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## To contact us:


**Western Pacific Surveillance and Response**
World Health Organization
Office for the Western Pacific Region
United Nations Avenue
1000 Manila, Philippines
wpsar@who.int
https://ojs.wpro.who.int/


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# Community first responders: A missing key to reducing the impact of injury and illness in low- and middle-income countries in the Western Pacific?

Andrew Hodgetts,[a] Peter Massey,[b] Michelle Redman-MacLaren[c] and Roxanne Bainbridge[a]

Correspondence to Andrew Hodgetts (email: a.hodgetts@cqu.edu.au)

The higher burdens of morbidity and mortality in low- and middle-income countries (LMICs) in the Western Pacific Region (WPR) could be reduced if there were community first responders qualified in first aid and trained according to the local context. In the WPR, the leading causes of death of people aged 5–49 years are violence and injury, which claim the lives of 1 million people each year.[1] Emerging data highlight the burden of violence and injury in the Region,[1] but there are no reliable data to indicate the potential benefits of having community first responders. Community first responders might make a significant difference in the rates of mortality and morbidity associated with injury and with other health issues for which timely, effective first aid could help.

In LMICs in the WPR, the recognition and initiation of basic first-aid measures fall to the community because of limited access to formal health services.[2] In this Region, cardiovascular disease, complications of diabetes and respiratory diseases account for the majority of adult deaths, contribute to an increasing burden on the health systems and slow development.[3] Community first responders who are trained to identify these medical conditions could start targeted primary management and provide early reports to formal health service providers. Potentially, first responders could significantly reduce the harm of delayed treatment of diseases and injuries in their communities.

Community first responders have been reported to make a difference in LMICs in Iraq, Nigeria and South Africa. In South Africa, participants from a township in the Cape Town region who were given a 1-day training session provide effective basic first aid to members of their communities until professional ambulance services arrive.[4] In a similar programme in Ibadan, south-west Nigeria, drivers of commercial passenger vehicles were trained for 2 days in basic first aid techniques.[5] As commercial drivers are most likely to encounter motor vehicle accidents, they are able to provide immediate initial first aid. Both programmes established that laypeople can successfully complete first aid training programmes, demonstrate skills and retain knowledge, as shown in re-testing.[4,5] In Iraq, village first responders worked in partnership with trained paramedics to treat victims of motor vehicle accidents, and a significant reduction in mortality was recorded among people who received such pre-hospital care.[6]

In most LMICs, the burden of injury and illness affects not only the victims but also their families, communities and future generations. Sickness or injury of the main income earner may reduce their ability to provide for the family, including food and education, with inherent negative effects.[7] The extra burden placed on family members of caring for the sick or injured person may also negatively affect the family unit. Sick or injured children can lose valuable time away from education,

[a] Central Queensland University, Cairns, Australia.
[b] Hunter New England Health, New Lambton, Australia.
[c] James Cook University, Cairns, Australia.
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affecting their future, which in turn can negatively affect the family unit and the community. Trained community first responders could reduce this burden.

Additional benefits of community first responders stem from their intimate knowledge of the culture, assets and needs of the community. An example is the work of community rangers in the Treaty Village Resilience Program in Papua New Guinea.[8] The rangers work with local nurses to deliver health and nutrition programmes and provide birthing assistance. All rangers complete first aid training and collaborate with villages to deliver projects to improve health, including water and sanitation.

Not only must community first responders understand the culture and needs of communities, but the community must trust the first responder programme and its participants. Trust in community first responders was a key factor in a study in the United Republic of Tanzania of the perceptions of trauma patients to the introduction of community first responders.[9] Family members and neighbours were trusted most to deliver first aid, and taxi drivers and police officers were considered the least trustworthy. Members of religious groups were also identified as a potential source of first responders, but this recommendation was not tested. Trust in community first responders is poorly understood in the WPR.

Community first responders can also monitor and report important diseases in communities, as evidenced in a recent outbreak of Ebola virus disease in West Africa. Contact tracing and reporting of early symptoms at district and local levels by community and religious leaders helped to identify and contain the outbreak in some communities.[10] Community and religious leaders also disseminated information and improved community cooperation in reporting disease presentations.[10] This experience shows the importance of local training and capacity-building and of tailoring programmes to the local context.[11]

High-income countries in the WPR, such as Australia, have a responsibility to support LMICs in improving their health systems and training community first responders as they move towards achievement of the Sustainable Development Goals.[12] The potential of locally designed and developed community first responder programmes to reduce the burden of injury and illness in the WPR is untapped. A first step could be to work with local communities to understand how best to conduct training that is culturally relevant, acceptable and effective. If lives are to be saved and disability reduced, LMICs in the Region must find ways to provide effective training for community first responders, systems to sustain training and monitoring and optimal incorporation of social and cultural contexts into training.

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## *Conflict of interest*

All authors declare no conflicts of interest.

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# Genomic surveillance of *Pseudomonas aeruginosa* in the Philippines, 2013–2014

Jeremiah Chilam,[a,†] Silvia Argimón,[b,†] Marilyn T. Limas,[a] Melissa L. Masim,[a] June M. Gayeta,[a] Marietta L. Lagrada,[a] Agnettah M. Olorosa,[a] Victoria Cohen,[b] Lara T. Hernandez,[a] Benjamin Jeffrey,[b] Khalil Abudahab,[b] Charmian M. Hufano,[a] Sonia B. Sia,[a] Matthew T.G. Holden,[d] John Stelling,[c] David M. Aanensen,[b,e,*] and Celia C. Carlos,[a,*] on behalf of the Philippines Antimicrobial Resistance Surveillance Program

Correspondence to Celia Carlos (email: ccarlosphl@gmail.com) and David M. Aanensen (email: David.aanensen@bdi.ox.ac.uk)

*Pseudomonas aeruginosa* is an opportunistic pathogen that often causes nosocomial infections resistant to treatment. Rates of antimicrobial resistance (AMR) are increasing, as are rates of multidrug-resistant (MDR) and possible extensively drug-resistant (XDR) infections. Our objective was to characterize the molecular epidemiology and AMR mechanisms of this pathogen.

We sequenced the whole genome for each of 176 *P. aeruginosa* isolates collected in the Philippines in 2013–2014; derived the multilocus sequence type (MLST), presence of AMR determinants and relatedness between isolates; and determined concordance between phenotypic and genotypic resistance.

Carbapenem resistance was associated with loss of function of the OprD porin and acquisition of the metallo-β-lactamase (MBL) gene $bla_{VIM}$. Concordance between phenotypic and genotypic resistance was 93.27% overall for six antibiotics in three classes, but varied among aminoglycosides. The population of *P. aeruginosa* was diverse, with clonal expansions of XDR genomes belonging to MLSTs ST235, ST244, ST309 and ST773. We found evidence of persistence or reintroduction of the predominant clone ST235 in one hospital, and of transfer between hospitals.

Most of the ST235 genomes formed a distinct lineage from global genomes, thus raising the possibility that they may be unique to the Philippines. In addition, long-read sequencing of one representative XDR ST235 isolate identified an integron carrying multiple resistance genes (including $bla_{VIM-2}$), with differences in gene composition and synteny from the *P. aeruginosa* class 1 integrons described previously.

The survey bridges the gap in genomic data from the Western Pacific Region and will be useful for ongoing surveillance; it also highlights the importance of curtailing the spread of ST235 within the Philippines.

*Pseudomonas aeruginosa* is an opportunistic pathogen that often causes nosocomial infections (e.g. pneumonia, bacteraemia and urinary tract infections), particularly in immunocompromised patients.[1] Eight Asian countries reported frequencies of isolation of *Pseudomonas* spp. of above 15% from hospital-acquired (HA) pneumonia cases, with the Philippines reporting *P. aeruginosa* as the most common etiological agent.[2] Also, Pseudomonas spp. were the second most common pathogen isolated from device-associated HA infections in a study of intensive care units in Philippine hospitals.[3]

*P. aeruginosa* infections are often resistant to treatment,[4] and carbapenem use has been strongly associated with resistance.[1] However, a study evaluating carbapenem restriction practices at a hospital in Manila found that 37% of the carbapenem prescriptions were non-compliant, highlighting challenges in antimicrobial stewardship.[5] Between 2010 and 2014, the Philippine Antimicrobial Resistance Surveillance Program (ARSP) reported increasing rates of resistance to antibiotics used to treat *P. aeruginosa* infections, such as carbapenems and extended-spectrum cephalosporins (**Fig. 1A-B**). In contrast, resistance to aminoglycosides and fluoroqui-

[a] Antimicrobial Resistance Surveillance Reference Laboratory, Research Institute for Tropical Medicine, Muntinlupa, Philippines.
[b] Centre for Genomic Pathogen Surveillance, Wellcome Genome Campus, Hinxton, England, United Kingdom of Great Britain and Northern Ireland.
[c] Brigham and Women's Hospital, Boston (MA), USA.
[d] University of St Andrews School of Medicine, St Andrews, Scotland, United Kingdom of Great Britain and Northern Ireland.
[e] Centre for Genomic Pathogen Surveillance, Big Data Institute, University of Oxford, Oxford, England, United Kingdom of Great Britain and Northern Ireland.
[†] These authors contributed equally to this work.
[*] These authors contributed equally to this work.
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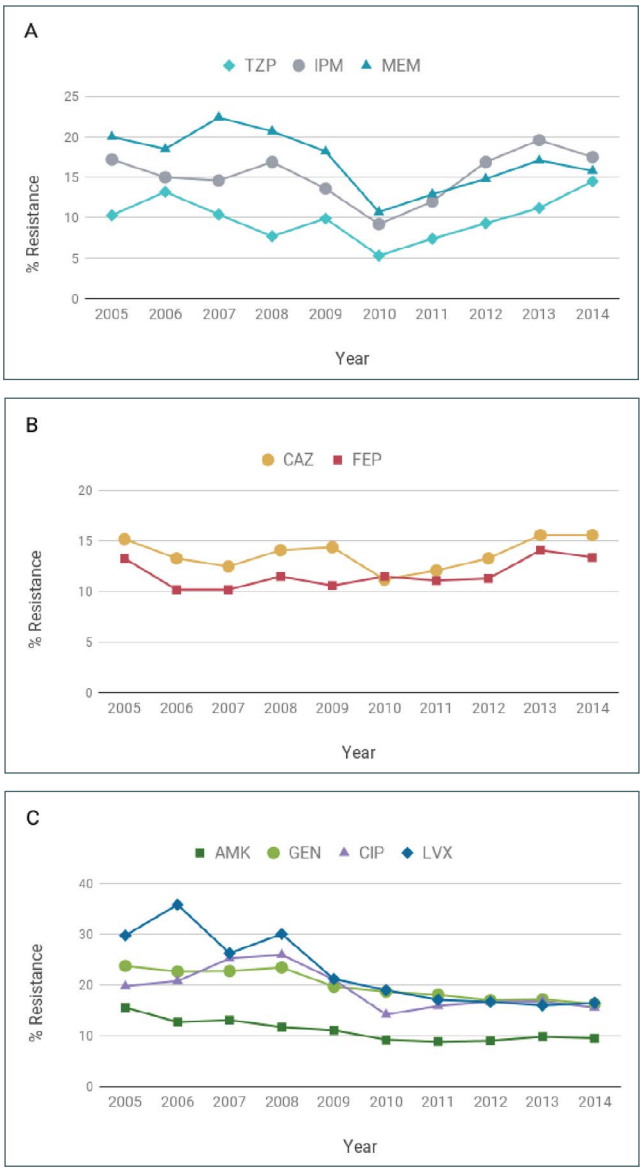
Fig. 1A-C. **Annual resistance rates to nine antibiotics of *P. aeruginosa* isolates referred to the ARSP, 2005–2014**




AMK: amikacin; CAZ: ceftazidime; CIP: ciprofloxacin; FEP: cefepime; GEN: gentamicin; IPM: imipenem; LVX: levofloxacin; MEM: meropenem; TZP: piperacillin-tazobactam.

nolones remained relatively stable or decreased slightly in the same period (**Fig. 1C**). The ARSP has also reported multidrug-resistant (MDR) rates of 21–23% and possible extensively drug-resistant (XDR) rates of 13–18% in recent years.[6–8]

The emergence of MDR *P. aeruginosa* with resistance to carbapenems, aminoglycosides and fluoroquinolones was followed by reports of isolates sensitive only to colistin[9] and, more recently, of colistin resistance in carbapenem non-susceptible isolates,[10] leaving few treatment options. These reports coincide with multi-locus sequence type (MLST) ST235,[9–11] the predominant global epidemic clone. The metallo-β-lactamase (MBL) genes $bla_{VIM}$ and $bla_{IMP}$ – usually associated with integrons carrying multiple resistance determinants – have been identified in ST235 *P. aeruginosa* isolates from Asian countries.[12–14]

While the resistance rates and profiles of *P. aeruginosa* in the Philippines have been well characterized,[15,16] the molecular epidemiology and AMR mechanisms of this pathogen remain largely unknown. Whole-genome sequencing (WGS) can identify transmission patterns, AMR mechanisms and the source of HA infections.[17] In this study, we characterized the clonal relatedness and resistance determinants of *P. aeruginosa* isolates from the ARSP using WGS.

## METHODS

### Bacterial isolates

A total of 7877 *P. aeruginosa* isolates were collected and tested for resistance by the ARSP from January 2013 to December 2014. Of the 443 and 283 isolates referred to the Antimicrobial Resistance Surveillance Reference Laboratory (ARSRL) for confirmation in 2013 and 2014, respectively, 179 isolates from 17 sentinel sites were selected for WGS, as previously described.[18] Briefly, 113 isolates of carbapenemase-producing *P. aeruginosa* were selected; also included were 66 available isolates that were susceptible to all antibiotics tested. We used a proxy definition for "infection origin", whereby initial infection isolates collected in the community or on either of the first 2 days of hospitalization were categorized as community-acquired (CA), and isolates collected on hospital day 3 or later were categorized as hospital-acquired (HA).[19]

### Antimicrobial susceptibility testing (AST)

All *P. aeruginosa* isolates from this study were tested for susceptibility to nine antibiotics representing five classes: amikacin (AMK), ceftazidime (CAZ), ciprofloxacin (CIP), cefepime (FEP), gentamicin (GEN), imipenem (IPM), meropenem (MEM), tobramycin (TOB), and piperacillin-tazobactam (TZP) (**Table 1**). Antimicrobial susceptibility of the isolates was determined at ARSRL using the Kirby-Bauer disk diffusion method, and gradient methods such as E-Test (bioMérieux, Marcy-l'Étoile, France) and Vitek 2

Table 1. **Total number of *P. aeruginosa* isolates analysed by the ARSP and referred to the ARSRL during 2013 and 2014, isolates submitted for WGS, and high-quality *P. aeruginosa* genomes obtained, discriminated by sentinel site and AMR profile**

| | Number of isolates | | |
|---|---|---|---|
| | 2013 | 2014 | Total |
| **Total ARSP** | 3591 | 4286 | 7877 |
| **Referred to ARSRL** | 443 | 283 | 726 |
| **Submitted for WGS** | 89 | 90 | 179 |
| **High-quality genomes** | 87 | 89 | 176 |
| *By sentinel site ** | | | |
| BGH | 2 | 4 | 6 |
| BRH | 0 | 5 | 5 |
| CMC | 0 | 1 | 1 |
| CVM | 2 | 3 | 5 |
| DMC | 5 | 2 | 7 |
| EVR | 2 | 2 | 4 |
| FEU | 2 | 2 | 4 |
| GMH | 4 | 4 | 8 |
| JLM | 2 | 5 | 7 |
| MMH | 3 | 5 | 8 |
| NKI | 10 | 16 | 26 |
| NMC | 3 | 8 | 11 |
| RMC | 2 | 0 | 2 |
| SLH | 0 | 1 | 1 |
| STU | 5 | 4 | 9 |
| VSM | 32 | 16 | 48 |
| *By AMR profile *** | | | |
| Susceptible | 36 | 30 | 66 |
| CAZ FEP IPM MEM TZP GEN TOB AMK CIP [XDR] | 30 | 29 | 59 |
| IPM MEM | 7 | 9 | 16 |
| CAZ FEP IPM MEM TZP GEN TOB CIP [XDR] | 4 | 7 | 11 |
| CAZ FEP IPM MEM TZP GEN TOB AMK | 1 | 4 | 5 |
| CIP | 3 | 2 | 5 |
| CAZ FEP IPM MEM TZP | 1 | 2 | 3 |
| IPM MEM TZP CIP | 0 | 1 | 1 |
| GEN TOB CIP | 1 | 0 | 1 |
| FEP TZP TOB CIP | 0 | 1 | 1 |
| CAZ FEP IPM MEM GEN TOB | 1 | 0 | 1 |
| IPM | 1 | 0 | 1 |
| CAZ FEP IPM MEM GEN TOB CIP | 1 | 0 | 1 |
| IPM MEM CIP | 1 | 0 | 1 |
| CAZ FEP GEN TOB AMK CIP | 0 | 1 | 1 |
| FEP IPM MEM GEN TOB CIP | 0 | 1 | 1 |
| CAZ | 0 | 1 | 1 |
| CAZ FEP TZP | 0 | 1 | 1 |

* AMK: amikacin; AMR: antimicrobial resistance; ARSP: Antimicrobial Resistance Surveillance Program; ARSRL: Antimicrobial Resistance Surveillance Reference Laboratory; CAZ: ceftazidime; CIP: ciprofloxacin; FEP: cefepime; GEN: gentamicin; IPM: imipenem; MEM: meropenem; TOB: tobramycin; TZP: piperacillin-tazobactam; XDR: extensively drug resistant; WGS: whole-genome sequencing.

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

Compact automated system (bioMérieux). To determine the resistance profile of the isolates, the zone of inhibition and minimum inhibitory concentration of antibiotics were interpreted according to guidelines from the Clinical and Laboratory Standard Institute (CLSI).[20] MDR phenotypes were classified according to standard definitions.[21]

## DNA extraction and WGS

A total of 179 *P. aeruginosa* isolates were shipped to the Wellcome Trust Sanger Institute for WGS. DNA was extracted from a single colony of each isolate with the QIAamp 96 DNA QIAcube HT kit and a QIAcube HT (Qiagen, Hilden, Germany). DNA extracts were multiplexed and sequenced on the Illumina HiSeq platform (Illumina, CA, USA) with 100-bp paired-end reads. Isolate 13ARS-VSM740 was also sequenced with the PacBio RSII platform (Pacific Biosciences). Raw sequence data were deposited in the European Nucleotide Archive (ENA) under the study accession PRJEB17615. Run accessions for Illumina data are provided on the Microreact projects. The PacBio data were deposited under run accession ERR3284501.

## Bioinformatics analysis

Genome quality was evaluated based on metrics generated from assemblies, annotation files and the alignment of the isolates to the reference genome of *P. aeruginosa* strain LESB58 (accession FM209186), as previously described.[18] Assemblies were produced from short-read Illumina data[18] and from long-read PacBio data with the HGAP v4 pipeline (Pacific Biosciences). A total of 176 isolates yielded high-quality *P. aeruginosa* genomes and were included in this study.

We derived the MLST of the isolates from the whole genome sequences. The sequence types (ST) were determined from assemblies with Pathogenwatch (https://pathogen.watch/) and with MLSTcheck v1.007001, and from sequence reads with ARIBA[22] and the *P. aeruginosa* database hosted at PubMLST.[23] The MLST calls were curated, as previously described.[18] Integrons were detected in the genome assemblies with IntegronFinder.[24]

Evolutionary relationships between the 176 isolates were inferred from core single-nucleotide polymorphism (SNP). A core gene alignment was performed with Roary v3.11.3, using the mafft aligner option and minimum percentage identity for blastp of 90%. Evolutionary relationships between 169 isolates from groups 1 and 2 were inferred from SNPs by mapping the paired-end reads to the reference genomes of *P. aeruginosa* strains LESB58 (ST146, FM209186) or NCGM2_S1 (ST235, AP012280.1).[18] Mobile genetic elements (MGEs) were masked in the alignment of pseudogenomes with a script available at https://github.com/sanger-pathogens/remove_blocks_from_aln. For the phylogenetic analysis of ST235 genomes, recombination regions detected with Gubbins[25] were also removed. Alignments of SNPs were inferred with snp-sites v2.4.1,[26] and were used to compute pairwise SNP differences between isolates from different patients (minimum $n = 3$) belonging to the same or to different hospitals, using a script from https://github.com/simonrharris/pairwise_difference_count. Maximum likelihood phylogenetic trees were generated with RAxML,[27] based on the generalized time reversible (GTR) model with GAMMA method of correction for among-site rate variation and 100 bootstrap replications.

To contextualize the Philippine genomes, we downloaded, assembled and quality controlled global *P. aeruginosa* genomes with linked geographical and temporal information, collected mainly between 2007 and 2017, for which raw Illumina paired-end sequence data were available at the ENA. A tree of 904 genomes was inferred with FastTree[28] from an alignment of 549 126 SNP positions, obtained after mapping the reads to the complete genome of strain LESB58 and masking regions with MGEs. A tree of 96 global ST235 genomes was inferred with RAxML from an alignment of 1993 SNP sites obtained after mapping the genomes to the complete genome of strain NCGM2-S1, and masking MGEs and recombination regions.

Known AMR determinants were identified with ARIBA[22] and a curated database of known resistance genes and mutations,[29] the Comprehensive Antibiotic Resistance Database,[30] and a custom database of mutations in the quinolone resistance-determining region of the *gyrA/B* and *parC/E* genes described for *P. aeruginosa*.[4] The output for the porin gene *oprD* was inspected to detect loss-of-function mutations. The *oprD* sequences were extracted from the whole-genome draft assemblies with blastn, using the oprD sequence from strain PAO1 (accession NC_002516.2, genome positions 1043982–1045314) as a query, then translated in silico to inspect the integrity of the coding frames. A 444 or

442 amino-acid protein that included a START and a STOP codon was considered functional.

The genomic predictions of AMR derived from the presence of known AMR genes and mutations (test) were compared with the phenotypic results (reference), and concordance was computed for each of six antibiotics (1056 total comparisons). Isolates with either a resistant or an intermediate phenotype were considered non-susceptible. An isolate with the same outcome for both the test and reference (i.e. both susceptible or both non-susceptible) was counted as a concordant isolate. Concordance was the number of concordant isolates as a percentage of the total number of isolates assessed.

All project data, including inferred phylogenies, AMR predictions and metadata were made available through Microreact.

### Ethics statement

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

## RESULTS

### Demographic and clinical characteristics of the *P. aeruginosa* isolates

Of the 179 *P. aeruginosa* isolates submitted for WGS, 176 passed quality control and were confirmed in silico as *P. aeruginosa* (**Table 2**). Patients were aged from under 1 to 96 years, with 27% ($n$ = 47) of the isolates from patients aged 65 years or older. Fifty-eight per cent ($n$ = 102) of the isolates were from HA infections. In terms of specimen type, 53% ($n$ = 94) of isolates were from respiratory samples (tracheal aspirates and sputum).

### Concordance between phenotypic and genotypic AMR

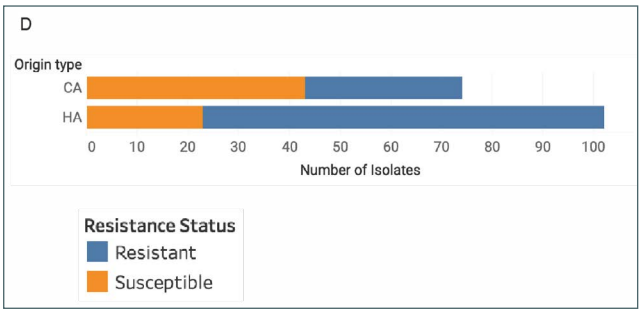
Isolates were tested for susceptibility to nine antibiotics representing five classes (**Fig. 1A-C**, **Table 3**). Most isolates were non-susceptible to carbapenems ($n$ = 100), 10 isolates were susceptible to carbapenems but resistant to other antibiotics, and 66 isolates were susceptible to all nine antibiotics (**Table 1**). CA infections

Table 2. **Demographic and clinical characteristics of 176 *P. aeruginosa* isolates**[a]

| Characteristic | No. isolates |
|---|---|
| **Sex** | |
| Male | 119 |
| Female | 57 |
| **Age (in years)** | |
| < 1 | 12 |
| 1–4 | 6 |
| 5–14 | 7 |
| 15–24 | 14 |
| 25–34 | 5 |
| 35–44 | 17 |
| 45–54 | 29 |
| 55–64 | 34 |
| 65–80 | 36 |
| ≥ 81 | 11 |
| Age unknown | 5 |
| **Patient type** | |
| Inpatient | 159 |
| Outpatient | 17 |
| **Specimen origin** | |
| Community-acquired | 74 |
| Hospital-acquired | 102 |
| **Submitted as** | |
| Carbapenem non-susceptible | 100 |
| Resistant to at least 1 antibiotic other than carbapenems | 10 |
| Susceptible | 66 |
| **Specimen type** | |
| Abdominal fluid* | 1 |
| Abscess | 1 |
| Blood* | 21 |
| Bronchial | 1 |
| Catheter | 2 |
| Cerebrospinal fluid* | 3 |
| Cornea | 2 |
| Dialysis fluid* | 1 |
| Drainage | 1 |
| Fluid | 3 |
| Inguinal | 1 |
| Other | 1 |
| Pleural fluid* | 1 |
| Sputum | 31 |
| Tissue | 5 |
| Tracheal | 1 |
| Tracheal aspirate | 63 |
| Urine | 12 |
| Wound | 25 |

[a] Invasive isolates were considered as those obtained from specimen types marked with an asterisk (*).

Fig. 1D. **Association between resistance and the origin of infection for 176 *P. aeruginosa* isolates sequenced in this study**



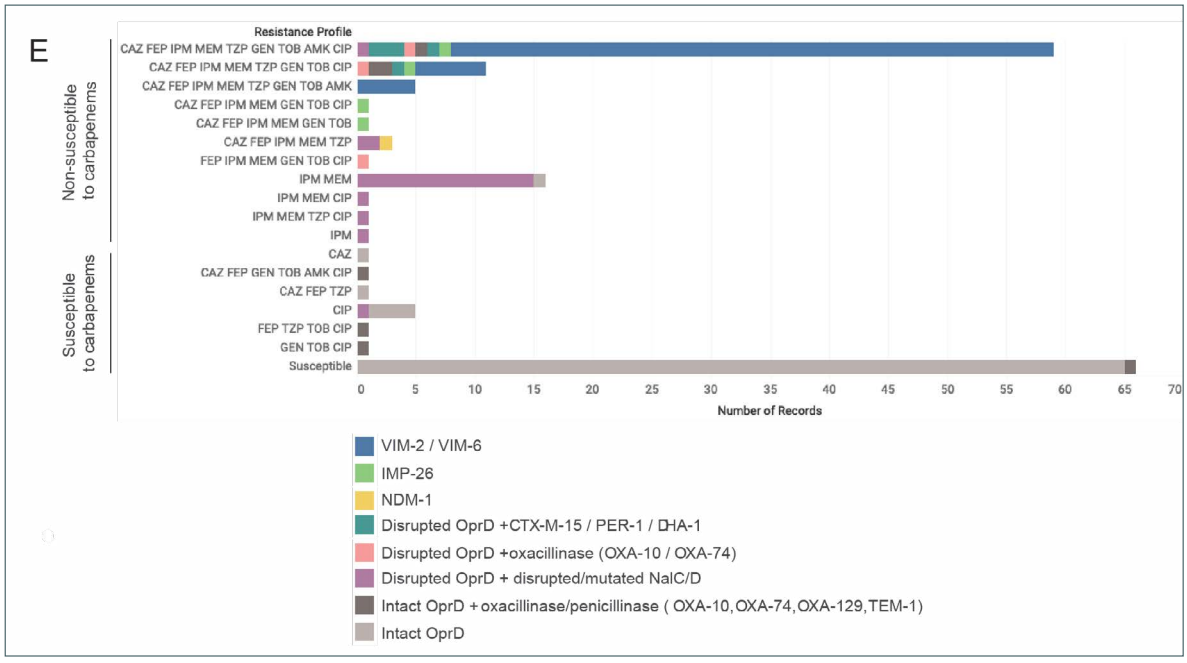

CA: community-acquired; HA: hospital-acquired; Resistant: Resistant to at least one antibiotic tested; Susceptible: Susceptible to all nine antibiotics tested.

were more frequently associated with susceptible isolates and HA infections with resistant isolates (**Fig. 1D**, two-tailed Fisher's exact test $P = 0.000002$).

Of the 18 isolates resistant to imipenem and meropenem but not to other β-lactam antibiotics, 17 carried both loss-of-function disruptions in the OprD porin, and disruptions or known non-synonymous mutations in the NalC (A186T, G71E, S209R) and/or NalD (S32N) regulators of the MexAB-OprM multidrug efflux pump, suggesting that their resistance is due to a combination of reduced influx and increased efflux of the carbapenem antibiotics (**Fig. 1E**). Among the 81 carbapenem-resistant isolates that were also resistant to third-generation cephalosporin ceftazidime and/or fourth-generation cephalosporin cefepime, 67 isolates carried acquired MBL genes $bla_{\text{VIM-2}}$ ($n = 61$ genomes), $bla_{\text{VIM-6}}$ ($n = 1$), $bla_{\text{IMP-26}}$ ($n = 4$) or $bla_{\text{NDM-1}}$ ($n = 1$), while five carried disrupted *oprD* genes plus acquired extended-spectrum β-lactamase (ESBL) genes $bla_{\text{PER-1}}$ ($n = 3$), $bla_{\text{CTX-M-15}}$ ($n = 1$) or AmpC-like gene $bla_{\text{DHA-1}}$ ($n = 1$). The remaining eight isolates harboured other β-lactamase genes, but their carbapenem-resistance mechanisms remain uncharacterized. Of the 76 isolates susceptible to carbapenems, 75 carried either a full-length OprD porin (444 amino acids) without any known mutations, or a 442 amino acid-long OprD protein with an intact reading frame, while one isolate was missing the STOP codon in the *oprD* gene.

The overall phenotypic and genotypic concordance was 93.27% for the six antibiotics analysed (**Table 3**). The concordance was above 96% for carbapenems.

Fig. 1E. **Mechanisms of resistance to carbapenems and other β-lactam antibiotics identified in the genomes of 176 isolates grouped by their resistance profile[a]**




[a] For simplicity, only the main mechanism is indicated.

AMK: amikacin; CAZ: ceftazidime; CIP: ciprofloxacin; FEP: cefepime; GEN: gentamicin; IPM: imipenem; MEM: meropenem; TOB: tobramycin; TZP: piperacillin-tazobactam.

## Genotypic findings

### *In silico genotyping*

A total of 79 STs were identified (**Table 4**), with 27.8% (*n* = 49) belonging to ST235, followed by ST309 (5.7%, *n* = 10), ST244 and ST773 (5.1% each, *n* = 9). The majority of the STs (79.7%, *n* = 63) were singletons (represented by only one genome), most of which (*n* = 42) were contributed by the susceptible isolates. Indeed, the resistant isolates (36 STs, *n* = 110) exhibited less clonal diversity than the susceptible isolates (56 STs, *n* = 66). ST235 represented 43.6% (*n* = 48) of the resistant isolates but only 1.5% (*n* = 1) of the susceptible isolates, and was predominantly a nosocomial clone in the Philippines (36 HA vs 13 CA isolates), spread across 13 hospitals.

### *Population structure of P. aeruginosa in the Philippines*

The phylogenetic tree of 176 genomes from the Philippines comprises three major groups,[31] group 1 (*n* = 64) including PA14, group 2 (n = 105) including PAO1 and the more distantly related group 3 (n = 7) including PA7 (**Fig. 2A**). All three groups included carbapenem-resistant isolates and susceptible isolates, though most isolates in group 2 were susceptible (*n* = 39, 60.9%) and most in group 1 were resistant (*n* = 75, 71.4%, **Fig. 2B**).

The population of *P. aeruginosa* comprises a limited number of widespread clones selected from a diverse pool of rare, unrelated genotypes that recombine at high frequency.[32] A phylogenetic tree of 169 genomes from groups 1 and 2 showed that the clonal expansions were mostly within the major group 1 – represented by ST235, ST309, ST773 and ST313 (**Fig. 2B**) – found across multiple hospitals and resistant to multiple antibiotics. Most of the XDR isolates (*n* = 61, 87%) were found in ST235, ST244, ST309 and ST773, and most (*n* = 44, 62.8%) carried $bla_{VIM}$ (an MBL that can degrade all anti-pseudomonal β-lactamases except for aztreonam),[1] AAC(6')-Ib (an aminoglycoside acetyltransferase conferring resistance to tobramycin and amikacin), and the non-synonymous mutation T83I on GyrA associated with resistance to fluoroquinolones.

The higher prevalence of ST235 prompted us to look further at this clone. The phylogenetic tree of 49 ST235 isolates comprised two distinct clades with different geographic distribution (**Fig. 2C**). Clade I (*n* = 10) was represented in five hospitals in the Luzon (north) and Visayas (central) island groups, while clade II (*n* = 39) was represented in 10 hospitals from north to south of the country. The phylogeographic structure of the tree and the relatedness between genomes showed evidence of dissemination of ST235 between hospitals. Within clade Ib (**Fig. 2C**), one genome from hospital NKI differed from two genomes from hospital BRH by seven and eight SNPs, respectively. Within clade IIb (**Fig. 2C**), the genetic differences between isolates from the same hospital (mean pairwise SNP differences 36.41 ± 20.84, range 0–64) were not significantly different to those between isolates from different hospitals (mean 45.36 ± 8.12, range 29–61, Mann–Whitney U test z-score = –1.49145, *P* = 0.13622). The close relationships and the common repertoire of resistance genes between isolates from different hospitals support inter-hospital transmission.

The genomes from the hospital VSM (*n* = 24) formed at least three clusters within clade IIb, two of which exhibited discrete temporal distribution (VSM-2 and VSM-3, **Fig. 2C**), suggesting that they could represent hospital outbreaks. In agreement with this, the genomes from different patients within clade VSM-3 differed by an average of 11.55 pairwise SNPs (range 0–24). We also identified isolates within VSM-3 that were collected nine or more months apart (**Fig. 2C**), suggesting that ST235 can either persist in or be reintroduced to the hospital environment.

The distribution of acquired resistance genes and mutations showed that resistance determinants differed between clades I and II, with patterns that were consistent with the acquisition of multiple genes simultaneously by mobile genetic elements. Long-read sequencing of isolate 14ARS-VSM0870, representative of the XDR resistant profile CAZ FEP IPM MEM TZP GEN TOB AMK CIP (marked with an asterisk on **Fig. 2C**), revealed the acquisition of $bla_{VIM-2}$, $bla_{OXA-10}$, *catB3*, *aadA1* (ANT(3")-Ia) and *acc(6')-Ib* within a class 1 integron integrated in the chromosome at position 977 774 (**Fig. 2D**). The ciprofloxacin resistance gene

Fig. 2. **Genomic surveillance of *P. aeruginosa* from the Philippines, 2013–2014**

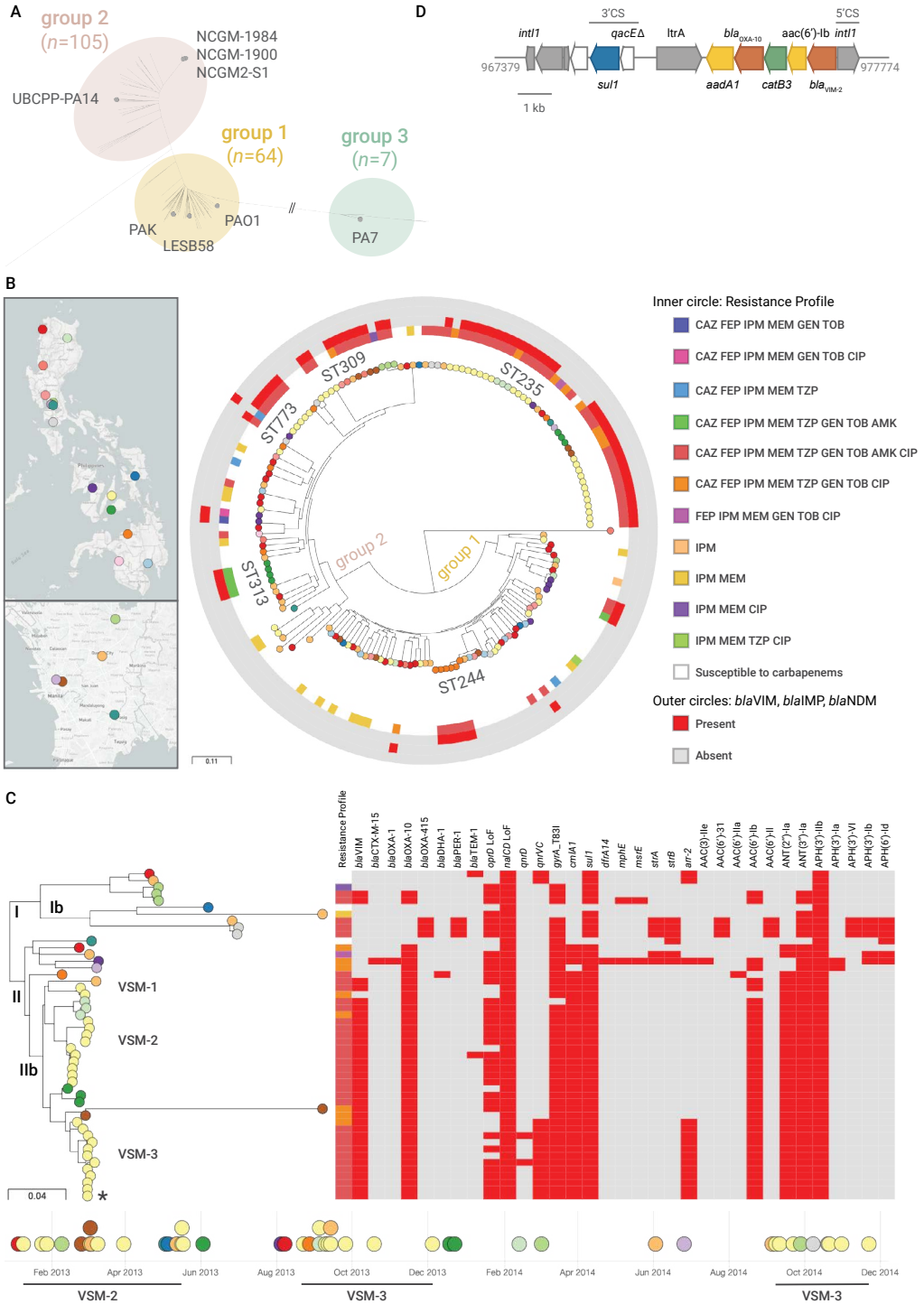



Fig. 2A. Phylogenetic tree of 176 isolates from the Philippines and eight reference genomes, inferred with RAxML from an alignment of 396 194 core SNP sites. The reference genomes are indicated by grey nodes.

Fig. 2B. Phylogenetic tree of 169 isolates from groups 1 and 2 inferred with RAxML from an alignment of 305 220 SNP sites obtained after mapping the genomes to the complete genome of strain LESB58 and masking mobile genetic elements from the alignment. The tree leaves are coloured by sentinel site and indicated on the map (left panels, top: Philippines, bottom: detail of the National Capital Region). Tree rings indicate (from inner to outer) the distribution of the carbapenem-resistant profiles and of carbapenemase genes *bla*$_{VIM}$, *bla*$_{IMP}$ and *bla*$_{NDM}$. The data, including the full distribution of resistance determinants, are available at https://microreact.org/project/ARSP_169PAE_2013–2014.

Fig. 2C. Phylogenetic tree of 49 ST235 genomes inferred from an alignment of 1066 SNP sites obtained after mapping the genomes to the complete genome of strain NCGM2-S1 (ST235) and masking mobile genetic elements and recombination regions. The tree leaves are coloured by sentinel site as indicated on the map from Fig. 2B. The tree blocks represent the distribution of the carbapenem-resistant profiles and of acquired resistance genes and mutations. The representative isolate sequenced with long reads is shown with an asterisk. The full data are available at https://microreact.org/project/ARSP_PAE_ST235_2013–14. The scale bars represent the number of SNPs per variable site.

Fig. 2D. Resistance genes acquired en bloc within a class 1 integron in *P. aeruginosa* strain 14ARS-VSM0870. Arrows indicate genes conferring resistance to β-lactamases (orange), aminoglycosides (yellow), chloramphenicol (green) and sulphonamides (blue), or related to DNA mobilization/integration (grey). 3′CS and 5′CS: conserved segments.

*qnrVC* and the rifampin-resistance gene *arr-2* were located on a different class 1 integron elsewhere in the genome.

### *P. aeruginosa from the Philippines in the global context*

We placed the genomes from our retrospective collection in the global context of 904 contemporary *P. aeruginosa* public genomes. This collection of public genomes represented 17 countries and 178 STs, with more than 60% of the genomes being from Europe ($n$ = 373) and the United States of America (USA) ($n$ = 205). The Philippine genomes were found throughout the tree, indicating that the *P. aeruginosa* population captured in our survey largely represents the global diversity of this pathogen. Notably absent were the epidemic clones ST111 and ST175 (**Fig. 3A**), which, together with ST235, are responsible for MDR and XDR nosocomial infections worldwide.

A more detailed tree of 96 ST235 genomes of global distribution showed three major clades: clade 1 was represented by isolates from Japan, the Philippines, Poland and Thailand ($n$ = 2); clade 2 showed the broadest geographic distribution across four continents and also included isolates from this study ($n$ = 3); clade 3 comprised exclusively isolates from the Philippines ($n$ = 44, **Fig. 3B**), which raises the possibility that this lineage of ST235 is characteristic to the Philippines; however, introductions from the other globally dispersed lineages may also occur, as shown in clades 1 and 2.

## DISCUSSION

In this study, we combined WGS and laboratory-based surveillance to characterize susceptible and resistant *P. aeruginosa* circulating in the Philippines in 2013 and 2014, with a particular emphasis on resistance to carbapenems, which increased in the years preceding this survey. Drug-resistant *P. aeruginosa* infections are difficult to treat, resulting in poor patient outcomes. In a tertiary hospital in Manila, severity of illness and mortality rates were significantly higher among patients infected with drug-resistant *P. aeruginosa* than among those infected with susceptible isolates, while median duration of hospital stay was significantly longer.[33]

*P. aeruginosa* strains exhibit a complex interplay between resistance mechanisms, both intrinsic and acquired.[34] The current gaps in understanding of some of these mechanisms were reflected in the variable concordance between phenotypic and genotypic resistance for the different antibiotics, even for those antibiotics belonging to the same class (aminoglycosides). Our characterization of the carbapenem resistance showed a combination of diverse known mechanisms, from inhibition of antibiotic influx into the cell, to upregulation of antibiotic efflux out of the cell and carbapenemase enzymes. The concordance between phenotypic and genotypic predictions of AMR was high for the carbapenems, but it required a degree of curation of results that is not practical within public health settings.

There are clear limitations in the genomic predictions of AMR for *P. aeruginosa*. First, publicly available, curated databases are not comprehensive of all the known mechanisms. We found no mutations leading to upregulation of the chromosomal cephalosporinase AmpC ($bla_{PAO}$), but an exhaustive search would require additional analyses. Second, the regulatory pathways of some mechanisms are not fully understood, such as those that regulate AmpC.[34,35] Third, extensive manual curation of some of the predictions is needed to ensure accuracy, for example of the loss-of-function mutations in the *oprD* gene.

The most prevalent clone in our data set was ST235 (27.8% of the isolates, $n$ = 49), found throughout the Philippines. ST235 is a well-characterized international epidemic clone causing drug-resistant nosocomial outbreaks.[32] Isolates carrying $bla_{VIM-2}$ and belonging to ST235 were reported from Malaysia, the Republic of Korea and Thailand.[13] Using WGS, we showed evidence of potential localized hospital outbreaks of ST235, as well as of persistence or reintroduction of this clone within one hospital. The number of SNP differences between genomes of isolates from different patients (0–24) were consistent with those reported for a persistent outbreak of *P. aeruginosa* in a hospital in the United Kingdom of Great Britain and Northern Ireland.[36] We also showed evidence of transfer of ST235 between hospitals, with isolates from different hospitals separated by as few as seven SNPs. Patient transfer between hospitals is not common in the Philippines, but the sampling for this

Fig. 3. ***P. aeruginosa* from the Philippines in the global context**

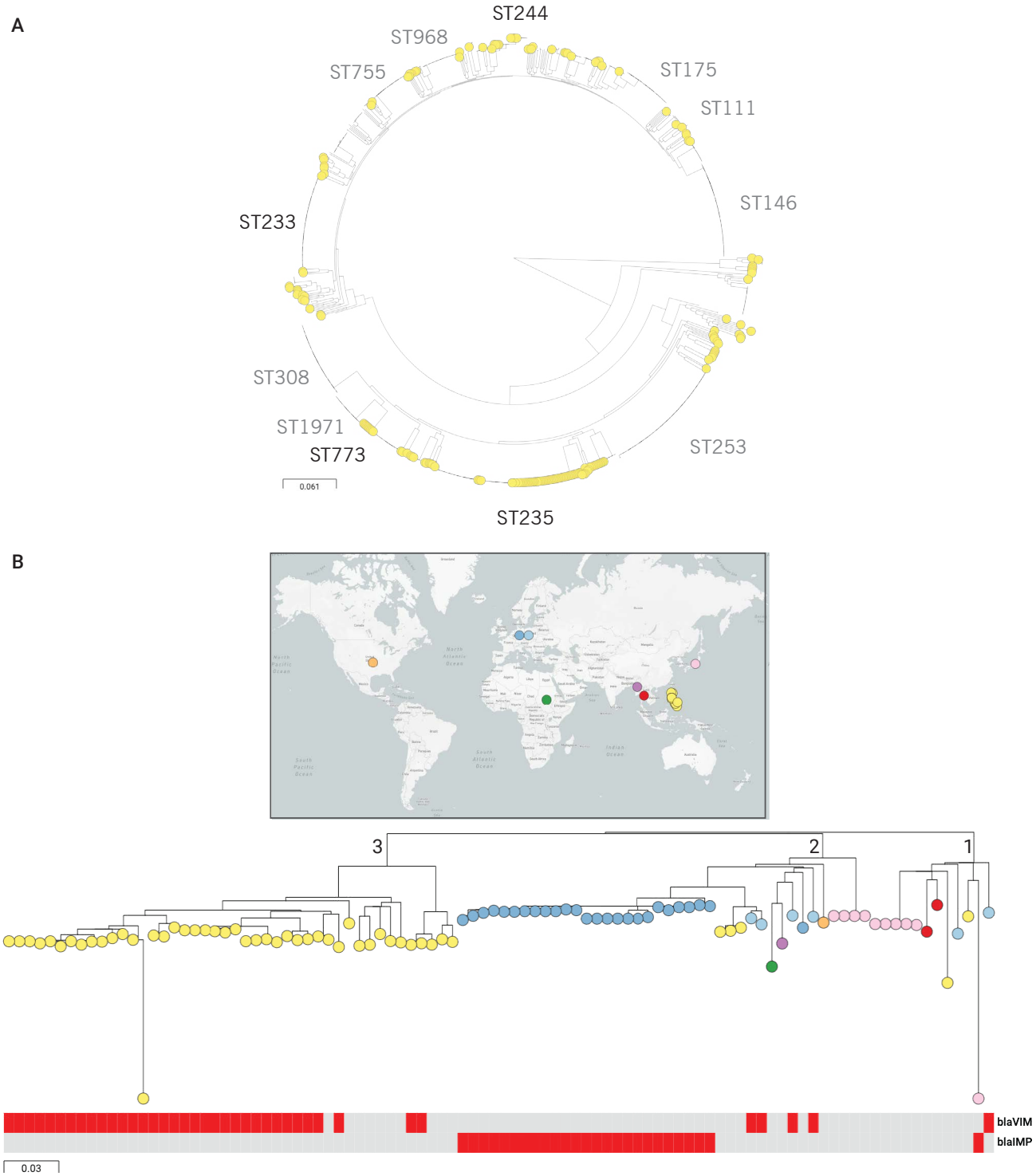



Fig. 3A. Phylogenetic tree of 904 *P. aeruginosa* isolates from the Philippines ($n$ = 176, this study) and from 57 other countries inferred from 549 126 SNP positions. The yellow tree nodes indicate the genomes from this study. The major lineages (STs) are labelled in black if represented by genomes of this study, or in brown if they are not. The data are available at https://microreact.org/project/ARSP_PAE_GLOBAL.

Fig. 3B. Phylogenetic tree of 96 ST235 isolates inferred from an alignment of 1993 SNP positions. The tree leaves are coloured by country as indicated on the map. The tree is annotated with the distribution of $bla_{VIM}$ and $bla_{IMP}$ genes (red: present, grey: absent). The data are available at https://microreact.org/project/ARSP_PAE_ST235_GLOBAL. The scale bars represent the number of SNPs per variable site.

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

| Antibiotic class | Antibiotic | Isolates tested | Resistant isolates (AST) | False positive | False negative | Concordance (%) | Acquired resistance mechanisms |
|---|---|---|---|---|---|---|---|
| Carbapenem | Imipenem | 176 | 100 | 1 | 4 | 97.16 | $bla_{VIM-2}$, $bla_{VIM-6}$, $bla_{NDM-1}$, $bla_{IMP-26}$, OprD loss-of-function (*oprD* interrupted, fragmented, or missing, presence of premature STOP, START codon missing), NalC/D loss-of-function (*nalC* missing, NalC_G71E, S209R, A186T, NalD_S32N) |
| | Meropenem | 176 | 99 | 2 | 4 | 96.59 | |
| Aminoglycoside | Gentamicin | 176 | 77 | 0 | 34 | 80.68 | AAC(3)-IIe, AAC(6')-31, AAC(6')-IIa, ANT(2")-Ia |
| | Tobramycin | 176 | 78 | 2 | 3 | 97.16 | AAC(3)-IIe, AAC(6')-31, AAC(6')-Ib, AAC(6')-Ib-cr, AAC(6')-IIa, ANT(2")-Ia |
| | Amikacin | 176 | 61 | 14 | 4 | 89.77 | AAC(6')-31, AAC(6')-Ib, AAC(6')-IIa, APH(3')-VI |
| Fluoroquinolone | Ciprofloxacin | 176 | 82 | 5 | 12 | 93.75 | *qnrD, qnrVC*, AAC(6')-Ib-cr, GyrA_D87N, D87Y, T83I, GyrB_E468D, S466F, ParC_S87L |

AST: antimicrobial susceptibility testing.

study only allows us to hypothesize about a possible role of the community, animals or the environment in the spread of this clone.

It was previously proposed that ST235 emerged in Europe around 1984, coinciding with the introduction of fluoroquinolones, and then disseminated to other regions via two independent lineages, acquiring resistance determinants to aminoglycosides and β-lactams locally.[14] Simultaneous acquisition of resistance to multiple antibiotics via integrons, transposons and integrative conjugative elements is well described in *P. aeruginosa*,[36] and is apparent in the distribution of resistance genes in our genomes. We have shown an example of a class 1 integron carrying six resistance genes in the genetic background of ST235. While this integron shared some features with others previously described in *P. aeruginosa*,[13,32] such as the 5′ and 3′ conserved segments,[37] the gene composition and synteny was different, supporting the hypothesis of local acquisition of resistance.

Country-specific ST235 lineages have been reported previously,[11,14] confirming that country-wide clonal expansions may occur in the context of the global circulation of this clone. A previous longitudinal study showed VIM-2-positive ST235 spreading throughout Belarus, Kazakhstan and the Russian Federation, albeit without the resolution of whole genome data.[38] The contextualization of our genomes with international ST235 genomes showed a distinct cluster of Philippine genomes with limited genetic variability, suggesting the clonal expansion and geographic dissemination of this lineage across the Philippines. Alternatively, this could be explained by the limited representation of the Western Pacific Region in the collection of global genomes, highlighting the need for public genome data with more even geographical coverage. Our retrospective survey contributed to bridging this gap by making raw sequence data available on public archives.

In conclusion, our detailed description of the epidemiology and resistance mechanisms of ST235 in the Philippines suggests that the burden of XDR *P. aeruginosa* infections in the Philippines may be largely driven by a local lineage of the international epidemic clone ST235. A recent study in a hospital in Jakarta, Indonesia analysed the population composition of *P. aeruginosa* before and after a multifaceted infection control intervention, with the relative abundance of ST235

Table 4. **Distribution of isolates, sequence types (STs), resistance profiles and acquired resistance mechanisms across the 17 sentinel sites[a]**

| Laboratory | No. of Isolates | No. of STs | Prevalent ST (no. of isolates) | Resistance profiles | Acquired resistance determinants |
|---|---|---|---|---|---|
| BGH | 6 | 5 | 309 (2) | Susceptible (2)<br>CAZ FEP IPM MEM TZP GEN TOB CIP (2)<br>CAZ FEP IPM MEM TZP GEN TOB AMK CIP (1)<br>IPM MEM (1) | NalC/D LOF (2)<br>IMP-26, AAC(6')-Ib, QnrVC1, OprD LOF, NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, ANT(3")-Ia, GyrA.D87Y, OprD LOF, NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, ANT(3")-Ia, QnrVC1, GyrA.T83I, OprD LOF, NalC/D LOF (1)<br>OprD LOF, NalC/D LOF (1) |
| BRH | 5 | 3 | 235 (2) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (3)<br>Susceptible (2) | AAC(6')-31, AAC(6')-II, ANT(3")-Ia, APH(3')-VI, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (2)<br>VIM-2, AAC(6')-Ib4, APH(3')-Ia, QnrVC1, NalC/D LOF (1)<br>NalC/D LOF (2) |
| CMC | 1 | 1 | 1121 | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (1) | ANT(2")-Ia, ANT(3")-Ia, QnrVC1, NalC/D LOF (1) |
| CVM | 5 | 3 | 235 (3) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (2)<br>Susceptible (2)<br>CAZ FEP IPM MEM TZP GEN TOB CIP (1) | VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (2)<br>NalC/D LOF (2)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1) |
| DMC | 7 | 7 | 9, 463, 381, 244, 639, 303, 357 (1) | Susceptible (3)<br>CAZ FEP IPM MEM TZP GEN TOB AMK CIP (2)<br>IPM MEM (2) | NalC/D LOF (2)<br>None (1)<br>ANT(2")-Ia, ANT(3")-Ia, APH(3')-VI, QnrVC1, gyrB.S466F, OprD LOF, NalC/D LOF (1)<br>IMP-26, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, QnrVC1, OprD LOF, NalC/D LOF (1)<br>OprD LOF, NalC/D LOF (2) |
| EVR | 4 | 4 | 1966~, 1978, 235, 1 823 (1) | Susceptible (2)<br>CIP (1)<br>CAZ FEP IPM MEM TZP GEN TOB CIP (1) | NalC/D LOF (2)<br>NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, APH(3')-Ia, NalC/D LOF (1) |
| FEU | 4 | 2 | 235 (3) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (2)<br>IPM MEM CIP (1)<br>Susceptible (1) | VIM-2, AAC(6')-Ib4, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (2)<br>GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1)<br>NalC/D LOF (1) |
| GMH | 8 | 3 | 313(4) | CAZ FEP IPM MEM TZP GEN TOB AMK (4)<br>CAZ FEP IPM MEM TZP GEN TOB AMK CIP (4) | VIM-2, AAC(6')-Ib4, NalC/D LOF (4)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (2)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, NalC/D LOF (1)<br>VIM-6, AAC(6')-Ib4, GyrA.T83I, ParC.S87L, NalC/D LOF (1) |
| JLM | 7 | 7 | 244, 1 597, 381, 261, 2 330, 309, 316 (1) | Susceptible (6)<br>FEP TZP TOB CIP (1) | NalC/D LOF (5)<br>None (1)<br>AAC(6')-Ib-cr, GyrA.T83I, ParC.S87L, NalC/D LOF (1) |
| MAR | 24 | 20 | 357 (3) | Susceptible (14)<br>IPM MEM (6)<br>CAZ FEP IPM MEM TZP (2)<br>CAZ FEP IPM MEM TZP GEN TOB CIP (1)<br>GEN TOB CIP (1) | NalC/D LOF (14)<br>OprD LOF, NalC/D LOF (4)<br>AAC(6')-Ib, OprD LOF, NalC/D LOF (1)<br>gyrB.E468D, OprD LOF, NalC/D LOF (1)<br>OprD LOF, NalC/D LOF (2)<br>ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, NalC/D LOF (1)<br>QnrVC1, NalC/D LOF (1) |
| MMH | 8 | 5 | 272~(3) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (2)<br>CAZ FEP IPM MEM GEN TOB (1)<br>CAZ FEP IPM MEM GEN TOB CIP (1)<br>CAZ FEP IPM MEM TZP (1)<br>CAZ FEP IPM MEM TZP GEN TOB AMK (1)<br>CAZ FEP IPM MEM TZP GEN TOB CIP (1)<br>IPM MEM TZP CIP (1) | VIM-2, AAC(3)-IIe, APH(3')-Ia, APH(3')-VI, OprD LOF, NalC/D LOF (2)<br>IMP-26, AAC(6')-Ib4, APH(3')-Ia, APH(3')-VI, NalC/D LOF (1)<br>IMP-26, AAC(6')-Ib4, APH(3')-Ia, APH(3')-VI, NalC/D LOF (1)<br>NDM-1, ANT(3")-Ia, APH(3')-VI, OprD LOF, NalC/D LOF (1)<br>VIM-2, AAC(3)-Iie, APH(3')-Ia, APH(3')-VI, NalC/D LOF (1)<br>AAC(3)-IIe, AAC(6')-Ib4, ANT(3")-Ia, APH(3')-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1)<br>gyrB.E468D, OprD LOF, NalC/D LOF (1) |

| Laboratory | No. of Isolates | No. of STs | Prevalent ST (no. of isolates) | Resistance profiles | Acquired resistance determinants |
|---|---|---|---|---|---|
| NKI | 26 | 21 | 235 (5) | Susceptible (15) | NalC/D LOF (14)<br>None (1) |
| | | | | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (3) | AAC(6')-31, AAC(6')-II, ANT(3")-Ia, APH(3')-VI, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, VIM-2, AAC(6')-Ib4, ANT(3")-Ia, QnrVC1, NalC/D LOF (1)<br>GyrA.D87N, OprD LOF, NalC/D LOF (1) |
| | | | | CIP (3) | NalC/D LOF (1)<br>QnrVC1, NalC/D LOF (1)<br>GyrA.T83I, ParC.S87L, NalC/D LOF (1) |
| | | | | CAZ FEP GEN TOB AMK CIP (1) | NalC/D LOF (1) |
| | | | | CAZ FEP TZP (1) | ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1) |
| | | | | FEP IPM MEM GEN TOB CIP (1) | OprD LOF, NalC/D LOF (1) |
| | | | | IPM (1) | ANT(3")-Ia, OprD LOF, NalC/D LOF (1) |
| | | | | IPM MEM (1) | |
| NMC | 11 | 6 | 244 (6) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (6) | VIM-2, AAC(6')-Ib4, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (4)<br>AAC(6')-Iia, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, QnrVC1, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1) |
| | | | | Susceptible (5) | NalC/D LOF (4)<br>None (1) |
| RMC | 2 | 2 | 1632, 235 (1) | CIP (1) | GyrA.T83I, ParC.S87L, NalC/D LOF (1) |
| | | | | Susceptible (1) | NalC/D LOF (1) |
| SLH | 1 | 1 | 235 | CAZ FEP IPM MEM TZP GEN TOB CIP (1) | AAC(6')-Ib4, ANT(3")-Ia, APH(3')-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1) |
| STU | 9 | 6 | 309 (3) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (3) | VIM-2, AAC(6')-Ib4, ANT(3")-Ia, QnrVC1, GyrA.T83I, OprD LOF, NalC/D LOF (3) |
| | | | | IPM MEM (3) | OprD LOF, NalC/D LOF (2)<br>NalC/D LOF (1) |
| | | | | CAZ FEP IPM MEM TZP GEN TOB CIP (2) | VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, NalC/D LOF (1)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (1) |
| | | | | Susceptible (1) | None (1) |
| VSM | 48 | 16 | 235 (24) | CAZ FEP IPM MEM TZP GEN TOB AMK CIP (30) | VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (9)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, QnrVC1, GyrA.T83I, ParC.S87L, OprD LOF, NalC/D LOF (8)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, QnrVC1, GyrA.T83I, ParC.S87L, NalC/D LOF (3)<br>VIM-2, AAC(6')-Ib4, APH(3')-Ia, QnrVC1, NalC/D LOF (3)<br>VIM-2, AAC(6')-Ib4, OprD LOF, NalC/D LOF (3)<br>VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, GyrA.T83I, ParC.S87L, NalC/D LOF (2)<br>VIM-2, AAC(6')-Ib4, QnrVC1, OprD LOF, NalC/D LOF (1)<br>gyrB.S466F, OprD LOF, NalC/D LOF (1) |
| | | | | Susceptible (12) | NalC/D LOF (12) |
| | | | | IPM MEM (3) | OprD LOF, NalC/D LOF (3) |
| | | | | CAZ FEP IPM MEM TZP GEN TOB CIP (2) | VIM-2, AAC(6')-Ib4, ANT(2")-Ia, ANT(3")-Ia, QnrVC1, GyrA.T83I, ParC.S87L, NalC/D LOF (1) |
| | | | | CAZ (1) | ANT(3")-Ia, GyrA.T83I, ParC.S87L, NalC/D LOF (1)<br>ANT(3")-Ia, NalC/D LOF |

[a] Only genes and mutations associated with the antibiotic classes tested are shown (β-lactamases, aminoglycosides, and fluoroquinolones). The full complement can be found in https://microreact.org/project/ARSP_176PAE_2013–2014.

LOF: loss-of-function.

almost halved in the 10 months post-intervention.[39] This highlights the importance of hospital infection control and of preventive measures to contain the spread of this high-risk clone.

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## *Conflicts of Interest*

The authors declare no conflicts of interest.

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# Estimating the national burden of hospitalizations for influenza-associated severe acute respiratory infection in the Lao People's Democratic Republic, 2016

Bouaphanh Khamphaphongphane,[a] May Chiew,[b] Joshua A. Mott,[c] Sombandith Khamphanoulath,[a] Viengphone Khanthamaly,[d] Keooudomphone Vilivong,[a,d] Thongchanh Sisouk,[a] Leila Bell,[e] Erica Dueger,[f,g,h] Sheena Sullivan,[i] Angela Daniella Iuliano,[g] Reiko Tsuyuoka[b] and Onechanh Keosavanh[a]

Correspondence to Bouaphanh Khamphaphongphane (email: bkhamphaphongphane@gmail.com)

**Objective:** Estimates of the burden of influenza are needed to inform prevention and control activities for seasonal influenza, including to support the development of appropriate vaccination policies. We used sentinel surveillance data on severe acute respiratory infection (SARI) to estimate the burden of influenza-associated hospitalizations in the Lao People's Democratic Republic.

**Methods:** Using methods developed by the World Health Organization, we combined data from hospital logbook reviews with epidemiological and virological data from influenza surveillance from 1 January to 31 December 2016 in defined catchment areas for two sentinel sites (Champasack and Luang Prabang provincial hospitals) to derive population-based estimates of influenza-associated SARI hospitalization rates. Hospitalization rates by age group were then applied to national age-specific population estimates using 2015 census data.

**Results:** We estimated the overall influenza-associated SARI hospitalization rate to be 48/100 000 population (95% confidence interval [CI]: 44–51) or 3097 admissions (95% CI: 2881–3313). SARI hospitalization rates were estimated to be as low as 40/100 000 population (95% CI: 37–43) and as high as 92/100 000 population (95% CI: 87–98) after accounting for SARI patient underascertainment in hospital logbooks. Influenza-associated SARI hospitalization rates were highest in children aged <5 years (219; 95% CI: 198–241) and persons aged ≥65 years (106; 95% CI: 91–121).

**Discussion:** Our findings have identified age groups at higher risk for influenza-associated SARI hospitalization, which will support policy decisions for influenza prevention and control strategies, including for vaccination. Further work is needed to estimate the burdens of outpatient influenza and influenza in specific high-risk subpopulations.

Globally, seasonal influenza is estimated to be associated with severe respiratory illness in 3–5 million people[1] and with 290 000–650 000 deaths from respiratory illness each year.[2] Although the majority of people infected with seasonal influenza recover, it can cause severe illness or death, particularly in high-risk groups, including pregnant women, children aged <5 years, older people and individuals with comorbidities.[1] In low- and middle-income countries and countries in the tropics, the burden of influenza is poorly understood.[3]

In the Lao People's Democratic Republic (Lao PDR), respiratory samples are collected to be tested for influenza at six sentinel sites monitoring severe acute respiratory infection (SARI). Aggregated

[a] National Center for Laboratory and Epidemiology, Vientiane, Lao People's Democratic Republic.
[b] WHO Health Emergencies Programme, World Health Organization, Vientiane, Lao People's Democratic Republic.
[c] Influenza Division, Thailand Regional Influenza Program, United States Centers for Disease Control and Prevention, Nonthaburi, Thailand.
[d] Influenza Division, United States Centers for Disease Control and Prevention, US Embassy, Vientiane, Lao People's Democratic Republic.
[e] Health Emergency Information and Risk Assessment, WHO Health Emergencies Programme, World Health Organization, Regional Office for the Western Pacific, Manila, Philippines.
[f] Infectious Hazards Management, WHO Health Emergencies Programme, World Health Organization, Regional Office for the Western Pacific, Manila, Philippines.
[g] Influenza Division, United States Centers for Disease Control and Prevention, Atlanta, GA, United States of America.
[h] Sanofi Pasteur, Lyon, France.
[i] WHO Collaborating Centre for Reference and Research on Influenza, Royal Melbourne Hospital, Melbourne, and the Peter Doherty Institute for Infection and Immunity, University of Melbourne, Melbourne, Australia.

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data at these sentinel sites are also collected by age and sex. At present, SARI sentinel surveillance operates in one central hospital in Vientiane, the capital, and five provincial hospitals that represent the central, northern and southern regions of the country. Influenza viruses have been found to circulate year-round in the country, with typical epidemic peaks from July to December.[4] This trend is consistent with trends seen in neighbouring countries with similar environments, such as Cambodia.[5]

In 2012, Lao PDR introduced a national seasonal influenza vaccination policy. Since then, the country has implemented this programme through a public–private partnership that offers influenza vaccine to pregnant women, persons aged ≥50 years, persons with chronic diseases and health-care workers. Although 90% of health-care workers are currently vaccinated, due to limited availability of the vaccine, coverage is only 35% among pregnant women and 12% among elderly people with chronic conditions.[6]

Estimating the burden of people hospitalized with influenza is a key step towards building the evidence base to inform decisions about influenza prevention and control policies. At present, the burden of people hospitalized with influenza is not well understood in the country. Our study aimed to estimate the burden of influenza-associated SARI hospitalizations to inform the evidence base for future decision-making about strategies to prevent and control influenza.

## METHODS

We used the World Health Organization (WHO) manual for estimating influenza disease burden[7] to identify a method to generate estimates of influenza-associated SARI hospitalizations. Following an assessment of all six SARI sentinel sites, we selected two: Champasack (CPS) Provincial Hospital and Luang Prabang (LPB) Provincial Hospital. We selected these two hospitals because they had catchment areas that were well circumscribed to allow their service populations to be assessed through hospital logbook reviews to obtain denominators for estimating hospitalization rates. These hospitals also represented populations in the northern and southern parts of the country.

### Data sources

#### *SARI influenza surveillance system for hospitalized patients*

In Lao PDR, patients are identified as having SARI if they have a history of subjective or measured fever of ≥38 °C and cough, with onset occurring within the last 7 days, and if they required hospitalization. All patients at the sentinel sites who met the SARI case definition were enrolled in the study, and nasal and throat swabs were collected. The data collected included information on the age, sex and clinical characteristics of the patient. Specimens collected from SARI patients were sent daily to the National Influenza Center at the National Center for Laboratory and Epidemiology in Vientiane where they were tested by real-time reverse transcription–polymerase chain reaction (RT–PCR) for influenza viruses.

#### *Health admission data*

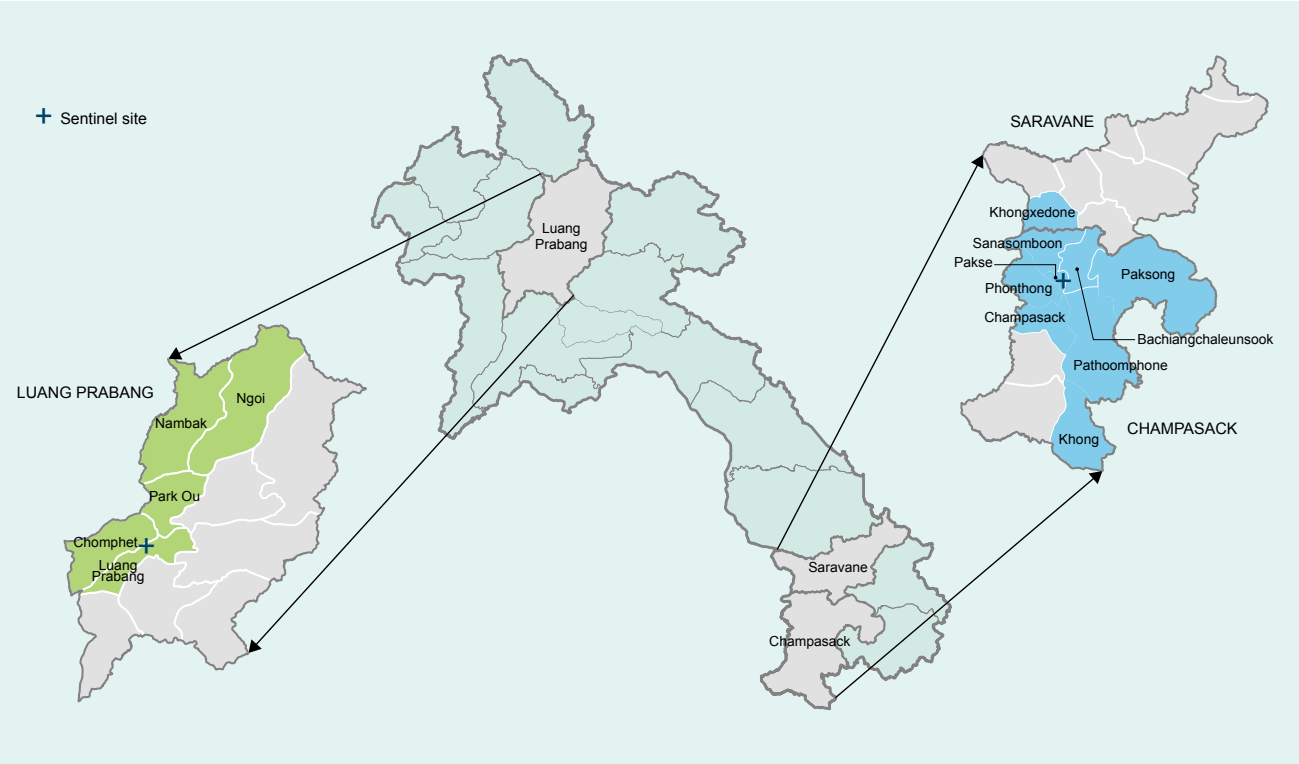
We reviewed health admission data to estimate the catchment areas of sentinel hospitals and to estimate annual cases of influenza-associated SARI in the country.

##### Estimating the catchment population of sentinel hospitals

At the time of the study, SARI sentinel surveillance in Lao PDR did not capture information about case patients' district of residence. To determine the catchment areas of the CPS and LPB provincial hospitals, we used data from an unpublished review of all hospital admission records from 2014 (Khampapongpane B, Musto J, Phengxay M, Ketmayoon P, Khamising A, Souphatsone Houatthongkham S, et al., unpublished data, 2017). The catchment area for each hospital was defined as the districts of residence from which ≥80% of SARI patients sought care, as guided by the WHO's manual for estimating the influenza disease burden.[7]

The catchment areas for the two sites are shown in **Fig. 1**. The catchment area for CPS Provincial Hospital covered nine districts: eight districts in CPS province (Bachiangchaleunsook, Champasack, Khong, Pakse,

Fig. 1. **Map of Lao People's Democratic Republic and the catchment areas of Champasack Provincial Hospital (blue) and Luang Prabang Provincial Hospital (green), by district**




Pathoomphone, Paksong, Phonthong and Sanasomboon) and one district in Saravane province (Khongxedone). For LPB Provincial Hospital, the catchment area covered five districts. All of the districts were part of LPB province (Chomphet, Luang Prabang, Nambak, Ngoi and Park Ou). All patients living outside these districts were excluded from the subsequent reviews of hospital admission logbooks.

### Identifying SARI patients residing within the catchment populations

We visited all health facilities that admit patients with respiratory illness within the identified catchment areas. At those facilities, we obtained and reviewed hospital admission logbooks from wards that admitted patients with respiratory illness (that is, internal medicine, inpatient, intensive care and paediatric units). We included admissions from 1 January to 31 December 2016. In Lao PDR, the International Classification of Diseases, tenth revision (ICD-10), is not used at the subnational level, including at health facilities in the catchment areas. Therefore, we recorded the clinical signs and symptoms from free-text entries in the admission and discharge logbooks to identify SARI patients residing in the catchment areas. Hospitalized patients who met the SARI case definition based on signs and symptoms were considered SARI patients. From the logbooks, we collected demographic data, the dates of admission and discharge, signs and symptoms, onset date, admitting diagnosis, discharge diagnosis and outcomes. To determine the proportion of total inpatient visits that were associated with SARI at LPB and CPS hospitals, we divided the total number of SARI patients identified by the logbook reviews by the total number of inpatient visits at the hospitals during the same period as was recorded in the District Health Information System.

### *Estimating annual cases of influenza-associated SARI, and correcting for missing records*

We obtained monthly age-specific numbers of SARI patients from the two sentinel sites and combined them. To account for variation in influenza circulation by month, we then divided the monthly SARI patient counts for each age group by the overall annual per-

centage of specimens testing positive for influenza at the two sentinel sites because there were too few age-specific data by month. From these calculations, we obtained estimates of the number of cases of influenza-associated SARI by month.

To assess the completeness of the identification of SARI patients in the logbooks, we compared the number of SARI patients detected from prospective sentinel surveillance data in 2016 to the number of SARI patients identified through logbook reviews at both sentinel sites. This was an aggregate-level comparison as it was not possible to link individual patients identified in logbook entries with those identified through SARI sentinel surveillance. Based on pooled results of record reviews from both sites, we calculated a correction factor to account for an underascertainment of SARI patients in the logbook reviews and applied it to the number of patients with influenza-associated SARI by age and month. Due to the absence of links between individual patients in the logbooks and in surveillance data, 95% confidence intervals (95% CIs) could not be estimated for each correction factor. However, as there was variability between the sites in the number of missing logbook records, we also calculated lower- and upper-bound correction factors based on the missing logbook data from each site.

### *Estimating the national burden of influenza-associated SARI*

We estimated age-specific populations for each district within the catchment areas using provincial-level age distributions from the 2015 population census (<5 years: 12.6%; 5 to <15 years: 23.3%; 15 to <65 years: 59.8%; and ≥65 years: 4.3%).[8] We then calculated the adjusted population denominator by multiplying the population of the catchment area of each sentinel site by the proportion of SARI patients that presented to that site compared with other health facilities in the catchment area, by age group. We estimated monthly influenza-associated hospitalizations due to SARI by combining estimated SARI patient counts (the numerator) at the two sites. We divided these combined SARI patient counts by the sum of the adjusted catchment populations for both sentinel sites (the denominator) and multiplied by 100 000. To create annual rates, we aggregated these monthly rates and weighted them by the proportion of SARI patients identified in the logbook review that occurred within a given month of the calendar year.

We adjusted the numbers and rates of influenza-associated SARI hospitalizations by applying the three correction factors for logbook underascertainment. To derive estimates of the national burden, we used the pooled hospitalization rates from the two sentinel site catchment areas and extrapolated these rates to the national 2015 census population. We calculated 95% confidence intervals by applying an error factor, as outlined in the WHO manual,[7] to account for variance in the percentage of cases positive for influenza and in the monthly SARI patient counts.

## RESULTS

The hospital logbook review was conducted in 8 of the 12 health facilities in the catchment area of LPB Provincial Hospital (that is, the provincial hospital, one private hospital, one military hospital and five district hospitals) and in 9 of the 10 health facilities in the catchment area of CPS Provincial Hospital (that is, the provincial hospital and eight district hospitals). From January through December 2016, 2060 SARI patients were identified from the review of logbooks, of whom 1513 were from the CPS catchment area and 547 were from the LPB catchment area.

Of the 1513 SARI patients in the CPS catchment area, 823 (54%) were <5 years; 265 (18%) were 5 to <15 years; 270 (18%) were 15 to <65 years; and 155 (10%) were ≥65 years. Within this catchment area, 746 (49%) SARI patients were identified from logbooks at CPS Provincial Hospital and 767 (51%) were identified from logbooks at district hospitals. Of the 746 cases identified in the CPS Provincial Hospital logbooks, the median length of stay at the hospital was 2 days.

Of the 547 SARI patients in the LPB catchment area, 313 (57%) were <5 years; 55 (10%) were 5 to <15 years; 126 (23%) were 15 to <65 years; and 53 (10%) were ≥65 years. Within this catchment area, 124 (23%) SARI patients were identified from logbooks at LPB Provincial Hospital; 329 (60%) were identified in logbooks at district hospitals; 66 (12%) were identified in logbooks at military hospitals; and 28 (5%) were identified in logbooks at private hospi-

Table 1. **Patients with severe acute respiratory illness identified from reviews of hospital logbooks, and catchment area populations, for Champasack Provincial Hospital and Luang Prabang Provincial Hospital, Lao People's Democratic Republic, January to December 2016**

| Hospital | Age group | | | | |
|---|---|---|---|---|---|
| | <5 years | 5 to <15 years | 15 to <65 years | ≥65 years | Total* |
| **Champasack Provincial Hospital** | | | | | |
| Number of SARI patients identified through logbook review | 344 | 81 | 202 | 119 | 746 |
| Percentage of SARI patients positive for influenza at sentinel surveillance site | 16% | 34% | 14% | 9% | 18% |
| Population of catchment area | 78 188 | 140 672 | 411 078 | 30 579 | 660 510 |
| Percentage of SARI patients in the catchment area admitted to the sentinel site | 42% | 31% | 75% | 77% | 49% |
| Adjusted population denominator | 32 681 | 42 998 | 307 547 | 23 477 | 325 671 |
| **Luang Prabang Provincial Hospital** | | | | | |
| Number of SARI patients identified through logbook review | 32 | 19 | 43 | 30 | 124 |
| Percentage of SARI patients positive for influenza at sentinel surveillance site | 5% | 6% | 9% | 5% | 6% |
| Population of catchment area | 31 067 | 57 404 | 147 329 | 10 569 | 246 370 |
| Percentage of SARI patients in the catchment area admitted to the sentinel site | 10% | 35% | 34% | 57% | 23% |
| Adjusted population denominator | 3176 | 19 830 | 50 279 | 5982 | 55 850 |

SARI: severe acute respiratory illness.

* Not all row totals equal the sum of columns.

tals. Of the 124 SARI cases identified in the logbooks at LPB Provincial Hospital, the median length of stay at the hospital was also 2 days.

The number of SARI patients identified, the estimated percentage testing positive for influenza by age, the estimated population of the catchment areas and the population denominators are summarized in **Table 1**. Compared with the LPB catchment area, in the CPS catchment area there was a greater number of SARI patients (746 versus 124), a higher percentage testing positive for influenza viruses (18% versus 6%) and a larger adjusted population denominator (325 671 versus 55 850). Based on inpatient data from the District Health Information System, the proportion of inpatient visits due to SARI was approximately 5% (746/15 144) in the CPS Provincial Hospital catchment area and approximately 1% (124/9172) in the LPB Provincial Hospital catchment area.

A total of 1253 SARI patients were detected from active sentinel surveillance compared with 870 identified by the logbook reviews, resulting in a correction factor of 1.44 (1253/870). At CPS Provincial Hospital, a total of 908 SARI patients were detected through active sentinel surveillance compared with 746 identified through logbook review. At LPB Provincial Hospital, the numbers of SARI patients identified through prospective surveillance and logbook review were 345 and 124, respectively. Therefore, we also applied the site-specific lower- and upper-bound correction factors for missing logbook data of 1.22 (908/746) and 2.78 (345/124) to the number of SARI patients identified from the logbooks at all hospitals within the catchment areas.

The estimated rate of influenza-associated SARI hospitalization was 48/100 000 population (95% CI: 44–51) (**Table 2**). However, given the variability in SARI patient underascertainment in hospital logbooks, we es-

Table 2. **National incidence estimates of rates of hospitalization for severe acute respiratory infection due to influenza in the Lao People's Democratic Republic, by age group, with adjustments to lower and upper bounds for underascertainment of the illness in hospital logbooks, January to December 2016**

| Age group (years) | Rate of influenza-associated SARI hospitalizations per 100 000 population (95% CI)* | | |
|---|---|---|---|
| | Corrected rate | Lower bound of estimate | Upper bound of estimate |
| <5 | 219 (198–241) | 186 (166–205) | 423 (390–457) |
| 5 to <15 | 33 (28–39) | 28 (23–33) | 64 (56–72) |
| 15 to <65 | 14 (13–16) | 12 (11–13) | 28 (25–30) |
| ≥65 | 106 (91–121) | 90 (76–103) | 204 (183–226) |
| All ages | 48 (44–51) | 40 (37–43) | 92 (87–98) |

CI: confidence interval; SARI: severe acute respiratory illness.

* The multiplier for case underascertainment was 1.44. The estimate of the lower bounds used a multiplier of 1.22, and the estimate of the upper bounds used a multiplier of 2.78.

Table 3. **National estimated number of hospitalizations for severe acute respiratory infection due to influenza in the Lao People's Democratic Republic, by age group, with adjustments to lower and upper bounds for underascertainment of the illness in hospital logbooks, January to December 2016**

| Age group (years) | Population of Lao PDR, 2015 | Number of influenza-associated SARI hospitalizations (95% CI) | | |
|---|---|---|---|---|
| | | Corrected | Lower bound of estimate | Upper bound of estimate |
| <5 | 681 983 | 1496 (1349–1642) | 1267 (1135–1400) | 2888 (2661–3115) |
| 5 to <15 | 1 397 815 | 465 (386–545) | 394 (322–467) | 898 (784–1013) |
| 15 to <65 | 4 137 333 | 593 (531–654) | 502 (446–558) | 1144 (1052–1236) |
| ≥65 | 275 097 | 291 (250–332) | 247 (209–284) | 562 (503–621) |
| All ages | 6 492 228 | 3097 (2880–3313) | 2623 (2431–2816) | 5978 (5625–6331) |

CI: confidence interval; Lao PDR: Lao People's Democratic Republic; SARI: severe acute respiratory illness.

* The multiplier for case underascertainment was 1.44. The estimate of the lower bounds used a multiplier of 1.22, and the estimate of the upper bounds used a multiplier of 2.78.

timated these overall SARI hospitalization rates to be as low as 40/100 000 population (95% CI: 37–43) and as high as 92/100 000 population (95% CI: 87–98). Our primary pooled incidence rates for the two catchment areas suggested that rates of influenza-associated SARI hospitalization per 100 000 population were highest in children aged <5 years (219; 95% CI: 198–241). The rates followed a U-shaped curve, declining to 33/100 000 (95% CI: 28–39) for the 5 to <15 year age group and to 14/100 000 (95% CI: 13–16) for the 15 to <65 year age group, but increasing to 106/100 000 among persons aged ≥65 years (95% CI: 91–121).

Applying these rates to the total population of the country gives the estimated number of influenza-associated SARI hospitalizations in 2016 as 3097 (95% CI: 2880–3313). Accounting for hospital logbook underascertainment, this number was estimated to be as low as 2623 (2431–2816) and as high as 5978 (5625–6331) (**Table 3**). Nearly half of these influenza-associated SARI hospitalizations were estimated to occur in children aged <5 years.

## DISCUSSION

Our findings are the first to estimate the national burden of influenza-associated SARI hospitalizations in Lao PDR and are important in understanding the health impact of influenza within the country. We found that children aged <5 years and adults aged ≥65 years

had the highest rates of hospitalization for influenza-associated SARI.

While every influenza season is different, our results suggest that influenza-associated SARI hospitalization rates for children aged <5 years in Lao PDR are higher than what has been documented in WHO's Western Pacific Region. In a recent systematic review and meta-analysis of the global burden of influenza in paediatric respiratory hospitalizations,[9] the pooled influenza-associated hospitalization rate among children aged <5 years was 150/100 000 population (95% CI: 105–216) compared with our estimate of 220/100 000 population. These findings are also similar to the results of a published study in Cambodia that estimated national rates of severe influenza were 323/100 000 population in infants aged <1 year and 196/100 000 population in children aged 1–4 years.[10] In contrast, the incidence of hospitalized patients with acute respiratory infection associated with influenza A in Viet Nam from 2007 through 2008 in children aged <5 years was much higher, at 870/100 000 population.[11] In the Viet Nam study, the case definition included all children presenting with cough or difficulty breathing, or both, with or without fever,[11] while our case definition was less sensitive and more specific. However, caution is required in comparing hospitalization rates across countries as case definitions, health-seeking behaviour, admission practices, logbook and medical charting, the methods of calculating population denominators, influenza vaccine policy, the general health of the population and influenza activity vary between countries and over time.

Our estimates suggest that in 2016 influenza represented a significant burden to hospitalizations in Lao PDR. Currently, the government is procuring seasonal influenza vaccine annually, using its own budget, with support from the Partnership for Influenza Vaccine Introduction.[12,13] These burden estimates will be useful for understanding the impact of influenza by age group. Ongoing work incorporating these estimates is exploring the economic costs of influenza and the cost–effectiveness of influenza vaccines. Understanding the impact of influenza virus infection on the population can support the expansion of influenza vaccine policies in Lao PDR in conjunction with national immunization laws and existing influenza vaccine policies.[13] These estimates can also support the government's decisions to purchase influenza vaccine in the future.

While our estimates will contribute to local and global efforts to estimate the burden of influenza, particularly in Asia, it is also important to acknowledge some limitations. Perhaps most importantly, data from other countries suggest that the SARI case definition used for these analyses may miss a substantial portion of influenza-associated illnesses and may be better suited to virus detection than burden estimation.[14] The inclusion of fever in the case definition may be one reason why these estimates are lower than those observed in Viet Nam[11] and why only half the burden was seen in children, for whom fever may be a more specific symptom.[15] Regardless of the case definition used, prospective sentinel surveillance also will not capture patients in whom an earlier influenza infection may have indirectly caused decompensation of another underlying chronic illness that leads to hospitalization and in whom nucleic acid from influenza viruses can no longer be detected with real-time RT–PCR. This could produce an underestimate of the influenza burden in certain populations, particularly older adults with underlying conditions.[16] It was not possible to calculate rates of influenza-associated SARI hospitalization among other recognized high-risk groups, such as pregnant women or patients with underlying conditions, due to the nature of the health systems and because the wards under surveillance in the SARI sentinel system do not necessarily admit those patients.

Because only two sentinel sites served well-circumscribed at-risk populations, these data also may not be fully representative of the national population. The variability of missing logbook data, coupled with the absence of ICD-10 coding, also complicated our ability to estimate the national burden of influenza-associated SARI, and these issues created uncertainty about the degree to which missing logbook data impacted these national estimates. We attempted to address this issue using sensitivity analyses.

We are also uncertain of how many people living in the catchment areas travel to other countries, such as Thailand, for medical treatment. Previous studies have demonstrated that people from Lao PDR seek health care in Thailand.[17] Furthermore, a study examining the characteristics of Lao nationals seeking health care in Thailand found that from 2009 through 2011, the diagnosis of unspecified pneumonia was one of the top five inpatient conditions for which Lao nationals were treated each year.[18] These findings could contribute to

our conservative estimates. Given these additional areas of uncertainty, we should note that the 95% confidence intervals presented here (and suggested in the WHO manual)[7] account for only random sampling variation and do not account for classification errors and other possible sources of bias.

Indeed, many of the limitations discussed here apply to similar, if not most, national estimates of influenza burden and meta-analyses globally. Notwithstanding, the estimated burden of hospitalizations for influenza-associated SARI in Lao PDR is comparable to those from other countries and highlights the need to maintain and further strengthen influenza surveillance systems. With proper consideration of these data and the case definition used, these findings contribute to understanding the potential impact of influenza in the country. These data can inform prioritization for influenza control and response activities, including vaccination programmes, in Lao PDR when combined with data on the costs of hospitalization, burden, cost of outpatient influenza, and data on vaccine effectiveness and costs.

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## *Conflicts of interest*

The authors of this manuscript have indicated no conflicts of interest.

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# Influenza epidemiology and burden of disease in Mongolia, 2013–2014 to 2017–2018

Oyungerel Darmaa,[a] Alexanderyn Burmaa,[a] Baataryn Gantsooj,[a] Badarchiin Darmaa,[a] Pagbajabyn Nymadawa,[a,b] Sheena G Sullivan,[c,d] James E Fielding[d,e]

Correspondence to James Fielding (email: James.Fielding@vidrl.org.au)

**Background:** Mongolia is a vast, sparsely populated country in central Asia. Its harsh climate and nomadic lifestyle make the population vulnerable to acute respiratory infections, particularly influenza. Evidence on the morbidity, mortality and socioeconomic impact of influenza in Mongolia is scarce; however, routine surveillance for influenza-like illness (ILI), severe acute respiratory infection (SARI) and laboratory-detected influenza is conducted. This paper describes the epidemiology of influenza and the estimated burden of influenza-associated illness in Mongolia in the five influenza seasons between 2013–2014 and 2017–2018.

**Methods:** Demographic and laboratory data from 152 sentinel surveillance sites on all patients who met the case definitions of ILI and SARI between October 2013 and May 2018 were extracted and analysed as described in *A Manual for Estimating Disease Burden Associated with Seasonal Influenza*.

**Results:** The estimated annual influenza-associated ILI and SARI rates, presented as ranges, were 1279–2798 and 81–666 cases per 100 000 population, respectively. Children aged <5 years accounted for 67% of all ILI cases and 79% of all SARI cases. The annual specimen positivity for influenza was highest (11–30% for ILI and 8–31% for SARI) for children aged 5–<15 years and children <2 years old, respectively. The annual mortality rate due to pneumonia and SARI was highest among children aged <2 years (15.8–54.0 per 100 000 population). Although the incidence of influenza-associated ILI and SARI was lowest for people aged ≥65 years, the mortality rate due to pneumonia and SARI (1.2–5.1 per 100 000) was higher than that for those aged 15–64 years.

**Conclusion:** The estimated influenza-associated ILI and SARI incidence rates are high in Mongolia, and children, especially those aged <5 years, have the highest influenza-associated burden in Mongolia. These findings provide evidence for decision-makers in Mongolia to consider targeted influenza vaccination, particularly for children.

Influenza is a highly infectious acute respiratory disease that is estimated to result globally in 3–5 million cases of severe illness and 290 000–650 000 deaths annually.[1,2] Children aged <5 years are more susceptible to infection, with an estimated annual attack rate of 20–30%, compared with adults at 5–10%, with the elderly having the highest risk of mortality.[3]

Syndromic and virological surveillance of influenza-like illness (ILI) and severe acute respiratory infection (SARI) are used to understand and estimate the burden of influenza. The data generated can be used to identify populations at high risk of infection and of complications, provide early warning of potential epidemics and guide preparedness, resource allocation, selection of preventive, treatment and control measures and selection of strains for seasonal flu vaccination.[4] In developing, low-income countries such as Mongolia, however, the burden of influenza is poorly quantified.[5,6] In 2015, the World Health Organization (WHO) published *A Manual for Estimating Disease Burden Associated with Seasonal Influenza* to guide comparable studies of disease burden with a uniform method.[7] The method is based on available data from national surveillance that countries may use annually and will result in comparable results across time and geography if the surveillance methods are applied consistently.

[a] National Influenza Centre, National Centre of Communicable Diseases, Ulaanbaatar, Mongolia.
[b] Mongolian Academy of Medical Sciences, Ulaanbaatar, Mongolia.
[c] World Health Organization Collaborating Centre for Reference and Research on Influenza, Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
[d] Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia.
[e] Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, at the Peter Doherty Institute for Infection and Immunity, Melbourne, Australia.
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Mongolia is a landlocked country in east and central Asia. The population of about 3 million people is relatively young with 65% aged <35 years. Children aged <5 years and people aged >65 years constitute 13% and 4% of the population, respectively.[8] The temperature ranges from approximately –30 °C to 40 °C, and the capital, Ulaanbaatar, in which nearly half the population resides, is considered the coldest capital city in the world.[9] One third of the population resides in rural areas, breeding livestock in nomadic and semi-nomadic pastoralism. The country's harsh climate and nomadic lifestyle make the population vulnerable to acute respiratory infections, particularly influenza.[10]

Several studies of sentinel surveillance of ILI and SARI and a cohort study conducted in a district family general practice 130 km east of Ulaanbaatar in 2010–2011 showed that, between 2007–2008 and 2011–2012, children aged <5 years had the highest incidence, accounted for almost all cases of ILI and SARI and had the highest attack rate of laboratory-confirmed influenza.[11–13] In this study, we sought to further elucidate the burden of influenza in Mongolia. Syndromic and laboratory surveillance data were used to compare morbidity and mortality, and to estimate the disease burden associated with seasonal influenza with the standardized protocol described in the WHO manual, in Mongolia between 2013–2014 and 2017–2018.

## METHODS

### Health facilities in Mongolia

Administratively, Mongolia is divided into nine districts in the capital, Ulaanbaatar, and 21 provinces; the provinces are divided into subregions called soums. Outpatients are managed in the capital districts in 218 family health centres and in the provinces and soums in 296 soum health centres. Data on ILI are collected from all outpatient sites in the country and reported weekly to the nine district health departments in the capital and 21 provincial health departments and then forwarded to the National Centre for Communicable Diseases (NCCD). The data collected and reported to the flu information system (www.flu.mn) consisted of the total number of outpatient visits to family group practices, the total number of ILI cases, the number of clusters, the total number of ambulance calls and the total number of calls due to ILI.

The largest hospitals in the country are general hospitals, regional centres for diagnosis and treatment and specialized hospitals known as reference centres. There are general hospitals in each of the capital districts and in 16 provinces and regional centres for diagnosis and treatment in five provinces. Although all public health facilities participate in influenza surveillance, cases diagnosed and treated in private hospitals are not reported. The proportions of patients treated in public and private facilities were not available.

### Sentinel surveillance

The WHO case definitions of ILI and SARI were used. An ILI case was defined as an acute respiratory infection with measured fever of ≥38 °C and cough with onset within the previous 10 days.[4] A SARI case was defined as an acute respiratory infection with a history of fever or measured fever of ≥38 °C and cough with onset within the previous 10 days and requiring hospitalization.[4]

ILI surveillance with specimen collection has been conducted at 115 sentinel outpatient sites throughout the country (23 in the capital and 92 in the provinces) since 2009. The sites report data on ILI daily. The sampling and testing methods are described under "Specimen collection and testing" below. SARI surveillance has been conducted at 37 hospitals since 2009, of which 16 are provincial general hospitals (located in provincial capital cities), five are regional centres for diagnosis and treatment, nine are district general hospitals in the capital, three are soum hospitals (one in the coldest part of the country, one in the south close to a major border crossing with China and the other in the north close to a major border crossing with the Russian Federation) and four are reference centres (National Centre of Maternal and Child Health, National Cancer Centre, State Hospital Number 3 and the NCCD hospital). The hospitals report data on SARI inpatients once a week. The data collected and reported to the flu information system consisted of the total number of patients at the end of the previous week, the total number of recovered and shifted patients, deaths, total number of newly admitted patients, number of patients at the end of the current week, total number of SARI patients at the end of the previous week, total number of recovered and shifted patients, deaths, total number of newly admitted SARI patients and total number of SARI patients at the end of the current week.

### Specimen collection and testing

The sentinel surveillance sites are classified into one of two categories according to the frequency of specimen collection. Category I sites ($n$ = 78: 61 outpatient sites and 17 hospitals) collect and send specimens for testing every week, and category II sites ($n$ = 74: 54 outpatient sites and 20 hospitals) collect and send specimens for testing only during the influenza season or if an outbreak or cluster is detected at the site.

Physicians at ILI and SARI sentinel sites were asked to collect nasopharyngeal swabs each week from 5–10 patients who met the case definitions within 3 days of disease onset and before treatment. The collected specimens were immediately immersed into sterile tubes containing virus transport medium, stored in refrigerators at the sentinel sites and transported to the Reference Virology Laboratory of the National Influenza Centre at the NCCD or to one of four participating branch laboratories.[12] Samples were shipped by car from the central region, by plane from the western and eastern regions and by train from the northern and south-eastern regions. Samples were tested for influenza virus by real-time reverse transcriptase polymerase chain reaction. Virus-positive samples were passaged in MDCK cells for isolation. Genetic sequencing analysis was done for five strains of A(H1N1)pdm09 and eight strains of A(H3N2) by ABI Big Dye terminator v.3.1 Cycle Sequencing and ABI 3130 xl Analyser.

### Analysis of epidemiological data and burden of disease

Data from the ILI, SARI and laboratory surveillance systems in the 2013–2014 and 2017–2018 influenza seasons were analysed to elucidate the epidemiology of influenza in Mongolia. As the annual influenza season crosses the new calendar year, seasons were defined as from week 40 of one year to week 39 of the following year. ILI incidence rates were calculated from population data for the whole country and total consultations and for the populations of the capital city districts and provincial capital cities.[8] SARI incidence rates were calculated from total hospitalizations and the populations of the provincial capitals and the districts of the national capital, representing the catchment populations of the SARI sentinel sites. An influenza season was defined as the period between the date on which the ILI rate crossed the median weekly ILI threshold rate for 2013–2014 to 2017–2018. Laboratory data were analysed by influenza type or subtype and the percentage of specimens tested that were positive for influenza.

These data were used to estimate overall and age-specific (age groups: <2, 2–<5, 5–<15, 15–<50, 50–<65, and ≥65 years) influenza-associated medically attended ILI and SARI incidence rates for each season between 2013–2014 and 2017–2018, as described in WHO's *A Manual for Estimating Disease Burden Associated with Seasonal Influenza*.[10]

Population mortality and case fatality rates were estimated from the ILI and SARI surveillance data collected throughout the season. Influenza-associated mortality and case fatality rates were not estimated, as samples were not taken from all people who died from SARI. Microsoft Excel® 2013 software was used for the data analyses.

## RESULTS

Between 2013–2014 and 2017–2018, 2 002 825 patients with ILI and 205 991 with SARI were reported per year (ranges, 371 491–440 389 for ILI and 33 136–50 759 for SARI). The seasonal peak rates were 50–70 ILI cases and 6–10 SARI cases per 10 000 population (**Fig. 1**). The peak rates were highest for both ILI and SARI in the 2016–2017 season, while the lowest peaks were in 2014–2015 and 2013–2014, respectively.

During the five seasons, the number of SARI patients increased, as both a proportion of hospital admissions and incidence rate, while the number of ILI patients decreased as a proportion of consultations and incidence rate (**Table 1**). The 5-year averages were 532.4 ILI cases and 42 SARI cases per 100 000 population.

Seasons started between weeks 40 and 44, but the timing of the peaks (weeks 51 to 9) and the ends (weeks 7 to 22) varied more widely (**Table 1**, **Fig. 1** and **2**). The longest season was that of 2013–2014 (35 weeks), and the shortest was that of 2016–2017 (16 weeks).

Influenza virus was detected in the population in each of the five seasons of 2013–2014 to 2017–2018.

Fig. 1. **ILI and SARI rates per 10 000 population by week, Mongolia, 2013–2014 to 2017–2018**

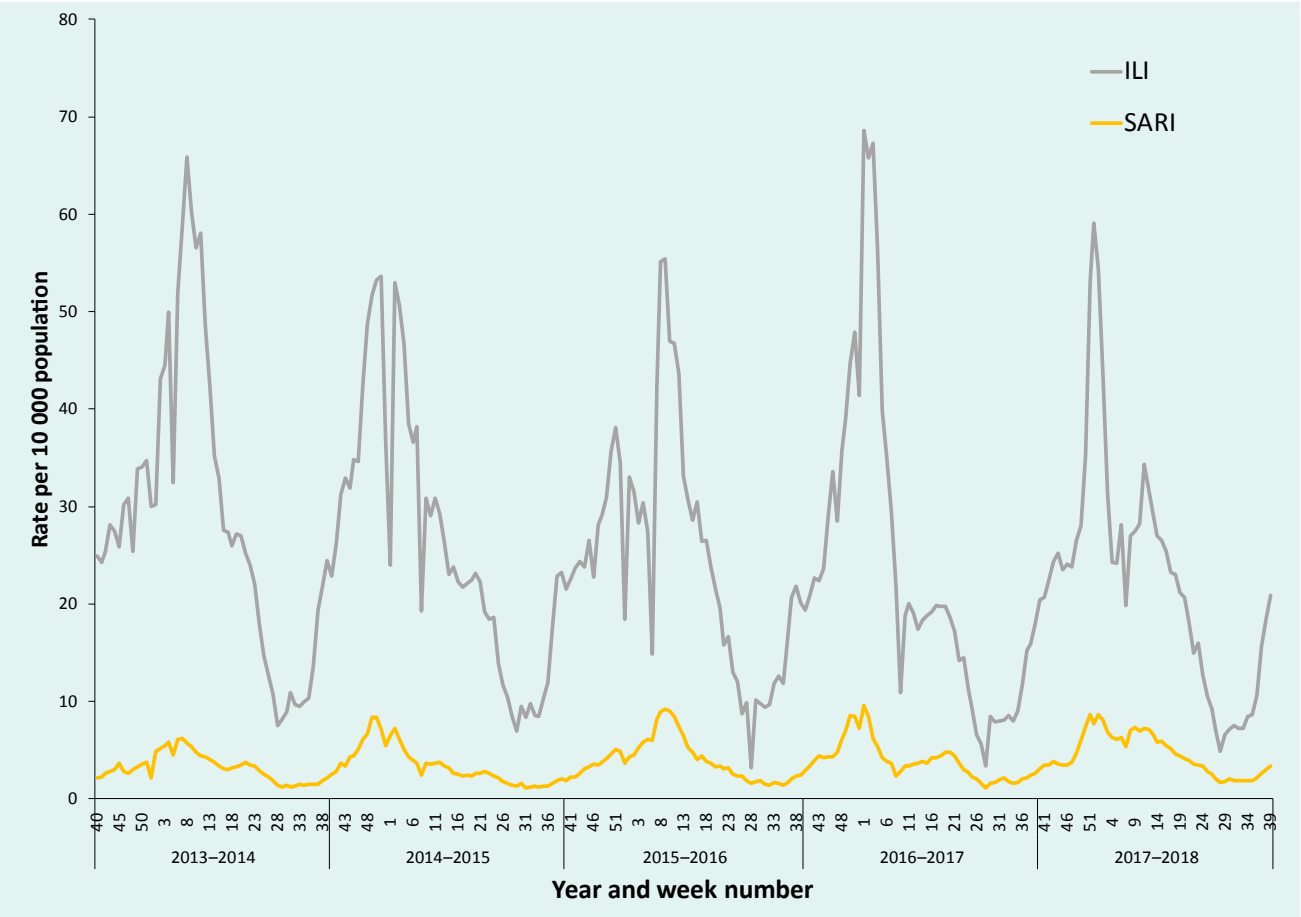
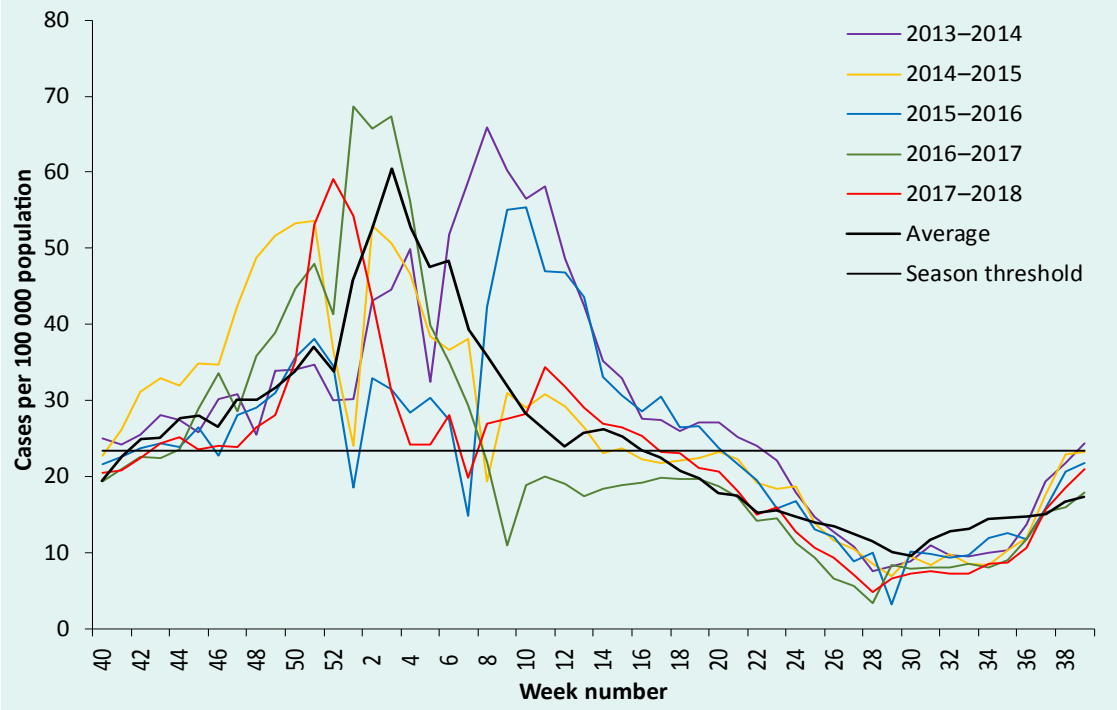



Table 1. **ILI consultations and SARI hospitalizations, incidence rates and season characteristics by year, Mongolia, 2013–2014 to 2017–2018**

| | Influenza season | | | | | 5-year average |
|---|---|---|---|---|---|---|
| | 2013–2014 | 2014–2015 | 2015–2016 | 2016–2017 | 2017–2018 | |
| ILI cases per total outpatient consultations (%) | 5.7 | 5.2 | 4.7 | 4.5 | 4.4 | 4.9 |
| No. of ILI cases per 100 000 population | 15 029 | 13 732 | 13 102 | 12 145 | 11 690 | 13 106 |
| SARI patients among total hospitalizations (%) | 8.4 | 9.2 | 10.3 | 11.1 | 11.8 | 10.2 |
| No. of SARI cases per 100 000 population | 1660 | 1780 | 2079 | 2029 | 2364 | 1990 |
| Season onset (week) | 40 | 41 | 42 | 44 | 43 | |
| Season peak (week) | 8 | 51 | 9 | 1 | 52 | |
| Season end (week) | 22 | 13 | 19 | 7 | 16 | |

Fig. 2. **ILI rates by week and year, Mongolia, 2013–2014 to 2017–2018**




Two seasons (2013–2014 and 2014–2015) started earlier, with most cases detected in weeks 2–17, peaking in weeks 3–11 (**Fig. 3**). Most cases in seasons 2015–2016, 2016–2017 and 2017–2018 were detected in weeks 47–17, with peaks in weeks 51–5. Trends in influenza positivity were similar for ILI and SARI patients. The 2014–2015 and 2016–2017 seasons were dominated by type A(H3N2), while type B co-circulated with type A(H1N1) in 2014–2015 and 2017–2018, with two distinct peaks in each season. All three types or subtypes co-circulated in 2013–2014. The percentage of tests positive for influenza virus was highest for both ILI and SARI patients in 2016–2017; however, over each full year, there was more variation in the percentage of ILI patients positive for influenza (range: 9–19%; lowest in 2014–2015 and highest in 2013–2014) than of SARI patients (range: 8–12%; lowest in 2014–2015 and highest in 2017–2018).

The highest proportions of the population positive for both ILI and SARI from 2013–2017 to 2017–2018 were reported in children aged <5 years (**Tables 2** and **3**). In seasons 2015–2016, 2016–2017 and 2017–2018, for which fewer data were available by age group, the proportions were highest among those aged <2 years. The proportions of age group-specific ILI generally decreased with age, whereas for SARI, the proportions decreased with age to 50 years and then increased for older age groups.

The estimated annual influenza-associated ILI and SARI rates, presented as ranges, were 1279–2798 and 81–666 cases per 100 000 population, respectively. (**Tables 2** and **3**) The rates were highest for children aged <5 years (especially those aged <2 years) and lowest for people aged 15–<50 years. There was wider variation between the minimum and maximum annual rates of SARI (42%) than for ILI (29%). The annual rates of ILI decreased each year during the study period, while the rates of SARI increased.

The annual mortality rate due to SARI ranged from 1.2 to 3.9 deaths per 100 000 population between 2013–2014 and 2017–2018. The rate was highest among children aged <5 years, in particular those aged <2 years (15.8–54.0 deaths per 100 000 population in 2015–2016 to 2017–2018). Annual mortality rates were <1.0 deaths among people aged 5–50 years, increasing to 1.2–5.1 deaths per 100 000 population for those aged ≥65 years (**Table 4**).

Fig. 3. **Numbers of ILI cases (3A) and SARI cases (3B) positive for influenza by type or subtype and percentages influenza positive, Mongolia, 2013–2014 to 2017–2018**

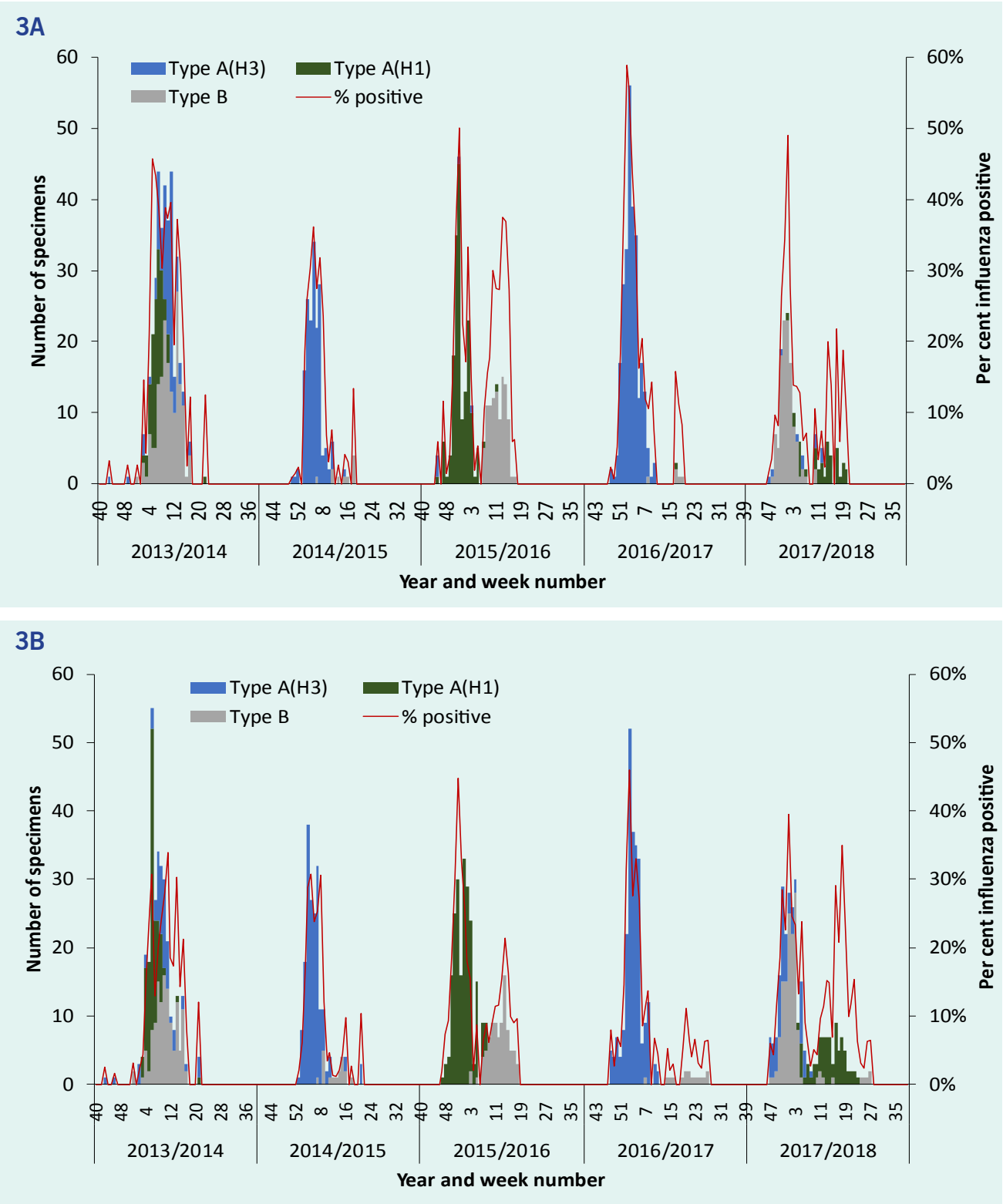


Table 2. **Range of annual ILI cases, incidence and per cent influenza positive by age group, 2013–2014 to 2017–2018**

| | Age group (years) | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <2* | 2–<5* | <5 | 5–<15 | 15–<50 | ≥50 | 50–<65* | ≥65* | |
| Total outpatient consultations | 1 228 239–1 354 384 | 765 072–804 931 | 1 955 342–2 180 652 | 877 738–1 086 993 | 2 632 829–3 666 852 | 1 714 868–2 135 206 | 1 117 744–1 322 442 | 721 168–812 764 | 7 734 051–8 502 958 |
| ILI cases | 148 950–174 258 | 100 979–104 964 | 249 929–285 412 | 71 670–101 315 | 34 472–41 364 | 9867–18 261 | 6170–7792 | 3727–4133 | 371 491–440 389 |
| ILI cases per 100 000 population | 96 575–108 028 | 42 118–46 535 | 63 436–87 486 | 13 097–20 981 | 2007–2411 | 2208–4430 | 1852–2108 | 3239–3368 | 11 690–15 029 |
| ILI cases sampled | 488–638 | 495–651 | 667–1289 | 295–736 | 230–417 | 76–380 | 55–68 | 17–32 | 1615–2447 |
| % specimens influenza positive | 10–13 | 14–18 | 6–15 | 11–30 | 9–19 | 9–24 | 9–25 | 10–18 | 9–19 |
| Estimated % total consultations for influenza-associated ILI | 1.3–1.6 | 1.8–2.5 | 0.8–1.9 | 0.9–2.8 | 0.1–0.3 | 0.0–0.1 | 0.1–0.1 | 0.0–0.1 | 0.5–1.1 |
| Estimated influenza-associated ILI per 100 000 population | 10 498–13 476 | 5786–8435 | 4958–10 079 | 1642–6313 | 191–457 | 203–618 | 168–500 | 308–582 | 1279–2798 |

* For seasons 2015–2016, 2016–2017 and 2017–2018 only

Table 3. **Range of annual SARI cases, incidence and per cent influenza positive by age group, 2013–2014 to 2017–2018**

| | Age group (years) | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <2* | 2–<5* | <5 | 5–<15 | 15–<50 | ≥50 | 50–<65* | ≥65* | |
| Total admissions | 54 095–66 759 | 20 389–28 077 | 72 470–87 148 | 20 209–49 594 | 154 586–204 850 | 105 027–122 039 | 62 124–69 403 | 41 738–52 636 | 384 711–432 053 |
| SARI cases | 25 018–27 392 | 9724–12,640 | 26 476–40 032 | 3003–6103 | 1391–2,654 | 1043–1961 | 758–1034 | 621–927 | 33 136–50 750 |
| SARI cases per 100 000 population | 23 315–26 197 | 6359–7777 | 12 226–14 988 | 894–1569 | 120–228 | 344–588 | 336–413 | 781–1114 | 1567–2,356 |
| SARI cases sampled | 756–804 | 434–563 | 1190–1725 | 124–209 | 66–337 | 17–119 | 13–51 | 4–25 | 1397–2390 |
| % specimens influenza positive | 8–31 | 11–30 | 4–30 | 12–22 | 4–17 | 4–21 | 8–16 | 5–50 | 5–28 |
| Estimated % total hospitalizations for influenza-associated SARI | 3.3–15.5 | 4.9–13.4 | 1.5–14.8 | 1.2–4.0 | 0.0–0.2 | 0.0–0.3 | 0.1–0.2 | 0.5–0.9 | 0.5–3.3 |
| Estimated influenza-associated SARI per 100 000 population | 1798–8039 | 697–2311 | 530–4547 | 103–316 | 8–23 | 14–104 | 32–57 | 65–557 | 81–666 |

* For seasons 2015–2016, 2016–2017 and 2017–2018 only

## DISCUSSION

In this first study of the influenza burden in Mongolia, estimated with WHO's *A Manual for Estimating Disease Burden Associated with Seasonal Influenza*,[7] the burden of influenza-associated ILI and SARI was highest among children aged <5 years, especially among those aged <2 years, consistent with a study conducted with the same methods on the epidemiology and impact of influenza in Mongolia between 2007 and 2012.[13] The estimated annual influenza-associated ILI and SARI rates, presented as ranges, were 1279–2798 and 81–666 cases per 100 000 population, respectively; the rates in children aged <5 years were 4958–10 079 and 530–4547 per 100 000 population, respectively. These rates are higher than those in other published studies of influenza in low- and middle-income countries (LMICs), as classified by The World Bank.[14] For example, the influenza-associated SARI rates per 100 000 population for all ages and for children aged <5 years, respectively, were: 115–142 and 2021–2349 in China;[15] 13–19 and 82–114 in Indonesia;[16] 21–82 and 147–469 (in children aged <2 years) in Kenya;[17] and 43.9 and 187.7 in Zambia.[18] The studies should be compared cautiously, as the same (WHO) SARI case definition was used only in Indonesia and Kenya, and the rates were from a relatively small number of hospitals and extrapolated to provincial or national levels.

The outcomes of influenza may be more severe in LMICs than in high-income countries, particularly in pregnant women, people living with HIV/AIDS and children aged <5 years,[19] contributing to a disproportionate proportion of the global burden of influenza.[6] There are several possible explanations for the very high rates observed in Mongolia. The extreme winter results in increased occupation of indoor spaces and may reduce immunity in some population groups. Increased population mixing also occurs in winter during public holidays, particularly the Lunar New Year and the beginning of the school year. Smoke and pollution caused by burning coal may exacerbate respiratory conditions and increase vulnerability to influenza infection.

The wide range of annual estimates of influenza-associated SARI in particular is partly driven by the marked, consistent increase in annual SARI rates over the 5-year study period. The reason for this increase has not been established, but hospitals may have changed the diagnostic and admission criteria for SARI to maximize government assistance payments for admitted SARI cases.

Only limited quantities of influenza vaccine are available in Mongolia, provided by the Government and the Partnership for Influenza Vaccine Introduction programme (https://pivipartners.org/). The Government subsidized influenza vaccination for health-care workers and staff in emergency agencies following the influenza A(H1N1)pdm09 pandemic in 2009, but vaccination remains voluntary and requires payment by other groups, so that very few people are vaccinated each year. The high influenza-associated ILI and SARI burden and mortality from pneumonia and SARI in children indicate that a vaccination programme for children could have an enormous impact on the burden of influenza in Mongolia. It would require considerable funding and resources in view of the high proportion of youth in the population. This population structure is common in developing countries, where 99% of deaths attributable to influenza-associated acute lower respiratory infection deaths in children aged <5 years occur.[20]

In the five influenza seasons between 2013–2014 and 2017–2018, ILI and SARI activity in Mongolia usually started in October and peaked during the coldest period of the year between late December and February. As measured by the percentage of samples from ILI and SARI patients who tested positive for influenza, the highest seasonal load was in 2016–2017 and the lowest in 2014–2015. In the 2015–2016 and 2017–2018 seasons, distinct secondary peaks were seen, associated with other influenza types and subtypes that dominated later in the seasons. The subtype distribution was consistent in the ILI and SARI surveillance systems each year, influenza A(H3) being the predominant circulating subtype in 2014–2015.

The timing and distributions of type and subtype in each of the five influenza seasons varied during the surveillance period and were not always consistent with observations from other regions of the northern hemisphere. Between 2013–2014 and 2016–2017, the subtype distribution in Mongolia was similar to those of North America and of north and east Asia (particularly China, Japan and the Republic of Korea) in each of the four seasons and to that of Europe in three seasons;[21–24] however, the timing of the seasons was similar to those

Table 4. **Range of annual deaths and rates of mortality due to pneumonia and SARI, 2013–2014 to 2017–2018**

| | Age group (years) | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|
| | <2* | 2–<5* | <5 | 5–<15 | 15–<50 | ≥50 | 50–<65* | ≥65* | |
| Deaths due to SARI | 17–59 | 4–6 | 21–65 | 1–2 | 0–5 | 1–8 | 1–4 | 1–4 | 25–80 |
| Mortality rate per 100 000 population | 15.8–54.0 | 2.5–3.9 | 7.9–24.8 | 0.3–0.6 | 0.0–0.4 | 0.3–2.6 | 0.4–1.8 | 1.2–5.1 | 1.2–3.9 |

* For seasons 2015–2016, 2016–2017 and 2017–2018 only

of these regions in only two of the four seasons. In 2017–2018, the timing and subtype distribution best matched that observed in western Europe.[25] The difference between the seasonal pattern in Mongolia and those in other countries in north and east Asia and elsewhere in the northern hemisphere highlights the importance of national surveillance in understanding influenza epidemiology and virology in Mongolia.

Our study had several limitations. A high staff workload, limited availability of swab kits, the absence of systematic sampling and the logistical challenges of transporting samples over long distances may have resulted in non-random sampling of ILI and SARI patients. The influenza-associated SARI mortality rate could not be estimated, as not all deaths were confirmed in the laboratory according to surveillance procedures. The positivity rate for influenza virus might have been underestimated due to delayed health care-seeking because of insufficient health literacy and improper use of antibiotics, lengthening the time to presentation to a doctor. Furthermore, reluctance among the elderly to seek health care may have resulted in underestimates of influenza-associated ILI, SARI and mortality rates for this age group. In contrast, SARI rates in the provinces might have been overestimated, as serious cases in soum hospitals are sometimes referred to provincial general hospitals. Lack of more detailed epidemiological and clinical data on cases prevented in-depth analysis of risk factors, such as underlying conditions and geographical distribution.

The estimated incidence of influenza-associated ILI and SARI in Mongolia over five seasons between 2013–2014 and 2017–2018 was higher than that in comparable countries; however, our finding that children under 5 years were the most affected is consistent with regional and global trends. The findings can inform influenza control policies. Targeted vaccination of children would dramatically decrease the burden of influenza in Mongolia. Further improvements to the surveillance system would allow more detailed analysis of risk factors and underlying conditions associated with the severity and economic burden of influenza.

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# Dengue at the time of COVID-19 in the Philippines

Xerxes T. Seposo[a]

Correspondence to Xerxes Seposo (seposo.xerxestesoro@nagasaki-u.ac.jp)

Cases of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), have been increasing since the virus emerged in Wuhan, China, in December 2019. As of 13 March 2021, confirmed COVID-19 cases have exceeded 119 million infected individuals across 188 countries, with more than 2.6 million recorded deaths.[1] National health systems have attempted to contain the pandemic through control measures such as community quarantine and isolation. In the Philippines, an enhanced community quarantine (ECQ) took effect on 15 March 2020 in an effort to flatten the epidemic curve.[2] ECQ involves placing stringent limitations on people's mobility and strict regulations on various industry operations, all of which are enforced by uniformed personnel.[3] In spite of the ECQ, active infections have been steadily increasing in the country, at 611 618 total cases and 12 694 deaths as of 13 March 2021.[1]

In 2020, the Philippines recorded a substantial decrease in the number of dengue cases, with a reduction in notified cases of about 70–90% during the rainy season[4] specifically from epidemiological weeks 28 to 40.[5] Apart from existing control and prevention measures implemented in the country – such as the establishment of dengue centres of excellence in tertiary hospitals and the creation of dengue fast lanes – the decrease in the number of cases during the COVID-19 pandemic may be largely due to the reduced mobility of the population. Several studies noted that reduction of localized household movement could lead to a reduction in transmission.[6] On a larger geographical scale, movement control measures reportedly slow or even prevent the spread of a dengue epidemic from locations with high transmission intensity to suburbs or remote areas.[7] Conversely, the decrease may have also been a result of reporting hesitancy due to the fear of contracting COVID-19 while visiting a health facility. In Caribbean and Latin American countries, an initial sharp decrease in dengue cases coincided with the start of reporting of COVID-19 cases.[8] The reduction in dengue trend may be due, in part, to the impact of the pandemic on health-seeking behaviour of the population, driven by fear of being infected. A similar reduction in health facility visits was also purported to be the reason behind the decrease in both infectious diseases and non-infectious diseases during the pandemic.[9] The Philippines has experienced several clusters of infection in hospitals. COVID-19 hospital transmissions have been widely documented in hospitals in various countries.[3] The existence of these hospital clusters has decreased medical-seeking behaviour due to the fear of contracting the disease, to the extent that it has impacted the reporting of other diseases and illnesses.

Several other countries in the World Health Organization (WHO) Western Pacific Region also noted a decrease in dengue cases in 2020.[5] However, this was not the case in Singapore, which has seen a substantial increase in cases, possibly associated with the country's physical distancing measures implemented in response to COVID-19.[10] For example, the work-from-home measure implemented may have contributed to the increase in dengue cases, compared with the usual workplace setting. Compared with workplaces, residences have a higher propensity for causing dengue infection, owing to the thriving conditions for mosquito breeding. The rise in dengue cases in Singapore and the reduction in the Philippines and other countries in the region show how different control measures (e.g. mobility restrictions) can vary in their effects on levels of dengue. These variations may be due to the extent and degree of control measures, coupled with prevention and control measures directed to either dengue or COVID-19, and inherent

[a] School of Tropical Medicine and Global Health, Nagasaki University, Japan.

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country-specific sociodemographic factors; thus, further investigation of these factors is warranted, subject to the availability of data.

The Philippines and other countries in the WHO Western Pacific Region did not see a similar increase in dengue cases in 2020. However, caution should be exercised, because a trend of increasing dengue cases could still develop in current conditions. The renewed rise of COVID-19 cases and the roll-out of COVID-19 vaccinations may have an impact on dengue cases in the latter part of 2021. The increase in COVID-19 cases may lead to more stringent control measures, but the strength of these measures will depend on the progress of vaccination coverage. According to the Philippines' current COVID-19 vaccination timeline, the general population will probably start receiving vaccinations in July 2021, after completion of the full master list of people to be vaccinated, which is expected by 30 June 2021.[1] The dengue season starts a month later, at the end of July.

In summary, although the Philippines has seen a decrease in dengue cases in 2020, a scenario in which cases increase is possible, as has happened in Singapore. Further investigation of countries in the region is needed to ascertain which factors have affected the varying impact on notified dengue cases from COVID-19-related measures, compounded by innate sociodemographic characteristics. Nevertheless, health managers can plan ahead and appraise the current conditions, including the rise in COVID-19 cases and vaccination progress, and consider how these may affect the number of dengue cases in the latter part of 2021.

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# Prioritizing mosquito-borne diseases during and after the COVID-19 pandemic

Shahmshad Ahmed Khan,[a] Cameron Ewart Webb[b] and Nur Faeza Abu Kassim[c]

Correspondence to Nur Faeza Abu Kassim (email: nurfaeza@usm.my)

The world is facing serious health and economic threats from the global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The burden of disease has been significant, with tens of millions of cases and more than 1.5 million deaths reported globally.[1] Since its emergence in Wuhan, China, in late 2019, COVID-19 has spread around the world, affecting almost all countries. COVID-19 is a highly contagious disease that is spread by direct contact and respiratory droplets, and patients can be infective while presymptomatic or asymptomatic.[2] To reduce opportunities for transmission, most developed countries have implemented lockdowns, causing significant social and economic disruption. Mosquito-borne diseases, such as malaria and dengue, are a substantial burden in many countries, especially those with developing economies. Malaria is the most significant mosquito-borne disease, with about 228 million cases reported in 2018 and 231 million in 2017, and 405 000 deaths in 2018 and 416 000 in 2017.[3] Dengue is the most commonly reported arboviral disease internationally, with Asia suffering a significant disease burden.[4] In countries facing endemic and epidemic malaria and dengue, disruption to government services (in health and non-health sectors) and to public health services could severely impact the ability to implement strategic responses to mosquito-borne diseases. As of 30 June 2020, all malaria-endemic countries in Asia had confirmed cases of COVID-19, and those with developing economies face a particularly serious threat to malaria control efforts. In these countries, local authorities responsible for malaria and dengue control must make strategic preparations for continuing with control measures, both during and after the COVID-19 pandemic.

Malaria and dengue control programmes in developing countries mainly focus on vector control by residual spraying of insecticides (other strategies include biological control of vectors and use of personal insect repellents and long-lasting insecticide-treated bed nets).[5] Between 2000 and 2015, malaria-endemic countries achieved remarkable success in malaria control, seeing about 60% reduction in malaria deaths and 37% reduction in cases. However, disrupting factors (e.g. war) can weaken malaria control programmes and result in a resurgent burden of malaria.[6]

Currently, there is uncertainty about the potential effects of the COVID-19 pandemic on existing malaria and dengue control programmes. For example, the dire global economic situation due to COVID-19 may reduce the ability of donor countries to continue their support of malaria and dengue control programmes in developing countries.

In recent years, donor countries have decreased their funding of malaria control programmes, prioritizing countries with higher disease burden; in addition, the resources available domestically for malaria and dengue control are limited. In many developing countries, malaria and dengue are major public health problems, with annual budgetary needs in the millions of dollars. However, control of these diseases is beneficial; for example, the 5-year growth of countries after malaria elimination is significantly more than in countries where malaria persists.[7] There is a precedent for emerging epidemics disrupting the response to existing public health threats. For example, the emergence of dengue in malaria-endemic countries can adversely affect malaria control programmes (e.g. the 2010 outbreak of dengue in Pakistan led to 702 000 more malaria

[a] Department of Entomology, Faculty of Crop and Food Sciences, Pir Mehr Ali Shah (PMAS) Arid Agriculture University Rawalpindi, Shamsabad, Pakistan.
[b] Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Camperdown, Australia.
[c] 129 Medical Entomology Laboratory, School of Biological Sciences, Universiti Sains Malaysia, Minden, Penang, Malaysia.
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cases in 2011).[8] It is already a challenge for countries to manage these two mosquito-borne diseases, with control often needing to be vector specific based on the distinct ecological requirements of the different mosquitoes.[9] Countries now face the challenge of focusing on dengue and malaria control during the COVID-19 pandemic. There is some uncertainty regarding how the COVID-19 pandemic will influence transmission rates of mosquito-borne pathogens. With the disruption to government services (e.g. through lockdowns or redeployment of government officials), control activities such as source reduction, community education and distribution of bed nets may cease or be significantly reduced. In residential and commercial buildings, efforts to reduce the risk of COVID-19 by creating more outdoor facilities and increasing circulation of indoor air may increase exposure to mosquitoes. Additionally, increased confinement at home during lockdowns, especially in metropolitan regions, may increase the risk of dengue virus transmission. If appropriate financial support is not maintained, the effectiveness of malaria and dengue control programmes will be compromised. Recent outbreaks of dengue have demonstrated the importance of adequately funding and implementing response strategies. In 2019, numbers of confirmed dengue cases increased compared with previous years in many countries in Asia and the Pacific, including Malaysia, the Philippines and Viet Nam.[10]

There is a need to distribute resources to simultaneously control dengue, malaria and COVID-19 in malaria-endemic countries. Given the possibility of reduced funding from donor countries, governments should consider earmarking funds for the support of malaria and dengue control programmes, both during and after the pandemic. The COVID-19 pandemic is likely to lead to strategic changes to public health policies in many countries, but prioritizing control of mosquito-borne diseases will remain critical. Many aspects of integrated mosquito control can be incorporated into existing and future public health strategies. These include community and household efforts to increase the use of sanitary water storage practices in homes, use of personal protection measures (e.g. bed nets and repellents) and protection of vulnerable populations (e.g. pregnant women, young children and older people). There has been significant international collaboration to develop responses to COVID-19. If the increased awareness of the importance of public health can lead to a greater focus on developing responses to mosquito-borne disease, there may be a positive outcome from the current situation. Although there may be competing public health priorities, especially for COVID-19, authorities must maintain the programmes designed to reduce the burden of malaria and dengue.

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# The first community outbreak of COVID-19 in Viet Nam: description and lessons learned

Tran Nhu Duong,[a] Le Thi Quynh Mai,[a] Nguyen Tran Hien,[a] Ngu Duy Nghia,[a] Nguyen Trong Khoa,[b] Nguyen Hai Tuan,[a] Tran Anh Tu,[a] Ngo Huy Tu,[a] Hoang Vu Mai Phuong[a] and Dang Duc Anh[a]

Correspondence to Dang Duc Anh (email: dda@nihe.org.vn).

**Objective:** At the time of this study, the prevention of novel coronavirus disease 2019 (COVID-19) relied solely on nonpharmaceutical interventions. Implementation of these interventions is not always optimal and, consequently, several cases were imported into non-epidemic areas and led to large community outbreaks. This report describes the characteristics of the first community outbreak of COVID-19 in Viet Nam and the intensive preventive measures taken in response.

**Methods:** Cases were detected and tested for SARS-CoV-2 by real-time reverse transcriptase polymerase chain reaction. Contact tracing and active surveillance were conducted to identify suspected cases and individuals at risk. Clinical symptoms were recorded using a standardized questionnaire.

**Results:** In Vinh Phuc province from 20 January to 3 March 2020, there were 11 confirmed cases among 158 suspected cases and 663 contacts. Nine of the confirmed cases (81.8%) had mild symptoms at the time of detection and two (18.2%) were asymptomatic; none required admission to an intensive care unit. Five prevention and control measures were implemented, including quarantining a community of 10 645 individuals for 20 days. The outbreak was successfully contained as of 13 February 2020.

**Discussion:** In the absence of specific interventions, the intensive use of combined preventive measures can mitigate the spread of COVID-19. The lessons learned may be useful for other communities.

In December 2019, an outbreak of a novel coronavirus disease was reported from Wuhan, China, in association with cases of severe pneumonia, and originally thought to be connected to a seafood market.[1] Novel coronavirus disease 2019 (COVID-19), caused by the pathogen severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has subsequently spread all over the world, with 1.5 million deaths as of early December 2020.[2,3] Viet Nam shares a 1200 km border with China, previously had multiple direct flights from Wuhan, and has had long-standing cultural and business ties with China, resulting in an increased risk of importation of SARS-CoV-2.

The first COVID-19 case in Viet Nam was detected in Ho Chi Minh City on 22 January 2020. The patient was a Chinese businessman from Wuhan visiting his son, who subsequently became infected. Shortly thereafter, a cluster of COVID-19 cases was detected among Vietnamese workers returning to the northern province of Vinh Phuc after 3 months of corporate training in Wuhan. In the absence of approved, effective vaccines or therapeutics, intensive preventive measures were the recommended response to cases of COVID-19.[4] This investigation describes the characteristics of the first community outbreak in Viet Nam and the intensive intervention and preventive measures taken in response.

## METHODS

### Setting

Vinh Phuc province has an area of 1370.7 km$^2$ and a population of 1 092 400 people. Binh Xuyen is one of seven districts in the province and includes 13 communes of approximately 10 000 people each. Vinh Phuc is approximately 51 km from Hanoi, the capital of Viet Nam, and home to 8 million people.

[a] National Institute of Hygiene and Epidemiology, Ministry of Health, Hanoi, Viet Nam.
[b] Agency of Health Examination and Treatment, Ministry of Health, Hanoi, Viet Nam.
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### Epidemiological investigation and laboratory methods

We defined cases of COVID-19 infection according to the Viet Nam Ministry of Health's guidelines in effect at the time of our investigation.[5] Specifically, suspected cases of COVID-19 infection were people with fever and cough, with or without shortness of breath, and either (i) a history of visiting Wuhan, China, during the 14 days before onset of illness or (ii) close contact (within 2 m) with confirmed or suspected cases occurring from 17 January through 3 March 2020.

This investigation was conducted from 20 January to 3 March 2020. Confirmed cases were those who had laboratory confirmation of SARS-CoV-2 virus by real-time reverse-transcriptase polymerase chain reaction (rRT–PCR),[6] regardless of whether they had symptoms. Imported cases were defined as confirmed cases with a history of travel to an epidemic area within the 2 weeks before the date of onset of symptoms or the date of their first sample testing positive. Locally transmitted COVID-19 cases were defined as cases in Vinh Phuc province without a history of travel to an epidemic area. Symptoms were recorded at onset or time of first positive test result. The duration of hospitalization and clinical outcomes were monitored for all confirmed cases.

A close contact was defined as any individual who was within 2 m of a confirmed or suspected case during the case's symptomatic period, including 3 days before symptom onset. A casual contact was defined as any individual who was further than 2 m from a confirmed or suspected case.

We conducted a descriptive epidemiological analysis by characterizing all cases in terms of their demographics, clinical symptoms, interval from onset to hospital admission, if applicable, number of contacts and history of travel to an epidemic area.

Oropharyngeal swabs were collected from suspected cases and all of their contacts, including those without symptoms. Testing by rRT–PCR was performed according to the Charité Institute of Virology's protocol, as recommended by the World Health Organization.[6]

### Ethical considerations

This investigation was approved by the Institutional Review Board of the Pasteur Institute of Ho Chi Minh City, the organization with oversight of national research protocols for COVID-19.

## RESULTS

The epidemiological characteristics were reported for 11 cases, 158 suspected cases and 214 close contacts. The intensive outbreak response, with its unique set of preventive measures, contributed to the successful containment of the COVID-19 outbreak.

### Epidemiology

The first community outbreak of COVID-19 occurred in Vinh Phuc province, where 11 cases were identified by contact tracing. To ensure complete case detection, attempts were made to identify all suspected cases between 30 January and 3 March 2020 – that is, from the day when the first case was detected to the last day of the lockdown.

#### *Confirmed cases*

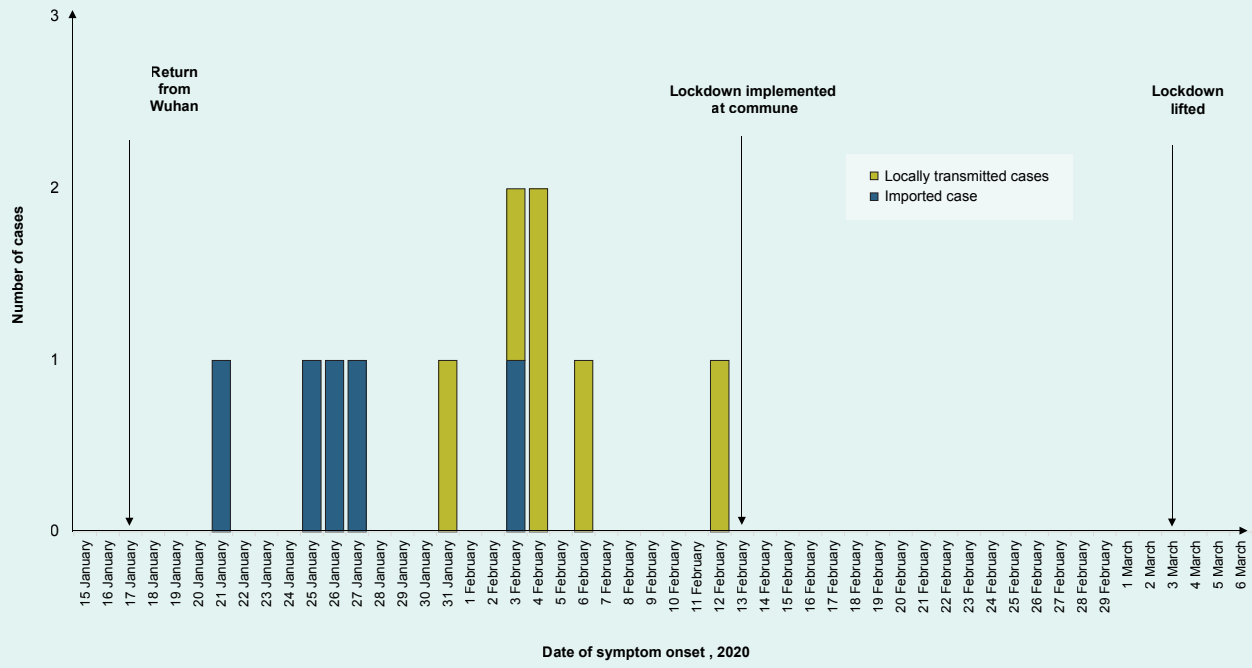
Of the 158 suspected cases of COVID-19, 11 cases were confirmed between 30 January and 3 March; the last confirmed case was identified on 12 February 2020 in Vinh Phuc province (**Table 1**). Five of these cases occurred among workers returning from Wuhan (imported cases) and the remaining six were close contacts (locally transmitted cases) of the imported cases (**Fig. 1**).

Nine of the confirmed cases (81.8%) occurred among Binh Xuyen residents: three cases were imported and six were locally transmitted (**Table 1**). Two subsequent cases (cases 10 and 11) were identified through contact tracing and regular follow up. Of the two additional imported cases, one was a resident of the Tam Duong and one of the Tam Dao district (**Fig. 2**). Notably, all six locally transmitted cases could be linked either directly or indirectly to imported case number 2 (**Table 2**, **Fig. 1**). Of the 11 confirmed cases, 8 were female (72.7%) and 3 were male (27.3%); the median age was 29.0 years (interquartile range [IQR]: 26.5–45.5).

Table 1. **Results of case finding and contact tracing for novel coronavirus disease (COVID-19), Vinh Phuc province, Viet Nam, January–March 2020**

| Location | No. of confirmed cases | No. of suspected cases with negative tests | No. of close contacts | No. of casual contacts |
|---|---|---|---|---|
| **All of Vinh Phuc province** | **11** | **147** | **214** | **449** |
| Binh Xuyen district | 9 | 99 | 149 | 200 |
| Son Loi commune | 6 | 40 | 70 | 52 |
| All other communes | 3 | 59 | 79 | 148 |
| All other districts | 2 | 48 | 65 | 249 |

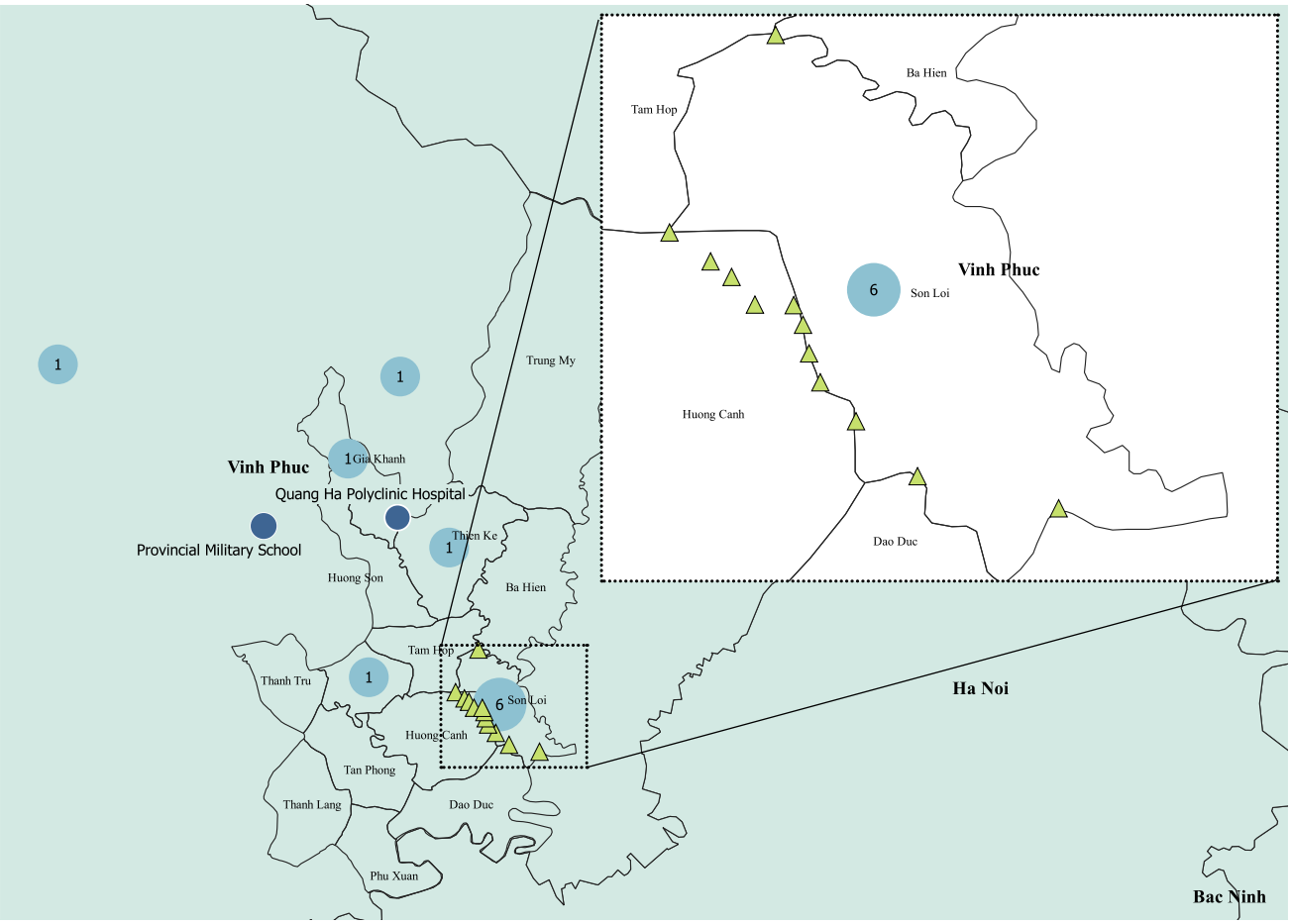
Fig. 1. **Epidemic curve of novel coronavirus 2019 (COVID-19) cases, by date of symptom onset, Vinh Phuc province, Viet Nam, January–February 2020**




Nine confirmed cases (81.8%) had mild symptoms at the time of detection; no cases required admission to an intensive care unit. Four out of five cases with imported COVID-19 who had travelled to Wuhan were symptomatic. The first case developed symptoms on 21 January 2020, 4 days after returning from Wuhan (**Table 2**). The most common symptoms were cough or fever, found in 8/11 cases (72.7%). Two patients (18.2%) had both cough and fever (**Table 2**). The less frequent symptoms of sore throat, headache, runny nose and fatigue were each found in one patient (9.1% for each of the four symptoms). Two other confirmed cases (18.2%) were asymptomatic at the collection date of their first specimen for testing by rRT–PCR, but the specimen tested positive.

Through case finding, we observed a decrease in the number of days that cases spent in the community before being hospitalized, with a median of 2 days (IQR: 2–3) for the five imported cases (cases 1, 2, 3, 4, 6) and 0 days (IQR: 0–0.75) for the six locally transmitted cases (cases 5, 7, 8, 9, 10, 11). The difference in delay in hospital admission between imported cases and locally transmitted cases was statistically

Fig. 2. **Map of Binh Xuyen district in Vinh Phuc province, Viet Nam, with an inset of Son Loi commune**




Bold text indicates names of provinces. Smaller text indicates commune names within the district. The circled numbers indicate the number of novel coronavirus 2019 (COVID-19) cases in the relevant commune. Green triangles indicate checkpoints. The dark blue dots indicate the locations of the Quang Ha Polyclinic Hospital and the Provincial Military School.

significant (Wilcoxon rank sum test: $P = 0.011$). The number of close contacts was not significantly different between the two groups (imported cases versus locally transmitted), with a median of 4 contacts (IQR: 4–6) of imported cases and 4.5 contacts (IQR: 4–5.75) of locally transmitted cases ($P = 0.92$). All cases recovered clinically, as assessed by the Vietnamese Ministry of Health's guidelines,[7] and were discharged following two negative rRT–PCR tests of upper respiratory specimens collected at least 24 hours apart (**Table 2**).

### *Close contacts*

A total of 214 close contacts were identified (**Table 1**). Six of these subsequently became confirmed cases, five of whom were tested and identified at home, and one, the father of case 2, who developed a sore throat and fatigue while quarantined at the local Provincial Military School (described below), who was immediately transferred to the Quang Ha Polyclinic Hospital where a specimen was collected and subsequently tested positive by rRT–PCR.

All 39 close contacts of the five imported cases were asymptomatic and were quarantined at the Quang Ha Polyclinic and the military school, as were 95 other close contacts without symptoms. The remaining 80 close contacts were quarantined at home.

## Outbreak response

The field outbreak response was led by the Vinh Phuc Provincial Centre for Disease Control with support from the National Institute of Hygiene and Epidemiology. The National Steering Committee for COVID-19 Prevention and Control also deployed an expert technical

Table 2. **Descriptive epidemiology of cases of novel coronavirus disease 2019 (COVID-19), Vinh Phuc province, Viet Nam, 17 January to 26 February 2020**

| Case | Gender | Age | Travel and contact history | Symptoms | Onset date | Hospital; date of admission | Date of discharge | Clinical outcome[b] |
|---|---|---|---|---|---|---|---|---|
| 1 | Male | 29 years | Travelled from Wuhan on 17 Jan | Cough | 21 Jan | NHTD; 23 Jan | 18 Feb | Survived |
| 2 | Female | 24 years | Travelled from Wuhan on 17 Jan | Fever, cough, sore throat | 25 Jan | NHTD; 26 Jan | 10 Feb | Survived |
| 3 | Female | 29 years | Travelled from Wuhan on 17 Jan | Fever | 26 Jan | NHTD; 2 Feb | 10 Feb | Survived |
| 4 | Male | 30 years | Travelled from Wuhan on 17 Jan | Fever, cough | 27 Jan | NHTD; 30 Jan | 10 Feb | Survived |
| 5 | Female | 42 years | Visited case 2's home on 22 and 28 Jan | Fever | 31 Jan | QH Poly; 31 Jan | 18 Feb | Survived |
| 6 | Female | 29 years | Travelled from Wuhan on 17 Jan | Asymptomatic | 3 Jan | QH Poly; 5 Feb | 20 Feb | Survived |
| 7 | Female | 49 years | Mother of case 2; same household | Cough | 3 Feb | QH Poly; 3 Feb | 18 Feb | Survived |
| 8 | Female | 16 years | Younger sister of case 2; same household | Asymptomatic | 4 Feb | QH Poly;[a] 5 Feb | 20 Feb | Survived |
| 9 | Female | 55 years | Visited case 2's home on 28 Jan | Fever, headache | 4 Feb | QH Poly;[a] NHTD, 5 Feb | 18 Feb | Survived |
| 10 | Female | 3 months | Stayed with case 2's family on 28–31 Jan | Cough, runny nose | 6 Feb | QH Poly;[a] NPH, 6 Feb | 20 Feb | Survived |
| 11 | Male | 50 years | Father of case 2; same household | Fatigue | 12 Feb | QH Poly; 11 Feb | 26 Feb | Survived |

NHTD: National Hospital for Tropical Diseases; QH Poly: Quang Ha Polyclinic Hospital; NPH: National Paediatric Hospital.

[a] These patients were first admitted to Quang Ha Polyclinic Hospital (QH Poly) then transferred to a national referral hospital to prevent complications; transfers included a patient with thrombocytopenia and a 3-month-old infant.

[b] The outcome "survived" refers to clinical outcome at the time of hospital discharge.

outbreak surveillance team, a rapid response team, an expert treatment team and an infection control team to Vinh Phuc province to support local authorities in directing, monitoring and implementing all prevention activities. Based on the descriptive epidemiology, interventions using a series of preventive measures were implemented.

Five doctors were deployed to each of the 13 commune health stations (CHSs) in the Binh Xuyen district (65 doctors in total) to ensure compliance with preventive measures. An additional 168 health-care workers at the district and commune levels were trained in case investigation, reporting, contact tracing, surface disinfection and the proper use of personal protective equipment (PPE).

### *Contact tracing*

Contact tracing was performed by the Provincial Centre for Disease Control. All suspected cases were interviewed to collect information about their close contacts, including health-care contacts, family members, co-workers, friends, neighbours, other social contacts and travelling companions. All contacts were subjected to quarantine and strict symptom monitoring.

### *Isolation and quarantine*

The five imported cases (cases 1–4, 6) were isolated and treated at the National Hospital for Tropical Diseases in Hanoi (**Table 2**), since they were among the first imported cases in Viet Nam.

The initial hospital isolation and treatment implemented in Vinh Phuc province occurred at the Quang Ha Polyclinic Hospital, a district hospital in Binh Xuyen. It was divided into six sections, one each for:

- isolation and treatment of laboratory confirmed cases;
- suspected cases with pending test results;
- family members of confirmed cases;
- symptomatic patients whose first COVID-19 test was negative but who required 14 days of observation;
- those who had recovered fully from COVID-19; and
- suspected cases and close contacts who tested positive for influenza or other respiratory viruses.

Patients in the isolation facility had their temperature and symptoms checked twice daily. For those with symptoms, temperature and symptom checks were performed four times per day. Suspected cases from other districts were isolated at the Vinh Phuc Provincial Hospital.

The local Provincial Military School was converted into a quarantine centre for close contacts who were not family members of cases. Beds were placed 1 to 2 metres apart. Those who were quarantined or isolated received three meals a day free of charge and full support and daily supplies. Waste was separated into potentially contaminated waste (e.g. masks and tissues) and all other waste. Temperature and symptom checks were conducted twice daily. We collected oropharyngeal specimens for laboratory testing from each contact under quarantine, once on day 2 and once on day 14 before discharge. We delivered risk communication messages to all quarantined contacts each day.

Four suspected cases were identified in the facility and were transferred to Quang Ha Polyclinic. One of these four suspected cases became case 11. All discharged contacts from the quarantine centre remained under home quarantine for 2 more weeks.

No locally transmitted cases were identified among health-care workers in the Quang Ha Polyclinic or among staff at the military school quarantine centre.

### *Community lockdown*

Intensive lockdown measures were taken after the identification of three locally transmitted cases in the Son Loi commune on 7 February. We worked with local authorities and implemented preventive control measures in the commune. A 20-day lockdown of the entire commune of 10 645 residents began with the establishment of eight checkpoints on 8 February and four more were added between 9 and 13 February. The lockdown officially started at midnight on February 13.

Twelve checkpoints were established by 14 February and were in place until 3 March (**Fig. 2**). The checkpoints were inspected regularly by 30 independent monitoring teams designated by the Provincial Steering Committee for COVID-19 Prevention and Control. Residents of Son Loi were permitted to leave for work in nearby fields or emergency purposes, but they were required to register at checkpoints and inform local authorities of when they would return. Visitors were only permitted to deliver supplies (e.g. food, water) to the checkpoints, from which they were collected and distributed within the commune. All task force staff and visitors without symptoms and with a forehead temperature <37.5 °C were permitted to enter.

Merchandise and vehicles entering and exiting Son Loi were inspected and disinfected with 0.1% chloramine B solution. Shops with fixed prices for staple foods, such as rice, noodles, meat and vegetables, were established during the lockdown in each of the six hamlets of Son Loi.

Each member of the commune received a daily allowance of 40 000 Vietnamese dong (US$ 1.70) for the 20-day duration of the lockdown. Residents were recommended to clean their houses and domestic surfaces daily with 0.1% chloramine B solution, wear masks and stay home as much as possible. Mass gatherings, such as festivals and weddings, were prohibited during the lockdown. Risk communication messages were delivered three times a day via loudspeakers throughout the commune.

A team of medical experts was sent to the Son Loi CHS to support the rapid identification of suspected cases and to meet any emergency needs of the residents. Two ambulances were always on duty at the CHS. A

mobile X-ray unit was acquired by the Son Loi CHS, a device not available at most CHSs in Viet Nam.

### *Active case finding*

Active case finding was performed during the lockdown. A total of 29 Community COVID-19 Prevention and Control Teams (CPCTs) were formally established. The teams consisted of three or four members, and included village health-care workers, volunteers and community or family representatives. The teams performed daily house-to-house health checks, including taking the temperature of all household members and delivering risk mitigation messages. Each household was provided with a thermometer so that symptomatic family members could have their temperature assessed and reported to the team by calling a dedicated phone number. No cases were identified during active case finding.

### *General preventive measures*

For people in the commune, general preventive measures were required at all times, including wearing masks, using other PPE, disinfecting surfaces and using hand sanitizer. In addition to the recommended general preventive measures, all hospitalized patients, quarantined individuals, suspected cases and close contacts of confirmed cases were also required to wear masks at all times.

All staff working at the CHSs, the military school and Quang Ha Polyclinic; members of the CPCTs; and personnel at other medical facilities in Vinh Phuc consistently wore a complete set of PPE, including a whole-body suit, gloves, eye protection and a surgical mask. All were encouraged to practice hand hygiene regularly, before and after meals, before and after caring for patients, and after using the toilet. Surface disinfection of hallways with 0.1% chloramine B solution was performed daily in health-care and quarantine facilities. All vehicles entering and exiting the military school campus, cars transporting suspected cases and ambulances were disinfected daily with 0.1% chloramine B solution.

## DISCUSSION

During the first community outbreak of COVID-19 in Viet Nam, 11 of 158 (6.9%) suspected cases tested positive for COVID-19, indicating a low rate of infection.[8] These 11 cases were identified in people who returned from Wuhan or were in close contact with one of these people. Given the transmissibility of SARS-CoV-2, this cluster had the potential to be much larger.[4,5]

The majority of clinical manifestations in the confirmed cases included cough or fever, or both.[9] About 20% of cases were asymptomatic, a low prevalence compared with previous reports.[10] The time from onset of symptoms or detection of a case to hospital admission for isolation and treatment was short, most likely due to the careful monitoring of suspected cases and close contacts at the hospital and at the quarantine centre. Since cases may be infectious for 1–3 days before symptom onset and thus contribute to community transmission,[11] it is crucial to identify both symptomatic and asymptomatic cases for isolation and quarantine.[12–14] The interval from symptom onset to hospital admission or isolation was reduced from 2 days to 0 during this outbreak as a result of efforts by local public health staff to limit the spread of cases. The delay between symptom onset and isolation has been shown to have the largest role in determining the degree of community transmission from imported cases.[15] Therefore, early detection and careful monitoring of suspected cases and close contacts can reduce the time that potential cases spend in the community; by committing to early detection and careful monitoring, Vinh Phuc province may have limited the spread of COVID-19 during the first community outbreak in Viet Nam.

The control measures implemented in response to this outbreak occurred 3 days after locally transmitted cases were identified in the community. This quick response was feasible with the government's assistance and because of the informed decisions made in near real-time by the National Steering Committee as its rapid response team was deployed to Vinh Phuc province. The establishment of quarantine and treatment facilities at the district level facilitated and supported timely case detection, contact tracing and quarantining of people at risk, which may have contributed to reducing the spread of COVID-19 in the community. The decision to implement a community lockdown for 20 days was supported by Vietnamese government Decree No. 101/2010/ND-CP.[16] Similar measures were implemented in China in 2003 in response to severe acute respiratory syndrome[17] and, more recently, in response to COVID-19 in Singapore.[11] Recent analysis suggests that increased compliance with community mitigation

strategies, including physical distancing, when the number of cases is increasing can reduce community transmission.[18] When first implemented, large-scale lockdown of communities can be highly disruptive. However, if it is implemented quickly and at a smaller scale, that disruption can be minimized and, importantly, disease transmission is more likely to be contained. In Son Loi commune, the lockdown was implemented for no longer than necessary, and the reason for it was to reduce pressure on the health, economic and social security of the people in the commune.[19]

Our investigation took place at a time when there was no effective vaccine or treatment and the national public health response in Viet Nam was still developing. This created several challenges. For example, at the time when the employees returned from Wuhan, there was no national or international guidance on how to detect or manage asymptomatic cases. Therefore, we had to adopt what we believed to be sensible public health interventions, assuming that asymptomatic cases could transmit SARS-CoV-2 and, thus, isolating them as if they were infectious. The conventional rRT–PCR assay was not readily available at central laboratories before 30 January 2020, so we often erred on the side of isolation and quarantine, knowing that suspected cases and contacts might have to wait several days for test results.

Our investigation began near the time of the annual Lunar New Year (Tet) holiday, the largest holiday in Viet Nam and a time when most government offices and businesses are closed. As such, we were not able to access all available resources. Nevertheless, despite these challenges, we were able to contain the outbreak in Vinh Phuc and prevent further transmission. The experiences gained through the response to this outbreak were indispensable for the development of subsequent national guidelines.[20–23]

This investigation has several limitations. The five cases with a history of travel to an epidemic area were considered imported cases; however, we were unable to determine when and where they were infected with the SARS-CoV-2 virus. The transmission of pathogens among these five cases was unclear. Furthermore, the effectiveness of each preventive measure was not separately assessed, so we do not know exactly which measures played key roles in the combined intervention.

In conclusion, in COVID-19 response activities, the government's assistance and the willingness of the community to adopt preventive measures are important in containing community outbreaks. When no vaccine is available, intensive interventions that involve a combination of preventive measures can mitigate spread of the disease. We believe that these experiences are useful for other communities that may need to respond to the COVID-19 pandemic.

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## *Conflicts of interests*

The authors declare that there are no conflicts of interest.

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# Use of movement restrictions during an outbreak of COVID-19 in Selangor, Malaysia

Anita Suleiman,[a] Shaari Ngadiman,[b] Mazliza Ramly,[a] Ahmad Faudzi Yusoff[c] and Mohamed Paid Yusof[d]

Correspondence to Mazliza Ramly (drmazliza@moh.gov.my).

**Objective:** Various public health and social measures have been used during the COVID-19 outbreak, including lockdowns, contact-tracing, isolation and quarantine. The objective of this manuscript is to describe outbreaks of COVID-19 in Selangor, Malaysia, the public health strategies used and the observed impact of the measures on the epidemic curve.

**Methods:** Information on all confirmed COVID-19 cases in Selangor between 25 January and 28 April 2020 was obtained. Clusters were identified, and cases were disaggregated into linked, unlinked and imported cases. Epidemic curves were constructed, and the timing of movement control orders was compared with the numbers of cases reported.

**Results:** During the study period, 1395 confirmed COVID-19 cases were reported to the Selangor Health Department, of which 15.8% were imported, 79.5% were linked and 4.7% were unlinked cases. For two main clusters, the number of cases decreased after control measures were instituted, by contact-tracing followed by isolation and home quarantine for the first cluster ($n$ = 126), and with the addition of the movement control order for the second, much larger cluster ($n$ = 559).

**Discussion:** The findings suggest that appropriate, timely public health interventions and movement control measures have a synergistic effect on controlling COVID-19 outbreaks.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in Malaysia on 25 January 2020; three cases were notified, all of which were imported from Wuhan, China. On 30 January 2020, WHO declared coronavirus disease 2019 (COVID-19) a public health emergency of international concern. On 6 February, the first local transmission was reported in Malaysia in a close contact of a confirmed COVID-19 case who had returned from Singapore. The first case in Malaysia with neither a history of contact with a confirmed case nor travel to an affected area was reported on 12 March 2020. By 28 April 2020, Malaysia had reported 5851 confirmed cases and 100 fatalities.

Selangor is the most densely populated state in Malaysia, with a population of 5.8 million and a population density of 780.3 people/km$^2$. It is situated in Peninsular Malaysia, bordering the capital, Kuala Lumpur, and the Federal Government Administrative Centre, Putrajaya. By mid-March 2020, there were more than 200 COVID-19 cases in Selangor, and the number increased to more than 1300 by mid-April 2020, largely due to two main clusters. The Malaysian Government instituted movement restrictions through a mandatory movement control order (MCO) under the Prevention and Control of Infectious Diseases Act 1988 and the Police Act 1967 to limit human movement from 18 March in an effort to prevent further COVID-19 cases.

A variety of containment strategies, used either in isolation or in combination, have been used for COVID-19, which can be broadly categorized as physical distancing measures, movement restrictions, public health measures and socioeconomic measures.[1] This paper describes the epidemiology and control measures used to control the outbreak of COVID-19 in Selangor, Malaysia, up to April 2020.

[a] Ministry of Health Malaysia.
[b] Selangor State Health Department, Malaysia.
[c] Institute for Medical Research, Malaysia.
[d] Petaling District Health Office, Malaysia.
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## METHODS

This observational study included all COVID-19 cases reported in Selangor between 25 January and 28 April 2020. By that time, Selangor had reported 25% of all COVID-19 cases in Malaysia.

A confirmed case was defined as an individual with a positive test for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction from nasopharyngeal swabs. We obtained demographic, clinical and exposure information from an online data collection form used by district health authorities in case investigation. Clusters were identified from detailed movement histories of confirmed cases and their contacts.

An epidemic curve was plotted, with the date of onset of illness used for symptomatic cases and the date of last exposure plus 5 days as the estimated "onset date" for asymptomatic cases. We defined cases as "imported" if they had travelled overseas in the 14 days before onset, as "linked" if the disease was acquired locally after a history of contact with a COVID-19 case and as "unlinked" for those with no history of contact with a confirmed COVID-19 case. Data were analysed in Microsoft Excel with SPSS version 26.

The control measures used during the period of measuring the epidemic curve are described.

### Ethics approval

The study protocol was reviewed and approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-20–1043–54912 [IIR]).

## RESULTS

As of 28 April 2020, 1395 confirmed COVID-19 cases had been reported to Selangor Health Department. Most (80%) were detected by contact-tracing, 13% were imported, 5% were detected by sampling of people with influenza-like illness or severe acute respiratory illness at sentinel surveillance sites, and 2% were found during routine passive case detection.

Most of the COVID-19 cases were in Malaysian citizens (85%) and males (59%). The age range was 1 month to 92 years (median, 35 years); 10.4% were aged <19 years, 46.5% 19–39 years, 27.2% 40–59 years and 14.5% ≥60 years. Of the 1395 cases, 15.8% were imported, 79.5% were linked cases and 4.7% were unlinked cases.

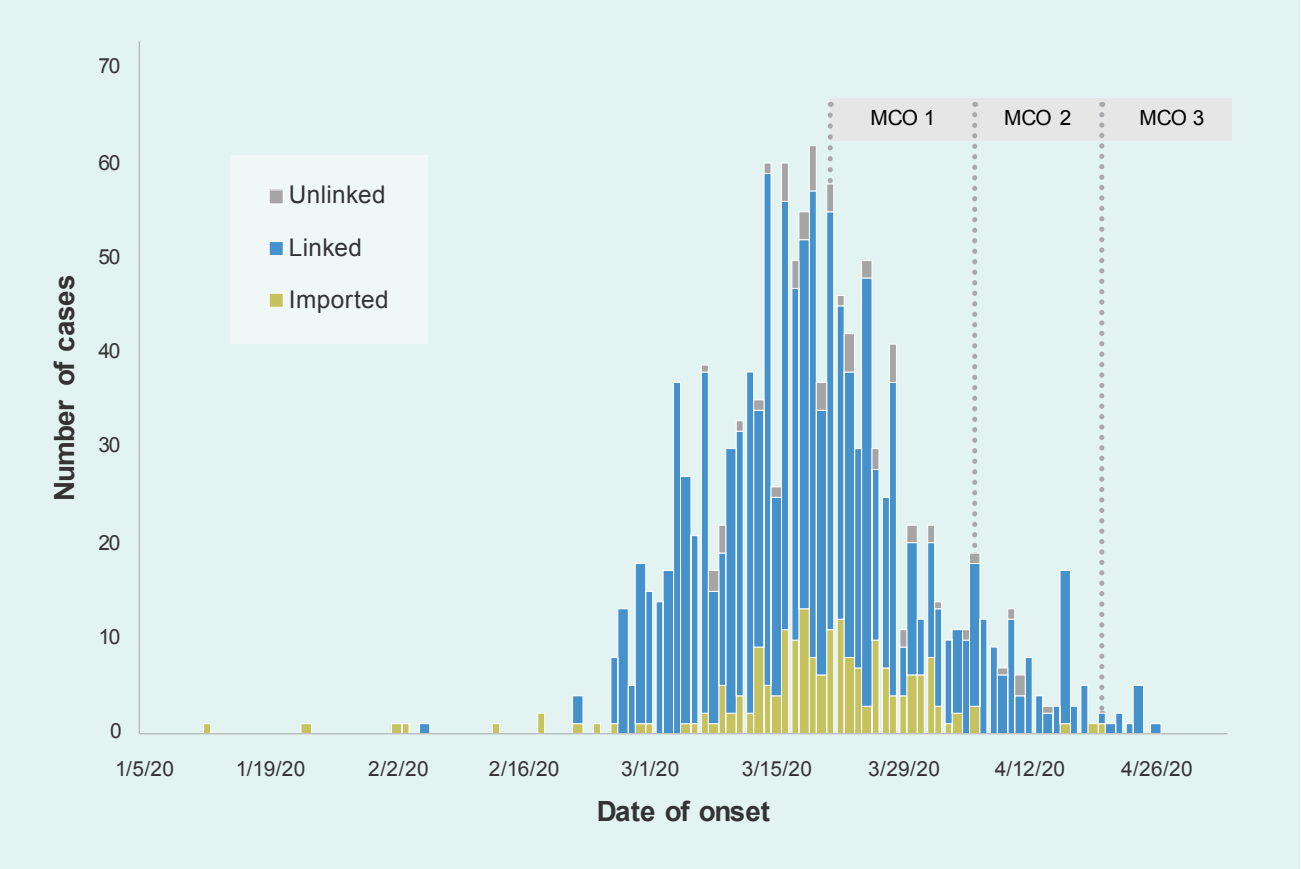
The epidemic curve (**Fig. 1**) shows an exponential increase in the number of cases in Selangor from early March 2020, which peaked on 19 March, followed by a steady decline by 28 April.

Initial case detection and control measures included contact-tracing, isolation of cases and home quarantining of contacts of cases. Travellers and returning Malaysians with either symptoms or fever detected with thermal scanners at points of entry were tested for SARS-CoV-2. Those found to be positive were isolated in a designated COVID-19 hospital, while those found to be negative and/or asymptomatic were quarantined in designated hotels for 14 days from the date of arrival.

The increase in the number of linked cases after 22 February was due to a workplace cluster. Extensive case investigations revealed 126 confirmed cases among 1715 contacts, for an attack rate of 7.3%. This attack rate was higher among work-related contacts (18.7%, 56 of 300) than among family and social contacts (4.9%). The case with the earliest onset of illness, on 18 February, was identified as the primary case for this cluster and was imported from a neighbouring country. The largest potential exposure event was on 27 February, at a meeting with approximately 300 people. The number of cases in this cluster peaked on 29 February and then declined, in line with public health measures initiated on 29 February (**Fig. 2A**).

At the time of the workplace cluster, mass gatherings were not banned. A second cluster was subsequently detected after a religious mass gathering in Kuala Lumpur of more than 10 000 people between 28 February and 2 March 2020, resulting in 559 COVID-19 cases in Selangor among attendees, their families and social contacts (**Fig. 2B**). Further links were made to a wedding on 6 March and the transfer of students from a school near the mass gathering location to another school in Selangor on 12 March. The earliest onset of disease after the latter event was on 26 February in a cook at the school in Selangor, who also attended the mass gathering.

Fig. 1. **Epidemic curve of COVID-19 cases by importation and linkage between 5 January and 28 April 2020, Selangor, Malaysia ($n$ = 1395)**




On 18 March, the first 14-day MCO was initiated, which prohibited public movement, including interstate and international travel and mass gatherings for religious, sports, social and cultural activities throughout the country. Businesses and services deemed non-essential, schools, universities and government offices were closed, and people were urged to work from home. Only essential services such as food and health care could operate, with strict operating procedures that ensured physical distancing and screening for fever. A second MCO was implemented from 1 April to 14 April. In addition, an enhanced MCO was enforced in certain locations with established large clusters, where all movement was restricted. Comprehensive testing of all residents for SARS-CoV-2 was conducted; residents and visitors in the area were forbidden to leave their homes, and all roads into the enhanced MCO area were blocked. Residents were provided with adequate food and medical supplies by authorities, with special arrangements to address any additional needs.

During the first 14 days of the first MCO, the number of COVID-19 cases decreased by 12.8%, with a further decline of 71% after the second and 72% after the third MCO. The number of imported cases fell after implementation of international travel restrictions during the first MCO and had almost disappeared by the third. Most unlinked cases were reported before and throughout the first MCO and had also fallen to almost 0 during the third.

## DISCUSSION

Lack of pharmacological treatment and vaccines against COVID-19 meant that public health and social measures were the mainstay of the initial COVID-19 response. Selangor initially adopted contact-tracing, isolation of cases and quarantine of contacts to manage the outbreak but added MCOs with closure of schools, universities and non-essential businesses and services. The MCOs appear to have flattened the epidemic curve. A modelling study conducted in the United Kingdom that included

Fig. 2A. **Distribution of cases by date of illness onset and date of exposure in a workplace cluster, Selangor, Malaysia (*n* = 126)**

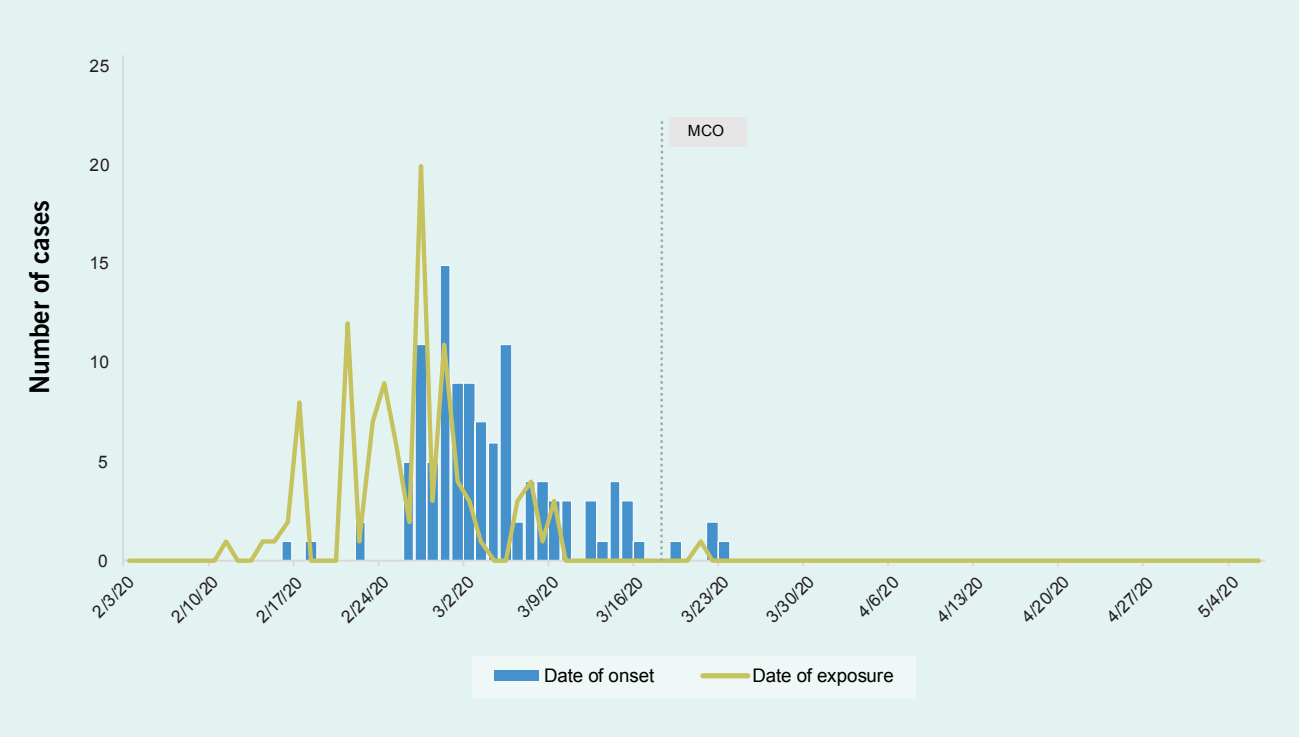
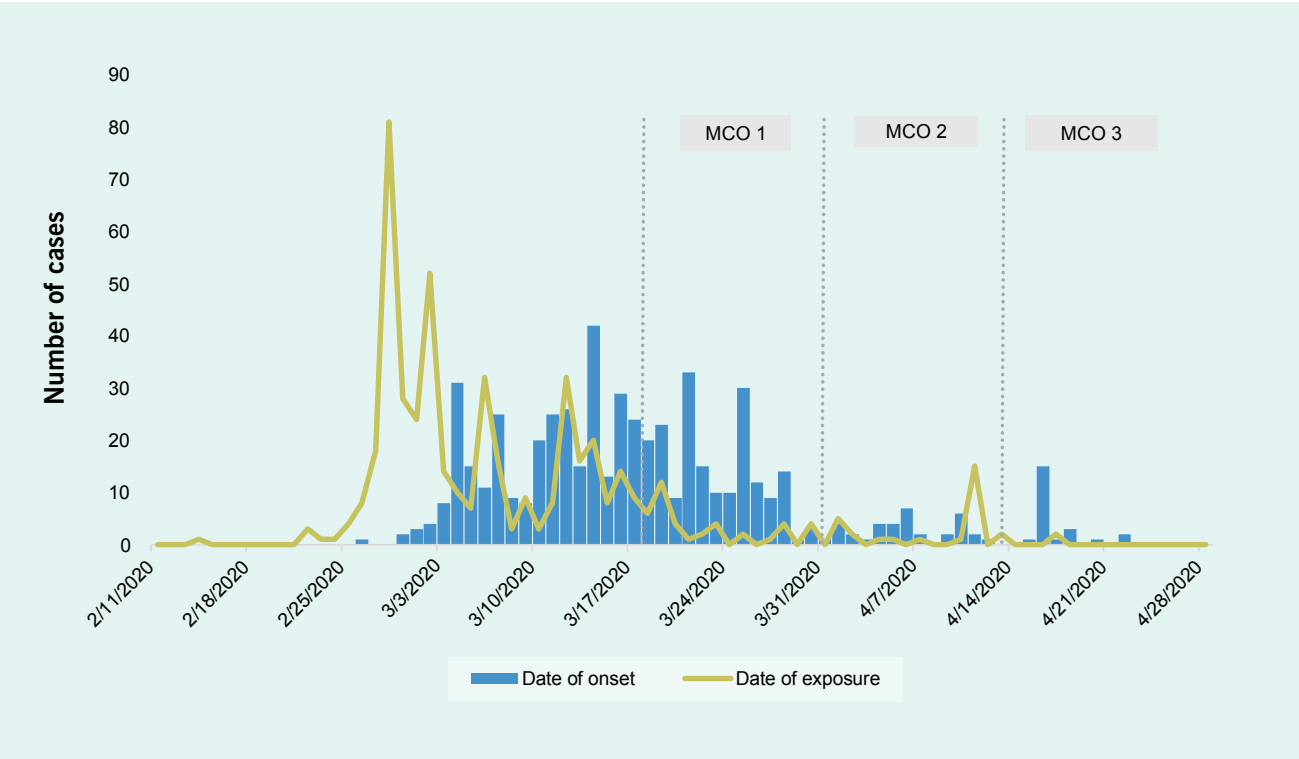



Fig. 2B. **Distribution of cases by date of illness onset and date of exposure in a cluster in Selangor after attendance at a mass religious gathering in Kuala Lumpur (*n* = 559)**



various transmission routes and mitigation measures suggested that lockdowns alone, particularly if short, will not eliminate transmission and that a combination of stricter measures is required.[2]

One of the main public health measures used to reduce importation of cases of COVID-19 was thermal body scanning and health declarations at points of entry. However, asymptomatic and presymptomatic cases can effectively shed the virus[3] and are unlikely to be detected by screening at points of entry. One study showed that half of infected travellers are not detected during airport screening.[4] In the initial workplace cluster in Selangor, the index case was an imported case that had not been detected at the point of entry. With a substantial proportion of asymptomatic cases (30%), additional control methods are required.

The initial workplace cluster in Selangor was successfully interrupted through the public health measures of contact-tracing, isolation of all confirmed cases and home quarantine of all contacts. Contact-tracing has been a key public health response during previous pandemics of influenza and other communicable disease outbreaks, as it identifies potentially infected individuals before symptoms emerge.[5] If conducted promptly, contact-tracing can prevent onward transmission from secondary cases.[6] Although contact-tracing can be highly effective for the control of COVID-19, it places substantial demands on the public health authorities, as reported in other studies.[7]

The second cluster, arising from the mass gathering in Kuala Lumpur, involved cases all around the country as attendees dispersed to their respective states. In Selangor, contacting and then testing the large number of potential contacts from this event stretched the state's capacity, and the response to the first cluster of 126 cases could not be replicated for the second cluster of 559 cases. Therefore, the first MCO was enforced, resulting in a reduction in the number of new cases, which continued during the second and third MCOs. Had mass gatherings been prohibited during the earlier phase of COVID-19, this outbreak could have been prevented. However, as a result of this cluster, MCOs were identified as a useful, practicable control measure, which can be implemented intermittently as required.

The objective of the MCO was to reduce contact of potential cases with others, thereby averting widespread community transmission and preventing the health care system from being overwhelmed by an influx of new patients. Extension of the MCO was made possible by government support through an economic stimulus package to ease the burden on businesses and individuals of the economic downturn.[8] Although costly, MCOs were seen to slow the epidemic. An interrupted time-series study in Hubei and Guangdong provinces in China before and after lockdown showed a significant reduction in the incidence of cases, indicating the effectiveness of lockdown in containing the outbreak.[9] A local modelling study with various contact rates during the phases of MCO found that MCO implementation flattened the epidemic curve,[10] and the effectiveness of lockdown in reducing transmission rates has been shown by modelling elsewhere.[2] It should be noted, however, that the decrease in the number of COVID-19 cases in Selangor might have also been the effect of the combined prevention strategies, such as isolation, quarantine, travel bans and closure of schools and universities, and not the MCO alone.

The study has several limitations. As Selangor implemented several public health measures concurrently, the relative impact of each intervention could not be evaluated. Nevertheless, our data show a temporal association between trends in the epidemic curve and MCO implementation. Additionally, we did not directly assess changes in human contact behaviour before and during the MCO.

Our study results support the conclusion that MCOs, in conjunction with other public health and social measures, played a key role in controlling the spread of SARS-CoV-2 in Malaysia.

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## *Conflicts of interest*

We know of no conflict of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

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# Challenges to implementation and strengthening of initial COVID-19 surveillance in Vanuatu: January–April 2020

Wendy Williams,[a,*] Caroline van Gemert,[b,c,d,*] Joanne Mariasua,[a] Edna Iavro,[a] Debbie Fred,[a,b] Johnny Nausien,[a] Obed Manwo,[a] Vincent Atua,[a,e] George Junior Pakoa,[a,e] Annie Taissets,[a] Tessa B Knox,[f] Michael Buttsworth,[f] Geoff Clark,[b] Matthew Cornish,[g] Posikai Samuel Tapo,[a] Len Tarivonda,[a] and Philippe Guyant,[f] on behalf of the Vanuatu Ministry of Health's National Health Emergency Operations Centre[h]

Correspondence to Caroline van Gemert (email: caroline.vangemert@unimelb.edu.au or caroline.vangemert@vhp.com.vu).

The Pacific island nation of Vanuatu is vulnerable to emerging infectious diseases, including epidemics and pandemics; chronic food and water insecurity; and natural hazards, including cyclones, earthquakes, tsunamis, landslides and flooding. In March 2020, the World Health Organization characterized the outbreak of novel coronavirus disease 2019 (COVID-19) as a global pandemic. By the end of April 2020, Vanuatu had reported no confirmed cases of COVID-19. Data from several sources are collected in Vanuatu's COVID-19 surveillance system to provide an overview of the situation, including data from case investigations and management, syndromic surveillance for influenza-like illness, hospital surveillance and laboratory surveillance. Review of data collected from January to the end of April 2020 suggests that there was no sustained increase in influenza-like illness in the community and no confirmed cases were identified. Lessons learnt from the early implementation of surveillance activities, the changing landscape of laboratory testing and pharmaceutical interventions, as well as the global experience, particularly in other Pacific island countries, will inform the refinement of COVID-19 surveillance activities in Vanuatu.

Pacific island countries and territories (PICTs) are marked by expansive geography, relatively small populations and diverse cultures. They are also vulnerable to emerging infectious diseases, including epidemics and pandemics, and to natural disasters, including cyclones, earthquakes and tsunamis. For these reasons, the World Health Organization's *Asia Pacific Strategy for Emerging Diseases and Public Health Emergencies* (APSED III) guides Member States to adopt an all-hazards approach, encompassing both disease outbreaks and natural disasters, to strengthen their capacity to detect, prepare for and respond to outbreaks of infectious diseases and public health emergencies.[1]

On 30 January 2020, the WHO Director-General declared that the outbreak of novel coronavirus disease 2019 (COVID-19) constituted a public health emergency of international concern. As of 30 April 2020, six PICTs had confirmed cases of COVID-19.[2] In Vanuatu, a country of approximately 290 000 people and composed of 83 islands, the response to COVID-19 is guided by the VanGov Plan (COVID-19 Health Sector Preparedness and Response Plan) developed in January 2020 and revised as the situation evolves.[3] Priority actions are categorized according to three scenarios: 1 (no cases), 2 (one or more cases or clusters) and 3 (community transmission). A strategic objective of the plan is to ensure that the surveillance system is active and functional. Since January 2020, the Government of Vanuatu has implemented several measures to prevent the importation of COVID-19 and contain and mitigate community transmission, including suspending the use of international ports of entry into Vanuatu on 23 March 2020 and declaring a state of emergency on 26 March 2020.

[a] Department of Public Health, Vanuatu Ministry of Health, Port Vila, Vanuatu.
[b] Vanuatu Health Program, Port Vila, Vanuatu.
[c] Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia.
[d] Burnet Institute, Melbourne, Victoria, Australia.
[e] Vila Central Hospital, Port Vila, Vanuatu.
[f] Country Liaison Office, World Health Organization, Port Vila, Vanuatu.
[g] Private physician, Port Vila, Vanuatu.
[h] Members of the Vanuatu Ministry of Health's National Health Emergency Operations Centre are provided in the Acknowledgements.
* These authors contributed equally.
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We describe the implementation of the initial COVID-19 surveillance system established in Vanuatu between January and April 2020, focusing on its design, challenges and the modifications required.

### Ethics statement

The Vanuatu Health Research Ethics Committee advised that ethics approval was not required because data were being collected as part of the pandemic response and in line with the Vanuatu Public Health Act No. 22 of 1994.

## THE SURVEILLANCE SYSTEM, MODIFICATIONS AND INTERVENTIONS

The objective of the COVID-19 surveillance system in Vanuatu is to rapidly identify and contain any imported or community-acquired cases of COVID-19 (**Table 1**). The framework for surveillance systems suggested by Heymann[4] was used to describe the system, which collates data from several sources.

### Existing data collection systems

The Vanuatu Public Health Sentinel Surveillance Network is part of the regional Pacific Public Health Surveillance Network.[5] Eleven sites in Vanuatu report weekly on five core syndromes: (i) acute fever and rash, (ii) prolonged fever, (iii) influenza-like illness (ILI), (iv) watery diarrhoea, and (v) illnesses that are like dengue, Zika or Chikungunya.[5] These syndromes are monitored as part of the all-hazards approach to tracking infectious diseases related to both outbreaks and natural disasters. Data are compiled weekly and sent to the national surveillance unit via e-mail, phone or short message service (that is, SMS or text), and they are manually entered into a custom Excel database. ILI data are monitored because the symptoms of COVID-19 are clinically similar to influenza (**Table 2**). A pre-established threshold was set ($N$ = 426 per week) to generate an alert and prompt action if the number of reported cases is greater than expected for seasonal influenza. Standard reporting is by epidemiological week (epi week), with week 1 ending 5 January 2020.

### Enhancement of systems for COVID-19 surveillance

A sentinel surveillance system for private clinics in Port Vila was established in March 2020 among general practitioners. The objective was to rapidly identify imported cases and monitor community-level transmission of COVID-19 among expatriates, who predominantly use private clinics. Clinics were requested to submit daily reports via a web form of the number of consultations and the number of people presenting with ILI (**Table 2**).

Active hospital-based surveillance activities were established in April 2020 to monitor and rapidly identify any cases of severe acute respiratory infection (SARI) or pneumonia-related presentations to emergency departments, and hospitalizations and deaths. Data were collected daily from the main referral hospital in Port Vila and five provincial hospitals (**Table 2**). In addition, data on the number of tablets of paracetamol dispensed through the emergency department were collected weekly. A surveillance officer contacted all hospitals daily to verbally collect information on new admissions for SARI or pneumonia, and weekly for paracetamol dispensing.

### Case investigation and management

Protocols were developed to investigate all suspected cases: a public health officer interviews all suspected cases to determine whether the person meets the case definition and the possible source of transmission, to identify close contacts and to implement steps to minimize ongoing transmission.

The initial protocol implemented in January 2020 was for suspected cases to be immediately isolated at home to prevent onward transmission; it has since been temporarily revised to implement hospital-based isolation of suspected cases in a specific ward. Hospitalization of suspected cases became necessary due to the length of time required to receive laboratory results (average: 4.1 days) and the need to control the risk of potential transmission during this time.

Table 1. **Main objectives and interventions of the surveillance response to the COVID-19 pandemic, as per the VanGov Plan (COVID-19 Health Sector Preparedness and Response Plan), Vanuatu, January–April 2020**

| Objectives | Scenario and interventions | | |
|---|---|---|---|
| | 1 (no cases) | 2 (≥ 1 case, imported or locally detected [sporadic], OR clusters of cases) | 3 (community transmission) |
| Early detection and isolation of suspected COVID-19 cases by an active and functional surveillance system | Use WHO definition to test suspected cases.<br><br>Train workers at sentinel sites, health-care workers and private practitioners about case definition and notification and reporting channels. | Use WHO definition to test suspected cases.<br><br>Provide refresher training to workers at sentinel sites, health-care workers and private practitioners about case definition and notification and reporting channels.<br><br>Enhance syndromic surveillance system, focusing on influenza-like illness and COVID-19 in public health facilities, and enhance event-based surveillance system in private health facilities.<br><br>Test if patient has symptoms, and implement contact tracing and monitoring. | Enhance syndromic surveillance system, focusing on influenza-like illness and COVID-19 in public health facilities, and enhance event-based surveillance system in private health facilities.<br><br>Implement sampling strategy for testing, depending on number of suspected cases. |

COVID-19: coronavirus disease 2019; WHO: World Health Organization.

Table 2. **Summary of sentinel and hospital surveillance activities related to the COVID-19 pandemic, Vanuatu, January–April 2020**

| Network or site | Number of sites | Coverage area | Site type (number) | Start date | Type of data used for COVID-19 surveillance |
|---|---|---|---|---|---|
| Vanuatu Public Health Sentinel Surveillance Network | 11 | National | Hospital (n = 6)<br>Health centre (n = 5) | Predated COVID-19 | ILI |
| General practitioner sentinel sites | 7 | Port Vila only | Private clinic (n = 5) | 23 March 2020 | ILI |
| Hospital-based surveillance | 6 | National | Hospital (n = 6) | 20 March 2020 | ILI (captured through the Vanuatu Public Health Sentinel Surveillance Network), SARI, pneumonia, deaths, number of paracetamol tablets dispensed |

COVID-19: coronavirus disease 2019; ILI: influenza-like illness; SARI: severe acute respiratory infection.

### Laboratory testing

Vanuatu's strategy for COVID-19 laboratory testing during the period of interest was to collect and refer for testing specimens from individuals who met WHO's definition of a suspected case.[6] In limited circumstances and in consideration of the global shortage of molecular testing reagents for COVID-19,[7] precautionary testing was undertaken for selected additional individuals.

### Isolation and treatment of cases

Since February 2020, the Vanuatu health ministry has undertaken significant measures to strengthen the country's medical capacity to manage patients with severe COVID-19, including establishing a dedicated intensive care unit for patients needing critical care and a ward for patients with mild disease who cannot isolate at home.

### Contact management, identification, case finding and quarantine

Protocols using WHO's definition of a close contact[6] were established for contact tracing to rapidly identify contacts of confirmed cases to determine possible sources of infection and to prevent onward transmission. The protocol specified that asymptomatic close contacts of confirmed cases were to be quarantined in a designated facility or at home for 14 days from their last date of exposure, as per Section 12 of the Vanuatu Public Health Act No. 22 of 1994, which allows for the isolation and detainment of a person recently exposed to infection or who may be in the incubation stage of any notifiable disease.[8] If close contacts developed symptoms, as per the WHO case definition,[6] they were to be referred to hospital for isolation and testing.

### Management of international arrivals

Quarantine in a government-designated facility for a period of 14 days is required for all people arriving in Vanuatu from 20 March 2020 onwards. Protocols were developed to monitor people in quarantine: provincial public health teams conducted daily visits to screen for symptoms of respiratory illness and fever. All people working in the quarantine facilities, including transport providers, hotel front desk clerks, cleaners, kitchen workers and security officers received training from the Vanuatu Ministry of Health.

## IMPLEMENTATION OF THE NEW SYSTEM JANUARY–APRIL 2020

### Existing systems

The number of ILI cases reported through the Vanuatu Public Health Sentinel Surveillance Network fluctuated between epi week 1 (EW1) and EW18 (range: 156–489; **Table 3**). In EW18, there were 212 reports of ILI, a decrease of 25 from the previous week ($n$ = 237). The number of ILI reports did not reach the threshold during the period (**Table 3**).

### Enhancement for COVID-19 surveillance

Among reports submitted from seven private clinics in the general practitioners' sentinel surveillance system between EW14 and EW18, there were also fluctuations in the number of consultations for ILI (range: 6–45), and a sustained increase was not observed (**Table 3**).

Only pneumonia-related hospitalization data were available for the period; SARI data were not available. Pneumonia hospitalization data were received from five of six hospitals in Vanuatu beginning in EW14. The number of new admissions for pneumonia decreased from four to one between EW14 and EW18 (**Table 3**). The number of paracetamol tablets dispensed through the emergency department was greatest in EW17 ($n$ = 1340, **Table 3**).

### Enhancing case investigation and management

Between January and April 2020, two people met the WHO case definition of a suspected case. Both patients had symptoms of ILI and had recently travelled overseas. Both of these patients isolated at home until the results of their COVID-19 tests were known. These patients were reported as suspected cases on 19 March and 30 March 2020.

### Laboratory testing of specimens

Between January and April 2020, COVID-19 testing was not available in Vanuatu, and all specimens were sent to New Caledonia for molecular testing. As of 30 April 2020, 24 specimens from 19 people had been sent to New Caledonia; of these, specimens were from eight people identified in private clinics (42%), two people from government-run health clinics (11%) and the remainder

Table 3. **Data collected through various surveillance activities for COVID-19, by epidemiological week (epi week), Vanuatu, January–April 2020**

| Week | | | Indicator (system) | | | |
|---|---|---|---|---|---|---|
| Start date | End date | Epi week | Influenza-like illness (Vanuatu Public Health Sentinel Surveillance Network) | Influenza-like illness (private clinic syndromic surveillance) | Pneumonia (hospital surveillance) | Number of tablets of paracetamol dispensed through emergency department |
| 30/12/2019 | 5/01/2020 | 1 | 489 | NC | NC | NC |
| 6/01/2020 | 12/01/2020 | 2 | 250 | NC | NC | NC |
| 13/01/2020 | 19/01/2020 | 3 | 205 | NC | NC | NC |
| 20/01/2020 | 26/01/2020 | 4 | 341 | NC | NC | NC |
| 27/01/2020 | 2/02/2020 | 5 | 191 | NC | NC | NC |
| 3/02/2020 | 9/02/2020 | 6 | 238 | NC | NC | NC |
| 10/02/2020 | 16/02/2020 | 7 | 205 | NC | NC | NC |
| 17/02/2020 | 23/02/2020 | 8 | 171 | NC | NC | NC |
| 24/02/2020 | 1/03/2020 | 9 | 319 | NC | NC | NC |
| 2/03/2020 | 8/03/2020 | 10 | 198 | NC | NC | NC |
| 9/03/2020 | 15/03/2020 | 11 | 292 | NC | NC | NC |
| 16/03/2020 | 22/03/2020 | 12 | 273 | NC | NC | NC |
| 23/03/2020 | 29/03/2020 | 13 | 268 | 18 | NC | NC |
| 30/03/2020 | 5/04/2020 | 14 | 224 | 45 | 4 | 50 |
| 6/04/2020 | 12/04/2020 | 15 | 156 | 40 | 4 | 170 |
| 13/04/2020 | 19/04/2020 | 16 | 209 | 14 | 2 | 915 |
| 20/04/2020 | 26/04/2020 | 17 | 237 | 6 | 1 | 1340 |
| 27/04/2020 | 3/05/2020 | 18 | 212 | 13 | 1 | 790 |

NC: data not collected prior to March 2020 when additional surveillance activities were implemented.

($n$ = 9; 47%) were identified through the Vila Central Hospital emergency department or outpatient clinic. Due to border control measures, each dispatch of samples required government approval and significant logistical coordination. The average number of days from specimen collection to test result was 4.1, with a range of 1–12 days. The samples from the two patients who met the WHO definition of a suspected case had test results in 2 and 5 days and both were identified by private clinics. The remainder of cases did not meet the WHO case definition and so had precautionary tests. None of the samples tested during this period was positive.

### Isolation and treatment

As there were no confirmed cases during the study period, the isolation and treatment of cases was not required.

### Contact management and quarantine

As there were no confirmed cases during the study period, contact tracing was not initiated.

### Managing international arrivals

As of 30 April 2020, a total of 98 people arriving from overseas had completed quarantine. The majority ($n$ = 61; 62%) were passengers on the two last flights arriving into Vanuatu on 21 March 2020 before the border was closed.

## DISCUSSION

The aims of a national surveillance system depend on a country's pandemic response strategy as well as the local

epidemiological context and laboratory and health facility capacities. The objectives may be to identify severe cases, asymptomatic cases, clusters of cases or a combination of these. Because no cases have been detected in Vanuatu as of 30 April 2020, the aims of surveillance for COVID-19 are to rapidly detect and contain any imported cases. Achieving these aims relies on timely and accurate laboratory testing. The absence of in-country testing between January and April 2020 significantly limited Vanuatu's initial capacity to respond effectively to the COVID-19 threat.

For most PICTs, including Vanuatu, in-country laboratory testing was not available until May 2020. If a case had been detected before May, the capacity of the country to implement timely containment and mitigation measures would have been reduced due to the lag between specimen collection and receiving results. In March 2020, a rapid molecular test using the GeneXpert platform (Cepheid, Sunnyvale, CA, USA), which provides fully automated, easy-to-use point-of-care molecular testing,[9] was approved for COVID-19 testing by the US Food and Drug Administration. The Joint Incident Management Team (coordinated by the WHO Representative Office in the South Pacific) procured GeneXpert cartridges and machines from the manufacturer for distribution across PICTs.[10] As a result, in-country laboratory testing in Vanuatu became available in May 2020, and this has strengthened Vanuatu's capacity to respond to COVID-19. A testing strategy has been developed that considers both the epidemiological situation in Vanuatu and the anticipated limited availability of cartridges due to staggered distribution and the global shortage of consumables, including swabs.

The absence of confirmed cases in Vanuatu and elsewhere cannot be interpreted as an absence of circulating virus, especially in countries where there is limited testing capacity. Currently, there is no international guidance about how to verify the absence of circulating virus. Data collected by the various syndromic surveillance systems in Vanuatu will continue to be used to monitor and verify the absence of confirmed cases. Internationally, severe and critical cases comprise around 20% of diagnosed cases of COVID-19[11] and, therefore, we assume that any undetected circulating virus would result in an increase in ILI in primary health care facilities and pneumonia in hospitals.

In the context of having no confirmed cases and in the absence of widespread availability of pharmaceutical interventions, such as treatment or vaccination, reopening the border may result in the importation of COVID-19 to Vanuatu. The various surveillance components described here are critical to rapidly detecting and containing any imported cases. Mathematical modelling data are not available to enable Vanuatu to predict the impact of imported cases using current population data and COVID-19 parameters, but they would be useful to guide the evolving response.

Several PICTs were also affected by Tropical Cyclone Harold in April 2020.[12] Harold impacted Vanuatu on 6–7 April 2020 as a category 5 cyclone. More than 160 000 people, approximately 55% of the population, reside in areas that were affected by the cyclone.[13] Harold occurred during a period of rapid scale-up and strengthening of COVID-19 surveillance activities. The implementation and strengthening of ILI surveillance in provinces affected by the cyclone were complicated by the emergence of several post-disaster outbreak-prone diseases that also have symptoms of ILI, such as dengue and leptospirosis. Where possible, the Vanuatu health ministry sought to harmonize surveillance activities, as demonstrated through the collection of data about ILI and injuries through pre-existing and new surveillance activities. Strategies to conduct disease surveillance for two events simultaneously at such a large scale is unprecedented in Vanuatu and elsewhere, and guideline developers should consider providing information about how to respond to a similar situation in the future.

Several additional limitations should be considered when assessing the implementation of Vanuatu's COVID-19 surveillance; these include pre-existing shortages of clinical and public health workers, limited pre-existing epidemiological capacity within Vanuatu's health ministry, the country's geographical isolation and small population, and its limited laboratory capacity. Nonetheless, the Vanuatu health ministry and its partners have rapidly scaled up surveillance activities in a complex, challenging and rapidly changing epidemiological landscape.

The COVID-19 response is continuing in Vanuatu and will adapt as the epidemiological context changes. Lessons from the early implementation of surveillance

activities during Scenario 1 (no cases), the changing landscape of laboratory testing and pharmaceutical interventions, as well as the global experience, particularly in other PICTs, will inform the refinement of COVID-19 surveillance activities in Vanuatu.

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All authors declare they have no conflicts of interest.

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# Early reports of epidemiological parameters of the COVID-19 pandemic

Keeley Allen,[a] Amy Elizabeth Parry[a] and Kathryn Glass[a]

Correspondence to Keeley Allen (email: Keeley.Allen@anu.edu.au)

**Background:** The emergence of a new pathogen requires a rapid assessment of its transmissibility, to inform appropriate public health interventions.

**Methods:** The peer-reviewed literature published between 1 January and 30 April 2020 on COVID-19 in PubMed was searched. Estimates of the incubation period, serial interval and reproduction number for COVID-19 were obtained and compared.

**Results:** A total of 86 studies met the inclusion criteria. Of these, 33 estimated the mean incubation period (4–7 days) and 15 included estimates of the serial interval (mean 4–8 days; median length 4–5 days). Fifty-two studies estimated the reproduction number. Although reproduction number estimates ranged from 0.3 to 14.8, in 33 studies (63%), they fell between 2 and 3.

**Discussion:** Studies calculating the incubation period and effective reproduction number were published from the beginning of the pandemic until the end of the study period (30 April 2020); however, most of the studies calculating the serial interval were published in April 2020. The calculated incubation period was similar over the study period and in different settings, whereas estimates of the serial interval and effective reproduction number were setting-specific. Estimates of the serial interval were shorter at the end of the study period as increasing evidence of pre-symptomatic transmission was documented and as jurisdictions enacted outbreak control measures. Estimates of the effective reproduction number varied with the setting and the underlying model assumptions. Early analysis of epidemic parameters provides vital information to inform the outbreak response.

Coronavirus disease 2019 (COVID-19) presents an enormous challenge to public health. By 18 April 2020, 140 million cases had been reported across 222 countries and areas, with an estimate of 3 million people having died.[1] The overwhelming attention placed on COVID-19 and the volume of research published in the early months of this pandemic (over 4100 papers in PubMed to the end of April 2020) create challenges for public health responders attempting to understand the epidemiology of this disease. There is a need to distil and synthesize the findings that are most relevant to inform public health interventions.

Estimates of the transmission parameters of a pathogen are required as soon as practicable, to inform the public health response. With known pathogens, public health responders can use data and estimates from previous outbreaks to make evidence-based decisions. However, with an emerging pathogen, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), past outbreaks may provide limited utility; hence, epidemic parameters must be estimated from early cases and detected transmission events. A successful outbreak response is informed by rapid data collection and analysis, to understand the dynamics of disease spread and identify appropriate, informed interventions.

Understanding disease transmission of a new pathogen requires knowledge of the incubation period, serial interval and reproduction number. The basic reproduction number is the expected or average number of secondary cases that result from one infected person if no individuals in the population are immune to the pathogen and no measures are in place to reduce spread. In practice, pathogens rarely propagate freely through a population because individuals change their behaviour or governments enact public health interventions. The effective reproduction number is the expected or average number of secondary cases in a population where some individuals are immune or interventions to limit spread are in place.

[a] National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory, Australia.
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The distribution of the incubation period is crucial for determining the length of quarantine for potentially exposed individuals and travellers.[2–4] Estimates of the serial interval provide public health responders with an idea of the time available to identify and isolate potential cases before they can spread the disease to others.[5,6] The reproduction number of a disease provides a population-wide estimate of the scale of a potential outbreak and a baseline to test the effectiveness of different interventions in limiting disease transmission.[7–9] Although highly influential, early estimates of the incubation period, serial interval and reproduction number are generally based on small sample sizes that may not be representative of the wider population at risk.[7,9,10]

Although some literature reviews have reviewed the epidemiology of COVID-19,[11–14] they have not collated the estimates of epidemic parameters from the initial period of the COVID-19 pandemic. The aim of this study was to collate and compare the characteristics of the COVID-19 pandemic up to 30 April 2020.

## METHODS

Studies that describe or estimate the epidemic characteristics of the COVID-19 pandemic until 30 April 2020 were collected. Epidemiological parameters were limited to the incubation period, the serial interval and the reproduction number. The incubation period is the length of time experienced by an individual case from the point of infection to the start of symptom onset. The serial interval refers to the mean length of time between successive cases in a chain of transmission, measured as the length of time from symptom onset in a primary case to symptom onset in a secondary case. Both the incubation period and serial interval in this analysis are measured in days.

Over the course of the COVID-19 pandemic so far, governments have enacted public health interventions at different times and to different extents. Individual behaviours have changed at different rates as individuals have learned about COVID-19 and responded to media reports, government messaging and their understanding of risk. Several estimates of the reproduction number overlap periods when governments have enacted significant public health interventions. Although this study focuses on estimates from the early stages of the outbreak, when most of the population were susceptible and potentially not modifying their behaviour, this study refers to all estimates of the reproduction number as the effective reproduction number.

We searched peer-reviewed published research articles from PubMed using the terms “coronavirus” AND “novel” OR “new” OR “covid” OR “Wuhan” OR “ncp” OR “ncov” for articles published online until 30 April 2020. The literature search ran from 24 February 2020 to 12 May 2020. All articles were imported to Zotero 5.0.87 for review. Eligible articles were reviewed for date of online publication, study period, sample size, setting, method of calculating epidemic parameters, assumptions used to inform these calculations and output measures (including the approach to estimating uncertainty).

Studies were included in this review if they reported estimates of at least one of the relevant epidemic parameters and were written in English. Any articles published before 1 November 2019, pre-prints, grey literature and case reports were excluded.

### Ethics and permissions

Ethical approval was not sought for this review of existing, publicly available peer-reviewed literature.

## RESULTS

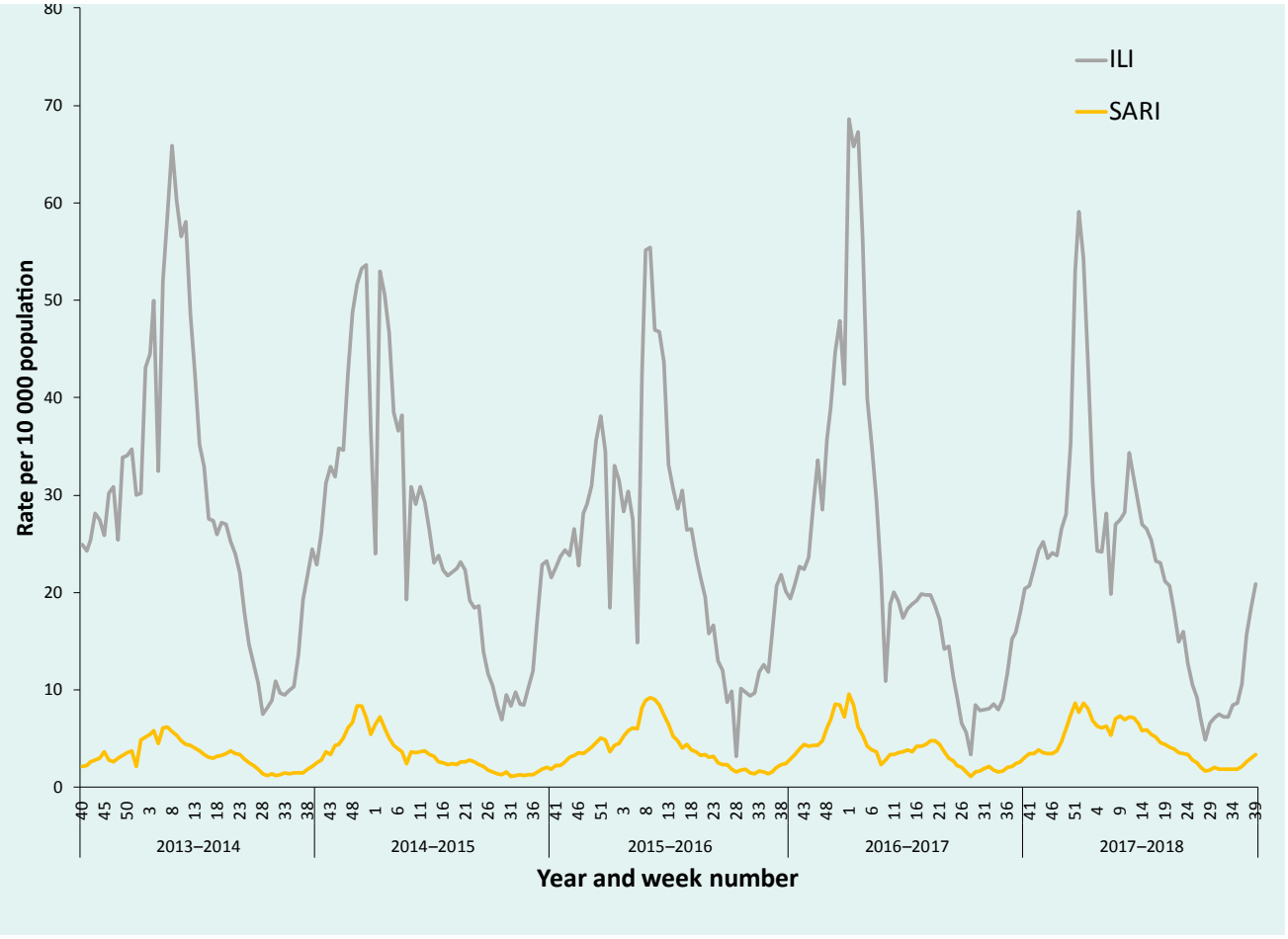
The PubMed search returned 4426 articles published online up to 30 April 2020. Of these articles, 3581 were excluded at the screening assessment and a further 759 at the eligibility assessment, giving a total of 86 included studies. The results of the search and eligibility assessment are shown in **Fig. 1**.

Of the 86 included studies, 15 calculated more than one epidemic parameter of interest. Sixty of the 86 studies used data from mainland China for part or all of their analysis, and 11 specifically analysed outbreak data from Hubei province or the city of Wuhan.

### Incubation period

A total of 33 studies estimated the incubation period of COVID-19 (**Table 1**). Mean estimates were reported in 15 studies, ranging from 1.8 to 9.9 days; however, 44% of the mean estimates were 5–6 days. The shortest mean estimate (incubation period = 1.8 days) was calculated

Fig. 1. **Preferred reporting items for systematic reviews and meta-analysis diagram of study selection**




from returned travellers from Hubei province in China, using their last day of travel as their date of exposure.[29] One study's mean estimate of 9.9 days was calculated from a series of 14 cases in Viet Nam.[33]

A further 22 estimates of the incubation period were summarized by their median. These studies were generally reporting on a specific cluster or outbreak investigation, and median estimates largely ranged from 4 to 7 days. Estimates outside of this range were calculated from case series; for example, a median range of 1–4 days was found among eight participants[39] and an estimated 8-day incubation period for a study involving 19 participants.[27] The distribution of the mean and median incubation estimates by sample size of the study is shown in **Fig. 2**.

A further three studies only included a range of observed incubation periods. The longest incubation period from these studies was 16 days, recorded in an outbreak investigation in mainland China.[36] Additional estimates of the 95th percentile of the incubation period ranged from 10.3 days (95% confidence interval [CI]: 8.6–14.1)[17] to 14 days (95% CI: 12.2–15.9).[47]

## Serial interval

Of the 15 studies that included a serial interval, eight were published in April 2020. Mean serial interval estimates were calculated in 14 studies and ranged from 3.1 to 7.5 days (**Table 2**).

The estimated serial intervals were longer in studies published at the start than at the end of the study period, with a mean interval of 7.5 days in late January 2020 and a mean of 4–5 days in early March 2020. Estimates published from March 2020 onwards included transmission pairs with negative serial intervals, or intervals shorter than the incubation period, suggesting possible pre-symptomatic transmission. Mean estimates

Table 1. **Estimated incubation period of COVID-19 from included epidemiological parameters studies published between 1 January and 30 April 2020**

| Study authors | Online publication date | Study period | Sample size | Setting | Estimate (days)* | Uncertainty estimate (days) | Uncertainty measure |
|---|---|---|---|---|---|---|---|
| Chan et al.[15] | 24 January 2020 | 26 December 2019 –15 January 2020 | 5 | Mainland China | - | 3–6 | Range |
| Li et al.[16] | 29 January 2020 | Up to 22 January 2020 | 10 | Wuhan/Hubei | 5.2 | 4.1–7.0 | 95% CI |
| Backer, Klinkenberg and Wallinga[17] | 6 February 2020 | 20 January 2020 –28 January 2020 | 88 | International | 6.4 | 5.6–7.7 | 95% CrI |
| Ki and Task Force for 2019-nCoV[18] | 9 February 2020 | 20 January 2020 –8 February 2020 | 28 | Republic of Korea | 3.9; [3.0] | 0–15 | Range |
| Jiang, Rayner and Luo[19] | 13 February 2020 | Up to 8 February 2020 | 50 | Mainland China | 4.9 | 4.4–5.5 | 95% CI |
| Linton et al.[20] | 17 February 2020 | 17 December 2019 –31 January 2020 | 158 | International | 5.6; [4.6] | 4.4–7.4; 3.7–5.7 | 95% CrI |
| Xu et al.[21] | 19 February 2020 | 10 January 2020 –26 January 2020 | 56 | Mainland China | [4] | 3–5 | IQR |
| Tian et al.[22] | 27 February 2020 | 20 January 2020 –10 February 2020 | 203 | Mainland China | [6.7] | ± 5.2 | SD |
| Cai et al.[23] | 28 February 2020 | 19 January 2020 –3 February 2020 | 10 | Mainland China | 6.5 | 2–10 | Range |
| Guan et al.[24] | 28 February 2020 | Up to 23 January 2020 | 291 | Mainland China | [4] | 2–7 | IQR |
| Liu et al.[25] | 3 March 2020 | 1 January 2020 –5 February 2020 | 58 | Mainland China | 6.0; [5.0] | 3–8; 1–16 | IQR; Range |
| Lauer et al.[26] | 10 March 2020 | 4 January 2020 –24 February 2020 | 181 | International | [5.1] | 4.5–5.8 | 95% CI |
| Zhao et al.[27] | 12 March 2020 | 23 January 2020 –5 February 2020 | 19 | Mainland China | [8] | 6–11 | IQR |
| Pung et al.[28] | 16 March 2020 | 18 January 2020 –10 February 2020 | 17 | Singapore | [4] | 3–6; 1–11 | IQR; Range |
| Leung[29] | 18 March 2020 | 20 January 2020 –12 February 2020 | 105 | Mainland China (travelled to Hubei) | 1.8 | 1.0–2.7 | 95% CI |
| | | | 70 | Mainland China (local transmission) | 7.2 | 6.1–8.4 | 95% CI |
| Chang et al.[30] | 23 March 2020 | 28 January 2020 –9 February 2020 | 15 | Mainland China | [5] | 1–6 | Range |
| Jin et al.[31] | 24 March 2020 | 17 January 2020 –8 February 2020 | 21 | Mainland China – GI symptoms | [4] | 3–7 | IQR |
| | | | 195 | Mainland China – No GI symptoms | [5] | 3–8 | IQR |
| Zhang et al.[32] | 2 April 2020 | 19 January 2020 –17 February 2020 | 49 | Mainland China | 5.2 | 1.8–12.4 | 95% CI |
| Le et al.[33] | 2 April 2020 | 17 January 2020 –14 February 2020 | 12 | Viet Nam | 9.9 | ± 5.2 | SD |
| Zhu and Chen[34] | 2 April 2020 | 1 December 2019 –23 January 2020 | Not specified | Mainland China, Hong Kong (SAR) China, Macau (SAR) China, Taiwan (China) | 5.67 | 1–14 | Range |

| Study authors | Online publication date | Study period | Sample size | Setting | Estimate (days)* | Uncertainty estimate (days) | Uncertainty measure |
|---|---|---|---|---|---|---|---|
| Han et al.[35] | 6 April 2020 | 31 January 2020 –16 February 2020 | 25 | Mainland China – adults | [5] | 3–12 | Range |
| | | | 7 | Mainland China – children | [4] | 2–12 | Range |
| Shen et al.[36] | 7 April 2020 | 8 January 2020 –26 February 2020 | 6 | Mainland China | [7.5] | 1–16 | Range |
| Sanche et al.[37] | 7 April 2020 | 15 January 2020 –30 January 2020 | 24 | Mainland China | 4.2 | 3.5–5.1 | 95% CI |
| Ghinai et al.[38] | 8 April 2020 | February–March 2020 | 15 | United States of America | 4.3; [4] | 1–7 | Range |
| Huang et al.[39] | 10 April 2020 | 23 January 2020 –20 February 2020 | 8 | Mainland China | [2] | 1–4 | Range |
| Zheng et al.[40] | 10 April 2020 | 17 January 2020 –7 February 2020 | 161 | Mainland China | [6] | 3–8 | Range |
| Xia et al.[41] | 12 April 2020 | 23 January 2020 –18 February 2020 | 10 | China incl. Hong Kong (SAR) China, Macau (SAR) China, Taiwan (China) | 7.0 | ± 2.59; 2–14 | SD; Range |
| Chen et al.[42] | 14 April 2020 | 28 January 2020 –11 February 2020 | 12 | Mainland China | 8.0 | 1–13 | Range |
| Song et al.[43] | 23 April 2020 | 16 January 2020 –29 January 2020 | 22 | Mainland China | - | 2–13 | Range |
| Jiang et al.[44] | 23 April 2020 | 23 January 2020 –13 February 2020 | 4 | Mainland China | - | 9–13 | Range |
| Nie et al.[45] | 27 April 2020 | 19 January 2020 –8 February 2020 | 2907 | Mainland China | [5] | 2–8 | IQR |
| Yu et al.[46] | 29 April 2020 | Up to 19 February 2020 | 132 | Mainland China | [7.2] | 6.4–7.9 | 95% CI |
| Bi et al.[47] | 30 April 2020 | 14 January 2020 –12 February 2020 | 138 | Mainland China | [4.8] | 4.2–5.4 | 95% CI |

*Mean estimates. Median estimates are shown in [square brackets]. Multiple estimates of incubation period for the same population within the same study are shown in the same row and separated by a semicolon. Estimates of the incubation period in the same study for different populations are shown in separate rows.

CI: confidence interval; CrI: credible interval; GI: gastrointestinal; IQR: interquartile range; SD: standard deviation.

Notes: Sample size reported in Table 1 is the sample size used to calculate the incubation period, not necessarily the whole study sample. All estimates are reported to one decimal place, except where stating findings from papers that did not provide that level of precision.

of the serial interval that included negative transmission pairs generally ranged from 3.9 to 5.8 days (**Table 2**).

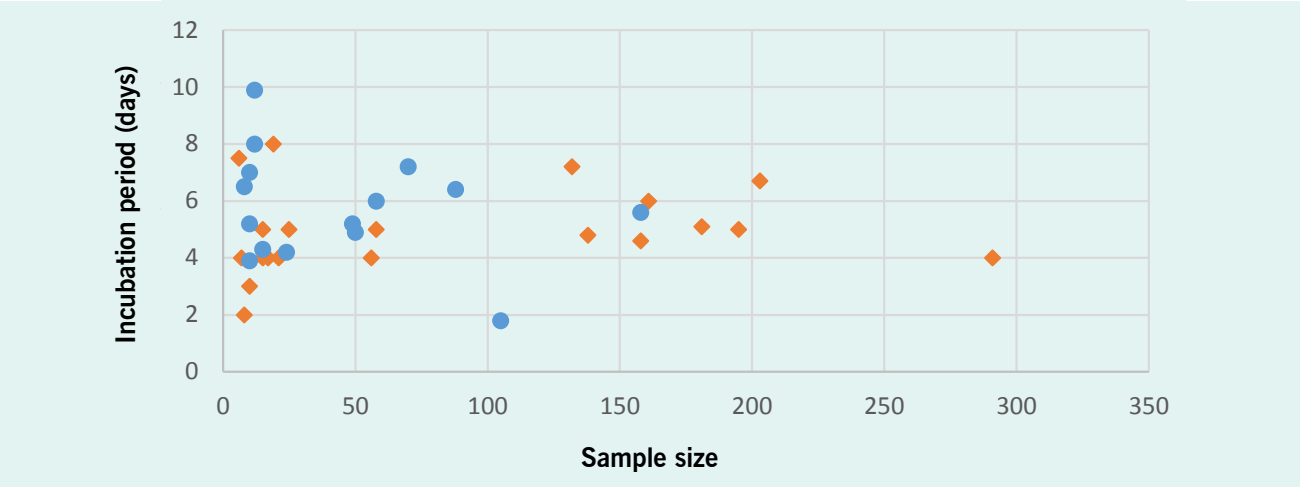
The four median serial interval estimates ranged from 1.0 to 5.4 days. Excluding the estimate of 2 days from a case series of eight cases,[39] the median serial interval ranged from 4.0 to 5.4 days (**Table 2**).

## Reproduction number

There were 90 estimates of the reproduction number from 52 studies across three World Health Organization (WHO) regions: Western Pacific Region, European Region and Region of the Americas. Reproduction number estimates ranged from 0.3 to 14.8. Of the 90 reported estimates, 33 estimates (37%) were between 2 and 3, and 20 estimates (22%) were between 3 and 4 (**Table 3**).

The initial low estimate of 0.3 relied on the early assumption that the pathogen was primarily spread through zoonotic transmission.[56] Other estimates of the reproduction number under 1 were reported in jurisdictions with rapid public health interventions during the study period, including the Republic of Korea and Singapore.[18,55,74] The highest reproduction number estimate (14.8) was from analyses of transmission dynamics onboard the Diamond Princess cruise ship.[67]

Fig. 2. **Incubation period estimates and sample size of study (*n* = 28 studies, 35 estimates) published between 1 January and 30 April 2020**




Note: The confidence intervals (CIs) of estimates are not shown in the figure. CIs are reported in Table 1. The estimate from Nie et al.[45] of a median of 5 days is not shown because the sample size (*n* = 2907) is significantly larger than other studies.

The distribution of reproduction number estimates by the assumed serial interval is shown in **Fig. 3**. Just over half (*n* = 50) of the 90 reproduction number results used an estimate of the serial interval to calculate the reproduction number. Serial interval estimates used to estimate the reproduction number ranged from 4[49] to 10 days, with the latter taken from the estimated serial interval for severe acute respiratory syndrome (SARS) in early outbreaks.[100] Studies generally applied serial intervals from the earliest COVID-19 estimate of 7.5 days[16] and the accepted serial interval of SARS of 8.4 days.[100]

## DISCUSSION

This study provides a review of estimated epidemic parameters of the COVID-19 outbreak up to 30 April 2020. Estimates of the incubation period were similar across the study period, with a mean estimated value of 5–6 days and a range of 2–14 days. Estimates of the serial interval shortened over the study period, from 7.5 days in late January 2020 to a mean of 4–5 days in early March 2020.

Estimates of the reproduction number varied in the studies collated up to 30 April 2020. Although some estimates of the reproduction number were as high as 14.8, over half were between 2 and 4. The higher estimates demonstrate the impact of the setting, individual behaviours and public health interventions – the highest estimates were associated with cruise ships,[64,67,68] whereas the lowest estimates were generally calculated in areas with a rapid response to an outbreak.[18,55,74,78]

The incubation period reflects the growth of a virus in an individual, and thus is largely a biological function that would not be expected to vary with changes in human behaviour and wider public health interventions. Variations in the incubation period reported in this study may, in part, result from the study designs adopted. Several estimates of the incubation period were reported directly from cluster investigations, often with low sample sizes. Studies with more than 20 participants had less variation between estimates than studies with smaller sample sizes. The definition of exposure, including the potential for continuous exposure in a household, may also have influenced results by artificially lengthening or shortening the incubation period, depending on study design and differences in local epidemiological reporting protocols.

The serial interval and reproduction number are likely to be influenced by public health interventions, social behaviours and political decisions. Estimates of these two epidemic characteristics are therefore setting-specific, which may explain the variance across the results in this study. The serial interval estimates also changed as new information about the pathogen came to light, primarily the potential for pre-symptomatic and pauci-symptomatic transmission.[101–106] However,

Table 2. **Estimated serial interval from included COVID-19 epidemiological parameters studies published between 1 January and 30 April 2020**

| Study authors | Online publication date | Study period | Sample size | Transmission pairs | Setting | Estimate (days)* | Uncertainty estimate (days) | Uncertainty measure |
|---|---|---|---|---|---|---|---|---|
| Li et al.[16] | 29 January 2020 | Up to 22 January 2020 | 10 | 6 | Wuhan/Hubei | 7.5 | 5.3–19.0 | 95% CI |
| Ki and Task Force for 2019-nCoV[18] | 9 February 2020 | 20 January 2020 –8 February 2020 | 28 | 12 | Republic of Korea | 6.6; [4.0] | 3–15 | Range |
| Liu et al.[25] | 3 March 2020 | 1 January 2020 –5 February 2020 | 15 single intracluster transmission cases | 12 clusters | Mainland China | 5.5 | - | - |
| | | | 56 single co-exposure cases | 56 clusters | Mainland China | 3.1 | - | - |
| Nishiura et al.[48] | 4 March 2020 | Up to 12 February 2020 | Not specified | 28 – all pairs | International | [4.0] | 3.1–4.9 | 95% CrI |
| | | | | 18 – most certain pairs | International | [4.6] | 3.5–5.9 | 95% CrI |
| Pung et al.[28] | 16 March 2020 | Up to 15 February 2020 | 4 | 3 | Singapore | | 3–8 | Range |
| Du et al.[49] | 19 March 2020 | 21 January 2020 –8 February 2020 | 752 | 468 | Mainland China | 4.0 | 3.5–4.4 | 95% CI |
| Wu et al.[50] | 19 March 2020 | 1 December 2019 –28 February 2020 | Not specified | 43 | International | 7 | 5.8–8.1 | 95% CI |
| Zhang et al.[32] | 2 April 2020 | 19 January 2020 –17 February 2020 | 63 | 35 | Mainland China | 5.1 | 3.1–11.6 | 95% CI |
| Ji et al.[51] | 7 April 2020 | 23 January 2020 –27 March 2020 | 51 | 32 | Wuhan/Hubei | 6.5 | 6.3 | SD |
| Huang et al.[39] | 10 April 2020 | 23 January 2020 –20 February 2020 | 9 | 8 | Mainland China | [1] | 0–4 | Range |
| Wang et al.[52] | 10 April 2020 | 11 January 2020 –16 February 2020 | 115 | 85 | Wuhan/Hubei | 5.5 | ± 2.7 | SD |
| He et al.[53] | 15 April 2020 | 7 January 2020 –4 March 2020 | Not specified | 77 | International | 5.8; [5.2] | 4.8–6.8; 4.1–6.4 | 95% CI |
| Kwok et al.[54] | 23 April 2020 | 23 January 2020 –13 February 2020 | 38 | 26 | Hong Kong (SAR) China | 4.6 | 3.4–5.9 | 95% bCI |
| | | | | 26 – adjusted for right truncation | Hong Kong (SAR) China | 4.8 | 3.5–6.9 | 95% CrI |
| Bi et al.[47] | 27 April 2020 | 14 January 2020 –12 February 2020 | Not specified | 48 | Mainland China | 6.3; [5.4] | 5.2–7.6; 4.4–6.5 | 95% CI |
| Ganyani et al.[55] | 30 April 2020 | 14 January 2020 –27 February 2020 | 54 | 4 clusters | Singapore | 5.2 | –3.4–13.9 | 95% CrI |
| | | | 114 | 16 clusters | Mainland China | 3.9 | –4.5–12.5 | 95% CrI |

*Mean estimates. Median estimates are shown in [square brackets]. Multiple estimates of serial interval for the same population within the same study are shown in the same row and separated by a semicolon. Estimates of the serial interval in the same study for different populations are shown in separate rows.

bCI: Bayesian confidence interval; CI: confidence interval; CrI: credible interval; SD: standard deviation.

Notes: Sample size reported is the sample size used to calculate the serial interval, not necessarily the whole study sample. All estimates are reported to one decimal place, except where stating findings from papers that did not provide that level of precision.

Table 3. **Estimated reproduction number from included COVID-19 epidemiological parameters studies published between 1 January and 30 April 2020**

| Study authors | Online publication date | Study period | Sample size | Method | Setting | Estimate | Uncertainty interval | Uncertainty measure |
|---|---|---|---|---|---|---|---|---|
| Wu et al.[56] | 23 January 2020 | 10 January 2020 –12 January 2020 | 41 | Zoonotic transmission – Cauchemez et al. 2013[111] | Wuhan/ Hubei | 0.3 | 0.17–0.44 | 95% CI |
| Li et al.[16] | 29 January 2020 | Up to 22 January 2020 | 425 | Transmission model with renewal equations | Wuhan/ Hubei | 2.2 | 1.4–3.9 | 95% CI |
| Riou and Althaus[57] | 30 January 2020 | Up to 18 January 2020 | 50 | Stochastic transmission model | Wuhan/ Hubei | 2.2 | 1.4–3.8 | 90% HDI |
| Zhao et al.[58] | 30 January 2020 | 10 January 2020 –24 January 2020 | 2033 | Exponential growth model method | Mainland China | 2.24 –3.58 | 1.96–2.55 to 2.89–4.39 | 95% CI |
| Wu et al.[59] | 31 January 2020 | 1 December 2019 –28 January 2020 | 55 | Differential equation – SEIR compartment model | International | 2.68 | 2.47–2.86 | 95% CrI |
| Zhao et al.[60] | 1 February 2020 | 1 December 2019 –24 January 2020 | 41 | Exponential growth model method | Mainland China | 2.56 | 2.49–2.63 | 95% CI |
| Tang et al.[61] | 7 February 2020 | 10 January 2020 –15 January 2020 | 41 | Differential equation – SEIR compartment model | Mainland China | 6.47 | 5.71–7.23 | 95% CI |
| Ki and Task Force for 2019-nCoV[18] | 9 February 2020 | 20 January 2020 – 8 February 2020 | 26 | Estimated from transmission chains | Republic of Korea | 0.48 | 0.25–0.84 | 95% CI |
| Zhou et al.[62] | 12 February 2020 | Up to 25 January 2020 | 2820 | Differential equation – SEIR compartment model | Mainland China | 2.83–3.28 | - | - |
| Jung et al.[63] | 14 February 2020 | 31 December 2019 –24 January 2020 | 92 | Exponential growth model method | Mainland China | 2.1; 3.2 | 2.0–2.2; 2.7–3.7 | 95% CI |
| Zhang et al.[64] | 22 February 2020 | Up to 16 February 2020 | 355 | Cori et al. methodology[112] | Cruise ship | 2.28 | 2.06–2.52 | 95% CI |
| Lai et al.[65] | 25 February 2020 | Up to 4 February 2020 | 52 | Coalescent-based exponential growth and a birth-death skyline method | Mainland China | 2.6 | 2.1–5.1 | 95% CI |
| Chen et al.[66] | 28 February 2020 | 7 December 2019 –1 January 2020 | Not specified | Bats-Hosts-Reservoir-People transmission network model | Wuhan/ Hubei | 3.58 | - | - |
| Rocklov, Sjodin and Wilder-Smith[67] | 28 February 2020 | 21 January 2020 –19 February 2020 | 3700 | Differential equation – SEIR compartment model | Cruise ship | 14.8 | - | - |
| Mizumoto and Chowell[68] | 29 February 2020 | 20 January 2020 –17 February 2020 | 3711 | Discrete time integral equation | Cruise ship | 5.8 | 0.6–11.0 | 95% CrI |
| Fang, Nie and Penny[69] | 6 March 2020 | 20 January 2020 –29 February 2020 | 35 329 | Differential equation – SEIR compartment model | Mainland China | 2.35–3.21 | - | - |

| Study authors | Online publication date | Study period | Sample size | Method | Setting | Estimate | Uncertainty interval | Uncertainty measure |
|---|---|---|---|---|---|---|---|---|
| Zhou et al.[70] | 10 March 2020 | 10 January 2020 –31 January 2020 | 44 | Differential equation – SEIR compartment model | Mainland China | 5.3167 | - | - |
| Kucharski et al.[71] | 11 March 2020 | 1 December 2019 –11 February 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 2.35 | 1.15–4.77 | 95% CI |
| Yang and Wang[72] | 11 March 2020 | 23 January 2020 –10 February 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 4.25 | - | - |
| Zhao and Chen[73] | 11 March 2020 | 20 January 2020 –30 January 2020 | Not specified | Differential equation – SEIR compartment model | Mainland China | 4.7092 | - | - |
| Choi and Ki[74] | 12 March 2020 | 29 December 2019 –3 January 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 4.028 | 4.010–4.046 | 95% CI |
| | | 20 January 2020 –17 February 2020 | 30 | | Republic of Korea | 0.555 | 0.509–0.602 | 95% CI |
| Kuniya[75] | 13 March 2020 | 15 January 2020 –29 February 2020 | 239 | Differential equation – SEIR compartment model | Japan | 2.6 | 2.4–2.8 | 95% CI |
| Remuzzi and Remuzzi[76] | 13 March 2020 | 19 February 2020 –8 March 2020 | Unclear | Exponential growth model method | Italy | 2.76–3.25 | - | - |
| Li et al.[77] | 16 March 2020 | 10 January 2020 –23 January 2020 | 801 | Differential equation – SEIR compartment model | Mainland China | 2.38 | 2.03–2.77 | 95% CrI |
| Shim et al.[78] | 17 March 2020 | 20 January 2020 –26 February 2020 | 6284 | Generalized growth model | Republic of Korea | 1.5 | 1.4–1.6 | 95% CI |
| Du et al.[49] | 19 March 2020 | 21 January 2020 –8 February 2020 | 752 | Not stated | Mainland China | 1.32 | 1.16–1.48 | 95% CI |
| Wu et al.[50] | 19 March 2020 | 1 December 2019 –28 February 2020 | 45 771 | Differential equation – SEIR compartment model | Wuhan/ Hubei | 1.94 | 1.83–2.06 | 95% CrI |
| Yuan et al.[79] | 28 March 2020 | 23 February 2020 –9 March 2020 | Not specified | Exponential growth model method; Wallinga time dependent method | Italy | 3.27; 3.10 | 3.17–3.38; 2.21–4.11 | 95% CI |
| | | | | | France | 6.32; 6.56 | 5.72–6.99; 2.04–12.26 | 95% CI |
| | | | | | Spain | 5.08; 3.95 | 4.51–5.74; 0–10.19 | 95% CI |
| | | | | | Germany | 6.07; 4.43 | 5.51–6.69; 1.83–7.92 | 95% CI |
| Anastassopoulou et al.[80] | 31 March 2020 | 11 January 2020 –10 February 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 4.6 | 3.56–5.65 | 90% CI |
| Ferretti et al.[81] | 31 March 2020 | Up to end March 2020 | 40 transmission pairs | Exponential growth model method | Mainland China | 2 | 1.7–2.5 | 90% CI |
| Huang et al.[82] | 31 March 2020 | 13 January 2020 –9 March 2020 | 80 754 | Differential equation – SEIR compartment model | Mainland China | 2.23–2.51 | - | - |

| Study authors | Online publication date | Study period | Sample size | Method | Setting | Estimate | Uncertainty interval | Uncertainty measure |
|---|---|---|---|---|---|---|---|---|
| Tian et al.[83] | 31 March 2020 | 31 December 2019 –23 January 2020 | Not specified | Differential equation – SEIR compartment model | Mainland China | 3.15 | 3.04–3.26 | 95% BCI |
| Zhu and Chen[34] | 2 April 2020 | 1 December 2019 –23 January 2020 | Not specified | Poisson Transmission Model | Mainland China | 2.47 | 2.39–2.55 | 95% CI |
| Sanche et al.[37] | 7 April 2020 | 15 January 2020 –30 January 2020 | 140 | Differential equation – SEIR compartment model | Mainland China | 5.7 | 3.8–8.9 | 95% CI |
| Zhao et al.[84] | 8 April 2020 | 1 December 2019 –8 January 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 2.5 | 2.4–2.7 | 95% CI |
| Pan, Liu and Wang[85] | 10 April 2020 | 5 December 2019 –8 March 2020 | 32 583 | Cori et al. methodology[112] | Wuhan/ Hubei | 3.82 | 3.72–3.93 | 95% CrI |
| Abbott et al.[86] | 14 April 2020 | Up to 25 January 2020 | 1975 | Stochastic branching process model | Mainland China | 2.8–3.8 | - | - |
| Puci et al. | 14 April 2020 | 22 March 2020 –29 March 2020 | 975 | Differential equation – SEIR compartment model | Italy | 1.82 | 1.51–2.01 | 95% CI |
| Du et al.[87] | 16 April 2020 | 1 December 2019 –22 January 2020 | 19 | Exponential growth method | Mainland China | 1.9 | 1.47–2.59 | 95% CrI |
| Torres-Roman et al.[88] | 17 April 2020 | 6 March 2020 –15 March 2020 | Not specified | Cori et al. methodology[112] | Peru | 2.97 | - | - |
| Tsang et al.[89] | 20 April 2020 | 15 January 2020 –3 March 2020 | Not specified | Exponential growth model | Mainland China | 2.8–3.5 | - | - |
| Muniz-Rodriguez et al.[90] | 22 April 2020 | 19 February 2020 –19 March 2020 | 978 | Exponential growth model; renewal equations method | Islamic Republic of Iran | 4.4; 3.5 | 3.9–4.9; 1.3–8.1 | 95% CI |
| Zhuang et al.[91] | 22 April 2020 | Up to 5 March 2020 | Not specified | Stochastic model, maximum likelihood estimation approach | Italy | 2.6; 3.3 | 2.3–2.9; 3.0–3.6 | 95% CI |
| | | | | | Republic of Korea | 2.6; 3.2 | 2.3–2.9; 2.9–3.5 | 95% CI |
| Gatto et al.[92] | 23 April 2020 | 24 February 2020 –23 March 2020 | 107 | Differential equation – SEIR compartment model | Italy | 3.6 | 3.49–3.84 | 95% CI |
| Han et al.[93] | 23 April 2020 | 21 January 2020 –15 February 2020 | 482 | Exponential growth model method | Mainland China | 2.9 | 1.8–4.5 | 95% CI |
| Caicedo-Ochoa et al.[94] | 25 April 2020 | Up to 23 March 2020 (first 10 days after reaching 25 cases in each location) | Not specified | Cori et al. methodology[112] Two serial intervals used: 7.5 days; 4.7 days | Spain | 6.48; 2.9 | 5.97–7.02; 2.67–3.14 | 95% CrI |
| | | | | | Italy | 6.41; 2.83 | 6.11–6.71; 2.70–2.96 | 95% CrI |
| | | | | | Ecuador | 12.86; 3.95 | 12.05–13.68; 3.70–4.21 | 95% CrI |
| | | | | | Panama | 7.19; 3.67 | 6.37–8.08; 3.25–4.13 | 95% CrI |
| | | | | | Brazil | 6.53; 2.91 | 5.85–7.25; 2.60–3.23 | 95% CrI |
| | | | | | Chile | 5.79; 2.67 | 5.32–6.28; 2.45–2.89 | 95% CrI |
| | | | | | Colombia | 5.65; 2.67 | 5.04–6.29; 2.38–2.98 | 95% CrI |
| | | | | | Peru | 5.24; 2.36 | 4.68–5.83; 2.11–2.63 | 95% CrI |
| | | | | | Mexico | 4.94; 2.42 | 4.37–5.56; 2.14–2.72 | 95% CrI |

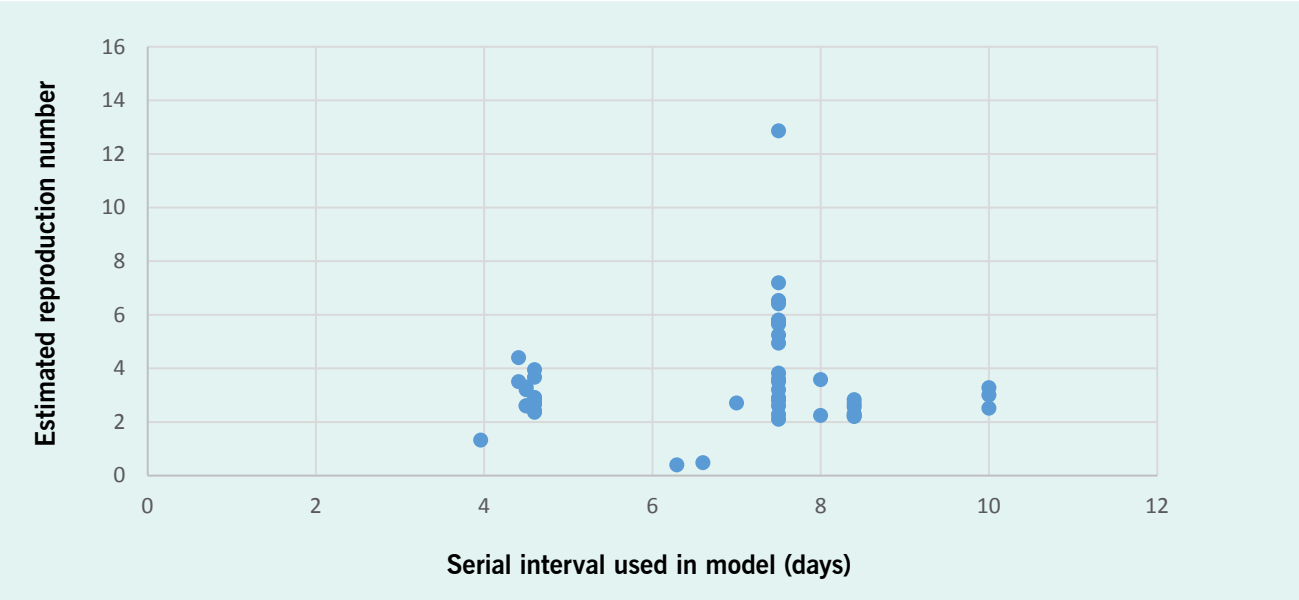
| Study authors | Online publication date | Study period | Sample size | Method | Setting | Estimate | Uncertainty interval | Uncertainty measure |
|---|---|---|---|---|---|---|---|---|
| Bi et al.[47] | 27 April 2020 | 14 January 2020 –12 February 2020 | 48 | Estimated from transmission chains | Mainland China | 0.4 | 0.3–0.5 | 95% CI |
| Distante et al.[95] | 27 April 2020 | Up to 29 March 2020 | Not specified | Exponential growth method | Italy | 3.6 | - | - |
| Ndairou et al.[96] | 27 April 2020 | 4 January 2020 –9 March 2020 | Not specified | Differential equation – SEIR compartment model | Wuhan/ Hubei | 0.945 | - | - |
| Peirlinck et al.[97] | 27 April 2020 | 21 January 2020 –4 April 2020 | 311 357 | Differential equation – SEIR compartment model | United States of America | 5.3 | ± 0.95 | SD |
| Adegboye et al.[98] | 28 April 2020 | 27 February 2020 –11 April 2020 | 318 | Cori et al. methodology[112] | Nigeria | 2.71 | - | - |
| Ganyani et al.[55] | 30 April 2020 | 14 January 2020 –27 February 2020 | 91 | Exponential growth model method | Singapore | 1.25 | 1.17–1.34 | 95% CrI |
| | | | 135 | Exponential growth model method | Mainland China | 1.41 | 1.26–1.58 | 95% CrI |
| Ivorra et al.[99] | 30 April 2020 | 1 December 2019 –29 March 2020 | Not specified | Differential equation – SEIR compartment model | Mainland China | 4.2732 | - | - |

Multiple estimates of the reproduction number for the same population within the same study are shown in the same row and separated by a semicolon. Estimates of the incubation period in the same study for different populations are shown in separate rows.

bCI: Bayesian confidence interval; CI: confidence interval; CrI: credible interval; HDI: high density interval; SD: standard deviation; SEIR: susceptible-exposed-infected-recovered.

Notes: Sample size reported is the sample size used to calculate the serial interval, not necessarily the whole study sample. All estimates are reported to the number of decimal places provided in each study.

Fig. 3. **Estimated reproduction number and serial interval of the model (*n* = 23 studies, 50 estimates) published between 1 January and 30 April 2020**




Note: The confidence intervals (CIs) of estimates are not shown in the figure. CIs are reported in Table 3.

these revised estimates of the serial interval were rarely used to revise reproduction number estimates. A longer serial interval results in a higher estimate of the reproduction number. The earliest published estimate by Li et al.'s study (first published online on 29 January 2020)[16] of six transmission pairs in Wuhan was higher than most of the later estimates. That estimate was applied as an assumed serial interval in 10 studies published in March and April 2020,[37,63–65,68,85,89,93–95] despite not being used in Li et al.'s own calculation of the reproduction number.[16] These early studies have been used to inform national and regional responses to the COVID-19 pandemic, and they demonstrate the importance of and reliance on early estimates to inform future research and public health decision-making.

Variations in the estimated reproduction number may also occur due to other assumptions applied in calculations. The initial estimate of the reproduction number of 0.3 assumed zoonotic transmission as the primary mode of transmission, based on the information available at the time.[56] The method applied may also influence the final estimate of the reproduction number. This is evident in the studies estimating the reproduction number of the Wuhan outbreak from December 2019 to mid-February 2020, which increased in later publications that used the same data sources and time periods. The reproduction number was estimated to be 2.2 in studies published in January and February 2020,[16,57] but increased to 4 in articles published in March and April 2020.[72,74,80]

The epidemiological parameters reviewed share some similarities to that of SARS and Middle East respiratory syndrome (MERS), two diseases caused by coronaviruses that have caused significant outbreaks in the early 21st century. The estimates of the range and mean of the incubation period of COVID-19 are similar to that of SARS (2–10 days, mean of 5–6 days)[2,100,107] and MERS (2–14 days, median of 5–6 days).[107,108] However, the estimated serial interval for COVID-19 is shorter than the observed intervals for SARS (8.4 days)[100] and MERS (7.6–12.6 days).[108,109] The later estimates of the COVID-19 serial interval published in April 2020 are shorter than the estimates for the incubation period, suggesting the potential for pre-symptomatic transmission, which has not been observed for SARS or MERS.[100,108,110] The estimated reproduction number of COVID-19 is similar to the estimates for the 2002–2003 SARS outbreak.[100]

This study has some important limitations. It provides a descriptive assessment and does not include meta-analysis or recalculations of results. The use of different methods and different outputs from each study limits the capacity for meta-analysis. This review may also be impaired by publication bias. Several included studies were based on small sample sizes, which led to imprecise results. The ongoing pandemic requires the active involvement of public health researchers to assess unfolding situations and advise on local responses. Fulfilling crucial roles as the pandemic unfolded may have limited the potential to publish findings, restricting our understanding of epidemic parameters in real time and reducing the representativeness of the results. This potential publication bias may also explain in part the overrepresentation of data from mainland China although COVID-19 has led to outbreaks worldwide. Nevertheless, the early published estimates included in this study have been used worldwide to inform public health responses, and they provide the best available evidence in the timeframe of this study.

Only studies written in English were included in this review. This excludes many early estimates written in Mandarin and Korean, which also limits the representativeness of this analysis. Furthermore, this analysis was limited to peer-reviewed published journal articles indexed in PubMed, which represents only a fraction of the literature published on the COVID-19 pandemic. The current pandemic has seen the proliferation of pre-print articles and increased attention on their results. Grey literature published by WHO, national governments and other organizations were also omitted. In times of emergency, pre-prints and grey literature may provide new information in a timely manner; however, this review focused only on estimations of epidemic parameters that have been subject to external peer review.

Pandemics are inherently uncertain times. The challenges of the ongoing COVID-19 pandemic are compounded by SARS-CoV-2 being a new pathogen, which public health and clinical professionals have had to rapidly assess, understand and respond to. Early estimates

can provide useful interim guidance for public health decision-making. This is particularly true for transmission that is driven by biological characteristics, such as the incubation period. Epidemic characteristics that are influenced by human behaviours and public health interventions are less certain and require interpretation within the context of data collection and analysis of the study. Reliance on data from small sample sizes and specific settings is necessary in the context of an outbreak, but it also limits the generalizability of findings to other contexts.

Uncertainty in epidemic characteristics should not mean that we do not act. Although earlier estimates may rely on less-than-ideal sample sizes and sample structures, they are necessary to facilitate decision-making in a timely manner. However, reliance on the first estimates published may limit or bias our understanding of new data. The increasing availability of pre-print articles provides an outlet for urgent distribution of findings during an outbreak of a novel pathogen, provided preliminary findings are interpreted with caution before peer review. This study underscores the ongoing challenge and ever-present need for outbreak investigations and research to be both timely and frequently updated, to provide the best evidence to guide interventions. Further research is required to refine estimates of the serial interval and reproduction number, to improve our understanding of this pandemic in different contexts, and to provide reference values to enable a timely response to potential future outbreaks of COVID-19 and any future emerging coronaviruses and other potential pandemic diseases.

## *Conflicts of interest*

None declared.

## *Funding*

None.

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# Descriptive epidemiology of the first wave of COVID-19 in Petaling District, Malaysia: Focus on asymptomatic transmission

Rama Krishna Supramanian,[a] Lavanyah Sivaratnam,[a] Arifah Abd Rahim,[a] Noor Dalila Inche Zainal Abidin,[a] Ong Richai,[a] Zazarida Zakiman,[a] Salina Md Taib,[a] Lee Soo,[a] Syed Hafeez Syed Ibrahim Jamalullai,[a] Muhammad Nur Asraf Khirusalleh[a] and Mohamed Paid Yusof[a]

Correspondence to Rama Krishna Supramanian (email: ramakrishna@moh.gov.my)

**Background:** COVID-19 was first detected in Malaysia on 25 January 2020. Multiple clusters were detected in Petaling District, with the first locally transmitted case reported on 8 February. Descriptive analyses of the epidemiology of the COVID-19 outbreak in Petaling are presented, from the first case to the end of the first wave.

**Methods:** All laboratory-confirmed COVID-19 cases reported to the Petaling District Health Office between 1 February and 26 June 2020 were analysed. Socio-demographic characteristics, symptoms, date of onset, date of exposure, travel history and history of comorbidities were obtained by phone interviews using one of two investigation forms. The descriptive analysis was conducted according to time, place and person.

**Results:** There were 437 COVID-19 cases, for an incidence rate of 24/100 000 population. Ten (2.3%) deaths and 427 recovered cases were recorded. Of the 437 cases, 35.5% remained asymptomatic and 64.5% were symptomatic. Common symptoms included fever (43.8%), cough (31.6%) and sore throat (16.2%); 67.3% had no comorbidities, 62.5% reported close contact with a confirmed case, and 76.7% were local infections. Transmission occurred in four main groups: religious gatherings (20.4%), corporations (15.1%), health facilities (10.3%) and a wholesale wet market (6.4%). In 31.9% of confirmed cases, an epidemiological link to an asymptomatic case was found.

**Conclusion:** Transmission of the disease by asymptomatic cases should be emphasized to ensure continuous wearing of face masks, hand hygiene and social distancing. Further research should be conducted to better understand the transmission of SARS-CoV-2 from asymptomatic cases.

Pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China was first reported to the World Health Organization (WHO) on 31 December 2019.[1] As of 16 August 2020, the virus, which causes coronavirus disease 2019 (COVID-19), had spread globally and infected more than 21 million people, with more than 700 000 deaths.[2] The outbreak of COVID-19 was declared a public health emergency of international concern by the WHO on 30 January 2020, following international spread of the disease. Malaysia's preparedness and response plan was instituted as early as February 2020. It included public health activities, intensified diagnostic capacity and early, appropriate treatment of confirmed COVID-19 cases.[3] The first cases of COVID-19 in Malaysia were detected on 25 January 2020 in three travellers from China,[4] and the first case in a Malaysian citizen was confirmed as the ninth case in early February 2020.[4] Localized clusters started to emerge in February, the largest cluster being linked to a religious gathering in Sri Petaling, which resulted in a major increase in the number of local cases and contributed to imported cases in neighbouring countries.[5] By 16 March, every state and federal territory in Malaysia had reported cases of COVID-19. Malaysia implemented a movement control order (MCO) on 18 March 2020 to contain the spread of the virus.[4] The government initiative included closing international borders, shutting down certain economic sectors and restricting social movement within and between states to protect the population.[6]

Many of the initial confirmed cases were connected to a wet market in Wuhan, and the SARS-CoV-2

[a] Petaling District Health Office, Selangor, Malaysia.
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pathogen was indicated to be zoonotic in origin. Reports have confirmed person-to-person transmission via respiratory droplets, as the virus was shown to spread in Wuhan by close contact with positive cases, without exposure to live animals.[7] The average incubation period for COVID-19 is 5 days but may be up to 14 days. The common reported symptoms include fever, cough, shortness of breath, fatigue and other flu-like symptoms.[8,9] Asymptomatic cases have also been documented.[10]

The first COVID-19 case in Petaling was documented on 3 February 2020 and was later confirmed to be the first case in a Malaysian citizen.[4] Following notification of a confirmed COVID-19 case, the District Health Office (DHO) implements control and prevention measures and conducts a thorough epidemiological investigation to identify the source of infection or index case. To break the chain of transmission, confirmed COVID-19 cases are isolated and treated in designated COVID-19 hospitals, while contacts are traced and identified for mandatory COVID-19 laboratory testing and a 14-day at-home quarantine. Early detection of cases among close contacts is crucial for early containment to prevent further seeding of community transmission. In early March 2020, the number of cases in Petaling increased due to a localized cluster of COVID-19 infections in one corporation, with more than 90 cases confirmed within 3 weeks.[11] The outbreak then increased exponentially, triggering a more rigorous control response from the Petaling DHO. As analysis of the COVID-19 cases in Petaling may provide critical information to help control the spread of similar infectious diseases at district and national levels, the objective of this paper is to describe the epidemiology of the COVID-19 epidemic in Petaling District between 1 February and 26 June 2020.

## METHODS

### Study design

This descriptive study is based on an exploratory analysis of all cases of COVID-19 notified to the Petaling DHO from the beginning of the outbreak in early February 2020 to the end of June 2020.

### Study setting

This study was conducted in the Petaling District, Selangor, Malaysia, a highly urbanized area with a dense population of over 2 million people.

### Case definition

The definition of a confirmed case of COVID-19 is a person with a reverse transcriptase polymerase chain reaction (RT-PCR) positive result, regardless of their symptoms. Only cases that met this case definition were included. People under investigation for COVID-19 are defined as having fever OR acute respiratory infection (sudden onset of shortness of breath, cough and/or sore throat) AND travel to or residence in an affected country (China, Islamic Republic of Iran, Italy, Japan, Republic of Korea) within 14 days before illness onset OR close contact within 14 days before illness onset with a confirmed case of COVID-19.

### Epidemiological investigation

Each notified case was verified by the Petaling DHO before an epidemiological investigation was undertaken to determine the source of infection, including contact tracing, active case detection and prevention and control measures, including quarantine. The primary objective of investigation was to identify the source of infection and close contacts of confirmed cases. Information on socio-demographic characteristics, symptoms, date of illness onset, date of exposure, travel history and co-morbidities was obtained by phone interview with cases and contacts using one of two investigation forms. The data were then shared with the Selangor State Health Department. Date of exposure was defined as the last date of contact with a known case of COVID-19 or last date of travel, if any, while date of onset was defined as the date the person self-reportedly developed any symptoms related to COVID-19. Details of close contacts were retrieved during case investigations and sent to the contact tracing team for further action. All cases and contacts were monitored daily for the next 14 days. All relevant data were captured within the COVID-19 surveillance system of Malaysia's Ministry of Health (MOH).

### Data management

Most notifications of confirmed cases were received from the Surveillance Unit of the Selangor State Health Department; some were received by phone, fax or email from hospitals and accredited laboratories. The MOH has a surveillance system for notification and monitoring of infectious diseases known as the Communicable Diseases Control Information System or eNotifikasi,[12]

and COVID-19 was added as a notifiable disease to this system at the end of March 2020 to ensure mandatory reporting of suspected and confirmed cases of COVID-19 to the nearest DHO. Reporting is compulsory under the Malaysia Prevention and Control of Infectious Disease Act 1988.[13] As all case records contain national identification numbers, all cases are recorded in the system without duplication. The inclusion criteria for this study were confirmed COVID-19 cases according to the case definition notified to the Petaling DHO between 1 February 2020 and 26 June 2020.

### Data analysis

The socio-demographic and clinical characteristics of all confirmed cases of COVID-19 were summarized with descriptive statistics. An epidemic curve of all cases was constructed by plotting the number of cases (y-axis) against the self-reported date of symptom onset (x-axis). For asymptomatic cases, the date of onset was considered to be the last date of known exposure.

### Ethical approval

The study protocol was approved by the Medical Research and Ethics Committee, MOH Malaysia (NMRR-20–1540–55803 [IIR]).

## RESULTS

Between 1 February 2020 and 26 June 2020, there were 437 confirmed cases of COVID-19 in Petaling District. The total population of Petaling District in the 2010 census[14] was 1 812 633. Therefore, the incidence rate of COVID-19 infection was 24/100 000 population. The baseline characteristics of the confirmed cases are presented in **Table 1**.

All 437 cases were admitted to the hospital for isolation and treatment. Ten cases (2.3%) died due to complications, and the other 427 cases were eventually discharged. Of all cases, 76.7% were local and 23.3% were imported. The mean age was 41 years, and 25.6% were in the 21–30 years age group. The gender distribution was relatively even, with 53.8% male and 46.2% female cases. Malaysian citizens accounted for 92%, and 64.5% of cases were symptomatic. The most commonly observed symptoms were fever (43.8%), cough (31.6%) and sore throat (16.2%). The total number of close contacts of confirmed COVID-19 cases was 7081. Among 160 close contacts who were later confirmed positive, 51 (31.9%) were close contacts of asymptomatic primary cases, and 109 (68.1%) were close contacts of symptomatic primary cases.

A total of 294 cases (67.3%) had no comorbidities, while 70 (16%) had hypertension and 46 (10.6%) had diabetes mellitus. Of all cases, 62.5% had reported close contact with a confirmed COVID-19 case, and 76.7% were classified as locally transmitted infections. In Petaling, four main clusters of cases were identified: at a religious gathering (20.4%), in a corporation (15.1%), in health facilities (10.3%) and at a wholesale wet market (6.4%). Other clusters included sporadic local and imported cases.

**Fig. 1** shows the dates of symptom onset for cases of COVID-19 in Petaling District between January and June 2020. The first cluster of COVID-19 was detected in a corporation in early February, which peaked in mid-February. A total of 66 cases were reported from this cluster. The highest peak of cases occurred in mid-March; the infection rate then tapered off and ended in mid-April. Most cases during the peak were linked to a mass religious gathering (89 cases). The third peak, seen at the end of April, involved vendors at a wholesale wet market, with a total of 28 cases reported. The epidemic curve in **Fig. 1** shows a pattern indicating person-to-person transmission.

## DISCUSSION

We report the epidemiological characterization of the initial COVID-19 outbreak in the most densely populated district of the State of Selangor, Malaysia. Most of the reported cases were aged 21–30 years (25.6%), and the distribution of cases by gender was similar. The age distribution of the cases in this study is consistent with that in the initial outbreak reported in China, i.e. mainly young adults.[15] About 65% of the cases were symptomatic, the three most commonly reported symptoms being fever, cough and sore throat. The pathogenesis of SARS-CoV-2 includes both upper and lower respiratory tract infections,[16] and the earliest outbreak in the epicentre, Wuhan, also included symptoms of respiratory tract infection in most reported cases.[17] Respiratory viruses are highly contagious when patients are symptomatic. In the outbreak reported here, more than half the

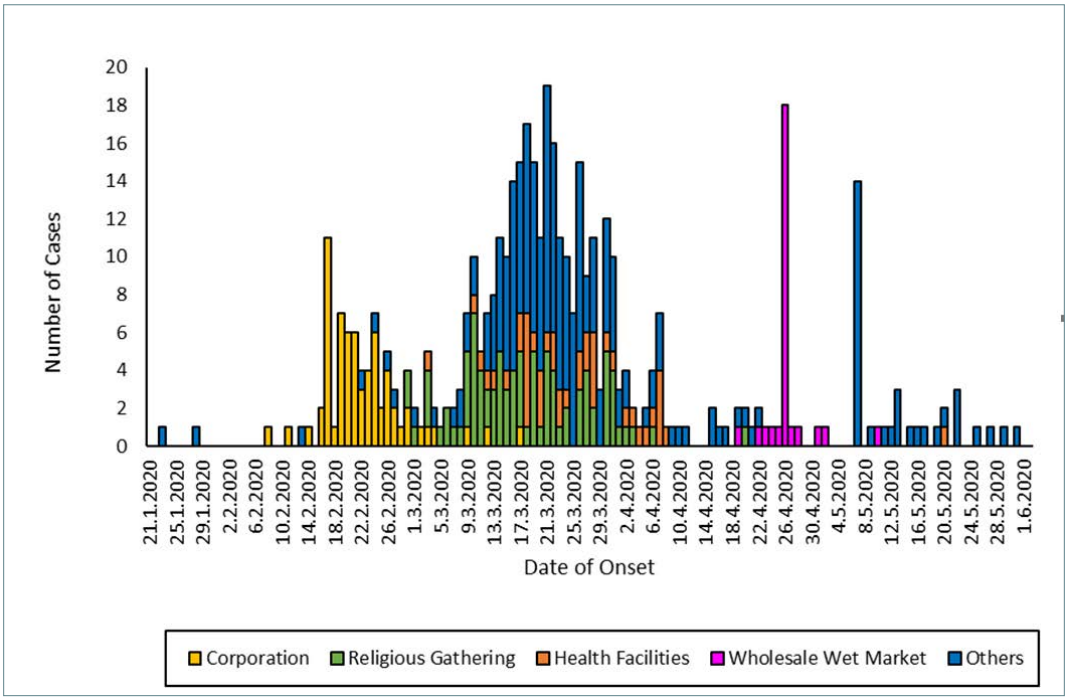
Table 1. **Baseline characteristics of COVID-19 cases in Petaling District**

| | N | % |
|---|---|---|
| **Total number of cases** | **437** | |
| **Attack rate** | | **0.024** |
| **Age (years, mean, SD)** | **41, 17.7** | |
| Age group | | |
| 0–10 | 15 | 3.4 |
| 11–20 | 28 | 6.4 |
| 21–30 | 112 | 25.6 |
| 31–40 | 77 | 17.6 |
| 41–50 | 59 | 13.5 |
| 51–60 | 77 | 17.6 |
| >60 | 69 | 15.8 |
| Gender | | |
| Male | 235 | 53.8 |
| Female | 202 | 46.2 |
| Nationality | | |
| Malaysian | 402 | 92.0 |
| Non-Malaysian | 35 | 8.0 |
| Symptom status | | |
| Symptomatic | 282 | 64.5 |
| Asymptomatic | 155 | 35.5 |
| Symptoms ($n$ = 282) | | |
| Fever | 187 | 43.8 |
| Cough | 137 | 31.6 |
| Sore throat | 71 | 16.2 |
| Headache | 22 | 5.0 |
| Loss of taste and smell | 21 | 4.8 |
| Myalgia | 18 | 4.1 |
| Gastrointestinal disturbances | 12 | 2.7 |
| Comorbidities or risk factors | | |
| None | 294 | 67.3 |
| Hypertension | 70 | 16.0 |
| Diabetes mellitus | 46 | 10.6 |
| Dyslipidaemia | 22 | 5.0 |
| Heart disease | 16 | 3.7 |
| Bronchial asthma | 10 | 2.3 |
| History of close contact with a confirmed COVID-19 case | | |
| Yes | 273 | 62.5 |
| No | 164 | 37.5 |
| Total number of close contacts | | |
| Symptomatic index cases | 4568 | 64.5 |
| Asymptomatic index cases | 2513 | 35.5 |
| Confirmed COVID-19 cases among close contacts | | |
| Symptomatic index cases | 109 | 68.1 |
| Asymptomatic index cases | 51 | 31.9 |
| Type of infection | | |
| Local | 335 | 76.7 |
| Imported | 102 | 23.3 |
| Clusters | | |
| Religious gathering | 89 | 20.4 |
| Corporation | 66 | 15.1 |
| Health facilities | 45 | 10.3 |
| Wholesale wet market | 28 | 6.4 |
| Others | 209 | 47.8 |
| Local council area subdivision | | |
| Petaling Jaya | 178 | 40.7 |
| Subang Jaya | 100 | 22.9 |
| Shah Alam | 157 | 36.0 |
| Others | 2 | 0.5 |
| Status | | |
| Alive | 427 | 97.7 |
| Dead | 10 | 2.3 |

cases were locally transmitted and had reported close contact with a confirmed COVID-19 case. COVID-19 is transmitted primarily in respiratory droplets[7] and by physical contact.[18] Evidence of human-to-human transmission among close contacts has been found since the beginning of the pandemic, in mid-December 2019.[19] Furthermore, the clusters of COVID-19 cases in Petaling District involved gatherings, further spreading the virus in the community.[20] In this outbreak, about 32% of cases had an epidemiological link to an asymptomatic case. As similar viral loads have been reported in symptomatic and asymptomatic cases,[17] community transmission of SARS-CoV-2 by asymptomatic cases is likely. The salivary glands could act as a potential reservoir for COVID-19; thus, infectious salivary droplets could be transmitted to a susceptible host from the mouth when an asymptomatic carrier is speaking, sneezing or even breathing, or from the eyes, and directly inhaled into the lungs.[21] Similar evidence of transmission from asymptomatic carriers to close contacts has been reported.[22,23] In view of the novelty of SARS-CoV-2, accumulation of evidence on transmission from asymptomatic people has contributed to understanding the dynamics and public health implications of the disease. In our study, almost one third of close contacts who became infected were contacts of asymptomatic cases. As asymptomatic individuals appear to be a common source of infection, strict monitoring of close contacts of asymptomatic cases is essential to contain potential outbreaks.

The fundamental characteristics of first-wave cases and the associated epidemic curves in Petaling

Fig. 1. **COVID-19 epidemic curve, with all clusters in Petaling District between January and June 2020**




District indicate that 282 (64.5%) cases were symptomatic, with appropriate dates of onset of illness. The epidemic curve of all clusters in Petaling District between January and June 2020 (**Fig. 1**) indicates that the outbreak had a propagated source pattern of spread. This trend is consistent with person-to-person spread in outbreaks of this newly introduced zoonotic viral pathogen that subsequently became capable of human-to-human transmission due to high mutation and recombination rates.[24] As shown in the epidemic curve, the outbreak in Petaling District had multiple surges of cases, resulting from several main clusters, including a corporation, a religious gathering, health facilities, a wholesale wet market and sporadic cases. The index case in the corporation cluster was believed to have been infected while travelling in Indonesia before the onset of symptoms. Subsequently, while symptomatic, the index case attended a meeting at the office, and transmission occurred to other workers. The religious gathering was attended by more than 19 000 people from various countries. It not only became a catalyst for subsequent spread of COVID-19 in Petaling District but also resulted in massive transmission throughout Malaysia and abroad.[25] The gathering involved sharing of communal spaces, such as prayer halls, collective eating from shared plates and sharing of sleeping areas, which increased the opportunities for transmission among participants. Transmission of COVID-19 in these two main reported clusters in Petaling District went beyond household contacts, and contact tracing revealed up to five generations of contacts. The epidemic curve shows that cluster transmission accounted for more than half of the confirmed COVID-19 cases in this outbreak; a similar phenomenon has been seen in other cities.[18]

Early implementation of the MCO in response to the COVID-19 pandemic played a vital role in controlling the outbreak and preventing disease transmission within the community. Closure of all universities, schools, places of worship and non-essential sectors during the MCO helped to break the chain of transmission in the community by prohibiting mass movement and gatherings nationwide. This federal response was successful in lowering the epidemic curve in Petaling District. The enhanced or targeted MCO, a cordon sanitaire implemented on 10 May 2020 by the federal government, slowed the COVID-19 outbreak in Petaling District during the wholesale wet market cluster.

Overall, this study provides valuable information on the first wave of the COVID-19 outbreak in Petaling District and the general epidemiological measures taken to curb the outbreak. Additionally, this study included a large number of cases, as Petaling is part of the state of Selangor, which had the second-largest number of confirmed COVID-19 cases in Malaysia during this pe-

riod of the pandemic. Nevertheless, the study had some limitations, such as lack of data on the severity and clinical outcomes of cases. Furthermore, the data were retrospective and self-reported by patients and may be inaccurate due to recall bias.

## CONCLUSION

This study provides key findings in the Petaling COVID-19 outbreak that are consistent with those reported in other studies. Most cases had a history of close contact with confirmed COVID-19 cases, confirming human-to-human transmission. The study also confirms that asymptomatic cases can transmit the disease to others. This should be emphasized to the community to ensure continuous wearing of face masks, hand hygiene and social distancing in public. Public health efforts should focus on surveillance for local transmission of cases and swift control measures to avert widespread community transmission. Active case detection and quarantine of close contacts of confirmed cases is a key prevention and control strategy to prevent spread of the disease, while strict monitoring of close contacts of asymptomatic infected cases is just as important as for symptomatic cases. Further research should be conducted to better understand the transmission of SARS-CoV-2 from asymptomatic cases.

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### *Conflicts of interest*

The authors declare that they have no conflict of interest in this publication.

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# Screening of hospital admissions for COVID-19 in Brunei Darussalam

Sanny Zi Lung Choo,[a] Hazirah Shafri,[a] Fatimah Al-Zahara Johan,[a] Norwani Basir,[a] Pui Ling Chong,[a] Muhammad Syafiq Abdullah,[a,b] Rosmonaliza Asli,[a] Jackson Tan,[a,b] Dilip Joseph Thottacherry,[c] Mohammad Ady Adillah Ahmad[d] and Vui Heng Chong[a,b]

Correspondence to Vui Heng Chong (vuiheng.chong@moh.gov.bn)

Since late December 2019, an outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, resulting in a pandemic. As of 30 March 2021, 126 million confirmed cases had been reported worldwide, with 2.7 million deaths.[1]

Brunei Darussalam reported its first case of COVID-19 on 9 March 2020, and as of 11 April 2021, there were 219 confirmed cases.[2] Apart from limited small clusters, Brunei Darussalam remains at WHO Level 2 of COVID-19 transmission with the last documented local infection on 6 May 2020. Several measures were taken by the Government, headed by the Ministry of Health, to prevent or contain community spread. These included active case identification (i.e. screening at points of entry and surveillance in clinics), contact tracing by the Department of Public Health, isolation of confirmed cases in a designated hospital (the National Isolation Centre, Tutong District), limiting public gatherings (closure of schools and places of worship, cancellation of public gatherings and banning of large private functions) and continued advice on physical distancing (through all media). In public and private hospitals and clinics, measures to prevent nosocomial spread of COVID-19 included limiting entry points, with compulsory risk assessment and temperature checks. In the three government hospitals (not the designated COVID-19 hospital), patients admitted for pneumonia and those with risk factors for COVID-19 were screened. In this paper, we describe this screening process from 9 March to 30 April 2020.

## MATERIALS AND METHODS

Screening for SARS-CoV-2 was implemented in the three government hospitals for all patients referred from clinics or who presented to the emergency departments for admission and who met the screening criteria. The standardized screening criteria were any of the following: community-acquired pneumonia (lower respiratory symptoms with no history of recent hospital admission), radiological changes consistent with pneumonia, previous quarantine within four weeks of contact with a confirmed COVID-19 case or travel to affected countries in the previous 14 days.

Patients were admitted to designated holding wards in each hospital, and nasopharyngeal swabs were taken and tested by reverse transcriptase polymerase chain reaction (RT–PCR) at the National Virology Reference Laboratory. Test results were usually available within 12 hours. While in the holding wards, patients continued to receive appropriate treatment and were screened for other infections, as indicated (dengue, malaria and various bacterial infections).

Patients who tested negative for SARS-CoV-2 were moved out of the holding wards to the main wards for continuation of care. Patients who tested positive were informed of their results, and transferred to the National Isolation Centre for further management. The Department of Public Health was informed of any positive results in order to initiate contact tracing without delay. Patients were interviewed according to the usual contact-tracing protocol, and family members and

[a] Raja Isteri Pengiran Anak Saleha Hospital, Brunei Darussalam.
[b] Institute of Health Sciences, Pengiran Anak Puteri Rashidah Sa'adatul Bolkiah, Universiti Brunei Darussalam, Brunei Darussalam.
[c] Suri Seri Begawan Hospital, Brunei Darussalam.
[d] Pengiran Isteri Hajah Mariam Hospital, Temburong, Brunei Darussalam.
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contacts were screened for SARS-CoV-2 with RT–PCR testing and quarantined for 14 days.

All positive SARS-CoV-2 cases, i.e. those detected by screening and those subsequently identified through contact tracing of cases, were transferred to the National Isolation Centre for treatment. Patients were admitted initially for a minimum of 14 days and were discharged only when they were symptom-free for three consecutive days and had two consecutive negative RT–PCR tests on days 12 and 14 of hospitalization. After discharge, patients were obliged to self-isolate for 14 days; a repeat swab was taken and tested on day 11 after discharge. Patients were considered cured once they had a negative swab and had completed 14 days of self-isolation. Patients who retested positive during self-isolation were readmitted for further management. Testing was repeated immediately, and the patients were discharged only after two consecutive negative swabs 24 hours apart. Our criteria have since changed and we no longer retest patients on day 11 after discharge.[3]

## RESULTS

During the study period, 225 patients had been admitted to the holding wards in the three government hospitals. Most of the patients (90%) were admitted from a medical specialty: eight from surgical and 14 from renal specialties. Seven had been admitted to an intensive care unit and 35 to a high-dependency unit (**Table 1**).

Of the 225 patients, only one (41-year-old man without comorbidities or travel history) was positive for SARS-CoV-2. This patient had presented five times to health-care services (four times to clinics and most recently to the emergency department of the main hospital) with fever and respiratory symptoms that had persisted despite symptomatic treatment. No contact with a possible or confirmed case was reported at any visit. After COVID-19 was confirmed, the contact history was reviewed, and the patient was linked to a confirmed case. The patient was immediately transferred to the National Isolation Centre for treatment. His course of illness was uncomplicated, and he was discharged after 15 days of hospitalization and two consecutive negative RT–PCR tests. A swab taken 11 days after discharge was negative. The 12 health-care workers involved in the care of this case at the original hospital were screened for SARS-CoV-2 and found to be negative.

Contact tracing for this case resulted in two additional COVID-19 cases: the patient's spouse and daughter. Both were tested the day after the index case was diagnosed. The daughter, who already had mild fever and headache for two days, tested positive. The spouse, who was then presymptomatic, tested negative and was placed under a 14-day quarantine. She was retested 7 days later during quarantine when she developed sore throat and rhinorrhea, and was then positive. Both were admitted to the National Isolation Centre soon after testing positive (daughter two days and spouse eight days after diagnosis of index case) and were discharged after 14 (daughter) and 20 days (spouse). The spouse was readmitted for a further four days after retesting positive on day 11 after discharge.

## DISCUSSION

Our experience highlights the importance of screening in hospitals during the COVID-19 outbreak. Although only one positive case was detected, we consider this programme a success, as, if the programme had not been carried out, nosocomial spread might have occurred. Nosocomial transmission has been reported, with significant consequences, including the deaths of health-care workers and other patients.[4–7] Hospitalized patients are usually older adults who have comorbidities that place them at higher risk for complications.[8] Screening for SARS-CoV-2 should therefore be maintained in health-care settings as the pandemic continues, with appropriate infection prevention and control (IPC) measures.

Our screening programme had implications not only for the hospitals but also for the community. Contact tracing for the case detected by screening led to the identification of two community cases, the patient's spouse and daughter. They became mildly symptomatic during their illness; the daughter was symptomatic at first testing, and the spouse became symptomatic 7 days after initially testing negative and later retested positive. Their symptoms resolved without treatment during hospitalization. These two cases could have been missed if the index patient had not been diagnosed, with a potential risk for community spread. Detection of the initial case upon hospital

Table 1. **Number of admissions isolated and screened for COVID-19 by hospital and specialty, Brunei Darussalam, 9 March–30 April 2020**

| Specialty | Hospital 1 | | Hospital 2 | | Hospital 3 | |
|---|---|---|---|---|---|---|
| | Holding ward 1 | Holding ward 2 (high dependency) | Holding ward | Intensive care unit | Holding ward | Total |
| Medical | 132 | 31 | 30 | 7 | 3 | 203 |
| Surgical | 8 | 0 | - | - | - | 8 |
| Renal | 10 | 4 | - | - | - | 14 |
| Total | 150 | 35 | 30 | 7 | 3 | 225 |

admission and isolation of the two additional cases prevented further community spread.

The limitations encountered included the continuously changing criteria for SARS-CoV-2 in the earlier part of the pandemic, especially with respect to countries of travel. Initially, we categorized countries by risk categories according to the level of infection and presence of community spread; however, as more countries became affected, any travel history was considered a risk factor. The selection of patients for screening partially depended on the admitting doctors' suspicion and interpretation of radiological changes. Even with set criteria, we relied on the vigilance and awareness of front-line workers of ever-changing guidelines and protocols. In addition, there will always be variation in doctors' threshold for screening, and the screening yield was low (only one positive of 225 screened; 0.44% yield), especially among those with chronic pulmonary problems, such as chronic obstructive pulmonary disease and past tuberculosis, who had the expected radiological changes. Simple, non-infective exacerbations would have been identified during screening. Unnecessary isolation in the holding wards, even for a short time, can be detrimental to patients, particularly those who require intensive medical care. The strict IPC measures required in these wards further burdens patients and staff. Inappropriate admission to the holding wards also incurs costs, with inappropriate use of limited resources. We consider, however, that use of resources was acceptable, despite the low rate of detection, given that there was community spread in the country.

The areas that would improve the screening programme include: rapid dissemination and implementation of revised criteria and other relevant documents to front-line health-care workers; maintaining open communication among team members in various departments; and continuous audits of screened patients to improve the screening process.

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