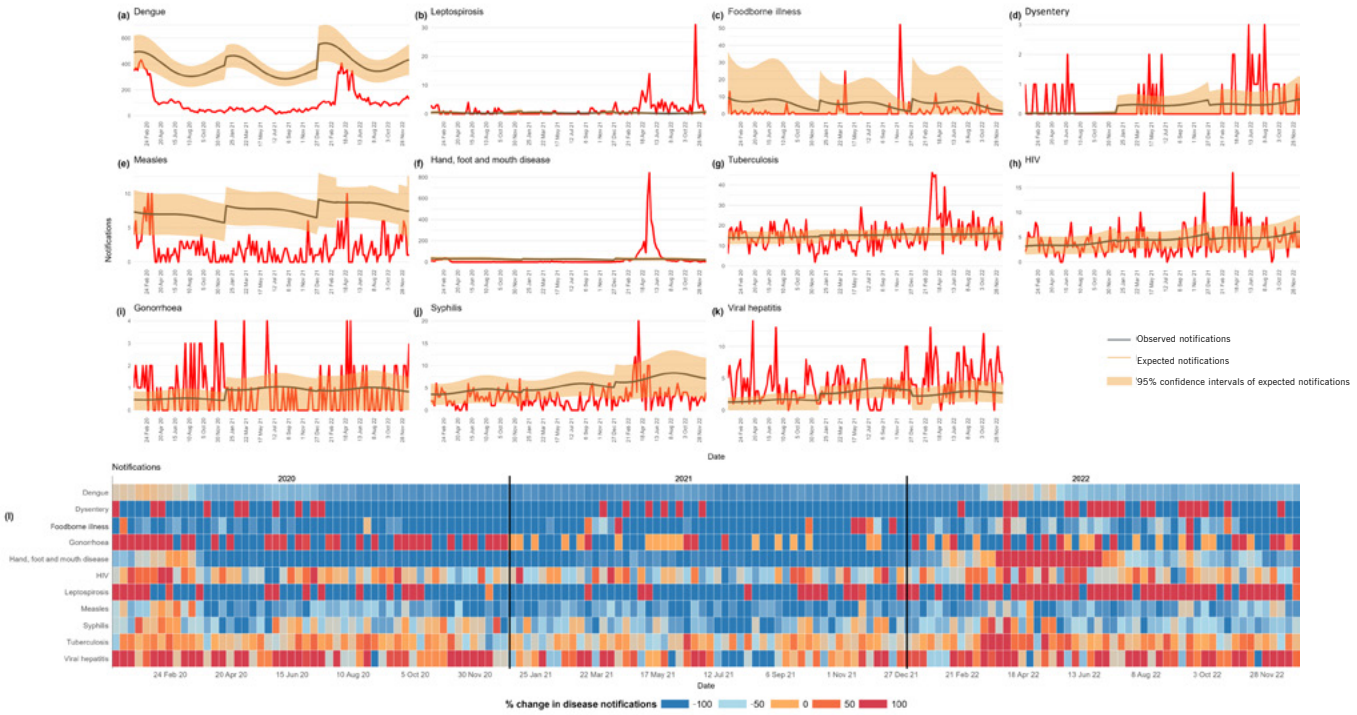
[a] Values are % (95% confidence interval).

were sporadic weeks in each year during which some diseases had 100% more registrations than expected, such as leptospirosis, measles and gonorrhoea (**Fig. 4**). The predicted number of notifications and registrations compared against the observed values are reported in **Supplementary Fig. 1** and **2**, respectively.

## DISCUSSION

The COVID-19 pandemic has had a staggering impact on global health systems, which affected their ability to respond to other diseases. The results of this study showed a decline in disease notifications and registrations

Fig. 3. **Differences in weekly notifications and percentage change between observed and expected notifications, by disease, Klang district, Malaysia, 2020–2022**



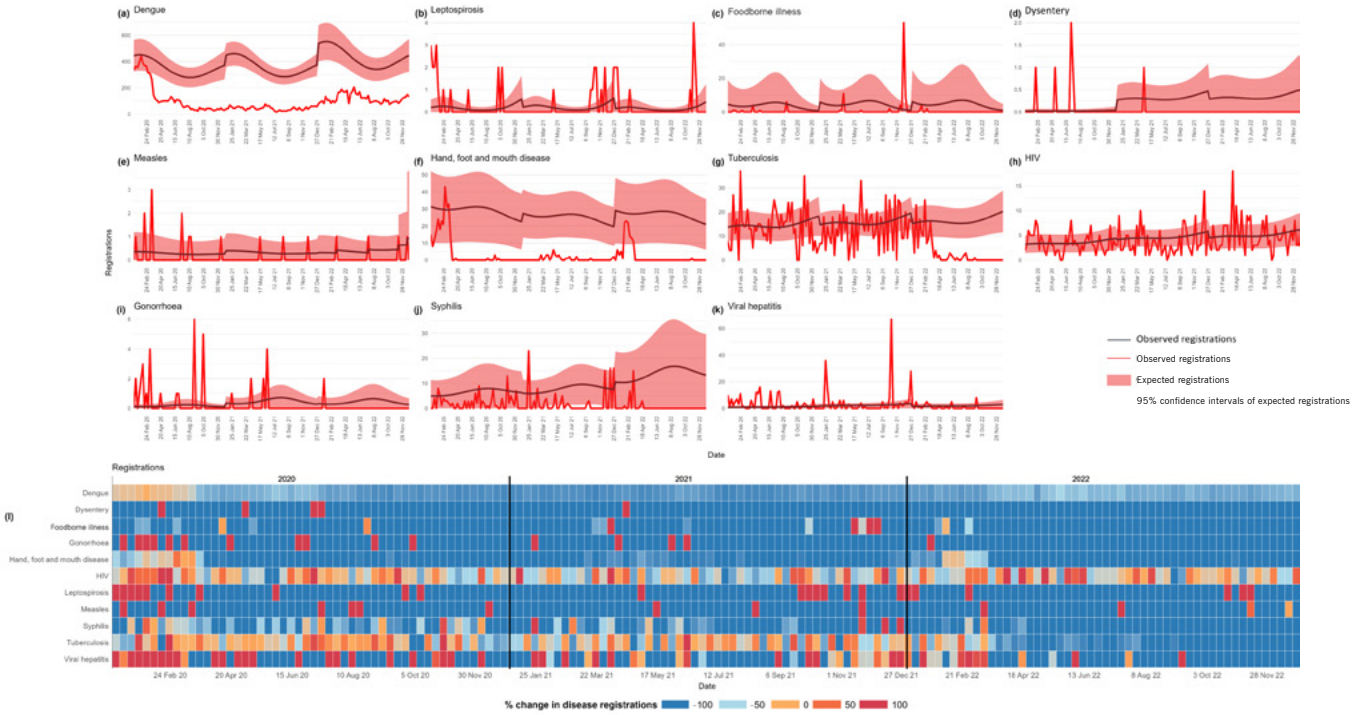

in 2020 and most of 2021 in Klang district, Malaysia, followed by increases in both between week 48 in 2021 and week 15 in 2022, compared with the reference period of 2014–2019. Since then, notifications and registrations have returned to near pre-pandemic levels for some, but not all, diseases.

The reductions in notifications and registrations for nearly all diseases across 2020 and 2021 were likely due to changes in interactions among people as a result of public health and social measures, which interrupted chains of transmission. Malaysia, in line with many other countries, introduced phased lockdowns and school closures during 2020 and 2021, intensifying these during each wave of COVID-19 and as variants emerged; these measures then eased as vaccinations were rolled out and policies shifted in early 2022. These types of interventions led to large reductions in the incidence of childhood diseases and foodborne and waterborne illnesses globally due to mobility restrictions.[1,9,14–16] Reductions in the incidence of childhood diseases, such as measles and HFMD, as well as foodborne illnesses and leptospirosis, in Klang district are consistent with these findings. The decline in mobility due to pandemic-related restrictions corresponded with decreased notifications of vector-borne diseases, such as dengue and malaria. These decreases occurred despite the likelihood that the vectors themselves remained unaffected by mobility restrictions. Similar patterns have been observed in other countries,[17,18] suggesting that this phenomenon is not unique to Malaysia but reflects a broader global trend.

Restrictive public health and social measures also likely modified the population's health-seeking behaviour. Due to fear of contracting COVID-19 in health-care facilities, visits to providers were reduced, likely contributing to the decrease in notifications and registrations.[1,19] This has been reported to be an important factor affecting reductions in notifications of sexually transmitted infections in other settings.[17,18,20] Similarly, the number of notifications of respiratory illnesses that have longer latencies, such as TB, also fell significantly during the COVID-19 pandemic.[21]

In addition to public health and social measures, broader societal and environmental factors have been suggested as modifying disease dynamics during the pandemic. The widespread adoption of work-from-home practices and a substantial reduction in international travel

Fig. 4. **Differences in weekly registrations and percentage change between observed and expected registrations, by disease, Klang district, Malaysia, 2020–2022**




likely altered traditional patterns of disease transmission, particularly for communicable diseases typically spread through close contact or travel.[22] Furthermore, environmental factors, such as urbanization and climate change, have been shown to affect disease vectors and transmission pathways, possibly also impacting the incidence of diseases during this period.[23]

The results of this study suggest that sexually transmitted infections, such as HIV and syphilis, as well as TB, which has a longer latency, had relatively constant reporting over time, indicating that surveillance systems for these diseases may have been less impacted by the pandemic than those for other diseases. Diseases with longer latency may have been less strongly impacted by acute shocks from changes in population mobility and behaviour. The health-care infrastructure for managing these diseases is often separate from acute care services, which may have shielded them from the resource redirection seen in other areas of health care during the pandemic. This separation could have enabled more consistent surveillance and reporting for these conditions. Consequently, surveillance programmes for these diseases maintained continuous reporting even during the pandemic.

Beginning in April 2022, there was a significant discrepancy between the number of notifications and the number of registrations during the time that public health and social measures were lifted completely in Malaysia. Much of this difference was driven by an increased circulation of diseases common in children, such as HFMD. The lifting of restrictions led to a large increase in notifications of HFMD during this period, and many of these were not subsequently registered as they did not meet the criteria for a confirmed case. This large increase in notifications signals a potential immunity-debt event, as has been described previously, whereby the reopening of schools led to the exposure of a large pool of immune-naive, susceptible children to diseases not actively circulating during the preceding 2 years.[24–26] However, this remains conjecture and requires further investigation. Conversely, discrepancies between notifications and registrations for TB, gonorrhoea, syphilis, viral hepatitis and leptospirosis in late 2022 were attributed to delays in laboratory confirmation, such as for testing repeat sputum

samples for TB and the wait times for microagglutination testing results for leptospirosis, as opposed to actual changes in disease patterns.

Finally, it is crucial to recognize that the pandemic's influence on disease surveillance systems may have been exacerbated by conflicting priorities in an overburdened health system. This can lead to gaps in surveillance reporting so that certain cases or data points are missed or unrecorded for various reasons, as has been documented elsewhere.[1,9] However, while this study primarily focused on reductions in notifications and registrations, these may have been influenced by changes in population mobility and behaviours. This speculation aligns with findings from studies exploring the impact of changes in mobility and behaviour on disease dynamics during the pandemic. These studies have suggested that factors such as fear, perception of health risk, and cultural differences in mobility and social behaviour could have significantly impacted disease notification rates.[1,18,27–29] The studies also suggested that many of the changes in disease notification and registration trends can be explained by changes in public health and social measures. Nonetheless, further studies will be necessary to disentangle the role of local surveillance in driving these trends.

Our findings have several implications for disease surveillance and response activities. First, adopting newer technologies and more comprehensive surveillance strategies – including the use of mobile health applications, alternative data sources, crowd-sourced data, community surveillance and telemedicine – may better facilitate disease reporting and surveillance during crises. Second, if a pandemic response is prolonged, it may be necessary to continually update health-care facilities about the importance of vigilance for all infectious diseases within the community, especially when a community is transitioning into endemicity. Finally, analytical frameworks that can differentiate between genuine reductions in disease incidence and perceived reductions due to changes in societal behaviour or mobility patterns should be developed further. Understanding this distinction may enable systems to generate more accurate public health responses and strategies, even during public health emergencies such as pandemics.

This study had several limitations. These included model fits being affected by very few case numbers for certain diseases and time frames, and complexities in trend analysis. Other challenges included lag times for registrations and bulk entry of registrations, false-positive notifications causing artificial spikes in data (notably in HFMD cases) and discrepancies between weekly notifications and registrations due to delayed case verification. The COVID-19 response also extended verification times. These factors may influence data interpretation. Despite these limitations, we believe these models are still useful if interpreted carefully.

In conclusion, our study found decreases in disease notifications and registrations during the COVID-19 pandemic compared with pre-pandemic years. The differential impact of the pandemic on disease notification and reporting suggests that the restrictive public health and social measures implemented for COVID-19 impacted other diseases, although changes to the surveillance system during the pandemic may have also had effects. This highlights the importance of building resilience into infectious disease surveillance systems.

## *Acknowledgements*

The authors thank the Director-General of Health, Malaysia, for permission to publish this paper.

## *Conflicts of interest*

The authors have no conflicts of interest to declare.

## *Ethics statement*

This study was registered with the National Medical Research Register (registration: NMRR-20-1208-55087), and ethical approval was obtained from the Medical Research and Ethics Committee, Ministry of Health, Malaysia.

## *Funding*

None.

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# Sociobehavioural factors associated with SARS-CoV-2 infection and COVID-19 vaccine effectiveness against medically attended, symptomatic SARS-CoV-2 infection in the Philippines: a prospective case-control study (FASCINATE-P study)

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**Objective:** We examined sociobehavioural factors associated with SARS-CoV-2 infection and estimated COVID-19 vaccine effectiveness against symptomatic SARS-CoV-2 infection in the Philippines. Such studies are limited in low- and middle-income countries, especially in Asia and the Pacific.

**Methods:** A case-control study was conducted in two hospitals in Manila, Philippines, from March 2022 to June 2023. Sociobehavioural factors and vaccination history were collected. PCR-positive individuals were cases, while PCR-negative individuals were controls. Adjusted odds ratios (aORs) were calculated to examine associations between sociobehavioural factors/vaccination and medically attended SARS-CoV-2 infection.

**Results:** The analysis included 2489 individuals (574 positive cases, 23.1%; 1915 controls, 76.9%; median age [interquartile range]: 35 [27–51] years). Although education and household income were not associated with infection, being a health-care worker was (aOR: 1.45; 95% confidence interval [CI]: 1.03–2.06). The odds of infection were higher among individuals who attended gatherings of five or more people compared to those who attended smaller gatherings (aOR: 2.58; 95% CI: 1.14–5.83). Absolute vaccine effectiveness for vaccination status was not estimated due to a high risk of bias, for example, unascertained prior infection. Moderate relative vaccine effectiveness for the first booster (32%; 95% CI: -120–79) and the second booster (48%; 95% CI: -23–78) were observed (both with wide CI), albeit with a waning trend after half a year.

**Discussion:** The higher odds of infection among health-care workers emphasize the importance of infection prevention and control measures. Moderate relative vaccine effectiveness with a waning trend reiterates the need for more efficacious vaccines against symptomatic infection caused by circulating variants and with longer duration of protection.

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in substantial morbidity and mortality globally.[1] Before COVID-19 vaccines were developed and widely rolled out, various public health and social measures (PHSMs) were the only countermeasures to limit the spread of SARS-CoV-2 and thus were implemented as obligations or strong recommendations

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Published: 15 January 2025
doi: 10.5365/wpsar.2025.16.1.1131

in each country.[2] Some of these PHSMs included lockdowns, mask mandates and border closures. Many studies have been conducted in various countries to evaluate the behavioural and social factors associated with SARS-CoV-2 infection to inform decision-making related to such PHSMs[3–5] However, such evidence is scarce in low- and middle-income countries (LMICs). Furthermore, once safe and effective vaccines were rolled out, concerns about waning immunity and the emergence of variants with immune escape capacity necessitated the monitoring of real-world vaccine effectiveness (VE).[6–14] There have been numerous studies to evaluate VE, mostly in high-income countries (HICs), but they have been limited in LMICs, including in Asia and the Pacific.[15] It would be valuable for more LMICs to conduct VE studies for the following reasons: (1) to evaluate vaccines that are mainly distributed in LMICs; (2) to confirm that the vaccines remain active through distribution networks, for example, no cold chain breaches; (3) to assemble data on the different cumulative infection burdens among countries, for example, to ascertain whether individuals with prior infection are protected against subsequent infection or disease; (4) to study substantial variations in PHSMs and policies or risk communication activities among countries; (5) to determine varied vaccine confidence within and among populations in surrounding countries; and (6) to build capacity to conduct operational research that would inform countries' public health response to COVID-19 as well as future epidemics and pandemics.

In Japan, several authors from the present report previously evaluated behavioural factors associated with SARS-CoV-2 infection, many of which were in line with local policy or risk communication implementation, and estimated VE against symptomatic infection.[5,14,16–18] We used the same design (multicentre case-control study) to examine: (1) behavioural factors associated with SARS-CoV-2 infection; and (2) VE against symptomatic SARS-CoV-2 infection in the Philippines.

# METHODS

## COVID-19 epidemiology and vaccination rollout in the Philippines

The epidemic curve of reported COVID-19 cases and vaccination rollout in the Philippines are illustrated together with the study period (22 March 2022 to 16 June 2023) in **Fig. 1**. In the Philippines, rollout of the primary series, that is, one vaccine dose from Janssen (J&J) or two doses of all other vaccine types, began on 1 March 2021.[19] The first booster dose rollout began on 16 November 2021 among health-care workers (HCWs), on 22 November 2021 among senior citizens and immunocompromised persons, and on 3 December 2021 among all adults aged ≥18 years. The second booster dose rollout began on 25 April 2022 among HCWs and individuals aged ≥60 years, and on 27 July 2022 among individuals aged ≥50 years and those aged 18–49 years with comorbidities. The primary series followed manufacturer-recommended intervals. During the study period from March 2022 to June 2023, Omicron subvariants B.1.1.529 and XBB.1.5 were reported to be dominant, while all the vaccines used were based on the ancestral strain, as variant-containing vaccines were not available at the time of the study.[20]

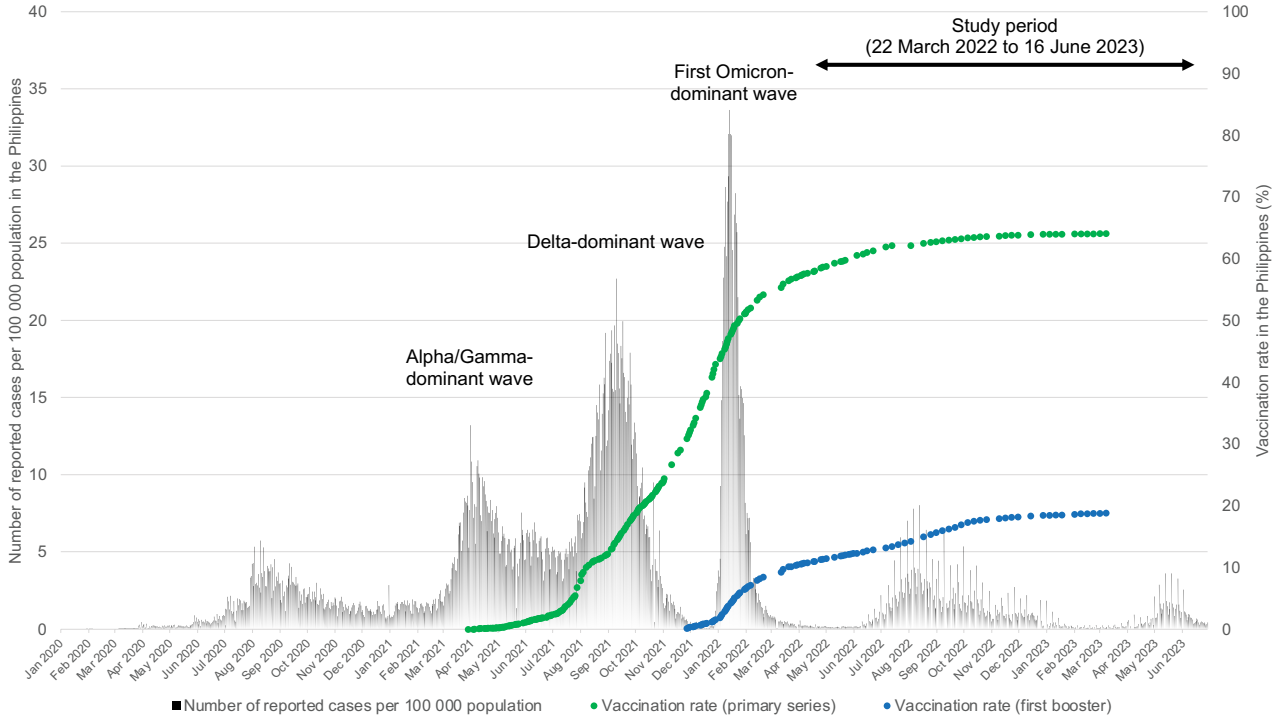
## Study design and setting

Our study, Factors Associated with SARS-CoV-2 INfection And The Effectiveness of COVID-19 vaccines in the Philippines (FASCINATE-P study), is a multicentre case-control study in health-care facilities with two objectives: (1) to elucidate behavioural and demographic risk factors associated with medically attended SARS-CoV-2 infection; and (2) to estimate the real-world effectiveness of COVID-19 vaccines used in the study country against symptomatic infection. This study was conducted at the Philippine General Hospital and San Lazaro Hospital in Manila, which had outpatient clinics that routinely tested individuals using polymerase chain reaction (PCR) for clinical diagnostic purposes and were functioning as two key COVID-19 response sites in the country.[21,22] We followed the same design as studies conducted in Japan and published previously.[5,14,16–18]

## Inclusion and exclusion criteria

All symptomatic individuals aged ≥18 years who sought care and had been tested for SARS-CoV-2 were included in the study. We defined symptomatic individuals as those with either fever ≥37.5 °C, malaise, chills, joint pain, headache, runny nose, cough, sore throat, shortness of breath, gastrointestinal symptoms (vomiting, diarrhoea or stomach ache), or loss of taste or smell. Individuals who did not or could not consent to participate in the study, individuals who required immediate life-saving treatment,

Fig. 1. **Number of reported COVID-19 cases since the beginning of the pandemic and COVID-19 vaccination rate with primary series and first booster, the Philippines[a]**




[a] The data are possibly underestimated due to reporting constraints. Testing/reporting intensity varied substantially over time. COVID-19 vaccination data are up to 9 March 2023.

*Source*: Our World in Data (https://ourworldindata.org).

and individuals who had previously participated in this study were excluded. At the analysis stage, we excluded individuals with unknown symptom onset date or who were tested ≥15 days after symptom onset.

## Classification of exposures and outcomes

Trained research nurses conducted face-to-face interviews before the PCR results were available to avoid social desirability bias, where individuals who tested positive were less likely to report potentially high-risk behaviours or more likely to report vaccination status. The interview collected general information (for example, sociodemographic factors) from the past 2 weeks relating to symptoms, preventive measures such as mask wearing, history of close contact, history of working or school attendance, history of behaviours such as social gatherings, and COVID-19 vaccination status. Patients were asked to present vaccination cards to ascertain the number of doses, vaccine manufacturer and date of each dose. Vaccination status was classified into 15 categories: (1) not vaccinated; (2) dose 1 or ≤13 days after dose 2 (partially vaccinated); (3) 14 days–3 months (14–90 days) after dose 2; (4) 3–6 months (90–180 days) after dose 2; (5) 6–9 months (181–270 days) after dose 2; (6) 9–12 months (271–360 days) after dose 2; (7) >12 months (>361 days) after dose 2; (8) ≤13 days after first booster dose; (9) 14 days–3 months (14–90 days) after first booster dose; (10) 3–6 months (90–180 days) after first booster dose; (11) >6 months (>181 days) after first booster dose; (12) ≤13 days after second booster dose; (13) 14 days–3 months (14–90 days) after second booster dose; (14) 3–6 months (90–180 days) after second booster dose; and (15) >6 months (>181 days) after second booster dose.

SARS-CoV-2 PCR was carried out at each medical facility for diagnostic purposes; PCR-positive individuals were considered cases, and PCR-negative individuals were controls.

## Sample size calculation

For risk factor analysis, assuming 10% positivity (based on data when the study was planned), 30–50% of controls with exposure of interest, a two-tailed significance level of 5%, and 80% power, enrolment of approximately 70–80 cases and 700–800 controls was needed for a

minimum detectable odds ratio of 2. For VE estimates, assuming 10% positivity, expected vaccine coverage of 30% and 90% VE (based on data from the ancestral strain when the study was planned), 207 cases and 1864 controls were needed for the lower confidence interval (CI) boundary of 10%. We planned to continue enrolment even after reaching this target to allow for subanalysis and continued assessment of factors that may be time-varying.

### Data analysis

Participant characteristics and vaccination status were described.

For risk factor analysis, individuals with a history of close contact were excluded because an infection, if confirmed, is usually most likely due to this specific contact rather than exposures solicited in the questionnaire. Logistic regression to identify associations between behavioural risk factors and SARS-CoV-2 infection was conducted, adjusting for age, sex, presence of comorbidities, prior SARS-CoV-2 infection, testing date (one categorical variable for every 2 weeks, for example, weeks 41–42 of 2022 as one variable), study site and vaccination status by dosage. These potential confounders were determined a priori based on published reports.[5]

For VE evaluation, to reduce confounding by various socioeconomic factors and priority of vaccination that can be confounders, we restricted the analyses to HCWs, older adults and individuals with comorbidities (who were also eligible for the fourth dose). Logistic regression was used to estimate the odds of being vaccinated among cases relative to controls. The model was adjusted for age, sex, presence of comorbidities, history of close contact, SARS-CoV-2 testing in the past month, prior SARS-CoV-2 infection, education, working or school attendance, going out to eat or drink in the evening/night without alcohol, testing date (one categorical variable for every two weeks, for example, weeks 41–42 of 2022 as one variable) and study site. These potential confounders were also determined a priori based on published reports.[14] VE against medically attended symptomatic SARS-CoV-2 infection was estimated using the following equation: $VE = (1 - aOR) \times 100\%$. In addition to absolute VE (aVE; VE comparing the vaccinated and unvaccinated), we planned to calculate relative VE (rVE; VE comparing individuals who received a booster of interest vs individuals who only received the previous dose 3 or more months earlier, for example, VE comparing three vs two doses and VE comparing four doses vs three doses) to evaluate the added effect of the booster.

Data analyses were performed using STATA version 18.0.

### Choice of controls in risk factor analysis

We considered that the behavioural and demographic traits among cases and controls would be most similar, as they were sourced from those presenting to the same medical facilities for testing (for example, health-seeking behaviours). Also, if controls were infected with other viruses due to similar exposures, the odds ratio for SARS-CoV-2 infection would be an underestimate of the true association. In other words, our design would detect differences in the magnitude of a particular risk factor or risk factors that would be specific to COVID-19. In fact, even though many respiratory pathogens (influenza virus, *Streptococcus pneumoniae*, etc.) were circulating at extremely low levels during the early phase of the pandemic, possibly due to PHSMs, SARS-CoV-2 epidemics occurred repeatedly. This suggests that SARS-CoV-2 has unique features that allow it to circulate even under strict PHSMs. Please see the Supplementary Methods of our previous report[5] for further detailed rationale.

## RESULTS

### Characteristics of the study participants

A total of 2691 symptomatic individuals were enrolled from two hospitals during the study period; we excluded 11 individuals due to unknown symptom onset date and 191 due to being tested ≥15 days after symptom onset (**Fig. 2**). The final analysis included 2489 individuals with 574 (23.1%) positive cases. The median interquartile age range (IQR) was 35 (27–51), 892 (35.8%) were male, and 877 (35.2%) had comorbidities (**Table 1**); 1743 (70.1%) were working. Although data on race and ethnicity were not collected, 2486 (99.9%; three missing) were Filipinos. All participants answered that they wore a mask when going out. Most had received COVID-19 vaccines (2246, 90.2%). Among the vaccine recipients, most had their vaccination cards (2123, 94.5%). Among those vaccinated with the primary

Table 1. Multicentre case-control study: demographic and clinical characteristics of participants, the Philippines

| Characteristic | All (*n* = 2489) | Test positive (*n* = 574) | Test negative (*n* = 1915) |
|---|---|---|---|
| Age in years, *n* (%) | 35 (27–51)[a] | 32 (26–43)[a] | 37 (28–52)[a] |
| 18–19 | 50 (2.0) | 16 (2.8) | 34 (1.8) |
| 20–29 | 830 (33.4) | 239 (41.6) | 591 (30.8) |
| 30–39 | 594 (23.9) | 158 (27.5) | 436 (22.8) |
| 40–49 | 352 (14.1) | 69 (12.0) | 283 (14.8) |
| 50–59 | 359 (14.4) | 62 (10.8) | 297 (15.5) |
| 60–69 | 194 (7.8) | 24 (4.2) | 170 (8.9) |
| 70–79 | 98 (3.9) | 6 (1.1) | 92 (4.8) |
| 80–89 | 12 (0.5) | 0 (0.0) | 12 (0.6) |
| Sex, *n* (%) | | | |
| Male | 892 (35.8) | 178 (31.0) | 714 (37.3) |
| Female | 1597 (64.2) | 396 (69.0) | 1201 (62.7) |
| Educational attainment, *n* (%) | | | |
| Master's degree and above | 158 (6.4) | 51 (8.9) | 107 (5.6) |
| College | 1570 (63.1) | 458 (79.8) | 1112 (58.1) |
| Vocational | 128 (5.1) | 18 (3.1) | 110 (5.7) |
| Secondary/high school | 526 (21.1) | 41 (7.1) | 485 (25.3) |
| Primary/elementary | 107 (4.3) | 6 (1.1) | 101 (5.3) |
| Comorbidity,[b] *n* (%) | | | |
| Yes | 877 (35.2) | 126 (22.0) | 751 (39.2) |
| No | 1612 (64.8) | 448 (78.1) | 1164 (60.8) |
| Occupation, *n* (%) | | | |
| Health-care worker | 1207 (48.5) | 400 (69.7) | 807 (42.1) |
| Other | 1282 (51.5) | 174 (30.3) | 1108 (57.9) |
| Smoking, *n* (%); missing = 7 (0.3%) | | | |
| Never smoked | 2042 (82.3) | 520 (90.8) | 1522 (79.7) |
| Past smoker | 346 (13.9) | 35 (6.1) | 311 (16.3) |
| Current smoker | 94 (3.8) | 18 (3.1) | 76 (4.0) |
| Days from onset to SARS-CoV-2 test | 3 (2–5) | 2 (2–3) | 3 (2–6) |
| History of close contact, *n* (%) | | | |
| Yes | 401 (16.1) | 149 (26.0) | 252 (13.2) |
| No/unknown | 2088 (83.9) | 425 (74.0) | 1663 (86.8) |
| SARS-CoV-2 diagnostic test in the past month, *n* (%); missing = 1 (0.0%) | | | |
| Yes | 599 (22.5) | 94 (16.4) | 465 (24.3) |
| No | 1929 (77.5) | 480 (83.6) | 1449 (75.7) |
| Past SARS-CoV-2 infection, *n* (%) | | | |
| No | 1801 (72.4) | 395 (68.8) | 1406 (73.4) |
| Once | 627 (25.2) | 164 (28.6) | 463 (24.2) |
| Twice | 57 (2.3) | 13 (2.3) | 44 (2.3) |
| Three times | 4 (0.2) | 2 (0.4) | 2 (0.1) |
| Vaccination card carrying, *n* (%) | | | |
| Yes | 2123 (94.5) | 532 (94.7) | 1591 (94.5) |
| No | 123 (5.5) | 30 (5.3) | 93 (5.5) |
| Number of COVID-19 vaccinations received, *n* (%) | | | |

| Characteristic | All (*n* = 2489) | Test positive (*n* = 574) | Test negative (*n* = 1915) |
|---|---|---|---|
| None | 243 (9.8) | 12 (2.1) | 231 (12.1) |
| Once (except for Ad26.COV2.S[c]) | 15 (0.6) | 2 (0.4) | 13 (0.7) |
| Twice or received Ad26.COV2.S | 682 (27.4) | 76 (13.2) | 606 (31.6) |
| First booster received | 820 (32.9) | 232 (40.4) | 588 (30.7) |
| Second booster received | 729 (29.3) | 252 (43.9) | 477 (24.9) |
| Vaccine type (primary series), *n* (%) | | | |
| AZD1222 (AstraZeneca) | 868 (38.6) | 265 (47.2) | 603 (35.8) |
| CoronaVac (Sinovac) | 828 (36.9) | 187 (33.3) | 641 (38.1) |
| BNT162b2 (Pfizer) | 249 (11.1) | 46 (8.2) | 203 (12.1) |
| mRNA-1273 (Moderna) | 159 (7.1) | 40 (7.1) | 119 (7.1) |
| Ad26.COV2.S (Janssen/J&J) | 50 (2.2) | 6 (1.3) | 44 (2.6) |
| Sputnik V (Gameleya) | 41 (1.8) | 7 (1.3) | 34 (2.0) |
| BBIBP-CorV (Sinopharm) | 7 (0.3) | 0 (0.0) | 7 (0.4) |
| BBV152 (Bharat BioTech) | 1 (0.0) | 0 (0.0) | 1 (0.1) |
| Unknown | 1 (0.0) | 1 (0.2) | 0 (0.0) |
| Heterologous | 42 (1.9) | 10 (1.8) | 32 (1.9) |
| Vaccine type (first booster), *n* (%) | | | |
| BNT162b2 (Pfizer) | 1149 (74.2) | 381 (78.7) | 768 (72.1) |
| mRNA-1273 (Moderna) | 250 (16.1) | 67 (13.8) | 183 (17.2) |
| AZD1222 (AstraZeneca) | 109 (7.0) | 26 (5.4) | 83 (7.8) |
| CoronaVac (Sinovac) | 39 (2.5) | 10 (2.1) | 29 (2.7) |
| Ad26.COV2.S (Janssen/J&J) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Sputnik V (Gameleya) | 1 (0.1) | 0 (0.0) | 1 (0.1) |
| Vaccine type (second booster), *n* (%) | | | |
| BNT162b2 (Pfizer) | 407 (55.8) | 141 (56.0) | 266 (55.8) |
| mRNA-1273 (Moderna) | 315 (43.2) | 111 (44.1) | 204 (42.8) |
| AZD1222 (AstraZeneca) | 6 (0.8) | 0 (0.0) | 6 (1.3) |
| Sputnik V (Gameleya) | 1 (0.1) | 0 (0.0) | 1 (0.2) |

*n*: number.

[a] Median (interquartile range).

[b] Comorbidities (self-reported) include hypertension, heart disease, diabetes mellitus, kidney disease, asthma, chronic obstructive pulmonary disease, obesity, cancer, immunodeficiency and immunosuppressant use.

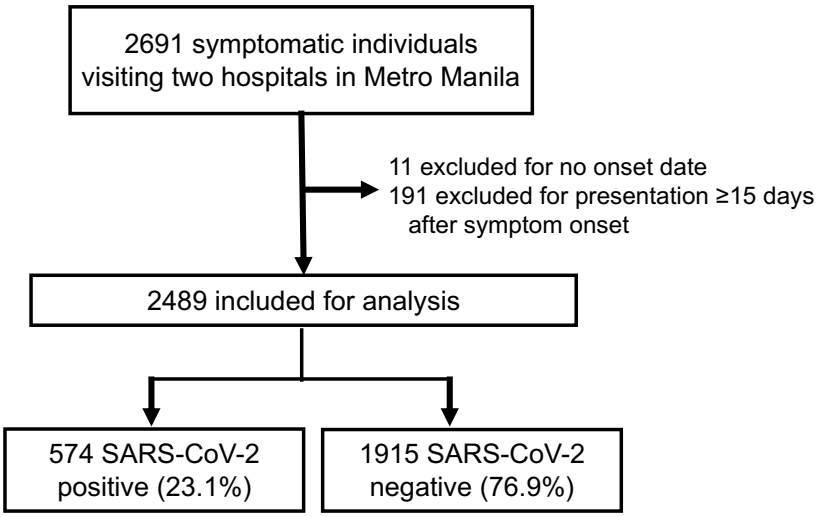
[c] Primary series is one dose, whereas other vaccine types are two doses.

series, 39% received AstraZeneca, 37% received Sinovac, 11% received Pfizer, 7% received Moderna, and 6% received other types. Among the recipients of booster doses, over 90% received mRNA vaccines.

## Association between sociobehavioural factors and medically attended SARS-CoV-2 infection

After excluding individuals with a history of close contact, 2088 individuals were included in this analysis. No apparent association was observed between SARS-CoV-2 infection and socioeconomic factors such as cohabitation status, education or household income (**Table 2**). On the other hand, interviewees who were working or attending school, especially HCWs, were associated with SARS-CoV-2 infection, with an adjusted odds ratio (aOR) of 1.83 (95% CI: 1.09–3.07) for those working or in school and an aOR of 1.45 (95% CI: 1.03–2.06) specifically for HCWs. No apparent association was observed between SARS-CoV-2 infection and various social gatherings with food or drinks, except for a statistically nonsignificant trend of higher infection risk among those who went out to eat or drink in the evening/night without alcohol (1.31 [0.94–1.82]; therefore, this was included as one of the

Fig. 2. **Flow diagram of the multicentre case-control study participants, the Philippines**




covariates for the VE analysis. However, among those who attended social gatherings, the odds of infection were higher among individuals who attended gatherings of five or more people compared to those who attended smaller gatherings (aOR: 2.58, 95% CI: 1.14–5.83). They were also higher among individuals who attended gatherings that lasted 2 hours or longer compared to individuals who attended shorter gatherings (aOR: 1.75, 95% CI: 0.95–3.22). The odds of infection were not higher among those who ordered takeaway, used food-delivery services or ate out alone compared to those who did not. Other behaviours unrelated to food or drink were also not apparently associated with SARS-CoV-2 infection, except that the odds of infection were slightly higher among those who reported having gone to the gym (aOR: 1.53, 95% CI: 0.94–2.49) or to karaoke (aOR: 1.74, 95% CI: 0.81–3.86) (**Table 2**).

### Association between COVID-19 vaccination (by doses and period since vaccination) and medically attended SARS-CoV-2 infection

After restricting to HCWs, older adults and individuals with comorbidities, 1890 individuals were included in this analysis. In the comparison between vaccinated and unvaccinated individuals, there were inconsistent odds of infection depending on the vaccination category. In the comparison between the first booster and 3 months after the primary series, there was a moderate effect 14 days to 3 months after the booster dose (rVE: 32%, 95% CI: -120–79), but VE seems to wane after half a year (rVE: -8%, 95% CI: -72–33). The comparison between the second booster and 3 months after the first booster showed a similar trend of moderate effect in the short-term (rVE: 48%, 95% CI: -23–78) with waning protection (**Table 3**).

## DISCUSSION

In this multicentre case-control study in the Philippines, we investigated the association between various sociobehavioural factors and medically attended SARS-CoV-2 infection. We also examined the association between COVID-19 vaccination and medically attended SARS-CoV-2 symptomatic infection. By following the same design as a similar study conducted in Japan by some of the authors, we aimed to look at country-specific differences in factors associated with SARS-CoV-2 infection.[5]

First, there was no apparent association between socioeconomic factors such as cohabitation status, education or household income and SARS-CoV-2 infection, suggesting that SARS-CoV-2 has spread regardless of socioeconomic status. However, working, especially in the health-care environment, had higher odds of SARS-CoV-2 infection compared to not working or not working in the health-care environment, respectively. This was also observed in other countries early in the pandemic.[23] With proper personal protective equipment (PPE) and infection prevention and control measures in the health-care setting, the risk of occupational exposure should have been minimized, but this trend was not

Table 2. **Multicentre case-control study: association between sociobehavioural factors and SARS-CoV-2 infection, the Philippines**

| Sociobehavioural factors | Test positive, *n* (%) | Test negative, *n* (%) | Crude odds ratios (95% CI) | Adjusted odds ratios (95% CI)[a] |
|---|---|---|---|---|
| **Cohabitation** | | | | |
| Living alone | 87 (28.9) | 214 (71.1) | 1 | 1 |
| Living with family | 244 (16.1) | 1276 (84.0) | 0.47 (0.35–0.63) | 0.86 (0.61–1.24) |
| Living with people other than family | 94 (35.2) | 173 (64.8) | 1.34 (0.94–1.90) | 1.12 (0.74–1.70) |
| **Education** | | | | |
| Primary/elementary | 6 (5.6) | 101 (94.4) | 1 | 1 |
| Secondary/high school | 38 (7.4) | 475 (92.6) | 1.35 (0.55–3.27) | 0.89 (0.34–2.34) |
| Vocational | 16 (13.7) | 101 (86.3) | 6.22 (2.71–14.31) | 1.30 (0.48–3.50) |
| College | 343 (27.0) | 928 (73.0) | 6.39 (2.45–16.65) | 1.12 (0.35–3.54) |
| Post-graduate/master's degree/PhD | 22 (27.5) | 58 (72.5) | 2.67 (1.00–7.09) | 1.20 (0.39–3.71) |
| **Monthly household income** | | | | |
| Unemployed/no income | 5 (2.9) | 166 (97.1) | 1 | 1 |
| < 10 000 (<US$ 176.50) | 17 (6.1) | 261 (93.9) | 2.16 (0.78–5.97) | 0.93 (0.25–3.51) |
| 10 000–<50 000 (US$ 176.50–882.60) | 169 (18.4) | 748 (81.6) | 7.50 (3.03–18.54) | 1.08 (0.29–3.97) |
| 50 000–<80 000 (US$ 882.60–1412.20) | 150 (34.1) | 290 (65.9) | 17.17 (6.90–42.71) | 1.31 (0.34–5.06) |
| ≥ 80 000 (≥US$ 1412.20) | 78 (34.8) | 146 (65.2) | 17.74 (6.99–45.00) | 1.39 (0.35–5.47) |
| **Work or school attendance** | | | | |
| No | 49 (6.7) | 682 (93.3) | 1 | 1 |
| Yes | 376 (27.7) | 978 (72.2) | 5.35 (3.91–7.32) | 1.83 (1.09–3.07) |
| **Health-care worker** | | | | |
| No | 153 (12.7) | 1055 (87.3) | 1 | 1 |
| Yes | 272 (30.9) | 608 (69.1) | 3.08 (2.47–3.85) | 1.45 (1.03–2.06) |
| **Going out to eat/drink in the daytime with alcohol** | | | | |
| No | 422 (20.4) | 1646 (79.6) | 1 | 1 |
| Yes | 3 (15.0) | 17 (85.0) | 0.69 (0.20–2.36) | 0.36 (0.09–1.38) |
| **Going out to eat/drink in the evening/night with alcohol** | | | | |
| No | 393 (19.9) | 1585 (80.1) | 1 | 1 |
| Yes | 32 (29.1) | 78 (70.9) | 1.65 (1.08–2.53) | 1.24 (0.74–2.06) |
| **Going out to eat/drink in the daytime without alcohol** | | | | |
| No | 259 (16.4) | 1322 (83.6) | 1 | 1 |
| Yes | 166 (32.7) | 259 (16.4) | 2.48 (1.98–3.12) | 0.90 (0.64–1.25) |
| **Going out to eat/drink in the evening/night without alcohol** | | | | |
| No | 296 (17.3) | 1421 (82.8) | 1 | 1 |
| Yes | 129 (34.8) | 296 (17.2) | 2.56 (2.00–3.28) | 1.31 (0.94–1.82) |
| **Going to a café** | | | | |
| No | 346 (19.5) | 1425 (80.5) | 1 | 1 |
| Yes | 79 (24.9) | 238 (75.1) | 1.37 (1.03–1.81) | 0.97 (0.69–1.35) |
| **Maximum number of people who attended the gatherings with food/drinks including oneself within 2 weeks of onset** | | | | |
| <5 people | 65 (22.9) | 219 (77.1) | 1 | 1 |
| ≥5 people | 15 (44.1) | 19 (55.9) | 2.66 (1.28–5.53) | 2.58 (1.14–5.83) |
| **Maximum time spent at the gatherings with food/drinks attended within 2 weeks of onset** | | | | |
| <2 hours | 27 (17.7) | 126 (82.4) | 1 | 1 |
| ≥2 hours | 53 (32.3) | 111 (67.7) | 2.23 (1.31–3.78) | 1.75 (0.95–3.22) |

| Sociobehavioural factors | Test positive, *n* (%) | Test negative, *n* (%) | Crude odds ratios (95% CI) | Adjusted odds ratios (95% CI)[a] |
|---|---|---|---|---|
| **Ordering takeaway** | | | | |
| No | 290 (21.3) | 1075 (78.8) | 1 | 1 |
| One | 13 (22.8) | 44 (77.2) | 1.10 (0.58–2.06) | 1.12 (0.52–2.39) |
| Twice | 59 (21.0) | 222 (79.0) | 0.99 (0.72–1.35) | 1.14 (0.78–1.67) |
| Three times or more | 63 (16.4) | 322 (83.6) | 0.72 (0.54–0.98) | 0.98 (0.68–1.40) |
| **Using food delivery** | | | | |
| No | 215 (15.3) | 1187 (84.6) | 1 | 1 |
| One | 5 (9.8) | 46 (90.2) | 0.60 (0.24–1.53) | 0.34 (0.12–0.93) |
| Twice | 35 (27.6) | 92 (72.4) | 2.10 (1.39–3.18) | 1.10 (0.67–1.80) |
| Three times or more | 170 (33.5) | 338 (66.5) | 2.78 (2.20–3.51) | 1.18 (0.85–1.62) |
| **Eating out alone** | | | | |
| No | 410 (20.6) | 1579 (79.4) | 1 | 1 |
| Yes | 15 (15.2) | 84 (84.9) | 0.69 (0.39–1.20) | 0.81 (0.43–1.53) |
| **Going to a mall** | | | | |
| No | 148 (14.4) | 878 (85.6) | 1 | 1 |
| Yes | 277 (26.1) | 785 (73.9) | 2.09 (1.68–2.61) | 1.07 (0.80–1.42) |
| **Going to a gym** | | | | |
| No | 390 (19.8) | 1578 (80.2) | 1 | 1 |
| Yes | 35 (29.2) | 85 (70.8) | 1.67 (1.11–2.51) | 1.53 (0.94–2.49) |
| **Going to karaoke** | | | | |
| No | 411 (20.1) | 1635 (79.9) | 1 | 1 |
| Yes | 14 (33.3) | 28 (66.7) | 1.99 (1.03–3.81) | 1.76 (0.81–3.86) |
| **Going to church** | | | | |
| No | 308 (22.4) | 1069 (77.6) | 1 | 1 |
| Yes | 117 (16.5) | 594 (83.5) | 0.68 (0.54–0.86) | 0.89 (0.66–1.20) |

: Philippine peso; CI: confidence interval; *n*: number; PhD: Doctor of Philosophy; US$: US dollar.

[a] Adjusted for age, sex, comorbidities, prior infection, week of testing, study site and vaccine by dosage.

observed in Japan, where strict infection prevention and control measures were in place.[5,24] Policies should also make sure that adequate supplies of PPE are available to protect those on the front line. We next examined various behaviours that may be associated with SARS-CoV-2 infection. Among those who attended social gatherings, the odds of infection were higher among individuals who attended gatherings of five or more people compared to smaller gatherings and individuals who attended for 2 hours or longer compared to shorter durations. Although not statistically significant, going to the gym or karaoke may be associated with higher odds of infection, while other behaviours such as ordering takeaway, using food-delivery services and eating out alone were not associated with infection. These findings were in line with findings from Japan and highlighted the nature of this pathogen where transmission can occur efficiently in specific situations.[5,25]

We examined the association between COVID-19 vaccination and medically attended SARS-CoV-2 infection to estimate COVID-19 VE against symptomatic infection. As for the comparison between vaccinated and unvaccinated individuals, there were inconsistent odds of infection depending on the vaccination category. We did include various covariates in the multivariable analysis, but we suspected that the risk of residual bias was high and, therefore, aVE was not presented. One bias that could have caused this is that, due to a substantial delay in the ethics approval process, enrolment began after a large Omicron wave in early 2022, when the majority of unvaccinated individuals were already or recently infected without having been tested, resulting in a protective effect at a level higher than that from vaccination several months earlier. Also, the presentation of vaccination cards was required in some stores and restaurants, which could have potentially underestimated VE.[18] This is in line

Table 3. **Multicentre case-control study: association between COVID-19 vaccination (by doses and time since vaccination) and SARS-CoV-2 infection, the Philippines**

| Vaccination status | Test positive | Test negative | Crude odds ratios (95% CI)[a] | Adjusted odds ratios (95% CI)[a] | VE% (95% CI) |
|---|---|---|---|---|---|
| **Comparison between vaccinated and unvaccinated** | | | | | |
| Unvaccinated | 11 | 171 | 1 | 1 | N/A |
| Dose 1 or ≤13 days after primary series | 2 | 11 | 2.83 (0.56–14.36) | 2.08 (0.35–12.4) | Not calculated[b] |
| 14 days to 3 months after primary series | 0 | 12 | N/A | N/A | Not calculated[b] |
| 3–6 months after primary series | 2 | 42 | 0.74 (0.16–3.47) | 0.69 (0.13–3.59) | Not calculated[b] |
| 6–9 months after primary series | 6 | 73 | 1.28 (0.46–3.59) | 0.78 (0.25–2.42) | Not calculated[b] |
| 9–12 months after primary series | 17 | 114 | 2.32 (1.05–5.13) | 2.57 (1.06–6.19) | Not calculated[b] |
| >12 months after primary series | 29 | 157 | 2.87 (1.39–5.94) | 1.43 (0.59–3.50) | Not calculated[b] |
| ≤13 days after first booster | 0 | 0 | N/A | N/A | Not calculated[b] |
| 14 days to 3 months after first booster | 5 | 23 | 3.38 (1.08–10.60) | 0.96 (0.25–3.64) | Not calculated[b] |
| 3–6 months after first booster | 12 | 69 | 2.70 (1.14–6.42) | 1.07 (0.38–3.02) | Not calculated[b] |
| >6 months after first booster | 160 | 348 | 7.15 (3.78–13.52) | 1.57 (0.66–3.72) | Not calculated[b] |
| ≤13 days after second booster | 2 | 3 | 10.36 (1.57–68.6) | 2.94 (0.35–24.55) | Not calculated[b] |
| 14 days to 3 months after second booster | 8 | 31 | 4.01 (1.49–10.77) | 0.77 (0.24–2.50) | Not calculated[b] |
| 3–6 months after second booster | 78 | 153 | 7.93 (4.06–15.45) | 1.46 (0.59–3.59) | Not calculated[b] |
| >6 months after second booster | 121 | 230 | 8.18 (4.28–15.64) | 2.05 (0.83–5.09) | Not calculated[b] |
| **Comparison between the first booster and 3 months after primary series** | | | | | |
| >3 months after primary series | 54 | 386 | 1 | 1 | N/A |
| ≤13 days after first booster | 0 | 0 | N/A | N/A | N/A |
| 14 days to 3 months after first booster | 5 | 23 | 1.55 (0.57–4.26) | 0.68 (0.21–2.20) | 32 (-120–79) |
| 3–6 months after first booster | 12 | 69 | 1.24 (0.63–2.44) | 0.73 (0.33–1.60) | 27 (-60–67) |
| >6 months after first booster | 160 | 348 | 3.29 (2.34–4.62) | 1.08 (0.67–1.72) | -8 (-72–33) |
| **Comparison between the second booster and 3 months after the first booster** | | | | | |
| >3 months after first booster | 172 | 417 | 1 | 1 | N/A |
| ≤13 days after second booster | 2 | 3 | 1.62 (0.27–9.76) | 1.96 (0.27–14.0) | Too few |
| 14 days to 3 months after second booster | 8 | 31 | 0.63 (0.28–1.39) | 0.52 (0.22–1.23) | 48 (-23–78) |
| 3–6 months after second booster | 78 | 153 | 1.24 (0.89–1.71) | 0.98 (0.66–1.43) | 2 (-43–34) |
| >6 months after second booster | 121 | 230 | 1.28 (0.96–1.69) | 1.34 (0.94–1.91) | -34 (-91–6) |

CI: confidence interval; VE: vaccine effectiveness; N/A: not applicable; d: day; mo: month.

[a] Adjusted for age, sex, comorbidities, history of close contact, SARS-CoV-2 testing in the past month, prior infection, education, work/school, going out to eat/drink in the evening/night without alcohol, week of testing, study site.

[b] Not calculated due to high risk of bias.

with reports from Canada, where negative effectiveness was observed.[26,27] On the other hand, moderate rVE for the first booster (32%) and the second booster (48%) against medically attended symptomatic SARS-CoV-2 infection was observed (although neither was statistically significant due to the small sample size). However, these effects seemingly have waned after half a year. These findings were consistent with the Japanese study and studies from other countries[10–17] and reiterate the need for vaccines that are more effective against symptomatic infection caused by circulating variants and with a longer duration of protection.

## Limitations

This study had several limitations. First, biases inherent in observational studies are possible. Using a detailed questionnaire, we attempted to minimize confounding that is not necessarily accounted for in studies that retrospectively evaluate routine surveillance data, but

unmeasured and residual confounding could have occurred. However, as explained above, the association between vaccination and medically attended SARS-CoV-2 infection has probably had residual bias with most unvaccinated individuals being infected, and thus aVE was not presented. Second, for the risk factor analyses, controls may have been infected with other viruses due to similar exposures, which can underestimate the odds ratio (see Methods for details). Third, identified risk factors may be country-, region-, culture- and population-specific and time-dependent due to changes in COVID-19-related policies and behaviours. Also, the determination of past infection was likely suboptimal, and this could have protected "truly high-risk groups" from getting infected during the study period. Specifically, our study population had a large proportion of HCWs, and thus the risk factor analyses may not be generalizable to the overall population in the Philippines. Fourth, our primary analyses were complete case analyses. However, due to the prospective nature of the study with thorough interviews, the amount of missing data was minimal, as shown in **Table 1**. Fifth, some estimates were calculated based on very low numbers, resulting in wide CIs that warrant careful interpretation. Finally, the study sites were two hospitals, which may limit the generalizability to the whole country.

## CONCLUSIONS

In this case-control study in the Philippines, school attendance or working, especially in the health-care environment, had higher odds of SARS-CoV-2 infection compared to not working or not working in the health-care environment, respectively, suggesting the importance of infection prevention and control measures in the health-care setting. Also, attending social gatherings with five or more people or for a longer duration was associated with SARS-CoV-2 infection. Although a comparison of COVID-19 VE versus unvaccinated groups could not be estimated due to the high risk of bias, moderate rVE against symptomatic SARS-CoV-2 infection was observed, albeit with a waning trend after half a year.

### *Acknowledgements*

The authors thank all staff members at the study sites for the SARS-CoV-2 testing and their administrative assistance.

### *Conflicts of interest*

The authors have no conflicts of interest to declare.

### *Ethics statement*

Ethics approval was obtained from each participating hospital. Before the interview, written informed consent was obtained from each participant.

### *Funding*

This work was supported by the World Health Organization and the Nagasaki University WISE Programme.

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# Foodborne illness from tuba-tuba seeds among school-aged children, Philippines: a call for community education

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**Objective:** On 2 September 2023, the Regional Epidemiology and Surveillance Unit of the Department of Health's Center for Health Development in Calabarzon, Philippines, received a report of foodborne illness due to the ingestion of tuba-tuba (*Jatropha curcas*) seeds in Talao Talao Village, Lucena City. The objective of this study was to describe the public health event.

**Methods:** A descriptive study was conducted. Cases were defined as previously well individuals who developed at least one of the following symptoms after eating tuba-tuba seeds: vomiting, abdominal pain, diarrhoea, headache or dizziness. Health records were reviewed, and key informant interviews and environmental surveys were conducted.

**Results:** Ten cases were identified, ranging in age from 10 to 12 years. The onset of symptoms ranged from 1 to 4 hours after consumption. Six of the cases were taken to the hospital, although two went home before being admitted; all recovered after 3 days. The most common symptom was vomiting (100%); other symptoms included abdominal pain, diarrhoea, dizziness and headache.

**Discussion:** This investigation confirmed that tuba-tuba seeds were the cause of symptoms among school-aged children in Lucena City. To prevent similar events in the future, we recommend intensifying educational campaigns at both the community and school levels, as tuba-tuba is common in the area.

*Jatropha curcas*, commonly known as tuba-tuba in the Philippines, is an inedible perennial shrub that grows in tropical and subtropical regions. The name is derived from the Greek words "jatros" (doctor) and "trophe" (nutrition). *J. curcas* has a strong root system, and in the Philippines and elsewhere it is used in reforestation, soil rehabilitation projects and to reduce soil erosion. It is also common in and around towns, where it is widely used as a live fence, giving rise to the common name, *tubang bakod*.[1] Its seeds can be used as an insecticide, while its leaves are used in traditional medicine as a remedy for many ailments, including cough, fever, chills, headache, stomach ache, constipation, arthritis, fractures, muscle pain, dermatitis, haemorrhoids, infection with helminths and even to treat tumours.[2–5]

Although parts of the plant are known to have therapeutic properties, the seeds contain toxic compounds such as curcin[2] and curcanoleic acid, which when ingested can cause headache, dizziness and severe gastrointestinal symptoms, including vomiting, abdominal pain and diarrhoea.[6,7] Several episodes of foodborne illness have been attributed to the ingestion of tuba-tuba seeds in the Philippines and other countries where this plant is common.[7–10]

On 2 September 2023, the Regional Epidemiology and Surveillance Unit of the Center for Health Development, Department of Health, Calabarzon, received a report of foodborne illness due to the ingestion of tuba-tuba seeds in Talao Talao Village, Lucena City. Talao Talao is a coastal village in Quezon Province with

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Published: 20 March 2025
doi: 10.5365/wpsar.2025.16.1.1186

a total population of 5234.[11] Lucena City, the capital city of Quezon Province, has a total population of around 278 924 as of the 2020 census.[11]

Given the widespread presence of *J. curcas* in the province and its potential health risks, an outbreak investigation was conducted by a team from the Department of Health's Regional Epidemiology Surveillance Unit in Calabarzon. This report summarizes the outcome of that investigation and provides recommendations to prevent future occurrences.

## METHODS

Following the report of a foodborne illness event in September 2023, disease surveillance officers and municipal personnel were deployed to Talao Talao on 8 September to carry out an initial investigation. A case was defined as a previously well individual who developed at least one of the following symptoms after eating tuba-tuba seeds in Talao Talao: vomiting, abdominal pain, diarrhoea, headache or dizziness. The investigation comprised a combination of medical records reviews, structured interviews and an environmental survey.

### Case investigation

On 8 September 2023, key personnel from a medical centre, local hospital and the Provincial Epidemiology and Surveillance Unit in Quezon were interviewed to gather historical data about similar events. During the investigation, pertinent data were also collected by interviewing cases and their legal guardians, and records were reviewed from the hospitals where cases were treated, with the help of the deployed disease surveillance officers. The data collected included sociodemographic characteristics (age, sex, place of residence, relationship to the index case, grade level), symptoms and clinical outcomes (if hospitalized or went home against medical advice, and whether recovered or not). Additionally, the Environmental Health and Sanitation Officer of the Lucena City Health Office and the village captain of Talao Talao were interviewed to determine whether they had relevant information about the public health event.

### Environmental assessment

An environmental survey of the site where the trees were located was conducted to determine the distribution and accessibility of the trees in the local area.

### Data analysis

This study employed a descriptive design. Case data were analysed using descriptive statistics; the environmental findings were summarized in a narrative review.

## RESULTS

### Case identification and interviews

Ten cases of foodborne illness due to ingestion of tuba-tuba seeds were identified, and a timeline of events was established (**Fig. 1**). On 2 September 2023, at around 13:00, a group of children aged 10–12 years went to Talao Talao Village to swim at a private resort. After a few hours and feeling hungry, seven children searched for trees bearing fruit. They found a tuba-tuba tree and, following a video they had seen on social media, harvested and consumed fresh tuba-tuba seeds at approximately 15:00, with some starting to show symptoms after 1 hour. They later shared the seeds with three additional friends who consumed them at around 16:00, and another friend started to show symptoms after 1 hour.

The onset of symptoms ranged from 1 to 4 hours after consumption, with an average onset of 1.75 hours. Six of the 10 children were taken to the hospital; four were admitted, but two went home against medical advice. All recovered after 3 days. All cases had vomiting. Additionally, some of the cases reported abdominal pain, diarrhoea, dizziness and headache (**Table 1**).

In this event, it was noted that ingesting only one seed was needed to cause symptoms. Four children ingested at least 10 seeds, one of whom developed hypovolaemic shock. The four children who ingested

Table 1. **Sociodemographic characteristics, clinical manifestations and outcome of foodborne illness due to ingestion of tuba-tuba (Jatropha curcas) seeds among 10 school-aged children, Talao Talao Village, Lucena City, Philippines, 2 September 2023**

| Characteristic | *n* (%) |
|---|---|
| Age (years) | |
| 10 | 1 (10) |
| 11 | 5 (50) |
| 12 | 4 (40) |
| Sought medical attention | |
| Yes | 6 (60) |
| No | 4 (40) |
| Admitted to hospital (among those who sought medical attention) | |
| Yes | 4 (67) |
| No, went home against medical advice | 2 (33) |
| No. of seeds ingested | |
| 1–3 | 3 (30) |
| 4–6 | 3 (30) |
| 10–15 | 4 (40) |
| Incubation period (hours) | |
| 1 | 6 (60) |
| 2–4 | 4 (40) |
| Symptoms | |
| Vomiting | 10 (100) |
| Abdominal pain | 3 (30) |
| Diarrhoea | 3 (30) |
| Dizziness | 2 (20) |
| Headache | 1 (10) |
| Hypovolaemic shock | 1 (10) |
| Outcome | |
| Recovered | 10 (100) |

fewer than six seeds were managed at home and did not experience serious complications.

### Interviews with health personnel

Interviews with personnel from the Provincial Epidemiology and Surveillance Unit revealed that foodborne illnesses from tuba-tuba seeds were recorded for the first time in Quezon Province during this outbreak investigation. Shortly after the Talao Talao incident, additional cases were reported in Wakas Village, Tayabas City, Quezon Province. In that instance, three cousins who were aged 4 years ingested the skin of the fruit, resulting in vomiting and diarrhoea. One child required medical evaluation at Quezon Medical Center.

Interviews with personnel from Quezon Medical Center, St. Anne General Hospital and the Lucena City Health Office indicated that the Talao Talao event was the first reported occurrence of foodborne illness in the municipality. The village captain of Talao Talao confirmed that tuba-tuba trees are common in the area, but this was the first documented event of foodborne illness associated with the trees.

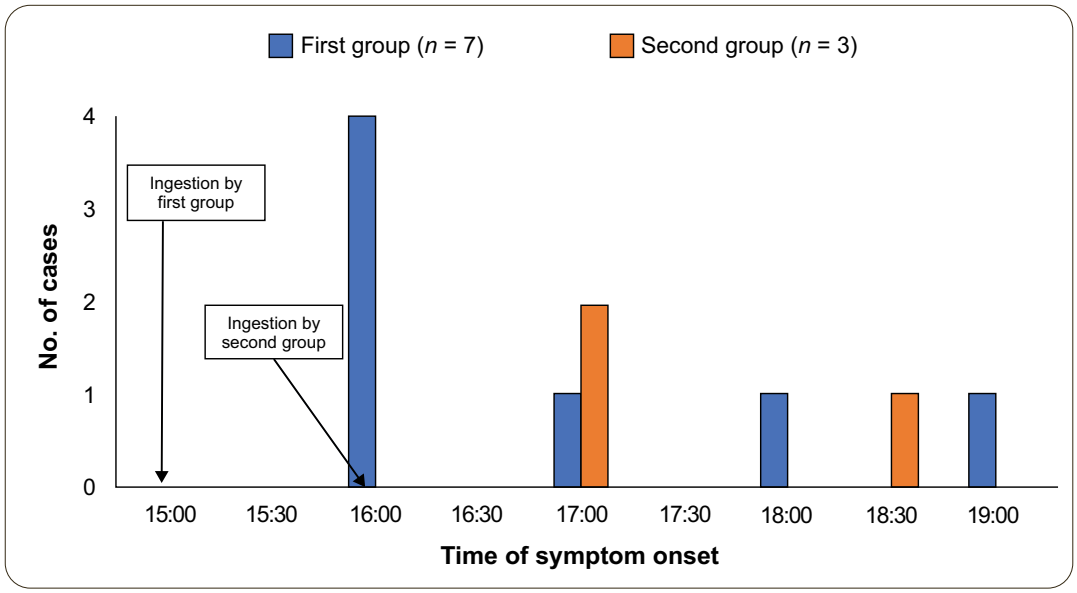
### Environmental survey

The environmental survey revealed that the tuba-tuba trees were located on private property near the coast along Eco Road. The trees serve as a natural fence for the private resort. No warning signs regarding the dangers of consuming tuba-tuba seeds or fruit were present in the area. The trees were approximately 2 metres tall, making the fruits easily reachable.

## DISCUSSION

This outbreak of foodborne illness caused by the consumption of tuba-tuba seeds in Talao Talao was the first to be recorded in Lucena City; shortly afterwards, another unrelated outbreak occurred in nearby Tayabas City. In other countries, such as India, foodborne illness due to tuba-tuba ingestion is more commonly reported.[6–10] Most of the cases reported globally have occurred in children, and vomiting is the most common initial presenting symptom.[6,7,12] The predominance of gastrointestinal symptoms is likely attributed to the presence of curcanoleic acid, a potent gastrointestinal irritant and a constituent of tuba-tuba seeds.[7] Symptom onset is typically rapid; we observed a minimum of only 1 hour between ingestion and symptoms, although a previous study by Shah and Sanmukhani reported an incubation period as short as 15–20 minutes.[7] Other studies have established that ingestion of tuba-tuba seeds can lead to gastrointestinal symptoms lasting up to 72 hours or longer,[13] which can lead to hypovolaemic shock. In this outbreak, 1 of the 10 cases suffered hypovolaemic shock. The risks associated with ingesting tuba-tuba

Fig. 1. **Foodborne illness from tuba-tuba (*Jatropha curcas*) seeds among 10 school-aged children, by time of symptom onset, Talao Talao Village, Lucena City, Philippines, 2 September 2023**




seeds should not be underestimated, especially in younger children who are more susceptible to dehydration.

Only one seed needed to be consumed to cause symptoms. Those who ingested fewer than six seeds were successfully managed at home and had no serious complications. Similar findings were noted in studies from India.[6,7,12] In this outbreak, children who ate six or more seeds were hospitalized, and among the four children who ingested at least 10 seeds, one had hypovolaemic shock. Ingestion of more than 10 seeds has been associated with more severe outcomes in a study from Israel, where two paediatric cases both developed hypovolaemic shock.[13] While it is tempting to conclude that the number of seeds ingested influences symptom severity, the weight of evidence does not yet support a dose–response relationship. For example, a large retrospective study from India[6] failed to find a dose–response relationship between the number of ingested seeds and the severity of symptoms. It is also noteworthy that in this event, the case who developed hypovolaemic shock was not the child who ingested the greatest number of seeds.

It is important to note that the children ingested tuba-tuba seeds after seeing a video clip on social media that led them to believe it was safe to do so. This finding should be a wake-up call to policy-makers to ensure that appropriate measures are in place to filter out dangerous content on social media platforms, especially content that is targeted at children during a period in their lives when they are explorative and impulsive. Other strategies that are important to consider include strengthening digital literacy programmes in schools and promoting awareness of the dangers of tuba-tuba through health clinics, and school-based and community health education programmes. A study on digital literacy showed that learning about the proper use of social media plays a role in preventing foodborne illness.[14] Signs warning of the dangers of consuming tuba-tuba seeds may also be effective. This recommendation is based on a study comparing the effectiveness of web and print media in communicating food safety practices to adolescents, which showed that the adolescents preferred the print-based media.[15]

This investigation has several limitations. First, we were not able to include laboratory testing to confirm the specific toxic compound responsible for the symptoms. However, the observed symptoms were consistent with those documented in the literature, supporting the conclusion that the seeds were the likely cause of the outbreak. In addition, given that the study relied on interviews with affected children and was conducted nearly a week after the incident, recall bias may have influenced the accuracy of reporting the number of seeds ingested. This potential inaccuracy likely impacted the study's ability to establish a clear dose–response

relationship between seed consumption and symptom severity.

Despite these limitations, our investigation has confirmed that ingesting tuba-tuba seeds, regardless of the exact number, causes illness, reinforcing that these seeds should never be ingested. Although foodborne illness due to tuba-tuba seeds is not common in the area, the risks and toxic effects are sufficiently acute, especially in children, to warrant conducting intensified health and educational campaigns regarding the dangers of ingesting the seeds to prevent similar events in the future.

## *Acknowledgements*

The authors are grateful for the cooperation of the staff of the Lucena City Health Office and the local governments of Talao Talao and Dalahican during the field visit.

## *Conflicts of interests*

The authors have no conflicts of interest to declare.

## *Ethics statement*

Ethics clearance was not required according to local regulations as this investigation was part of an emergency response to an outbreak.

## *Funding*

None.

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# Satellite communications in health emergencies: no longer a luxury

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In health emergencies, communication is a lifeline. Rapid coordination and information-sharing are critical for needs assessments, resource allocation and effective emergency response. In recent years, satellite communications have evolved from being prohibitively expensive to becoming an essential and affordable tool for emergency responders. Recent disasters, such as the 7.3 magnitude earthquake and resulting temporary communications blackout in Vanuatu on 17 December 2024, and a similar event following the 2022 volcanic eruption and tsunami in Tonga, underscore the importance of reliable satellite communications during emergencies.[1–5] In both instances, terrestrial cellular and data networks were down for the first several days after the event, and only those with access to satellite communications devices could contact counterparts and partners outside of the affected areas.

When disasters strike, traditional networks often collapse, leaving satellite communications as the only reliable option.[6] Tools such as satellite telephones, satellite messaging, geolocation devices and portable satellite internet devices generally remain operational, even in the most remote areas or when conventional networks are unavailable. These enable critical tasks, such as relaying information, coordinating medical referrals and logistics, addressing urgent needs and enhancing coordination through real-time data-sharing. These benefits were demonstrated by satellite communications devices in the hours and days following the December 2024 earthquake in Vanuatu, when the Ministry of Health and the National Disaster Management Office, the World Health Organization (WHO) and other United Nations agencies, as well as other partners, leveraged satellite technology to call for and coordinate international assistance.

Satellite communications, once costly and complex, are now both affordable and user-friendly. Subscription costs are similar to those of cellular phones and terrestrial mobile and data service providers, and many suppliers offer flexible plans that can be easily changed when needed following initial activation. WHO has procured satellite communications devices for some countries to strengthen emergency response communications readiness. However, in several cases, upon follow-up, these devices have remained inactive months after delivery, limiting their operational impact when emergencies arise. There are a few reasons for this. While basic costs may be modest – approximately US$ 150 per year for standby (limited use) satellite messaging – government or partner budgeting delays, administrative bottlenecks and lack of routine maintenance (e.g. software updates) sometimes prevent these devices from being deployment-ready. Moving forward, emergency responders should integrate satellite communications into field deployment kits and standard operating procedures from the outset. Devices must be activated, tested regularly and maintained, with clear budgeting for subscriptions and updates. Governments and partners must proactively finance and facilitate ongoing maintenance and address operational barriers to ensure that satellite devices are fully functional and

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Published: 27 March 2025
doi: 10.5365/wpsar.2025.16.1.1217

ready to deploy when they're needed the most. Routine monitoring or drills are needed to confirm the readiness of this critical resource.

Satellite communications are no longer a luxury: they are a critical component of disaster preparedness and emergency responses, helping to save lives and ensure efficient coordination. However, their use remains inconsistent across countries and partners. Prioritizing procurement, subscriptions for maintenance and training for personnel can help to ensure that satellite communications support more effective health emergency responses in the future.

## *Conflicts of interest*

The authors have no conflicts of interest to declare.

## *Ethics statement*

Ethics approval was unnecessary as no research was undertaken.

## *Funding*

None.

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