Applied epidemiology of COVID-19 and other respiratory diseases, Victoria, 2020-2021

A thesis submitted for the Degree of Master of Philosophy (Applied Epidemiology) of The Australian National University

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Field placement:

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Statement of originality

I hereby declare that this submission is my own work and to the best of my knowledge contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at the Australian National University or any other educational institution, except where due acknowledgment is made in the thesis. Any contribution made to the research by others is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation or linguistic expression is acknowledged.

Signed ……..

Date ……...

Abstract

This thesis demonstrates achievement of the competency requirements of the Australian National University's Master of Philosophy in Applied Epidemiology (MAE). My MAE placement was at the WHO Collaborating Centre for Reference & Research on Influenza in Melbourne from March 2020 to October 2021. I participated in four projects fulfilling the four major competencies of the MAE program, including: 1) an early epidemiologic study of the spectrum of COVID-19 describing a high attack rate and low symptomatic fraction in a cohort of adults exposed to SARS-CoV-2 on an Antarctic cruise; 2) investigation and contact tracing of multiple COVID-19 outbreaks affecting health care workers at a major Melbourne hospital, from which one in ten close contacts tested positive for SARS-CoV-2 while in quarantine; 3) an investigation of the short-term effects of ambient fine particulate matter on healthcare encounters for respiratory illness in Melbourne; and 4) an evaluation of two systems for COVID-19 surveillance in residential aged care in Victoria, aimed at informing ongoing respiratory outbreak surveillance efforts. I present each project together with reflective discussion of relevant population health implications and lessons learned. I address achievement of all minor MAE competencies at various points throughout the thesis.

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I had a great group of MAE classmates who proved an excellent source for camaraderie and commiseration, even though we only got to meet together as a class in person once. The MAE staff need to be commended for keeping the program running and managing a difficult transition to online course blocks, while at the same time juggling additional COVID-19 related responsibilities.

Finally, I would like to thank my family for their support; my parents and aunt for feeding my interest in population health, my brother James for statistical advice, and my partner Janina for providing a sympathetic ear via telephone during Australia's extended international border closure.

Introduction

This thesis demonstrates achievement of the competency requirements of the Australian National University's Master of Philosophy in Applied Epidemiology (MAE). I joined the MAE program as a student in February 2020, and completed my field placement in Melbourne at the WHO Collaborating Centre for Reference & Research on Influenza, part of the Victorian Infectious Diseases Reference Laboratory (VIDRL) at the Peter Doherty Institute for Infection & Immunity.

This thesis is organised into five chapters. Chapters 1 through 4 each detail a project addressing one of the four main MAE competencies. Chapter 5 demonstrates achievement of the teaching competencies, and outlines some of the additional activities I had the pleasure of participating in during my time in the MAE program, but which are not directly relevant to the main competencies. A piece of public communication writing, conference presentation slides from one project, and peer teaching material, are included as appendices.

The first chapter describes an epidemiological study I was part of while on secondment to the Victorian Department of Health in April 2020. We investigated symptoms and serologic features of SARS-CoV-2 infection in a cohort of Australians repatriated from an Antarctic cruise. Studies like this one are useful in understanding the full clinical spectrum of new infectious diseases, including in paucisymptomatic cases, when routine case detection methods tend towards finding infected individuals with more severe disease.

Chapter 2 describes my involvement in the investigation and management of multiple COVID-19 outbreaks at the Royal Melbourne Hospital between June and September 2020. At the time I helped set up an information system to facilitate case and contact follow-up. I subsequently worked on a retrospective analysis of the performance of the hospital contact tracing system, which forms the bulk of the chapter.

The third chapter addresses the 'analysis of a public health dataset' MAE competency. I investigated the short-term effects of outdoor fine particulate air pollution on emergency presentations and hospitalisations for respiratory illness in Melbourne. This project builds on a large body of evidence on the adverse health effects of air pollution by providing more details on healthcare utilisation impacts in a city with relatively good air quality by international standards, and provided me an opportunity to learn about environmental epidemiology.

The Australian residential aged care sector has been disproportionately impacted by COVID-19, with traditional respiratory outbreak surveillance and response measures proving inadequate to prevent large outbreaks. For my surveillance project, I evaluated two surveillance activities implemented in

residential aged care in response to the COVID-19 pandemic for their usefulness to ongoing respiratory outbreak surveillance. A report based on this evaluation is included as Chapter 4.

The final chapter deals with the MAE teaching competencies and summarises some of the additional population health activities I was involved in over my time as an MAE student. My teaching experiences included participation in peer-to-peer teaching ("Lessons from the field"), and teaching for first-year MAE students during their first course block. I ran a peer-teaching session discussing the use of causal diagrams in epidemiological research. MAE classmates Steph Curtis, Fran Sheehan, and I conducted a first-year teaching session on antimicrobial resistance and healthcare-associated infections. Additional population health activities included a three month secondment to the Victorian Department of Health to assist with the COVID-19 response at the start of 2020, and participation in a working group tasked with investigating healthcare worker infections with COVID-19 at the Royal Melbourne Hospital.

For our cohort, the MAE provided an especially interesting time to work in epidemiology and population health, coinciding with a once in a hundred year pandemic. For better or worse, COVID-19 pervaded both professional and personal aspects of the MAE experience for myself and many of my classmates. For most of us, the "field" of field epidemiology was largely restricted to an area bounded by the edges of our computer monitors. At the same time, the field of epidemiology itself expanded (at least temporarily) from an apparently niche science to a central matter in public and political discourse.

This shift embodies the deserved centrality of population health to society, since health is an essential resource for a fulfilled life. Faced with broad and fundamental issues affecting all of society, it is surprising to no one that epidemiology alone, despite being recognised as the basic science of population health, is unable to provide comprehensive answers to the most pressing current health problems. In short, there is no "pump handle" for a pandemic.

Though an interdisciplinary and multi-perspective approach to population health is far from a new idea, the MAE experience gave me a much better appreciation for its role in addressing urgent health issues. Moving on with my post-MAE career, I am particularly interested in further exploring how interplay between health sciences including epidemiology, and fields such as mathematics, computer science, cognitive science, economics, ecology, and ethics, can inform rational decision making around health threats posed by emerging infectious diseases.

Table 1: MAE competencies and relevant thesis chapters.

MAE Competency	Chapter					
Major competencies	**1**	**2**	**3**	**4**	**5**	**Appendices**
Investigate an acute public health problem		✓				
Analyse a public health dataset			✓			
Establish or evaluate a surveillance system or other health information system				✓		
Design and conduct an epidemiological study	✓					
Minor competencies						
Conference abstract and presentation	✓					✓
Peer-reviewed publication	✓	✓				
Teaching requirements					✓	✓
Summary of public health information for lay audience						✓
Literature review				✓		

Chapter 1: Spectrum of COVID-19 in a repatriated cruise ship cohort, 2020

Prologue

At the end of first MAE course block in March 2020, I began my field placement on secondment to the COVID-19 response at the Victorian Department of Health. While there, I was fortunate to be part of a study involving a cohort of Australian travellers exposed to SARS-CoV-2 on board a cruise ship.

The ship had left Argentina en route to Antarctica on 16 March with approximately 220 passengers and crew on board including 99 Australians. About a week into the voyage the ship was struck by an outbreak of respiratory illness. The cruise was abandoned and the ship diverted from its planned course and attempted to disembark in Uruguay. One of the passengers was medically evacuated to a Montevideo hospital with respiratory distress, and was the first confirmed case of COVID-19 on board. Subsequent testing of the entire ship's remaining passengers and crew by Uruguayan public health authorities on 3 April revealed almost two-thirds were positive for SARS-CoV-2 by PCR despite only a minority reporting symptoms. A flight was chartered to bring the Australians home on April 10, and the Uruguayans arranged transfer to the airport.

Managing this group of returned travellers posed several challenges. First, though a large proportion had reportedly tested positive for SARS-CoV-2, prior to their arrival into Australia there was limited information available on the prevalence and timing of COVID-19 compatible symptoms to guide assessment of infectiousness. Further, the travellers did not have formal laboratory reports with their test results, only letters from the ship's physician who had either sighted them or been informed of the results by Uruguayan authorities. Thus, the risk of onward transmission of COVID-19 in Australia was somewhat unclear but potentially high. Finally, Australia's hotel quarantine system was in its early infancy, having been established only a couple of weeks prior, and protocols for testing and release from isolation/quarantine were still being fine-tuned.

My role

The immediate objectives in this situation were protecting the health of the returning travellers and minimising risk of transmission to the broader Australian population. Fortunately, there was also recognition of an opportunity to learn more about COVID-19, particularly as this was a group with high incidence of disease that was identified based on exposure and surveillance testing rather than clinical presentation, so were more likely to represent the full spectrum of disease.

My involvement in the acute public health response was in collating and summarising data on symptoms and PCR testing in the cohort, in order to inform plans for safe release from quarantine. In terms of the study, I helped write the study protocol, consent form, and ethics application, and led recruitment with the help of the COVID-19 operations team. I prepared an internal report for the Victorian Department of Health summarising the outbreak and results of virological and serological testing in hotel quarantine. For the published manuscript, I performed the data analysis, prepared the initial draft, and managed submission and revisions. I gave a short presentation on the study at the PHAA Australasian COVID-19 Virtual Conference in December 2020 (slides included as Appendix 2).

Population health implications

Although many of the findings of this study were no longer novel by the time it was published, they corroborated important results of other studies that became available as we were performing the research. These include very high attack rates in cruise ship settings, an asymptomatic fraction for COVID-19 significantly higher than had been estimated earlier in the pandemic, and the wide variation in antibody response observed after natural infection. Subsequent to publication of the study, we continued to follow almost all of the infected members of the recruited cohort up for another year to investigate trends in the immune response to infection, and then response to vaccination in a smaller subset. I have included a second manuscript (currently under review) at the end of the chapter, based on some of this data, and containing a discussion of antibody kinetics in mild and asymptomatic COVID-19 and serosurveillance.

Lessons learned

Through this investigation, I gained some experience in risk assessment and planning in response to acute communicable disease threats. I developed skills in theoretical and practical aspects of study design, planning, and coordination, and learned to use the statistical software R to do basic plotting and statistical analysis.

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Symptoms and laboratory manifestations of mild COVID-19 in a repatriated cruise ship cohort

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Abstract

Much of our current understanding about novel coronavirus disease 2019 (COVID-19) comes from hospitalised patients. However, the spectrum of mild and subclinical disease has implications for population-level screening and control. Forty-nine participants were recruited from a group of 99 adults repatriated from a cruise ship with a high incidence of COVID-19. Respiratory and rectal swabs were tested by polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Sera were tested for anti-SARS-CoV-2 antibodies by enzyme-linked immunosorbent assay (ELISA) and microneutralisation assay. Symptoms, viral shedding and antibody response were examined. Forty-five participants (92%) were considered cases based on either positive PCR or positive ELISA for immunoglobulin G. Forty-two percent of cases were asymptomatic. Only 15% of symptomatic cases reported fever. Serial respiratory and rectal swabs were positive for 10% and 5% of participants respectively about 3 weeks after median symptom onset. Cycle threshold values were high (range 31–45). Attempts to isolate live virus were unsuccessful. The presence of symptoms was not associated with demographics, comorbidities or antibody response. In closed settings, incidence of COVID-19 could be almost double that suggested by symptom-based screening. Serology may be useful in diagnosis of mild disease and in aiding public health investigations.

Background

The spectrum of novel coronavirus disease 2019 (COVID-19) ranges from asymptomatic infection to death due to respiratory failure or other complications. However, most cases appear to experience mild illness [1], with estimated case-hospitalisation rate varying from 0% to 18% depending on age [2]. Fever and cough are common symptoms in hospitalised patients [3]. In mild cases, fever is less common, and gastrointestinal (GI) symptoms, and loss of taste or smell are reported frequently [4–6]. A minority of studies examining symptom profiles have investigated non-hospitalised cases [4].

Respiratory viral shedding peaks around the time of symptom onset, then decreases, reaching the limit of detection by polymerase chain reaction (PCR) on average about 2 weeks later [7, 8]. Longer duration of shedding is correlated with more severe illness [8, 9]. Prolonged faecal PCR positivity has been reported in mild or asymptomatic illness, raising the possibility of faecal–oral transmission from undetected carriers [10, 11]. However, most attempts to recover virus from faecal samples or rectal swabs have been unsuccessful, and the role of faecal–oral transmission remains unclear [10, 12].

Use of serologic assays for the detection of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been suggested as an aid to clinical diagnosis, for estimation of population wide attack rates, and for retrospective investigation of transmission chains [13, 14]. Immunoglobulin (Ig) G assays have reported sensitivity of 85–95% at >14 days since symptom onset and specificity of 92–99%, while IgA assays are less specific but have higher sensitivity earlier in the disease course [15, 16]. However, serum used for

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validation has mostly come from symptomatic patients [15–17], and it is unclear whether these results are generalisable to people without symptoms. Emerging evidence suggests that asymptomatic cases may have a less robust IgG response and that antibody titres decay rapidly [18, 19]. Older age and presence of comorbidities predispose towards severe disease [20], and the risk of symptomatic disease appears to increase with older age [21]. However, other determinants of developing symptomatic *vs.* asymptomatic illness are not well understood.

Because outbreaks of COVID-19 on cruise ships occur in closed settings with high rates of exposure, they provide opportunities to study a broader spectrum of illness than that which may be apparent from active or passive case finding in the community [22]. On 3 April, all 217 people on board a cruise ship off the coast of Uruguay known to have COVID-19 cases were tested for SARS-CoV-2. Fifty-nine percent tested positive [23]. Most were reported to be asymptomatic [23]. Passengers had been confined to their cabins from 22 March. On 12 April 2020, 99 adult passengers and crew were repatriated to Australia [23]. They were separated according to their test results on the repatriation flight. On arrival in Melbourne, Australia, all were required to undertake 14 days of isolation or quarantine in a designated hotel.

This study aimed to describe the attack rate, symptoms, viral shedding patterns and serologic response in this cohort of Australian returned travellers, to investigate possible determinants of symptomatic illness, and to examine differences in antibody response between symptomatic and asymptomatic cases.

Methods

Public health response

Because of the high proportion of passengers and crew reported to have tested positive in Uruguay, all returned travellers were treated as suspected cases upon arrival in Melbourne. They were interviewed by phone to collect demographic information, information on relevant symptoms and past medical history. They were also asked to provide copies of letters they had received stating their PCR test result from Uruguay. Victorian authorities subsequently did not accept these letters confirming infection status as proof of infection because laboratory reports were not included. Therefore, all returned travellers were requested by the public health authority to provide a nasopharyngeal swab for SARS-CoV-2 testing. These swabs were collected between days 1 and 7 after arrival in Australia. The state public health unit contacted returned travellers daily to monitor for signs and symptoms of COVID-19 until they were cleared from isolation or quarantine.

During their interviews, the returned travellers were invited to participate in the study. Participants provided consent for the study team to access data collected in routine case follow-up, including their PCR test results, and for the collection of additional biospecimens. The study was approved by the Human Research Ethics Committee of the Department of Health and Human Services, Victoria (HREC 05-20).

Data collection

Data collected as part of case follow-up were abstracted from the Department of Health and Human Services' Public Health Events Surveillance System. Nurse-collected respiratory swabs (nasopharyngeal and pharyngeal) and self-collected rectal swabs were requested on recruitment, if not already provided. Participants with an initial PCR-positive respiratory swab were asked to provide follow-up swabs every 1–2 days until they returned two consecutive negative swabs, or reached the end of their isolation or quarantine period, whichever occurred sooner. Results of additional swabs collected for public health or clinical reasons during the isolation or quarantine period were collated and included in the analysis. Two blood samples were requested from each participant, the first on either 16 April or 17 April, and the second on 24 April.

Virus characterisation

Respiratory and rectal swabs were tested for the presence of SARS-CoV-2 RNA using real-time PCR (RT-PCR) targeting the RdRp, E and N genes [24]. Virus isolation in Vero cells was attempted for all PCR-positive samples [24].

Serology

Sera were tested using commercial kits manufactured by EUROIMMUN AG (Lübeck, Germany) for the detection of IgA and IgG by enzyme-linked immunosorbent assay (ELISA), using the S1 domain of the SARS-CoV-2 spike protein as antigen, according to the manufacturer's instructions [25]. For these kits, the ratio between the extinction value for the sample and calibrator provides a semi-quantitative measure of antibody response (14). The sensitivity of the IgA and IgG kits using sera collected between 10 and 21 days after symptom onset was calculated by the manufacturer as 100.0% and 87.5%, respectively, with the sensitivity of the IgG assay increasing to 100.0% for samples collected at least 21 days after symptom onset [25, 26]. Specificity was reported as 90.5% and 99.3%, respectively [25, 26].

An in-house microneutralisation (MN) assay was used to detect neutralising antibody against SARS-CoV-2. SARS-CoV-2 isolate CoV/Australia/VIC01/2020 passaged in Vero cells was stored at −80 °C. Serial twofold dilutions of heat-inactivated serum were incubated with 100 median tissue culture infectious doses ($TCID_{50}$) of SARS-CoV-2 for 1 h and residual virus infectivity was assessed in quadruplicate wells of Vero cells; viral cytopathic effect was read on day 5. The neutralising antibody titre was calculated using the Reed/Muench method. Based on prior validation of this assay using SARS-CoV-2 positive and negative (pre-2019 sera), a titre of 40 or more was taken to indicate a positive antibody response. The sensitivity and specificity of this assay at this threshold were estimated at 70% (95% confidence interval (CI): 55–82%) and 74% (95% CI 60–85%), respectively (unpublished data).

Statistical methods

Data analyses were performed in R version 3.6.1. Because timing of swab collection correlated poorly with symptom onset, cases were defined as participants with evidence of any positive PCR result, or a positive IgG result from either blood sample. The attack rate was calculated using the total number of participants as the denominator. Summary statistics for presence and timing of symptoms were calculated for symptomatic cases. Pearson correlation coefficients (r) were calculated to examine correlation between MN titres and ELISA results. Two-sided Mann–Whitney U tests were performed to test the hypotheses that the distributions of MN titres and ELISA results differed between

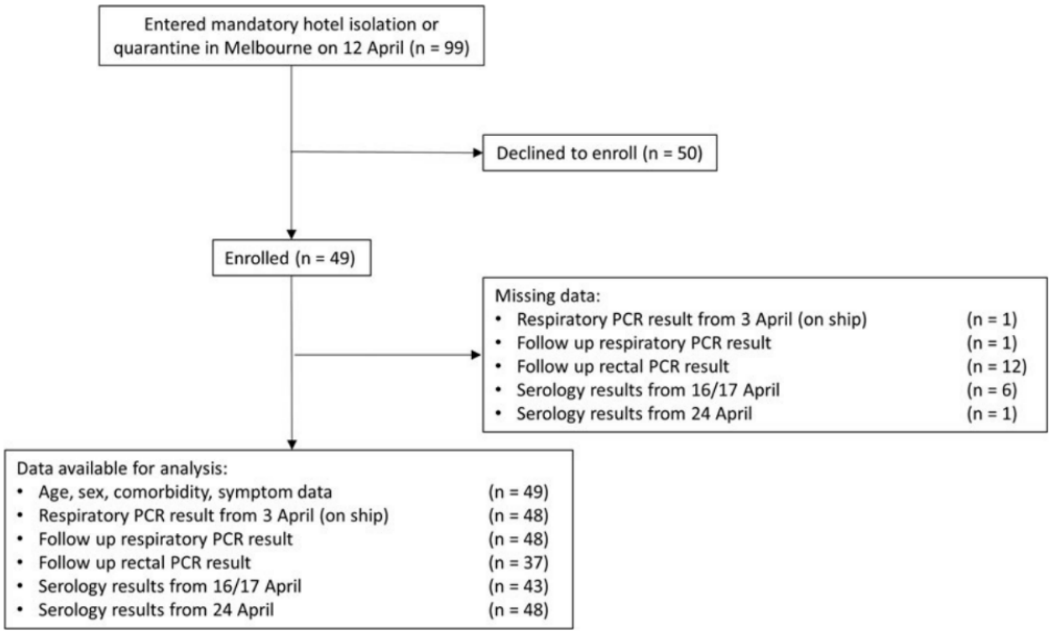

Fig. 1. Flow diagram showing enrolment of cohort, data available for analysis and missing data.

symptomatic and asymptomatic PCR positive participants, at each time point.

For participants meeting the study case definition, the relationships between the presence of symptoms as outcome, and binary predictors (sex, age group and presence of comorbidities), were examined independently. After constructing binary dummy variables for each age group, the risk of symptoms was calculated for cases with and without each predictor. Relative risk was calculated as the ratio between these two values. The 'EpiStats' package was used to calculate two-sided 95% CIs, and to compute *P*-values using chi-squared tests.

Results

Forty-nine participants were recruited from the 99 Australians repatriated to Melbourne (49%, Fig. 1). Forty-three were initially recruited, with a further six recruited for follow-up blood collection only. Demographic and health information are summarised in Table 1. The median age was 67 years (range: 36–81), and 31 (63%) were female. Nearly half of participants reported a comorbid condition. One participant was hospitalised in Uruguay. Twenty-seven participants (55%) reported symptoms either on the ship or in hotel quarantine.

Testing reports from Uruguay were provided by 48 participants, of whom 36 were stated to have tested positive (73% of total). Forty-eight participants provided at least one respiratory swab for testing in Melbourne, with the first collected a median 23 days (range: 13–27 days) after symptom onset. Five (10%) tested positive (Fig. 2), but only three of these five reported symptoms on the ship or during the follow-up period. By the end of the 14-day quarantine period, only one of these participants had returned two consecutive negative swabs.

Thirty-seven participants provided rectal swabs, two of which were positive (5%). Respiratory swabs collected from these two participants on the same date were negative. Both had previously experienced respiratory symptoms, but neither reported diarrhoea. For the 14 PCR-positive respiratory and rectal swabs collected from the seven participants who were PCR positive in

Table 1. Demographics, comorbidities, hospitalisation, presence of symptoms and previous SARS-CoV-2 PCR results for study participants (*n* = 49)

Age in years – median (range)	67 (36–81)
Sex	
Female – *n* (% of total)	31 (63.3)
Male – *n* (% of total)	18 (36.7)
Comorbidities	
None – *n* (% of total)	26 (53.1)
Any – *n* (% of total)	23 (46.9)
Chronic respiratory disease – *n* (% of total)	6 (12.2)
Cardiac disease (excluding uncomplicated hypertension) – *n* (% of total)	5 (10.2)
Other – *n* (% of total)	19 (38.8)
Symptoms	
Present – *n* (% of total)	27 (55.1)
Absent – *n* (% of total)	22 (44.9)
Hospitalised	
Yes – *n* (% of total)	1 (2.0)
No – *n* (% of total)	48 (98.0)
Respiratory PCR result on ship (3 April 2020)	
Positive – *n* (% of total)	36 (73.5)
Negative – *n* (% of total)	12 (24.5)
Not available – *n* (% of total)	1 (2.0)

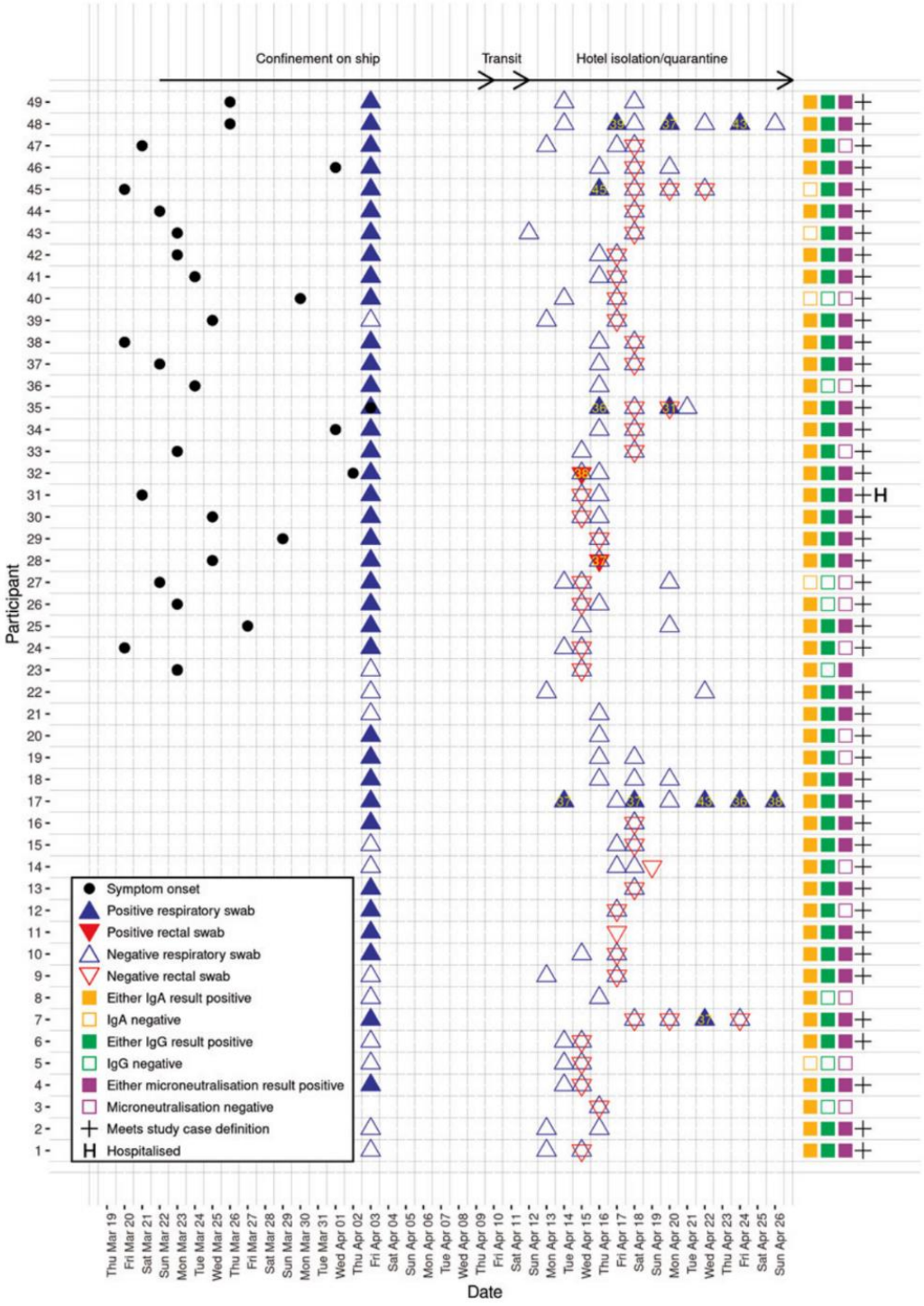

Fig. 2. Timing of symptom onset, SARS-CoV-2 PCR testing and anti-SARS-CoV-2 serology, for 49 study participants. Participants were members of a cohort exposed to SARS-CoV-2 on board a cruise ship. Yellow numerals show cycle threshold (Ct) values. Serology results, case status and hospitalisation are presented on the right-hand side of the plot for readability, blood samples were collected on 16–17 April 2020 and 24 April 2020. Ig, immunoglobulin.

Melbourne, the median cycle threshold (Ct) value for the RdRp gene was 37 (range: 31–45). Virus isolation was unsuccessful for all samples.

Consecutive blood samples were collected a median of 24 and 31 days after symptom onset, respectively. There was wide variation in antibody responses, even among PCR-negative

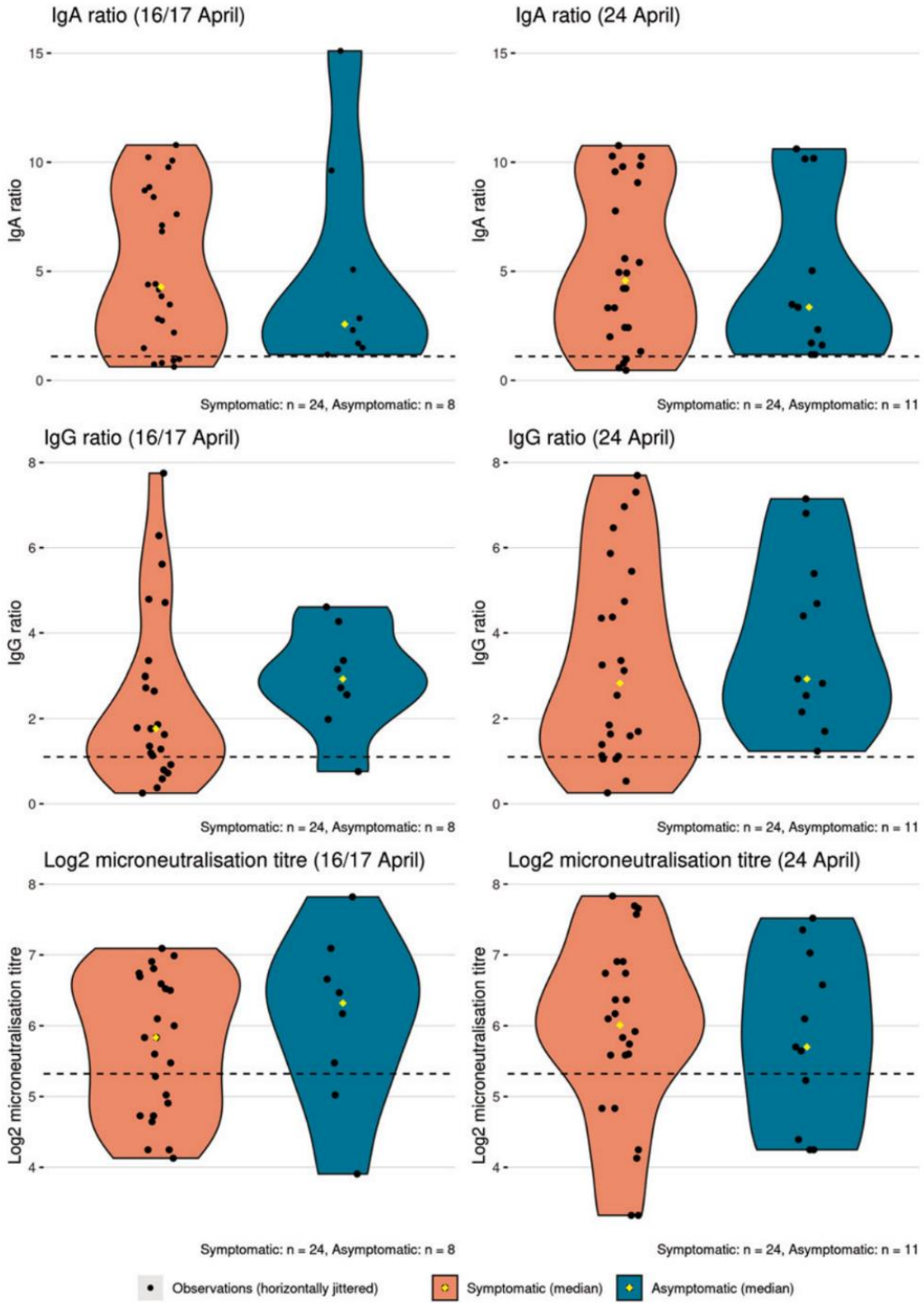

Fig. 3. Distribution of SARS-CoV-2 serology results in 36 study participants testing positive by PCR, by the presence of symptoms. Participants were members of a cohort exposed to SARS-CoV-2 on board a cruise ship. Median symptom onset was 24 March 2020. Dashed lines show threshold above which a result is considered positive. Ig, immunoglobulin.

participants (Fig. 3, Supplementary figure). For the 42 participants who provided two blood samples, the number with a positive IgA result increased from 36 (86%), on the first sample to 37 (88%) on the second sample, while the number with a positive IgG result increased from 30 (71%) to 34 (81%). MN assay positivity increased from 28 (67%) to 30 (71%). The MN was highly

Table 2. Symptom profiles in 26 symptomatic cases of mild COVID-19, disaggregated by sex

Symptom	Number reporting symptom (% of total)		
	All cases ($n = 26$)	Male cases ($n = 8$)	Female cases ($n = 18$)
Cough	15 (58%)	4 (50%)	11 (61%)
Sore throat	7 (27%)	2 (25%)	5 (28%)
Diarrhoea	6 (23%)	2 (25%)	4 (22%)
Headache[a]	6 (23%)	2 (25%)	4 (22%)
Runny/blocked nose[a]	5 (19%)	2 (25%)	3 (17%)
Lethargy[a]	5 (19%)	1 (12%)	4 (22%)
Fever	4 (15%)	1 (12%)	3 (17%)
Body aches[a]	4 (15%)	0 (0%)	4 (22%)
Loss of taste or smell[a]	3 (12%)	0 (0%)	3 (17%)
Shortness of breath	1 (4%)	0 (0%)	1 (6%)

[a]Participants were not routinely asked about these symptoms but volunteered them when asked about 'other' symptoms.

correlated with the IgG results ($r = 0.85$), and less well with the IgA ($r = 0.6$, data not shown).

Despite a trend towards higher IgA, and lower IgG response in symptomatic *vs.* asymptomatic PCR-positive participants, the overall distribution of IgA and IgG ratio and $\log_2$ MN titre appeared similar in both groups for samples collected 24 and 31 days after median symptom onset (Fig. 3). No statistically significant differences were detected between groups in the results of any assay on either sample (two-sided Mann–Whitney U test, IgA: $P = 0.85$, $P = 0.76$; IgG: $P = 0.21$, $P = 0.38$; MN: $P = 0.49$, $P = 0.78$; first and second samples, respectively).

Based on positive PCR or IgG results, 45 participants were estimated to have been infected, giving an attack rate of 92% among participants. However, 42% of cases reported no symptoms on the ship or during the follow-up period. One of the four study participants not meeting our composite case definition reported having been unwell with 1 day of fever in late March. The median date of symptom onset for the 26 symptomatic cases was 24 March (range: 20 March–3 April). Among the symptomatic cases, cough, sore throat, diarrhoea and headache were the most common symptoms (Table 2). Only four (15%) reported fever. Non-specific symptoms of lethargy or headache were the only symptoms reported by three cases (12%). Among the 45 cases, the presence of symptoms was not associated with age, sex or presence of comorbidities (Table 3).

Of the 36 participants with a letter reporting a positive PCR result from Uruguay, 32 (89%) were IgG positive. Of the 12 with a letter reporting a negative result, three (25%) were IgG negative but nine (75%) were IgG positive, while the one participant who did not provide a letter was IgG negative.

Discussion

This study synthesised symptoms, demographic and health data with the results of PCR and serology testing from a cohort of returned travellers exposed to SARS-CoV-2, among whom the attack rate was 92%. The asymptomatic fraction was 42%, similar to the estimated asymptomatic fraction on Diamond Princess [27], and of the remainder only one was hospitalised. Cough and sore throat were the most common symptoms. Self-reported fever was present in only 15% of symptomatic cases, underscoring the fallibility of temperature checks for screening [28].

A minority of participants had positive respiratory (10%) swabs when tested in Melbourne. This was not surprising as these tests were performed around 3 weeks after median symptom onset, and respiratory viral shedding has been reported elsewhere to persist for 1–2 weeks in most cases [7, 8]. That only 2 of 37 (5%) of participants had positive rectal swabs was somewhat unexpected given previous findings that about half of patients appear to shed RNA in faeces [10], for a median duration of almost 1 month after symptom onset [10]. This discrepancy might be due to the low disease severity in our cohort, or may be related to technique when self-collecting rectal swabs. Neither of the two participants with positive rectal swabs reported GI symptoms and both tested negative on respiratory swabs from the same day as rectal swab collection. In patients with positive rectal or stool samples, GI shedding tends to persist after clearance from the upper respiratory tract [10, 12] and only a minority report GI symptoms [10].

Although four participants continued to shed virus at the end of their hotel period, the high Ct values and inability to isolate live virus suggest the risk of onward transmission was low. The study team was notified by two of these cases that they tested positive again roughly 5 weeks after their first positive tests. Persistent viral shedding has been reported elsewhere [10]. In a Korean report of 285 cases who had a repeat positive PCR result after being released from isolation, there were no confirmed episodes of onward transmission after isolation, live virus isolation was unsuccessful in all 108 cases where it was attempted, and neutralising antibody was detected in the serum of all 23 cases who provided samples [29]. Persistent shedders present a problem for public health because it can be unclear whether they are at transmission risk and therefore require isolation. If isolation criteria are based solely on the timing of a positive PCR result, as may be the case for those without symptoms, it is possible that many people will be required to isolate unnecessarily.

At 1 month after median symptom onset, IgA and IgG ratios and MN titre were comparable between symptomatic and asymptomatic PCR-positive participants. This finding contrasts with recently published research, which found significantly lower IgG levels in 37 asymptomatic patients compared to 37 age- and sex-matched symptomatic patients during both the acute and early convalescent phases [19]. There are several possible explanations for this difference. First, because asymptomatic cases in that study were detected through testing of contacts of known cases, the interval from exposure to testing may have been shorter than for matched symptomatic cases, meaning asymptomatic cases would have had less time for a measurable IgG response to develop [19]. This is supported by the authors' finding that time from first to last positive PCR result was longer in the asymptomatic group. In our study, date of exposure should have been on average the same for symptomatic and asymptomatic participants. Second, asymptomatic patients in the abovementioned study were treated with α-interferon, ribavirin and additional supportive treatments according to local protocol [19], possibly clouding the natural history of disease.

Table 3. Results of univariable analysis for cases of COVID-19 with presence of symptoms as outcome ($n = 45$)

Predictor	Number with predictor	Number with predictor symptomatic	Risk of symptoms with predictor (%)	Number without predictor	Number without predictor symptomatic	Risk of symptoms without predictor (%)	RR (95% CI)	*P* value (χ^2)
Sex								
Female	29	18	62	16	8	50	1.24 (0.70–2.19)	0.43
Male	16	8	50	29	18	62	0.81 (0.46–1.42)	0.43
Comorbidities								
None	24	13	54	21	13	62	0.88 (0.53–1.44)	0.60
1 or more	21	13	62	24	13	54	1.14 (0.69–1.88)	0.60
Age group								
Age <55	6	5	83	39	21	54	1.55 (0.98–2.45)	0.17
Age 55–64	12	6	50	33	20	61	0.82 (0.44–1.55)	0.52
Age ≥65	27	15	56	18	11	61	0.91 (0.55–1.50)	0.71

RR, relative risk; CI, confidence interval; χ^2, chi-squared test.

This particular group of returned travellers presented a problem for public health authorities. Cruise ship outbreaks were particularly prominent in the media at the time after more than a hundred cases were identified linked to passengers allowed to disembark from Ruby Princess [30]. Participants in our study were not provided formal laboratory results confirming infection but few remained positive in Melbourne. IgG testing confirmed the overseas test reports for 35 participants and suggested a further nine had been infected despite the absence of a positive PCR report. In this cohort, there appears to have been utility in using serology to confirm infection, where the prevalence of disease was high and sufficient time had passed to permit development of detectable antibodies. However, its utility in other cohorts may be limited if the prevalence of infection is lower (therefore negatively influencing the positive predictive value), or during acute infection before antibody is detectable.

This study had several limitations. First, the relatively low participation rate raises the possibility that participation bias affected the study results. Specifically, individuals who had already tested positive, or those who had experienced symptoms but not received a positive result, may have been disproportionately motivated to participate in order to have confirmation of infection through antibody testing, leading to overestimation of the attack rate and underestimation of the asymptomatic fraction. Indeed, PCR positivity on 3 April was slightly higher in the study population than among all people on the ship (73% *vs.* 59%), based on another report on this outbreak [23]. According to the same report, only 19% of PCR-positive individuals on board were symptomatic. However, it is unclear whether this number reflects the proportion that was symptomatic only at the time of testing, and if not, for how long cases were followed to determine if they went on to develop symptoms [23]. Furthermore, because symptom data in the present study were recorded about 3 weeks after onset, poor recall may have contributed to overestimation of the asymptomatic fraction, countering some of the effect of the hypothesised participation bias. In addition, some symptoms, including headache or loss of taste or smell were not explicitly queried in our study. Second, the identification of risk factors for symptomatic disease was limited by the small sample size. For example, to detect statistically significant differences, the true relative risk for the effect of sex would need to be at least 3.11 or no more than 0.32, and for the presence of comorbidities at least 2.71 or no more than 0.37. Finally, the study population was mostly aged over 50 years, so caution should be exercised in generalising the findings to the broader population.

To conclude, in this cohort, asymptomatic infection with SARS-CoV-2 was common and the humoral immune response was not dependent on the presence of symptoms. By 3 weeks after disease onset, viral load in respiratory and GI samples was low or undetectable, but serology was useful for confirming prior infection. Demographics and presence of comorbidities were not strong predictors of symptomatic *vs.* asymptomatic disease within this study population. Study of other potential predictors of symptomatic illness, for example genetic or immunologic factors, could inform screening strategies or therapeutics. Research involving longitudinal follow-up of seropositive individuals will help to predict duration of immunity and the utility of sero-surveys in estimating population exposure.

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Data availability statement. Readers should contact the authors if they would like to access the data included in this publication.

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Trend in sensitivity of SARS-CoV-2 serology one year after mild and asymptomatic COVID-19: unpacking potential bias in seroprevalence studies

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Abstract

A key aim of serosurveillance during the COVID-19 pandemic has been to estimate the prevalence of prior infection, by correcting crude seroprevalence against estimated test performance for PCR-confirmed COVID-19. We show that poor generalisability of sensitivity estimates to some target populations may lead to substantial underestimation of case numbers.

Introduction

During the current SARS-CoV-2 pandemic, public health agencies have used serology to investigate the clinical spectrum, distribution, and determinants of COVID-19 across time and place to inform a range of interventions [1]. Serology is the preferred method for determining past infection with SARS-CoV-2, because pathogen-specific antibodies are detectable in serum long after clearance of viral RNA or antigen from accessible sites [1]. The prevalence of prior infection (PPI) has been estimated from cross-sectional sero-surveys, corrected for test sensitivity and specificity against PCR-confirmed infection [2]. However, there are two obvious limitations of this approach.

First, serological assay sensitivity estimates have primarily been derived using samples obtained from symptomatic—usually hospitalised—patients [3-6]. Yet a large proportion of cases have only mild illness, and more than one-third remain asymptomatic [7]. Given the strong correlation between COVID-19 severity and magnitude of antibody response [8, 9], sensitivity estimates derived from moderately and severely ill patients may not represent the broader SARS-CoV-2-infected population.

Second, most sensitivity estimates are based on samples obtained in early convalescence [3-5], yet serum antibodies have been shown to decline substantially within a few months of infection [10]. The kinetics of antibody decay may differ between mild and severely ill patients. Nevertheless, antibody decay is not considered in most published seroprevalence estimates.

In light of these limitations, we hypothesised that estimates from seroprevalence studies would underestimate PPI because of differences between test sensitivity in target populations and sensitivity estimates used for correction. To assess the possible magnitude of this bias, we investigated the longitudinal trend in results of one commercial serological assay in a cohort of individuals with mild and asymptomatic COVID-19 over one year, and modelled changes in sensitivity.

Estimation of test sensitivity over time

The cohort consisted of 48 older adults (median age 67 years, range 36-81), recruited from a previously-described group exposed to SARS-CoV-2 on an Antarctic cruise [11], with SARS-CoV-2

infection confirmed by PCR and/or serology (Supplementary table). Notably, 21/48 (44%) remained asymptomatic during 14 days of active monitoring. We collected 207 serum samples between 16 April 2020 and 14 April 2021; after excluding three samples collected after COVID-19 vaccination, 204 samples were available for analysis (median per participant: 4.5; range: 1-5). All participants provided informed consent. The study was approved by the Human Research Ethics Committee of the Department of Health and Human Services, Victoria (HREC 05-20).

Longitudinal analysis of antibody data requires estimating time since infection or illness onset, a challenging prospect for asymptomatic individuals. This cohort were almost certainly all exposed to SARS-CoV-2 over a 4-week period, between boarding the ship on 15 March 2020 and entering a managed quarantine facility in Australia on April 12 2020 [11]. All symptomatic participants became ill between 20 March and 3 April 2020, with the median date of onset 24 March (Figure 1a). For symptomatic participants we considered date of illness onset to be the same as symptom onset. For asymptomatic participants we set the date of illness onset to the median date of symptom onset, an assumption which is necessarily imprecise at the individual level but which we expected, on average, to hold true for the cohort.

We tested samples using the EUROIMMUN (EI) Anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) kit for the detection of immunoglobulin G (IgG), as per the manufacturer's instructions. The EI kit uses recombinant S1 domain of SARS-CoV-2 spike as antigen [3]. Results are expressed as the ratio of the measured optical density (OD) for the sample to that of a supplied calibrator, with ratios ≥ 1.1 considered positive. Published sensitivity estimates for samples obtained >14 days after symptom onset range from about 70-100%, and specificity 97-100% [3-6].

We modelled OD ratios obtained using the EI IgG kit in a hierarchical mixed-effects framework, using a non-linear model proposed by Simonsen et al. [12]. The model accommodates an initially rapid but gradually diminishing increase in antibody from illness onset, followed by exponential decay towards a steady state level [12]. To simulate the longitudinal trend in test sensitivity, we used parameter estimates from the fitted model to construct a hypothetical population of 1000 infected individuals. We simulated OD ratios for these individuals over a three year period from illness onset, and calculated sensitivity as the proportion of individuals with an OD ratio ≥1.1. We constructed 95% confidence intervals (95%CI) by repeating the model fitting and simulation procedures on 1000 bootstrap resamples of the original dataset. Details of the model specification, fit, and simulation methods are provided as supplementary material.

Predictions from the fitted model provided a reasonable representation of the underlying data (Figure 1b). Our simulation procedure and data were compatible with a maximum sensitivity of 81%

(95%CI: 74-84%) 40 days post-illness onset in the simulated population (Figure 1c-d). Simulated sensitivity declined to 76% at 3 months (95%CI: 69-79%) and 53% at one year (95%CI: 47-57%). Based on extrapolation of exponential decay, our simulation was consistent with a decline in sensitivity to 37% at three years (95%CI: 27-42%).

Example application to serosurveillance

When the proportion of previously infected individuals in the target population is high, correction based on biased sensitivity estimates may have a non-negligible effect on estimated PPI and, by extension, decisions affecting public health. We used Murhekar et al. [13] to demonstrate this problem. They conducted a serosurvey of 28,598 individuals between 18 December 2020 and 6 January 2021, to estimate the proportion of the Indian population previously infected with SARS-CoV-2. Their population-weighted, but unadjusted, seroprevalence was 21.7% using the Siemens S1-RBD IgG assay, with a PPI of 21.5% after correcting for the manufacturer-reported sensitivity of 100%, and specificity of 99.9% [13]. Based on this adjusted seroprevalence, they estimated the true number of infected individuals in the Indian population to be 242,124,000, indicating that there had been 23.8 infected individuals for each reported case as of 19 December 2020 [13].

In order to roughly estimate the possible degree of bias in these findings, we considered the following simplistic assumptions: 1). All infected individuals had onset of illness on 15 September 2020, the date of peak reported cases in India's first wave [14]; 2). All individuals in the study were sampled on 24 December, 100 days later; 3). The temporal profiles of the true sensitivities of the EI and Siemens assays were equivalent; 4). The reported specificity for the Siemens assay was generalizable to the target population.

Our simulation was compatible with a true sensitivity of 74% 100 days post-illness onset. Correcting the crude seroprevalence for this value and the reported specificity of the Siemens assay gave a PPI of 29.0% (equation 3 in the supplementary material), equivalent to 326,426,000 infected individuals, or an infection-case ratio of 32.1, 1.35 times higher than the initial estimate. Interestingly, Murhekar et al. noted that seropositivity among a subgroup of 664 participants who reported testing positive for SARS-CoV-2 by PCR was only 64%, a finding they suggested might be due to antibody decay [13].

Limitations

Our study had several limitations. The age and sex structure of our cohort differed substantially from most serosurveillance target populations. We have previously discussed the possibility of selection bias due to differential participation based on symptoms [11]. However, given population estimates of a relatively low infection:hospitalisation ratio [15], and high asymptomatic proportion [13], we believe our sample to be more applicable to seroprevalence studies than most others used to derive

estimates of serological assay sensitivity. Longitudinal trends in sensitivity may vary depending on the assay used. Our model has not been validated and relies on unverified assumptions including multivariate log-normality in parameter distribution, and continuing exponential decay past one year. Consequently, we intended to illustrate the potential for biased incidence estimates arising from serosurveillance studies, rather than to provide a precise quantification of this bias.

Conclusion: improving the utility of serosurveillance for COVID-19

In attempting to infer population prevalence of prior COVID-19 from seroprevalence studies, careful consideration should be given to bias due to non-generalisability of assay sensitivity estimates to target populations, leading to substantial underestimation. The effect of this bias increases with time from infection to sampling.

At a minimum, seroprevalence studies seeking to estimate SARS-CoV-2 infection should include sensitivity analyses allowing for much lower test sensitivity than those reported by kit manufacturers. The utility of seroprevalence surveys to infer patterns of COVID-19 might be further improved by the application of methods to recover incidence by applying models of test kinetics to cross-sectional data [12, 16]. To our knowledge, such methods are yet to be successfully implemented for SARS-CoV-2, but practically would require: 1). Cross-sectional testing using multiple assays with distinct kinetics, for example serological assays targeting various antigen-isotype combinations, possibly in combination with PCR [9]; 2). Reporting of individual results on continuous rather than binary scales [16]; 3). Longitudinal models of test kinetics derived from population-representative cohorts [16]. Future, studies seeking to estimate infection rather than population immunity must now distinguish between vaccine- and infection-induced antibody responses. This might be achieved by the development of new multiplex assays, but in the interim may require collection of vaccination status for sensitivity analyses [17].

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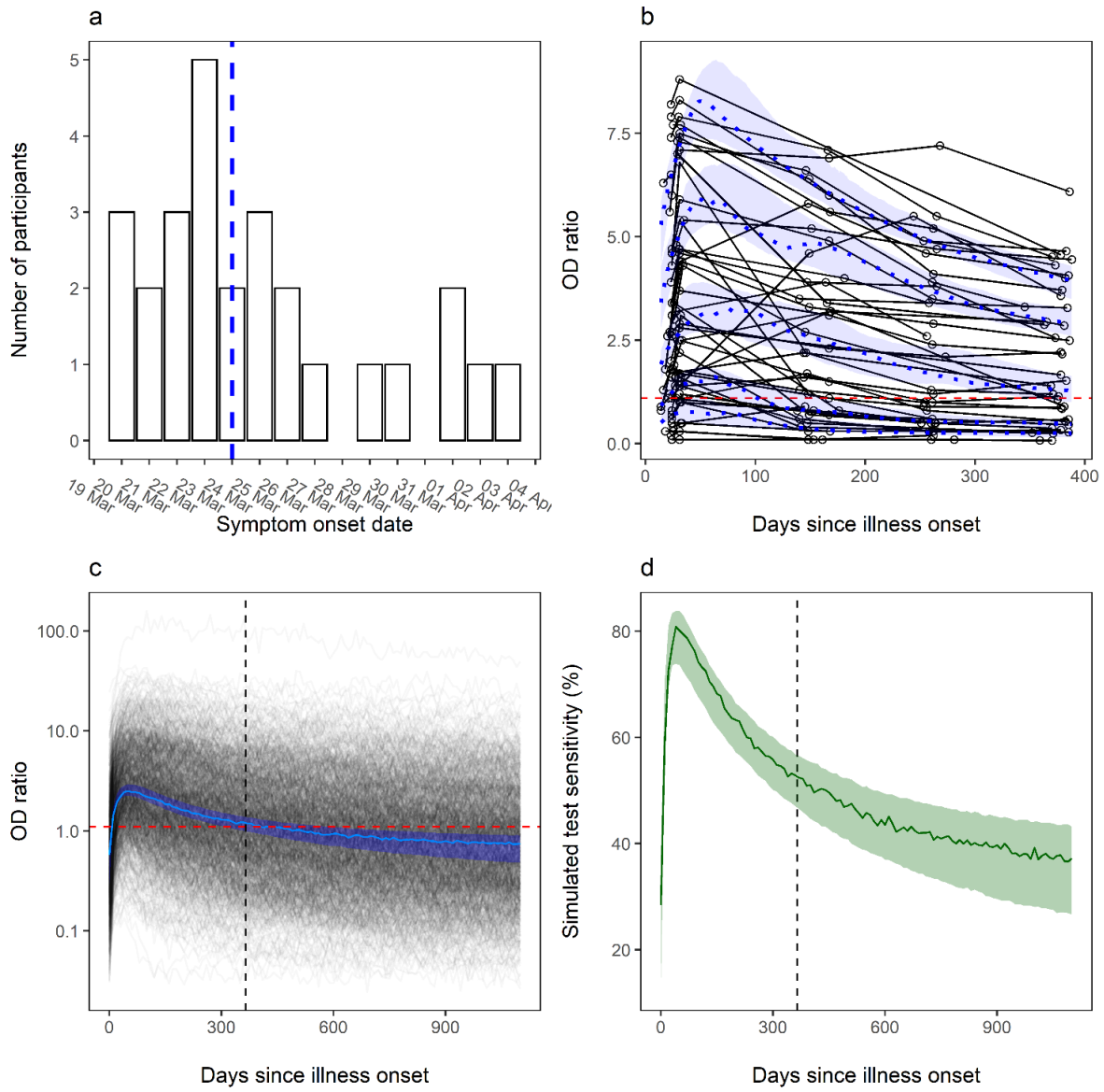

Figure 1. Estimation of the impact of antibody decay on assay sensitivity.

a: Distribution of symptom onset in 27 symptomatic participants, vertical dashed blue line shows the median date of onset used to infer disease onset in the remaining 21 asymptomatic participants; **b:** Optical density (OD) ratios obtained using the EUROIMMUN Anti-SARS-CoV-2 immunoglobulin G kit on samples from all 48 SARS-CoV-2 infected participants. Blue dotted lines show the 10th, 25th, 50th, 75th, and 90th centiles of the individual model predictions with the light blue shaded regions their corresponding 95% confidence bands; **c:** OD ratios for a simulated population of 1000 infected individuals. The blue line shows the median, with the darker blue shaded region showing the corresponding 95% confidence bands; **d:** Test sensitivity of the EUROIMMUN kit in the simulated population (green line) with 95% confidence band (green shaded region). Vertical black dashed lines are drawn at one year, the approximate time from which ongoing estimates are based on assumed ongoing exponential decay. All horizontal red dashed lines show the test positivity threshold (1.1).

Supplementary methods

Model specification and fit

To model decay in serum antibody levels over time we employed a non-linear two-phase model proposed by Simonsen et al. [1]. The model accommodates a rapid rise in serum antibodies after disease onset, followed by a second phase of first-order decline. In this model the antibody level for an individual i, on their j^{th} measurement, at time t after disease onset is given by the function:

$$f(t_{ij},\psi_i) = \begin{cases} X^* + \dfrac{(S + aS(t_1^* - t))}{t_1^* a^2} - \dfrac{S + aSt_1^*}{t_1^* a^2} e^{-at} & if\ t < t_1^* \\ X^* + \dfrac{Se^{at_1^*} - S - aSt_1^*}{t_1^* a^2} e^{-at} & if\ t \geq t_1^* \end{cases} \quad (1)$$

Where S is a measure of the product of the amount of serum antibody produced per unit time per unit of antigen and the amount of antigen present at the time of illness onset, a is the decay rate of serum antibodies towards a steady-state level X^*, and t_1^* is the time at which antibody production in response to ongoing antigen exposure stops. ψ_i is a vector of the individual parameters, which are assumed to be independently sampled from a multivariate lognormal probability distribution. The predicted response y_{ij} is given by [2]:

$$y_{ij} = f(t_{ij},\psi_i) + bf(t_{ij},\psi_i)\varepsilon_{ij} \quad (2)$$

Where $\varepsilon_{ij} \sim$ i.i.d. $N(0,1)$ and b is a fixed error parameter, thus assuming error that is proportional to the predicted response.

We fit the model to our data using the "saemix" package [2] in R version 3.6.1 [3], estimating fixed and random effects for all parameters. We assumed a covariance model allowing for correlation between random effects for X^* and S, which improved model fit over our starting assumption of uncorrelated random effects.

Simulation

We used the "saemix" model object to construct a simulated population of 1000 infected individuals. We simulated OD ratios for these individuals over a three year period from illness onset, sampling from the residual error model and calculating sensitivity every ten days, as the proportion

of individuals with an OD ratio ≥1.1. We constructed 95% confidence intervals for all estimates by repeating the model fitting and simulation procedures on 1000 bootstrap resamples of the original dataset, then applying the "bca" function from the "coxed" package to each vector of bootstrap estimates [4].

Correction of crude seroprevalence for test sensitivity and specificity

The estimated proportion of infected individuals q in a population is given by [5]:

$$q = \frac{w + r - 1}{s + r - 1} \tag{3}$$

Where w is the crude seroprevalence, s is the estimated test sensitivity and r the estimated specificity. Writing the same equation with q^* as the true proportion of infected individuals and s^* as the true sensitivity in the target population, substituting for w, and assuming that the true and estimated specificities are equivalent, gives the ratio of the estimated to true previously infected proportion:

$$\frac{q}{q^*} = \frac{s^* + r - 1}{s + r - 1} \tag{4}$$

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Supplementary table: Characteristics of study cohort (n = 48)

Age in years - median (range)	67 (36-81)
Sex	
Female - n (%)	30 (62%)
Male - n (%)	18 (38%)
Comorbidities	
Any reported comorbidity - n (%)	28 (58%)
No reported comorbidity - n (%)	20 (42%)
Symptoms	
Symptomatic - n (%)	27 (56%)
Asymptomatic - n (%)	21 (44%)
Admitted to hospital - n (%)	1 (2%)
Method of laboratory confirmation	
PCR[1] - n (%)	36 (75%)
ELISA[2] (IgG & IgA) - n (%)	9 (19%)
ELISA (IgG only) - n (%)	0 (0%)
ELISA (IgA only[3]) - n (%)	3 (6%)

[1] PCR: polymerase chain reaction. Participants were tested on 3 April 2020 regardless of symptoms.
[2] ELISA: enzyme-linked immunosorbent assay. IgG: immunoglobulin G. IgA: Immunoglobulin A. Participants were tested on 16-17 April 2020 and/or 24 April 2020.
[3] All three participants showed convincing evidence of IgA seroconversion i.e. optical density ratio greater than two times positivity threshold on both initial samples, falling to below positivity threshold on subsequent follow-up (data not shown).

Chapter 2: Hospital-based COVID-19 contact tracing during Australia's "second wave", Melbourne, 2020

Prologue

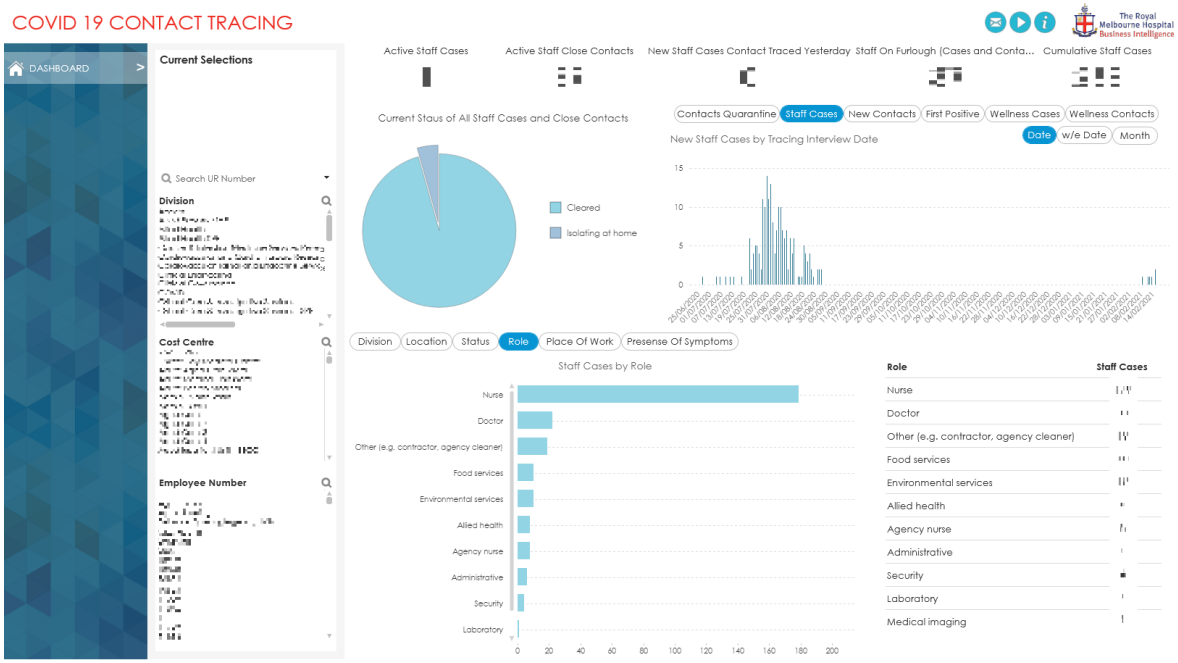
Early in July 2020 I had the opportunity to assist the infection control team at Royal Melbourne Hospital (RMH) with investigation of cases of COVID-19 amongst staff. Case numbers across Melbourne had been rising since mid-June, with a corresponding increase in the number of health care workers who either had COVID-19, or were required to quarantine as close contacts.

My role

Our first priority was to improve capability to accurately track and count cases. Hospital contact tracers were recording and accessing data on cases and close contacts in a series of separate Microsoft Excel spreadsheets. This system had previously been adequate for influenza or norovirus outbreaks, and earlier in the pandemic when there had been sporadic cases of COVID-19 in health care workers. However, the system was poorly suited for reporting summary information for a large number of cases and contacts, and for recording and accessing data involving serial instances of follow-up for the same individual.

We worked with the Business Intelligence team at RMH to rapidly develop a REDCap database intended to meet the information requirements of the contact tracing team, and reporting requirements of the Victorian Department of Health. I drew on experienced gained through working at the Department of Health to provide input on what fields should be included, tested the database, and imported data for existing cases and contacts. After implementation I was involved in modifying the database to address shortcomings and changing information demands, and set up a process for data checking which could be completed daily by staff in the infection control team. This database was linked to a live dashboard designed by the Business Intelligence team (see figure next page), which provided a summary of staff cases and furloughed close contacts by status, role, and location. This was used by decision makers in the hospital executive to access near real-time information on the status of staff affected by COVID-19. The database is currently still in use at RMH.

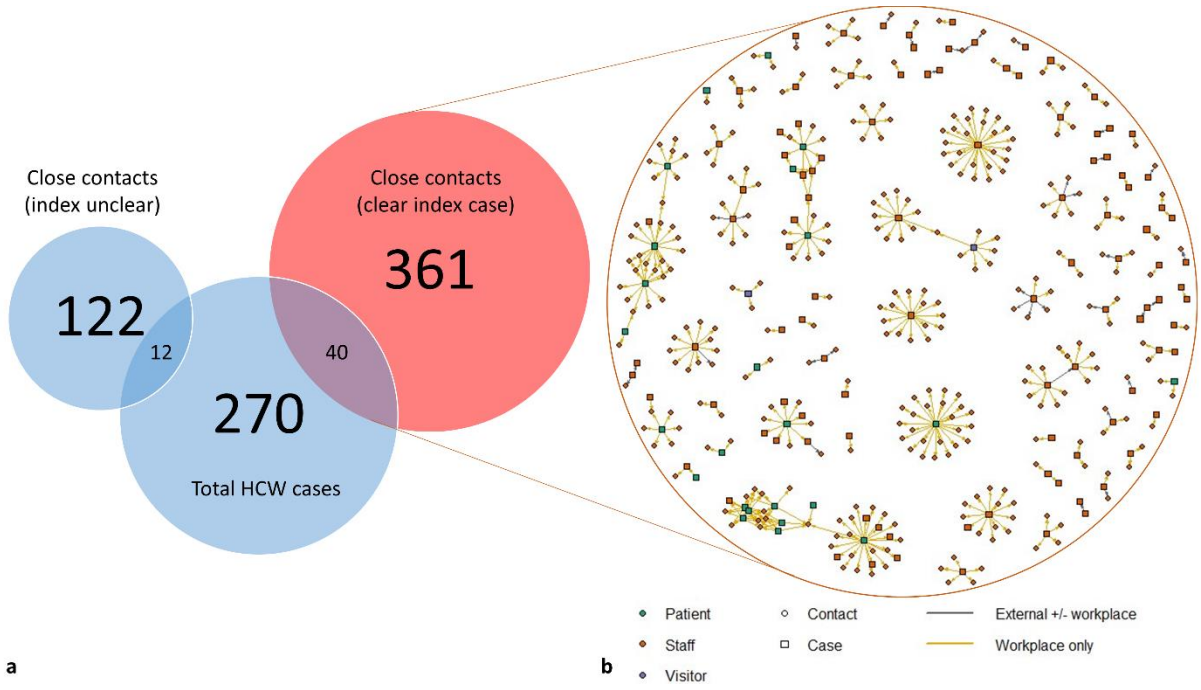
As our ability to understand the distribution and characteristics of cases and their contacts increased, new questions arose, including how well the system was working to detect infected staff members, and which exposures presented higher risk of infection. The following chapter describes a retrospective analysis I undertook of the hospital contact tracing data from the "second wave" in Melbourne, with the aim of providing evidence to refine the process of hospital-based contact tracing for COVID-19.



Snapshot of the live COVID-19 contact tracing dashboard developed by the Royal Melbourne Hospital Business Intelligence team.

Population health implications

Identification and quarantine of close contacts is key to control of outbreaks of COVID-19, but furlough of essential healthcare workers can put significant pressure on health systems. Internationally, there has been wide variation in the ways healthcare worker SARS-CoV-2 exposures have been managed, depending on assessment of risk and pressure on the system. In extreme overseas cases, infected staff have been asked to continue working (1). This analysis was important because it provided reassurance that the processes in place for classifying contacts at the time of the investigation were not unnecessarily restrictive, with about 1 in 10 quarantined close contacts subsequently testing positive (see figure next page), and likely preventing substantially more infections within the hospital. Viral evolution and changing infection control and prevention practices make it important to continue to monitor the performance of contact tracing systems in critical high-risk settings such as healthcare facilities.



COVID-19 cases and their close contacts identified through hospital-based contact tracing at Royal Melbourne Hospital; a). Overlap of health care worker (HCW) cases and close contacts; b). Network diagram showing contact between HCW close contacts and linked cases.

Lessons learned

The traditional stereotype of a 'field' outbreak investigation involving a small team of epidemiologists undertaking a pseudo-step-wise process, including confirmation of an outbreak, identification of an aetiologic organism or substance, development of case definitions, hypothesis testing, and implementation of targeted control measures, has limited relevance in the setting of an established pandemic. Instead, outbreaks are usually fairly simple to identify and define, the organism is known, and the impetus is the rapid implementation of broad control measures involving a large team from a variety of sectors. In this setting, one of the primary roles of the epidemiologist is to provide timely and accurate information and advice to those with the power to make important decisions. I gained valuable practical experience working as an epidemiologist within one of these teams, developed skills in the implementation and use of health information systems, and broadened my skills in statistical analysis and scientific communication.

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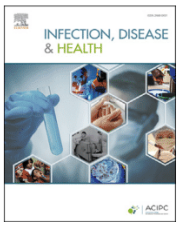

Research paper

Performance of hospital-based contact tracing for COVID-19 during Australia's second wave

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KEYWORDS
COVID-19;
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Healthcare;
Hospital

Abstract *Background:* Hospital-based contact tracing aims to limit spread of COVID-19 within healthcare facilities. In large outbreaks, this can stretch resources and workforce due to quarantine of uninfected staff. We analysed the performance of a manual contact tracing system for healthcare workers (HCW) at a multi-site healthcare facility in Melbourne, Australia, from June–September 2020, during an epidemic of COVID-19.
Methods: All HCW close contacts were quarantined for 14 days, and tested around day 11, if not already diagnosed with COVID-19. We examined the prevalence and timing of symptoms in cases detected during quarantine, described this group as proportions of all close contacts and of all cases, and used logistic regression to assess factors associated with infection.
Results: COVID-19 was diagnosed during quarantine in 52 furloughed HCWs, from 483 quarantine episodes (11%), accounting for 19% (52/270) of total HCW cases. In 361 exposures to a clear index case, odds of infection were higher after contact with an infectious patient compared to an infectious HCW (aOR: 4.69, 95% CI: 1.98–12.14). Contact with cases outside the workplace increased odds of infection compared to workplace contact only (aOR: 7.70,

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95% CI: 2.63—23.05). We estimated 30%, 78% and 95% of symptomatic cases would develop symptoms by days 3, 7, and 11 of quarantine, respectively.
Conclusion: In our setting, hospital-based contact tracing detected and contained a significant proportion of HCW cases, without excessive quarantine of uninfected staff. Effectiveness of contact tracing is determined by a range of dynamic factors, so system performance should be monitored in real-time.

Highlights

- Health care workers were identified as close contacts by hospital-based contact tracing on 483 occasions.
- 11% developed COVID-19 in quarantine, accounting for 19% of all healthcare worker cases.
- Odds of COVID-19 were higher after contact with infectious patients compared to infectious healthcare workers.
- Odds of COVID-19 were higher if close contact occurred outside of work.

Introduction

Contact tracing is a key part of the public health response to novel coronavirus disease 2019 (COVID-19) [1]. Modelling suggests that effective case isolation, contact tracing and quarantine can effectively control outbreaks, and that these strategies provide additional benefit when combined with population wide non-pharmaceutical interventions (NPIs) to limit physical contact [2]. In Australia, implementation of coordinated contact tracing, together with strict border measures, has allowed easing of NPIs without sustained community transmission [3].

Health care workers (HCWs) are at significantly elevated risk of COVID-19 [4, 5], so implementation of effective contact tracing in health care settings should be prioritised. However contact tracing is resource intensive [6], and in the context of large outbreaks quarantining large numbers of HCW can heavily impact health systems [7].

Various frameworks have been suggested to guide contact tracing in health care settings [6, 8]. However, there is a need to determine the most effective, and least restrictive, strategies for isolation, testing, and return to work [9]. We conducted a retrospective analysis of contact tracing data during an outbreak to examine the rate and timing of COVID-19 onset among HCW close contacts identified through hospital-based contact tracing, and to identify factors associated with increased risk of infection in this group.

Methods

Setting

We sourced data from a large public tertiary hospital in Melbourne, Victoria. The facility includes a 550 bed tertiary campus, a 150 bed aged care and sub-acute campus, a large mental health service and four residential aged care facilities. Around 10,000 staff were employed across 32 sites, although about 70% worked at the two main metropolitan campuses.

Victoria experienced a second epidemic of COVID-19 between June and October 2020, driven largely by local transmission within Melbourne. Stage 3 restrictions (including the closure of bars, entertainment venues, and places of worship, limiting restaurants to take-away only, and prohibiting public gatherings of more than two people) were implemented in 10 postcodes from 2 July, and expanded to all of metropolitan Melbourne from 8 July. From 2 August, Stage 4 restrictions were introduced (including an overnight curfew, limits on movement to within a 5 km radius of one's residence except for essential activities, and a 1 h limit on outdoor exercise). The epidemic included around 18,650 cases and peaked on 4 August with 687 new diagnoses [10]. The temporal distribution of new diagnoses of COVID-19 in HCWs across the facility over this period resembled the shape of the epidemic curve for Victoria as a whole [10, 11].

Use of NPIs to reduce transmission risk to HCWs at the facility changed significantly over the same period. In particular, mandatory universal mask wearing, even in non-clinical settings, was introduced and expanded from early July (Supplementary table 1). From mid-July, staff were required to wear N95 masks at all times in high-risk areas such as wards dedicated to the care of COVID-19 patients.

Contact tracing

For the purposes of this report, we define isolation as separation of suspected or confirmed cases from the general population, and quarantine as separation of non-cases deemed to be at elevated risk of infection based on exposure history. Furlough refers to the temporary removal of HCW from the workforce, while in isolation or quarantine.

Hospital-based contact tracing was undertaken by the Infection Prevention and Surveillance Service (IPSS) in accordance with guidelines provided by the Victorian Department of Health and Human Services (DHHS) [12]. Cases were notified to IPSS by the hospital laboratory, if tested at the facility. If tested elsewhere, cases were

notified by DHHS, the positive staff member themselves, or their manager.

An IPSS staff member interviewed each HCW case via phone as soon as practical after they were notified. Contact tracing was performed for the infectious period from 48 h prior to symptom onset, or first positive test if asymptomatic at notification, until the case was isolated. Close contacts were defined by DHHS as people who had either:

a) ≥15 min cumulative face-to-face contact during the prior week,
b) ≥2 h in a confined space shared with a confirmed or probable case during the prior week, or
c) been exposed to a particular setting judged by IPSS to be associated with a high risk of infection (such as a ward experiencing a widespread outbreak) [12].

HCWs wearing appropriate personal protective equipment (PPE) during care of suspected, probable or confirmed patient cases were not considered close contacts unless a breach in PPE was identified [12]. From 11 July, following advice from DHHS, mask use was considered when risk assessing contact between HCWs. In instances where both case and contact were HCWs, and both were masked, the above close contact definition was no longer applied. Instead, designation as a close contact was subject to individual risk assessment by IPSS, considering nature and duration of contact, as well as whether the case was symptomatic. Data were collected on all close contacts within the facility, and any close contact with other staff that occurred external to the facility. Data were entered into a REDCap database at the time of contact tracing.

HCW close contacts were contacted via phone and furloughed for 14 days from the last date of close contact. IPSS staff or a wellbeing team staff member provided regular follow up over the quarantine period and assisted contacts to seek testing if they developed symptoms. Return to work was contingent on a negative test result on or after day 11 and completion of quarantine, regardless of test results, although some staff also underwent asymptomatic testing earlier in the quarantine period. Testing was performed using polymerase chain reaction (PCR) on upper respiratory tract samples (nose and throat swab). Testing for respiratory viruses other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was not routinely performed.

Data source and study population

We extracted data from the REDCap database used by IPSS for case and contact management. We defined HCWs as anyone working or undertaking study in the facility and who could be exposed either directly or indirectly to SARS-CoV-2 in that setting. We included data from June—September 2020 for all cases of COVID-19 diagnosed in HCWs who attended the facility, and all HCW close contacts of another HCW, patient, or visitor case. We excluded records for HCW close contacts of a case in the community who was not also a HCW, because these contacts were not identified through hospital-based contact tracing. We also excluded records where there were insufficient data to determine why the HCW had been designated a close contact. Individual HCWs could have multiple instances in the database if they were furloughed on multiple occasions.

Data analysis

Data analysis was performed in R version 6.3.1 [13]. We calculated the overall proportion of HCW close contact instances resulting in diagnosis of COVID-19 during quarantine. We excluded from further analysis instances where HCW were furloughed without a clear index case, i.e. they were defined as a close contact according to definition c) above, but there were insufficient data to identify details and timing of specific cases they were exposed to.

For each HCW close contact instance, we extracted data on age, sex, role, symptom onset, test dates and results, number of linked potential source cases, whether the linked case first resulting in the HCW being quarantined (index case) was another HCW, a patient, or a visitor, place of contact with the index case, and date of last close contact. We classified role as "clinical" for HCWs involved directly with patient care, for example nurses, doctors, and allied health staff. Other staff, for example cleaning, administrative, security, or food handling staff we classified as "non-clinical". We classified place of close contact into either "workplace only", or "external ± workplace" where there had been close contact external to the facility, for example in a household or social setting, regardless of whether there was also contact within the facility.

We used univariate and multivariate logistic regression models to assess potential factors associated with increased odds of testing positive during quarantine, based on data available from the contact tracing database. We included HCW role, number of linked cases, place of contact with the index case, and type of index case as categorical predictors in both univariate and multivariate models, based on a priori assumptions of possible independent causal effects. We tested interactions between these variables, but none were statistically significant, and we did not include them in the multivariate model (data not shown). We included sex and age group in the multivariate model in an attempt to reduce confounding due to unmeasured behavioural factors.

For HCW close contacts who tested positive during quarantine and developed symptoms, we plotted a histogram of symptom onset by days since last close contact. We fitted gamma, Weibull and lognormal distributions using the R package "fitdistrplus" [14]. We chose the best fitting model based on the Akaike information criterion (AIC), calculated 95% confidence intervals by bootstrapping with 1000 iterations, and calculated 95% prediction intervals for developing symptoms by days 3, 7, and 11 post last close contact.

Results

We screened 506 HCW close contact records, excluded 13 due to missing data, and a further 10 identified through community rather than hospital-based contact tracing (Fig. 1). In the remaining 483 instances, HCWs were designated as close contacts and furloughed through hospital-

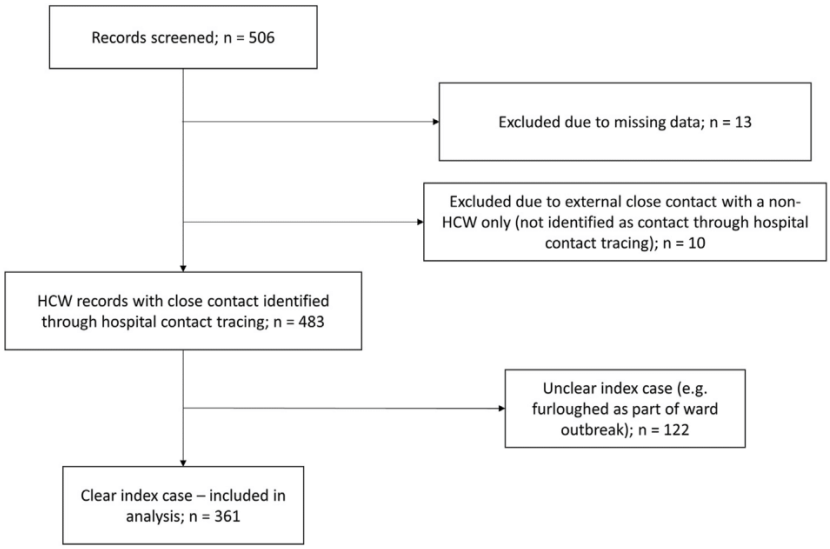

Figure 1 Selection of health care worker (HCW) database records for inclusion.

based contact tracing. Of these, 11% (52/483) resulted in diagnosis of COVID-19 during quarantine, which represented 19% (52/270) of HCW cases identified in the facility. In 25% (122/483) of instances, HCWs were furloughed without recorded contact with an index case, while in 75% (361/483) of instances, HCWs were furloughed following close contact with an index case. Twelve of 122 instances (10%) where there was no known contact with an index case resulted in a diagnosis of COVID-19. These instances were not analysed as specific index case data were not available. Forty of the remaining 361 instances (11%) where there was known contact with an index case resulted in a diagnosis of COVID-19. These 361 instances represent data from 357 unique HCWs, as 4 were quarantined more than once.

The median age of these 357 furloughed HCWs was 32 years (range 21—70), 283 (79%) were female, and 314 (88%) worked in clinical roles (218 nurses, 58 doctors, 26 allied health staff, and 12 students). These HCWs were furloughed due to close contact with at least one of 97 source cases, including 71 HCW cases, 24 patient cases where contact occurred without appropriate PPE, and two visitor cases. In 28 instances HCWs were identified as close contacts of more than one case and in 333 as close contacts of one case only (Table 1). In the multivariate model, odds of infection were higher for close contact with a patient versus a HCW index case (aOR: 4.69, 95% CI: 1.98—12.14), and for close contacts with any close contact occurring external to the workplace (aOR: 7.70, 95% CI: 2.63—23.05, Table 1). For sex, age group, role of the HCW contact, and the number of linked cases, estimated effect sizes were small, and confidence intervals included an odds ratio of 1.

The timing of testing and symptom onset was analysed in 39 of 40 HCW cases diagnosed in quarantine (Fig. 2, test dates were missing for one HCW). Seventeen cases were initially tested within 3 days of furlough either because of symptoms (8/17) or as part of asymptomatic screening (9/17), among whom 65% (11/17) were positive (Fig. 2).

Symptoms developed in 63% (25/40) of cases during the quarantine period. For these cases, the distribution of days from last contact to symptom onset was best approximated by a gamma distribution, with marginally lower AIC than the lognormal distribution (Supplementary figure 1). Based on the fitted model parameters we estimated 30% (95% CI: 16—46%) of symptomatic infected HCWs would develop symptoms by 3 days since last close contact, 78% (95% CI: 65—92%) by 7 days and 95% (95% CI: 88—100%) by 11 days (Supplementary table 2).

In 9% (31/361) of instances, HCWs reported COVID-19 compatible symptoms in quarantine but were not identified as cases. However, all reported onset prior to 11 days since last close contact and tested negative around day 11. Of these 31 HCWs, 27 had also earlier tested negative at onset of symptoms.

Discussion

In our study, approximately one in ten close contact HCWs tested positive for SARS-CoV-2 during quarantine, representing 19% of all HCW infections. We identified close contact with infected patients compared with infected HCWs, or close contact outside the health-care facility as possible risk factors for infection in quarantined HCWs. More than a third of cases diagnosed in quarantine did not develop symptoms. We estimated that almost all symptomatic infected HCWs developed symptoms by 11 days after their most recent close contact with an infectious case.

Strategies for contact tracing and quarantine should consider both individual and workforce impacts of furloughing staff, as well as the benefits associated with preventing transmission. In our setting, approximately 9 non-infected close contacts were furloughed for every case contained in quarantine. Given the substantial proportion

Table 1 Characteristics of health care workers (HCWs) furloughed due to close contact on 361 occasions, results of univariate and multivariate logistic regression predicting diagnosis of COVID-19 by polymerase chain reaction (PCR) during 14 day quarantine.

	HCW characteristics		Univariate models	Multivariate model
	Total number of close contacts	Number PCR positive (% of total)	Odds ratio (95% confidence interval)	
Sex				
Female	287	30 (10%)	Reference	Reference
Male	74	10 (14%)	1.34 (0.60–2.8)	1.35 (0.57–2.99)
Age group				
<30	142	17 (12%)	Reference	Reference
30-39	110	8 (7%)	0.58 (0.23–1.35)	0.63 (0.24–1.55)
≥ 40	109	15 (14%)	1.17 (0.55–2.47)	1.29 (0.58–2.88)
HCW role				
Non-clinical	43	4 (9%)	Reference	Reference
Clinical	318	36 (11%)	1.24 (0.47–4.32)	1.12 (0.37–4.3)
Number of linked cases				
1	333	35 (11%)	Reference	Reference
≥2	28	5 (18%)	1.85 (0.59–4.83)	1.03 (0.31–2.93)
Place of contact with index case				
Workplace only	327	31 (9%)	Reference	Reference
External ± workplace	34	9 (26%)	3.44 (1.41–7.82)*	7.70 (2.63–23.05)**
Type of index case				
Staff	218	17 (8%)	Reference	Reference
Patient	133	23 (17%)	2.47 (1.27–4.89)*	4.69 (1.98–12.14)**
Visitor	10	0 (0%)	–	–

*$p < 0.01$, **$p < 0.001$.

of overall SARS-CoV-2 transmission from asymptomatic and presymptomatic cases to (estimated to be between 20% and 70%) [15], we believe this represents a favourable trade-off. The consequences of transmission in a high-risk setting are serious, although these have to be balanced with the risks of furloughing a significant proportion of a critical workforce.

This study was conducted in the setting of widespread community transmission, with increasing HCW infections mirroring an increase in cases in the community. Our finding that risk of infection was increased with contact outside the healthcare setting is in keeping with previous investigations of infected HCWs [16], and the known propensity of SARS-CoV-2 to spread within households [17]. Our investigation highlights that hospital infection control and prevention teams need to effectively cooperate with and conduct joint risk assessments with public health authorities conducting community contact tracing.

During the COVID-19 epidemic in Victoria, about 70% of HCW or aged-care worker infections were thought to be acquired at work [18]. However, the minority of cases in our facility were detected through workplace contact tracing, with the majority detected either through symptomatic testing or wider asymptomatic screening [11]. Clearly, effective contact tracing should be accompanied by other strategies to reduce workplace transmission. Such strategies include targeted asymptomatic testing, screening everyone entering the workplace for symptoms of COVID-19, as well as optimising air flow and use of PPE [19].

Our findings suggest that among those quarantined, contact with known infected patients presented higher risk of infection than contact with known infected HCWs. This might reflect generally higher viral loads among admitted patients, associated with more severe disease [20], and differences in nature and extent of HCW-HCW and HCW-patient close contact. Several studies have attempted to follow-up HCWs exposed to COVID-19 patients, and have generally found low rates of infection [21–24]. However these typically involve a small number of selected patients [21–24], and hospital seroprevalence studies suggest many HCW cases go undiagnosed [25, 26]. Thus, there is a need for systematic prospective research involving follow-up and testing of casual contacts of hospitalised COVID-19 patients to better define risk of infection and to refine quarantine requirements.

We estimated that 88–100% of HCWs who develop symptoms after being quarantined will do so within 11 days of last close contact. This is consistent with data on the incubation period of SARS-CoV-2 [27], accounting for some HCWs being infected prior to the most recent exposure. Given SARS-CoV-2 viral load in upper respiratory tract samples peaks around symptom onset [20, 28], and that viral load appears to be similar in asymptomatic and mildly symptomatic cases [29–31], testing on day 11 could be expected to detect the vast majority of HCW cases who would otherwise pose a risk of onwards transmission. Our findings suggest that a strategy involving testing on days 3 or 7 might fail to detect a substantial proportion of

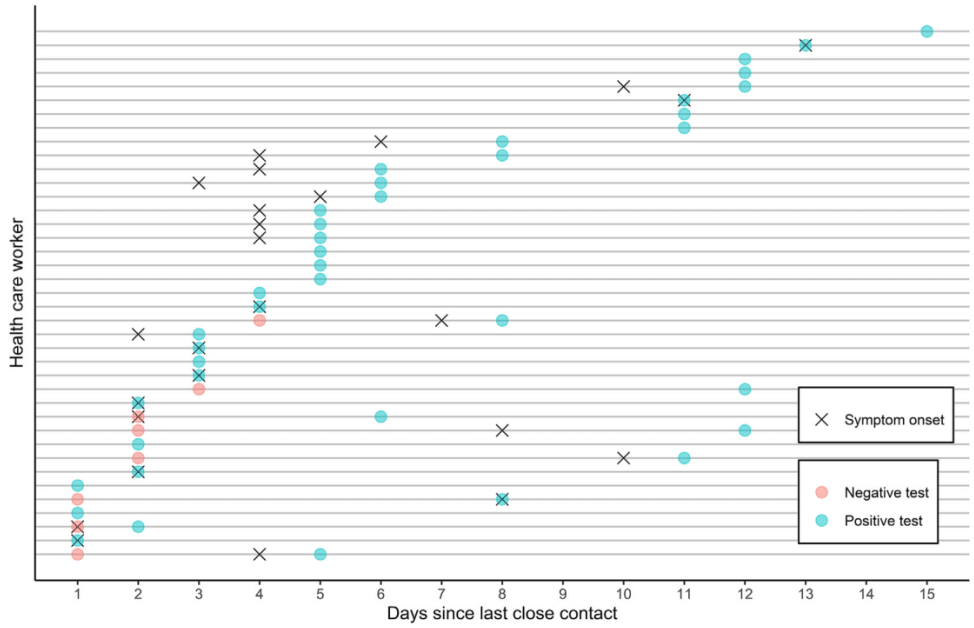

Figure 2 Timing of symptom onset and testing in 39 health care workers diagnosed with COVID-19 during quarantine.

asymptomatic or pre-symptomatic cases. Indeed, a number of HCW cases in our study were PCR-negative when tested early in the quarantine period. However, earlier identification of infected HCWs in quarantine would have facilitated earlier identification of their contacts, providing opportunities to prevent further transmission.

Our study has several limitations. First, due to the substantial workload on contact tracing staff, data sometimes contained limited information on nature of contact or possible exposures outside of the workplace, preventing more detailed analysis. Further, during the peak of the second epidemic, delays of up to several days in both turnaround time of results from some external pathology services, and in case follow-up and reporting by the DHHS, in turn led to unavoidable delays in initiating contact tracing, which may have affected the ability of cases to provide an accurate history of contact at the time of interview.

Second, when investigating factors associated with risk of infection in close contacts, we considered information about the index case, but not other cases the HCW was subsequently identified as having been exposed to. While this approach may be helpful in informing risk assessment in real-time, it does not account for possible sources of infection other than the index case. While exposure misclassification due to undocumented contact is likely to have occurred, we did not set out to make inferences based on a complete picture of each individual's exposures, but to determine how contact tracing data could be used to better define risk.

Third, it is possible some asymptomatic cases with long incubation periods may have gone undetected on day 11 testing, biasing estimates around symptom onset towards earlier in the quarantine period. However, this seems unlikely based on current incubation period data [27], and we are not aware of any study HCWs being diagnosed in the immediate period following quarantine.

Fourth, caution should be used in attempting to apply our findings to other settings, as a range of dynamic and difficult to measure factors affect generalisability. These include HCW factors, such as the proportion of staff vaccinated or previously infected, facility factors including close contact definitions and workplace practices, and pathogen factors including the presence of more infectious variants.

The COVID-19 pandemic has demonstrated the critical importance of systems for hospital contact tracing, but has also put them under unprecedented strain. In our setting, contact tracing detected and contained a substantial proportion of HCW cases, without requiring furlough of an excessive number of non-infected staff. These data demonstrate that our contact tracing and furlough procedures likely prevented many more cases in HCWs, although there were significant impacts on the workforce. Collection of large amounts of data for contact tracing purposes poses logistical challenges, but it also provides opportunities to gain insight into how systems are performing and may be improved. This requires hospitals to implement robust processes for data collection and storage, facilitating near to real-time analysis. This may be aided by better integrating systems for contact tracing run by hospitals and other public health agencies, and by exploring novel methods for automated contact tracing [32]. Planning for hospital-based contact tracing should be accompanied by workforce planning that can accommodate furlough of large numbers of staff.

Ethics

This study was assessed by the Melbourne Health Human Research Ethics Committee (HREC) as an evaluation activity not requiring HREC review (QA2020192).

Authorship statement

CB: formal analysis, investigation, methodology, visualisation, writing — original draft. VL: data curation, investigations, writing — review & editing. EO: investigation, writing — review & editing. ES: data curation, software. CK: writing — review & editing. KLB: writing — review & editing. BCC: writing — review & editing. MDK: supervision, writing — review & editing. SGS: supervision, writing — review & editing. CM: conceptualisation, investigation, methodology, writing — review & editing.

Conflict of interest

The authors have no conflicts of interest to report.

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Provenance and peer review

Not commissioned; externally peer reviewed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.idh.2021.09.001.

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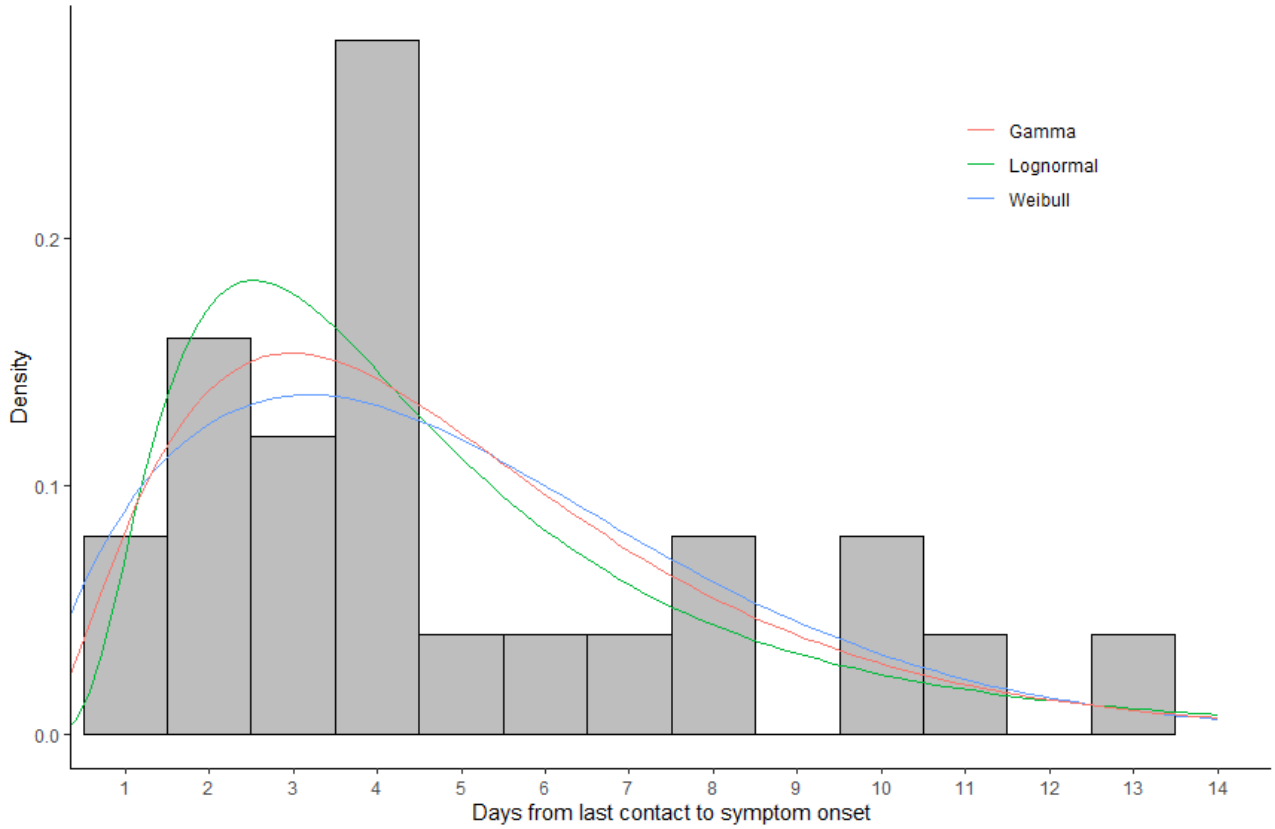
Supplementary table 1. Changes to personal protective equipment (PPE) requirements for staff over the study period at The Royal Melbourne Hospital

Date	Changes to staff PPE requirements
Prior to 4 July 2020	For care of suspected, probable, or confirmed COVID-19 patients: • Long sleeved gowns, gloves, eye protection and surgical mask. • Airborne precautions for aerosol-generating procedures (AGPs). No requirement for staff mask wearing in other situations other than mandated by transmission-based precautions.
4 July 2020	All staff: surgical masks required for all clinical and non-clinical areas when physical distancing cannot be maintained.
9 July 2020	Public-facing staff: surgical masks required, other than when eating or drinking. Non-public-facing staff: surgical masks or face shields required when physical distancing cannot be maintained.
14 July 2020	Emergency department staff working in "hot" zone: N95 masks required (in addition to long sleeved gowns, gloves and eye protection already in place).
17 July 2020	Public-facing staff: surgical masks and eye protection required, other than when eating or drinking. Non-public-facing staff: surgical masks or face shields required, other than when eating or drinking.
20-21 July 2020	Selected high-risk wards (caring for COVID-19 confirmed, suspected or quarantined patients and outbreak wards): Long sleeved gowns, gloves, eye protection and N95 masks at all times.
24 July 2020	N95 masks required for care of all patient during AGPs (regardless of COVID-19 status). Long sleeved gowns, gloves and eye protection during care of patients identified as close contacts or in quarantine. Non-public-facing staff: surgical masks required, other than when eating or drinking, or alone in an office. Additionally, face shield or goggles required when physical distancing cannot be maintained.

Supplementary table 2. Parameters of probability distributions used to estimate days from last close contact to symptom onset in 25 health care workers with COVID-19.

	Gamma	**Lognormal**	**Weibull**
Parameters (95% CI)	*Shape = 2.47 (1.63 - 4.80)*	*ln(μ) = 1.39 (1.14 - 1.67)*	*Shape = 1.64 (1.29 - 2.42)*
	Rate = 0.49 (0.31 – 1.01)	*ln(σ) = 0.68 (0.49 - 0.85)*	*Scale = 5.62 (4.25 - 6.96)*
Probability of symptoms by:	**95% confidence interval**		
Day 3	16-46%	18-48%	15-45%
Day 7	65-92%	66-91%	64-90%
Day 11	88-100%	84-99%	89-100%



Supplementary figure 1. Distribution of symptom onset by days since last close contact in 25 health care workers diagnosed with COVID-19 during quarantine. Lines show gamma, lognormal, and Weibull distributions fitted by maximum likelihood. The Akaike information criterion values were 125.3, 125.4, and 126.1 respectively.

Chapter 3: Short-term effects of ambient fine particulate air pollution on respiratory illness, Melbourne, 2014-2019

Prologue

I became interested in the relationship between air pollution and respiratory health for several unrelated reasons. The first was a selfish one of personal experience with intractable runny nose and cough while holidaying in New Delhi in the winter of 2017. Second, like many people I was shocked by the extremely poor air quality affecting Australian cities as a result of massive bushfires over the 2019-2020 summer. However, primarily I was interested in learning more about research methods in environmental epidemiology. How could scientists claim to determine the effects of often imperceptible changes in concentrations of airborne pollutants on incidence of illness at some later date, when studies involving interventions in much more controlled settings, such as hospitals, were already complicated by so many potential biases?

Environmental epidemiology faces unique challenges. It must deal with numerous intercorrelated exposures, most with relatively small effects on health outcomes. It is rarely practical to conduct experimental studies of environmental exposures, and observational studies are further complicated because exposures are seldom measured at the individual level. Nevertheless, it is becoming increasingly important to quantify the health effects of changes to the environment and climate that result from human activity.

Apart from during bushfire events Melbourne generally does not suffer from poor air quality by international standards. I was interested in whether low-level fluctuations in outdoor fine particulate matter that result from everyday sources of pollution have effects on acute respiratory illnesses in our population.

My role

I performed a literature review, developed the study protocol and ethics submission, collated and analysed the data and drafted the chapter.

Population health implications

Findings of this analysis build on previous literature describing the short term effects of fine particulate matter air pollution on respiratory illness by providing additional detail on the differing effects across age groups and impact on hospital use in a setting with generally low levels of outdoor air pollution. They provide some additional justification for efforts to improve ambient air quality over-and-above previous guideline levels, in line with recent changes to the WHO air quality

guideline values made in September 2021. More evidence on the most effective interventions to reduce the impact of air pollution on human health would be useful.

Lessons learned

I gained a much better appreciation of techniques and challenges in environmental epidemiology, including: observational study designs; management of large datasets, approaches to handling missing data; analysis of time-series data, and some complexities in causal inference.

Effect of ambient $PM_{2.5}$ on healthcare utilisation for acute respiratory illness, Melbourne, Victoria, 2014-2019.

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Abstract

Ambient fine particulate matter ($PM_{2.5}$) is an important component of natural and human-generated air pollution and a major contributor to the global burden of disease. Short-term effects of $PM_{2.5}$ exposure on respiratory illness have been described but most evidence arises from high pollution settings. We used case-crossover methods to estimate effects of outdoor $PM_{2.5}$ levels on emergency department (ED) presentations and hospital admissions for a range of acute respiratory illnesses and age groups in Melbourne, Australia from 2014-2019. We performed analyses with and without adjustment for other pollutants and weather conditions, using daily and one-week averaged lags. We estimated incidence rate ratios for a 10 $\mu g/m^3$ increase in 7-day average ambient $PM_{2.5}$ of 1.043 (95% CI: 1.000 – 1.089) on ED presentation and 1.013 (95% CI: 0.971 – 1.056) on hospital admissions for acute respiratory illnesses for patients of any age. We observed distinct temporal patterns in daily lag effect by disease. The largest effects on acute lower respiratory tract infection and asthma were observed in children. Ambient $PM_{2.5}$ levels rarely exceeded standards in place at the time. Although uncertainty around most point estimates was relatively wide, these findings are most compatible with adverse health effects of ambient $PM_{2.5}$ at levels below currently established Australian national standards.

Background

The World Health Organization (WHO) considers air pollution the most serious environmental risk to human health, through its contribution to the burden of stroke, ischemic heart disease, chronic obstructive pulmonary disease (COPD), lung cancer, and acute respiratory illnesses (1). Fine particulate matter 2.5 microns in diameter or smaller ($PM_{2.5}$) is an important component of outdoor air pollution. In Melbourne, the human contribution to $PM_{2.5}$ arises mainly from wood burning (including for domestic wood heaters, land burning, and bushfires), motor vehicles, and industry (2). Ambient $PM_{2.5}$ is estimated to have been responsible for 4.2 million deaths worldwide in 2015 (3).

In addition to its contribution to chronic disease, numerous epidemiological studies have demonstrated short-term relationships between ambient $PM_{2.5}$ and healthcare encounters for respiratory diseases (4-12). However, most studies have focussed on cities in the northern hemisphere, and there is evidence for region-specific effects (12, 13). Mechanisms by which exposure to elevated $PM_{2.5}$ might lead to acute respiratory illness include induction of bronchial hyperreactivity, acute pro-inflammatory effects, direct cytotoxicity, pathogen transfer via particulate matter, and effects on individual behaviour which in turn might increase exposure to respiratory viruses, for example through causing people to spend more time together indoors (14-16).

Justifiably, many recent studies have been conducted in areas where air quality falls below national or international standards (6, 7, 9). Despite a recognition among scientists that there is no known "safe" level of $PM_{2.5}$ exposure (1), public perception of air pollution risk is often linked to immediate harm experienced as a result of extreme pollution events (17), including extreme bushfires. This may in part be due to public reporting of air quality in terms of value-based categories such as "good" or "poor" (18). Although much attention has been given to the impacts of air pollution during extreme fire events, an individual's typical $PM_{2.5}$ exposure is far more likely to be at routine air pollution levels rather than the very high concentrations seen during air pollution events. Therefore, understanding the impacts of lower-level exposures is still highly relevant.

In September 2021, WHO issued new global air quality guidelines to replace those previously updated in 2005 (19). Under the new guidelines, targets for ambient $PM_{2.5}$ were reduced from an annual mean of 10 $\mu g/m^3$ to 5 $\mu g/m^3$, and a maximum 24-hour mean of 25 $\mu g/m^3$ to 15 $\mu g/m^3$ (20, 21). These changes represent accumulating evidence for adverse health effects of air pollution at lower concentrations (21). However, in assessing short-term respiratory effects of ambient $PM_{2.5}$, WHO considered only impacts on mortality (21, 22), and there remains limited evidence for effects on healthcare utilisation across the age range at lower levels of exposure. We used case-crossover methods to estimate the effects of ambient $PM_{2.5}$ on healthcare encounters for acute respiratory illness in Melbourne, Australia, a relatively unpolluted city by international standards (23), from 2014-2019.

Methods

Target population and setting

We chose the population and setting based largely on the availability of air monitoring data in Victoria. Because there is a relatively higher concentration of regulatory monitoring stations measuring $PM_{2.5}$ in Melbourne compared to regional Victoria (23), we limited our analysis to metropolitan Melbourne, an area with an estimated population of 5,079,123 residents as of 2019 (24), spanning approximately 9990 km^2 (25), and divided into 31 local government areas (LGAs) (Figure 1). We chose a study period of 2014-2019 inclusive, based on relative availability of complete air monitoring data, including data on $PM_{2.5}$.

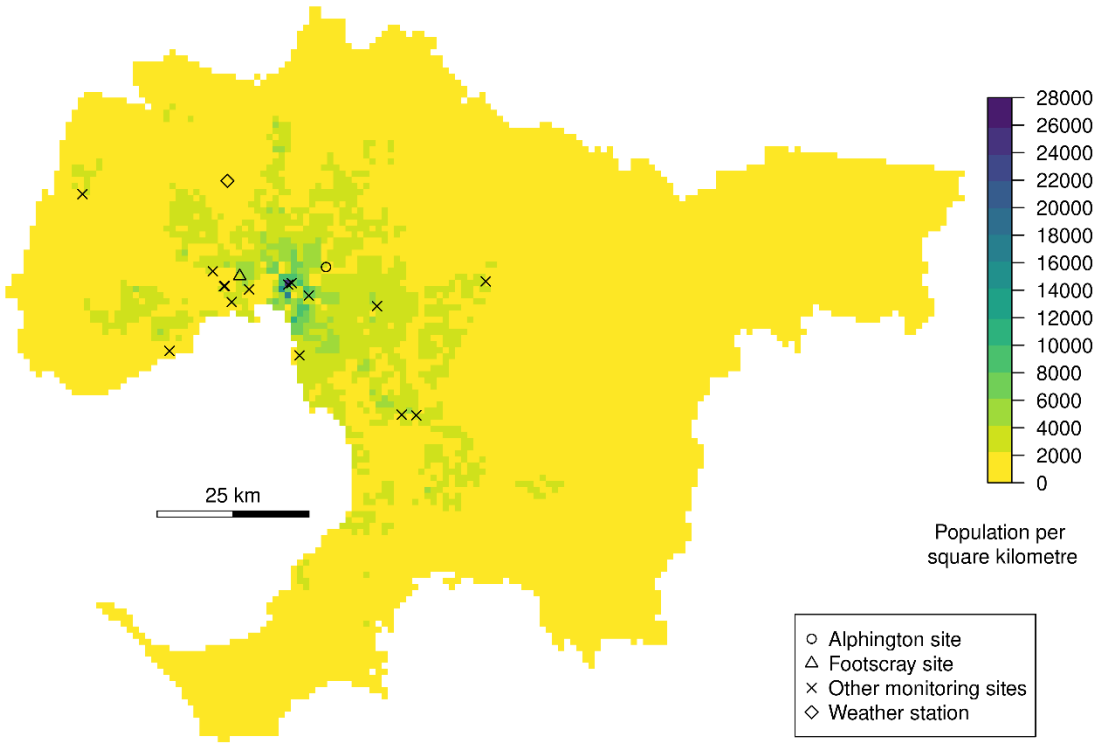

Figure 1. Map of metropolitan Melbourne showing population density (2017), and the location of air quality and weather monitoring stations for which data was obtained. *Analysis was based on data from the Alphington and Footscray sites and Melbourne airport weather station. Other monitoring sites were used to impute missing data.*

Data sources

Healthcare encounters for acute respiratory illness

From the Victorian Department of Health, we obtained daily counts of inpatient admissions to public and private hospitals (26), and emergency department (ED) presentations to public hospitals (27), for all episodes in 2014-2019 where the patient resided within metropolitan Melbourne, and a primary diagnosis consistent with acute respiratory illness was recorded. Data on residential location was provided at the LGA level.

We classified ED presentations and hospital admissions into the following diagnosis groups based on the International Statistical Classification of Diseases and Health Related Problems, 10th revision, Australian Modification (ICD-10-AM) primary diagnosis codes: acute upper respiratory infection (AURI), acute lower respiratory infection (ALRI), and asthma/COPD. A list of codes included in each group is included as supplementary material. In addition, because patterns of respiratory illness differ by age, patient age was aggregated into the following categories: 7 days - 4 years, 5-17 years,

and 18 years or older. We assessed subgroup outcomes separately for each combination of diagnosis group, age group, and healthcare encounter (ED presentation or hospital admission).

Exposure data

We obtained publicly available air monitoring data from the Environmental Protection Authority Victoria for 16 monitoring stations located within metropolitan Melbourne (28). We obtained hourly measurements of ambient $PM_{2.5}$, as well as other ambient pollutants which might confound the effect of $PM_{2.5}$ exposure on respiratory health outcomes, due to their shared sources and independent effects on human health (16). These included fine particulate matter less than or equal to 10 microns in diameter (PM_{10}), ozone (O_3), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2). Meteorological conditions, including temperature and humidity, may affect concentrations of airborne pollutants (29), as well as incidence of acute respiratory illness (30), and may therefore confound the effect of $PM_{2.5}$ on healthcare encounter. We obtained hourly measures of dry bulb and dew point temperature at Melbourne Airport from the Australian Bureau of Meteorology (31). We calculated 24 hour means (midnight to midnight) for each set of hourly measures.

Exposure assignment

Pollutant data were most complete for two long-term ambient monitoring sites at Alphington and Footscray. We therefore limited the analysis to data from these two sites. Most other stations collected data on a limited set of pollutants and/or were temporary monitors set up in response to local pollution concerns (23). For the primary analysis, we assigned pollutant exposure for each event based on the station closest to the centroid of the patient's residential LGA. We explored alternative exposure assignments in sensitivity analyses.

Handling of missing exposure data

In the original dataset, 9% of hourly measurements for the Alphington site and 25% for the Footscray site were missing. Handling of missing data by calculating 24 hour means for periods with a minimum proportion of non-missing data (e.g. 75% complete), followed by list-wise deletion, would have resulted in a substantial proportion of observations being dropped from the analysis. Instead, we used multiple imputation by chained equations, implemented in the "mice" package in R (32), to impute missing hourly data for all independent variables based on available data from all 16 air quality monitoring sites and the weather station. We pooled estimates from analyses performed on 10 imputed datasets to incorporate uncertainty associated with imputed observations into the final parameter estimates (32).

Study design

We used a time-stratified case-crossover design commonly applied to studies of the short-term effects of environmental exposures (6, 10, 11, 33). In this design, each day is matched to several referent, or control days within the same stratum (33). We selected referent dates as the 3-4 dates in the same month and year that shared the same weekday with each event date. This design offers some advantages over a time-series analysis in the form of intrinsic adjustment for time-invariant confounding through individual factors such as age and comorbid conditions, as well as control for long-term trends in exposure and outcome (33, 34), but at the cost of reduced statistical precision (34). It relies on the assumption that the outcome of interest is rare at the individual level, i.e. that the same individual does not experience multiple events during the period for referent selection.

Statistical analysis

Model specification

Under the conditional quasi-Poisson model, the number of events on day i in stratum s, $Y_{i,s}$, conditional on the sum of events in each stratum, $Y_{.,s}$, is given by (35):

$$Y_{i,s}|Y_{.,s}\ Multinomial(\{\pi_i\}), \pi_i = \frac{e^{\beta^T x_i}}{\sum_{j \in S} e^{\beta^T x_j}} \quad \text{Eq. 1}$$

Where other days in the same stratum are denoted by j, and β^T is the transposed vector of model parameters to be estimated. x_i is a vector of variables corresponding to day i, in this case the exposure and covariates measures for the corresponding lag. We considered individual models with between 0 and 6 days' lag between exposure and outcome, as well as a model with exposures averaged across one week from days 0-6.

We ran separate conditional quasi-Poisson models for each combination of age group (including a combined age category), outcome, and lag, using the "gnm" package (36) in R version 3.6.1. Analysis using the conditional quasi-Poisson model is computationally more efficient than with the conditional logistic regression model traditionally applied to case-crossover studies and provides more robust uncertainty estimates in the presence of overdispersed count data (35). Our primary analysis models adjusted for all pollutant and weather covariates for the same lag period. We excluded one highly influential outlier count from the regression models arising from an extreme thunderstorm asthma event in November 2016 (37). We expressed results of the analysis in the form of incidence rate ratio (IRRs), obtained by taking the exponent of estimated model coefficients for a 10 μg/m^3 increase in $PM_{2.5}$ (21).

Sensitivity analyses

We conducted sensitivity analyses for the method of exposure assignment, including restricting analysis to only those events where the patient lived in an LGA less than 10km from the Alphington or Footscray sites, as well as assigning exposure for all events from the site with the highest proportion of complete data (Alphington). We also conducted analyses examining the effects of removing from the models all pollutant covariates, all weather covariates, or both sets. Because ambient pollen exposure has been suggested to confound the effects of pollutants on respiratory illness (38-40), we conducted a sensitivity analysis by excluding all events occurring between 1 October and 31 January, months when outdoor grass pollen levels are elevated in Melbourne (41).

Ethics approval

The study protocol was approved by the Australian National University Science and Medical Delegated Ethics Review Committee (protocol 2021/076).

Results

The average median 24 hour mean concentrations of $PM_{2.5}$ over the study period were 6.9 $\mu g/m^3$ at the Alphington site and 6.7 $\mu g/m^3$ at the Footscray site (Table 1). Yearly mean $PM_{2.5}$ concentrations remained below the 2005 WHO guideline (20) for an upper limit annual mean of 10 $\mu g/m^3$, but above the 2021 WHO guideline (21) level of 5 $\mu g/m^3$ in every year at both sites. At the Alphington site, the 2005 guideline for an upper limit 25 $\mu g/m^3$ 24-hour mean $PM_{2.5}$ was exceeded on a median of 5 days per year (range: 4-9 days), and the 2021 24 hour-hour mean limit of 15 $\mu g/m^3$ was exceeded on a median of 26 days per year (range: 21-41 days). There were no obvious long-term trends in concentrations of $PM_{2.5}$, other pollutants, or weather variables across the study period (Tables 1 & 2).

Overall, ED presentations with a primary diagnosis classified as ALRI (n = 184,205) were more common than those classified as AURI (n = 164,365), or asthma/COPD (n = 121,714; Table 3). Patterns differed by age group, with AURI being the most common classification for individuals aged <18 years. ALRI was the most common classification for hospital admission overall (n = 207,671), followed by asthma/COPD (n = 148,187), and AURI (n = 61,258), but asthma was the most common primary diagnosis for the 5-17 year age group.

Table 1. Summary of original and imputed hourly pollutant measurements for the Alphington and Footscray monitoring sites, 2014-2019.

Measure	Year	% missing[4]		24-hour mean: Median (interquartile range)				Yearly mean			
				Imputed		Original		Imputed		Original	
		Alphington	Footscray	Alphington	Footscray	Alphington	Footscray	Alphington	Footscray	Alphington	Footscray
$PM_{2.5}$ ($\mu g/m^3$)	2014	9	100	7.4 (4.1)	7.4 (3.1)	7.3 (4.3)	-	8.6	8.1	8.7	-
	2015	21	26	7.1 (3.7)	7 (3.6)	7 (4.4)	6.8 (3.6)	8.3	7.7	8.4	7.6
	2016	14	5	6.4 (3.8)	6.1 (3.8)	6.3 (4)	6.1 (3.9)	7.4	6.9	7.4	6.9
	2017	6	2	7.3 (4.5)	6.5 (3.9)	7.4 (4.7)	6.5 (4)	8.9	7.8	8.9	7.8
	2018	10	10	6.6 (3.9)	6.4 (3.5)	6.5 (3.9)	6.4 (3.9)	8.1	7.6	8	7.7
	2019	32	1	6.3 (4)	6.5 (3.9)	6.4 (4.7)	6.5 (3.9)	7.5	7.5	7.6	7.5
	Overall	15	24	6.9 (4.1)	6.7 (3.7)	6.9 (4.5)	6.5 (3.8)	-	-	-	-
PM_{10} ($\mu g/m^3$)	2014	3	1	15.4 (7.6)	17.3 (10.1)	15.4 (7.5)	17.3 (10)	16.5	18.9	16.6	18.9
	2015	6	2	14.3 (7.8)	15.3 (11.1)	14.5 (7.7)	15.3 (11.3)	15.5	16.9	15.5	16.9
	2016	4	4	13.7 (8.7)	14.1 (9.2)	13.5 (8.7)	13.7 (9.7)	14.5	15.2	14.5	15.2
	2017	2	6	14.3 (8.2)	16.1 (9.5)	14.3 (8.1)	16.2 (9.8)	15.3	17	15.4	17.1
	2018	8	3	15.8 (10.2)	16.6 (10.4)	16 (10.8)	16.5 (10.5)	18.1	18.4	18.3	18.4
	2019	3	19	15.4 (11.2)	16.4 (12.7)	15.7 (11.3)	15.7 (11.5)	18.2	20.1	18.3	19
	Overall	4	6	14.8 (8.7)	15.9 (10.4)	14.8 (8.8)	15.8 (10.5)	-	-	-	-
CO (ppm)	2014	8	6	0.3 (0.2)	0.2 (0.2)	0.3 (0.2)	0.2 (0.2)	0.3	0.2	0.3	0.2
	2015	12	30	0.3 (0.1)	0.3 (0.2)	0.3 (0.1)	0.4 (0.1)	0.3	0.3	0.3	0.4
	2016	9	9	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.3	0.1	0.3	0.1
	2017	6	9	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.2	0.2	0.2	0.1
	2018	6	15	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.2	0.1	0.2	0.1
	2019	6	5	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.2	0.1	0.2	0.1
	Overall	8	12	0.2 (0.1)	0.1 (0.1)	0.2 (0.1)	0.1 (0.2)	-	-	-	-
O_3 (ppb)	2014	6	5	14.8 (7.2)	15.6 (7.4)	14.8 (8)	15.6 (7.7)	15.2	16.1	15.2	16.1
	2015	15	5	14.3 (7.7)	14.7 (6.6)	14.5 (8.3)	14.7 (7)	15	15.5	14.9	15.4
	2016	6	38	13.4 (6.5)	14.5 (6)	13.3 (7.2)	13.7 (6.4)	13.8	14.7	13.7	14.5
	2017	16	5	14.4 (9.1)	15.3 (7.6)	13.6 (9.3)	15.2 (8)	15	15.8	14.2	15.8

[4] Of hourly measures in original dataset

	2018	6	52	15.3 (9.1)	16.2 (7.6)	15.4 (9.5)	16.2 (7.5)	16.1	16.9	16.1	18.1
	2019	6	5	16 (7.5)	15.3 (6.9)	16 (7.9)	15.3 (7.2)	16.6	16	16.6	16
	Overall	9	18	14.7 (7.7)	15.4 (6.9)	14.7 (8.2)	15.2 (7.1)	-	-	-	-
NO_2 (ppb)	2014	8	7	9 (5.7)	9.6 (7)	9.1 (6.2)	9.7 (7.2)	9.7	10.6	9.8	10.7
	2015	12	5	8.9 (5.7)	9.8 (6.7)	9.1 (6)	10 (7)	9.6	10.6	9.7	10.7
	2016	9	8	8 (5.3)	8.8 (6.4)	8 (5.6)	8.8 (6.7)	8.9	9.9	8.9	10
	2017	9	10	9.2 (6.4)	10.3 (7.8)	9 (6.9)	10.4 (8.3)	9.8	11.1	9.7	11.5
	2018	6	5	8.6 (6.2)	9 (6.2)	8.7 (6.4)	9.2 (6.8)	9.5	10.2	9.6	10.3
	2019	8	5	8.2 (5.7)	9.5 (6.5)	8.1 (5.9)	9.3 (7)	9	10.4	9	10.4
	Overall	9	7	8.6 (5.9)	9.5 (6.8)	8.6 (6.2)	9.6 (7.1)	-	-	-	-
SO_2 (ppb)	2014	8	11	0.5 (0.8)	0.8 (1.3)	0.5 (0.8)	0.8 (1.5)	0.6	1	0.6	1.1
	2015	17	82	0.4 (0.5)	0.8 (0.8)	0.4 (0.6)	0.8 (1.1)	0.5	1	0.5	1
	2016	9	100	0.2 (0.4)	0.8 (0.8)	0.2 (0.5)	-	0.4	0.9	0.4	-
	2017	7	100	0.3 (0.5)	0.9 (0.8)	0.3 (0.5)	-	0.4	1.1	0.4	-
	2018	6	100	0.3 (0.5)	0.9 (0.7)	0.3 (0.5)	-	0.4	1	0.4	-
	2019	6	100	0.2 (0.5)	1 (0.7)	0.2 (0.5)	-	0.4	1.1	0.4	-
	Overall	9	82	0.3 (0.6)	0.9 (0.9)	0.3 (0.6)	0.8 (1.4)	-	-	-	-

Table 2. Summary of original and imputed hourly meteorological measurements for the Melbourne airport weather station, 2014-2019.

Measure	Year	% missing[5]	24-hour mean: Median (interquartile range)		Yearly mean	
			Imputed	Original	Imputed	Original
Dry bulb temp (°C)	2014	0	14.6 (6.6)	14.7 (6.7)	15.1	15.1
	2015	0	13.9 (7.5)	13.8 (7.5)	14.7	14.7
	2016	1	14.1 (7)	14.2 (7.1)	14.8	14.9
	2017	0	14 (8.9)	14 (8.9)	14.9	14.9
	2018	0	14.5 (7.8)	14.5 (7.8)	14.9	14.9
	2019	0	14.1 (7.9)	14.1 (7.9)	14.9	14.9
	Overall	0	14.2 (7.5)	14.2 (7.5)	-	-
Dew point temp (°C)	2014	0	7.8 (4.4)	7.8 (4.4)	8.2	8.2
	2015	0	7 (4.4)	7 (4.4)	7.5	7.5
	2016	1	7.8 (4.5)	7.8 (4.5)	8.3	8.3
	2017	0	7.6 (6)	7.6 (6)	8.1	8.1
	2018	0	7 (5.7)	7 (5.7)	7.5	7.5
	2019	0	6.9 (4.1)	6.9 (4.1)	7.3	7.3
	Overall	0	7.3 (4.8)	7.3 (4.9)	-	-

[5] Of hourly measures in original dataset

Table 3. Recorded emergency department presentations and hospital admissions for acute upper respiratory infection (AURI), acute lower respiratory infection (ALRI), and asthma or chronic obstructive pulmonary disease (COPD), for residents of metropolitan Melbourne 2014-2019, by age.

Event type	Diagnosis group	Number of events (% of total)			
		7 days - 5 years	5-18 years	>=18 years	Total
Emergency department presentations	AURI	88491 (54)	26620 (16)	49254 (30)	164365 (100)
	ALRI	52450 (28)	8866 (5)	122889 (67)	184205 (100)
	Asthma/COPD	28997 (24)	21869 (18)	70848 (58)	121714 (100)
Hospital admissions	AURI	23788 (39)	6707 (11)	30763 (50)	61258 (100)
	ALRI	32845 (16)	5706 (3)	169120 (81)	207671 (100)
	Asthma/COPD	15588 (11)	10950 (7)	121649 (82)	148187 (100)

Our analysis was consistently most compatible with positive short-term effects of elevated ambient $PM_{2.5}$ on both ED presentations (day 0-6 lag; IRR: 1.043, 95% CI: 1.000-1.089) and hospital admissions (day 0-6 lag; IRR: 1.013, 95% CI: 0.971-1.056) for acute respiratory illness (Figure 2). For ED presentations, IRR estimates from all daily lag models were >1 and were highest for the day 4 lag (IRR: 1.022, 95% CI: 1.001-1.044). For admissions, all estimates were >1 except for the day 1 and day 5 lag models, although all 95% CIs crossed the null except for in the day 1 lag model (IRR: 0.979, 95% CI: 0.959-0.999).

For asthma/COPD, the largest effects were estimated for the day 4 lag for both ED presentations (IRR: 1.045, 95% CI: 1.008-1.084), and admissions (IRR: 1.034, 95% CI: 1.004-1.065). Comparatively larger effects were estimated in the 7 days – 4 years and 5-17 years groups (Figure 3). For ALRI, larger estimates generally arose from longer lag models, with the largest daily effects estimated for the day 6 lag for both ED presentations (IRR: 1.030, 95% CI: 1.001-1.059), and admissions (IRR: 1.034, 95% CI: 1.007-1.062). The largest effects on ALRI events were estimated for the 7 days – 4 years group. Day 0 lag ALRI models produced estimates <1 (ED presentations: IRR: 0.980, 95% CI: 0.953-1.008. Admissions: IRR: 0.979, 95% CI: 0.954-1.005).

For AURI, IRR estimates for the effect of elevated ambient $PM_{2.5}$ were >1 for ED presentations (0-6 day IRR: 1.037, 95% CI: 0.973-1.104), but <1 for admissions (0-6 day IRR: 0.910, 95% CI: 0.832-0.995). There were no clear patterns in AURI age effects or tends in daily lag estimates.

Altering the method of exposure assignment had only small and inconsistent effects on model point estimates (Supplementary figure S3). Estimates obtained from models excluding weather covariates were similar to those from the primary analysis; however, exclusion of pollutant covariates typically led to substantially higher IRR estimates (Supplementary figure S4). Excluding pollen-season months from the analysis led to similar or slightly higher estimates (Supplementary figure S5).

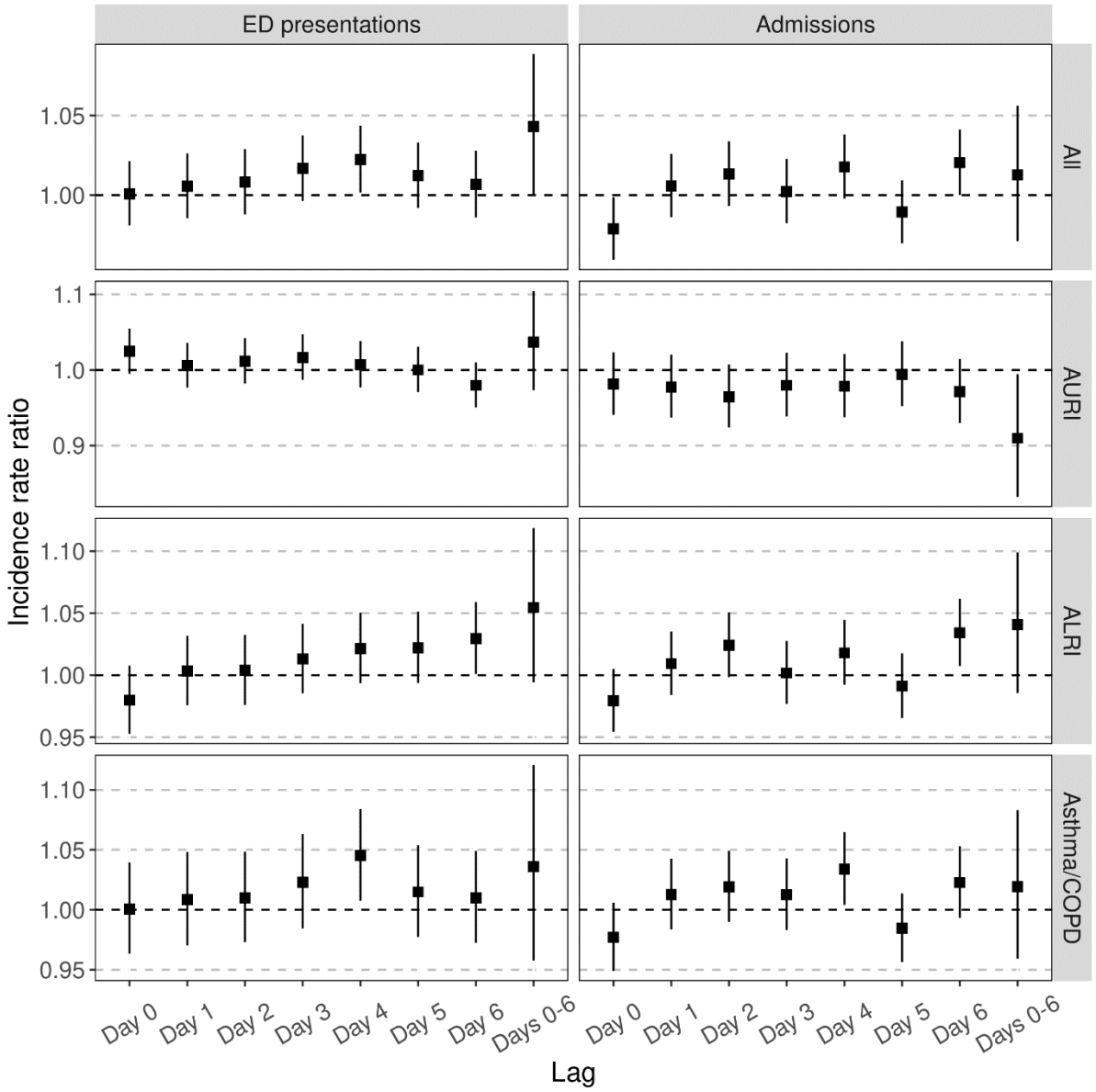

Figure 2. Incidence rate ratios for the estimated short-term effects of for a 10 µg/m³ increase in ambient $PM_{2.5}$ concentration on emergency department (ED) presentations and hospital admissions for acute respiratory illnesses. *Lags refer to the number of days from exposure/covariate measurement to outcome. Lag "Days 0-6" refers to the effect of exposures averaged across days 0-6 prior to outcome measurement. AURI: acute upper respiratory infection, ALRI: acute lower respiratory infection, COPD: chronic obstructive pulmonary disease. Vertical lines represent 95% confidence intervals.*

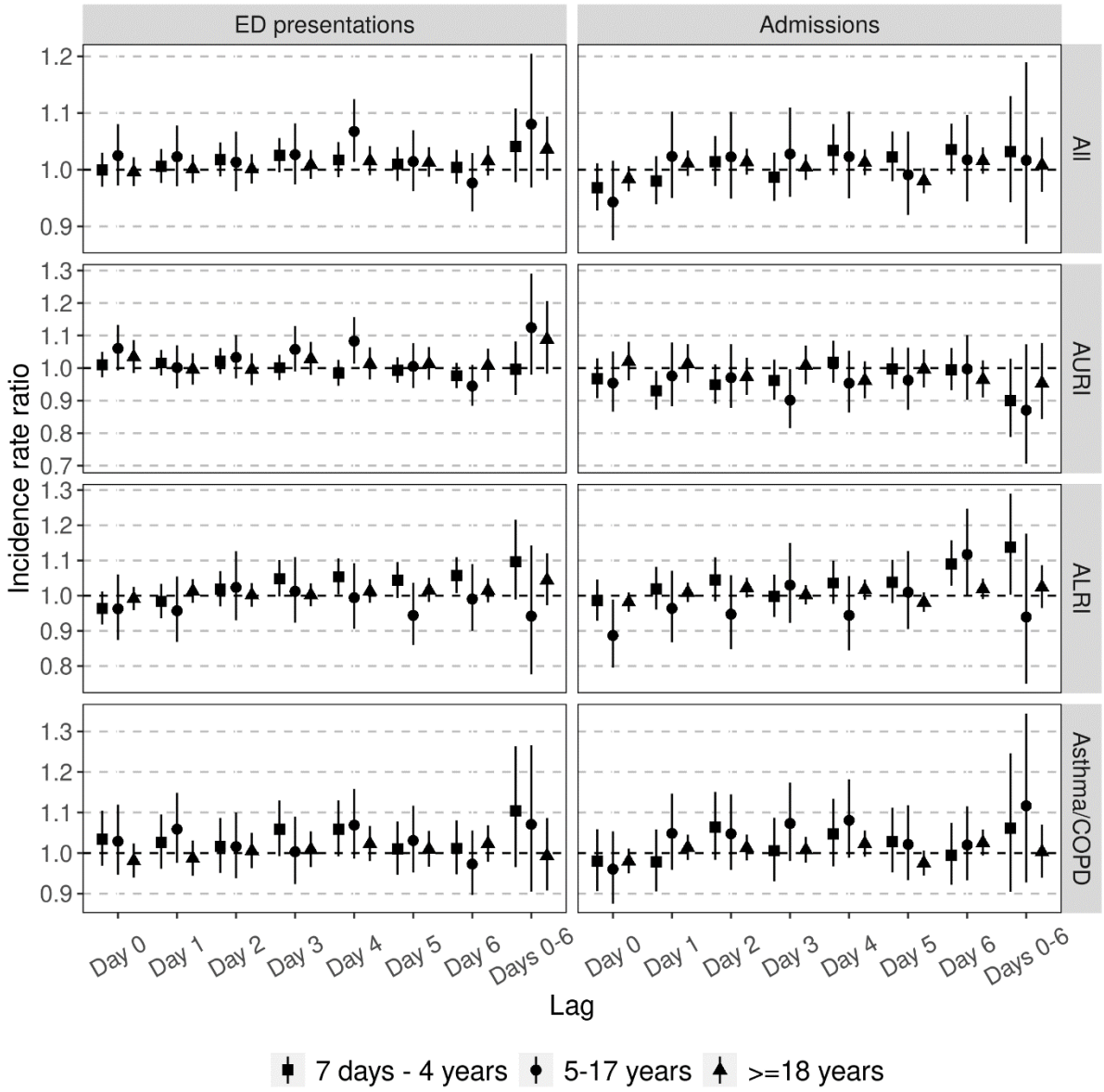

Figure 3. Incidence rate ratios for the estimated short-term effects of for a 10 µg/m³ increase in ambient $PM_{2.5}$ concentration on emergency department (ED) presentations and hospital admissions for acute respiratory illnesses by age group. *Lags refer to the number of days from exposure/covariate measurement to outcome. Lag "Days 0-6" refers to the effect of exposures averaged across days 0-6 prior to outcome measurement. AURI: acute upper respiratory infection, ALRI: acute lower respiratory infection, COPD: chronic obstructive pulmonary disease. Vertical lines represent 95% confidence intervals.*

Discussion

Our results provide further evidence for short-term exposures of ambient $PM_{2.5}$ increasing the overall number of healthcare events for acute respiratory illness, including both increased ED presentations and hospital admissions for ALRI and asthma/COPD, as well as on increased ED presentations but not hospital admissions for AURI across the age range. Larger effects were generally observed among children compared with adults aged 18 years or older. Confidence intervals for the primary analysis were wide, generally including an IRR of 1, but taken together with

previous research on respiratory healthcare encounters (12, 13, 42) and other respiratory outcomes (22, 43, 44), our findings provide further support that relatively low-level exposures to ambient $PM_{2.5}$ increase healthcare utilisation for acute respiratory illnesses. We provide additional evidence on how these effects might differ across age groups and impact hospital use in a city with generally low levels of outdoor air pollution.

Meta-analyses of time-series and case-crossover studies on short-term effects of ambient $PM_{2.5}$ on respiratory healthcare events have produced relatively consistent estimates, with 1-3% increased risk associated with a 10 $\mu g/m^3$ increase in 24-hour PM2.5 for hospitalisations (12), COPD-specific admissions (13), ED presentations or hospitalisations (42), pneumonia admissions (45), and asthma ED visits and hospitalisations (46). Walter *et al.* (47) published a recent systematic review of 72 epidemiologic air pollution studies conducted in Australia up to January 2019, however did not undertake a meta-analysis due to significant heterogeneity in design and reporting. Ten of the included studies examined effects of $PM_{2.5}$ on respiratory ED presentations, admissions, or mortality, three of which studied only children. Most describing positive effects which were generally largest for 0-1 day lags (47).

In contrast, we observed distinct lag patterns peaking on day 4 for asthma/COPD and day 6 for ALRI. These differences could reflect distinct primary short-term pathogenic mechanisms of $PM_{2.5}$, for example induction of bronchial hyperreactivity for asthma and increased susceptibility to infection for ALRI. For ALRI and asthma/COPD events we observed IRRs slightly less than 1 for the day 0 lag. In our setting a substantial proportion of day of hospital admission is likely spent in an air-conditioned hospital, and therefore not exposed to ambient pollution, so we do not find this finding overly surprising. Most of the proposed mechanisms for the respiratory effects of $PM_{2.5}$ are most consistent with at least 1-2 days between exposure and the need for hospital admission (14-16). There has been significant heterogeneity in lag selection strategies for air pollution case-crossover studies (42). An agreed standardised approach to lag specification might reduce the potential for selective reporting of “statistically significant” outcomes and simplify the process of meta-analysis.

In our study, effects on ALRI and asthma were generally larger among children. Childhood exposure to air pollution has been associated with long-term reductions in lung function (48), impaired neurological development (49), and a trend towards increased mortality (50). Worryingly, the full scale of long-term sequelae of childhood exposure to ambient air pollution remains unknown due to the challenges inherent in linking early life exposures to effects that might not become apparent until late adulthood, such as heart disease, stroke, or malignancy (1).

We did not detect a clear effect of ambient $PM_{2.5}$ on hospital admissions for AURI. This is hardly surprising, given many people will not seek care for uncomplicated upper respiratory tract infections, and those who do are probably more likely to see a general practitioner at lower overall cost to the healthcare system. A recent survey of Polish children found a clear association between short- and medium-term outdoor particulate matter ($PM_{2.5}$ and PM_{10}) and upper respiratory symptoms (51). It is plausible that most AURI hospital admissions were for later suppurative complications. However, we were unable to confirm this as 45% of these admissions were coded as "infections of multiple and unspecified sites" (Supplementary table S2).

Bushfires can cause massive spikes in ambient $PM_{2.5}$ and other pollutants, resulting in significant short-term increases in morbidity and mortality (52, 53). Such events rightly attract public and media attention due to obvious changes in perceptible air quality (54). The reduction in air quality in Melbourne in January 2020 as a result of the 2019-20 bushfire season far outstrips anything recorded over the period of our study, with the 24-hour average $PM_{2.5}$ concentration reaching 233.6 $\mu g/m^3$ (55). However, the important effects of routine lower-level exposures may be underappreciated by some policy makers and members of the public due to lack of obvious (to human sensory perception) change in air quality. Australia's current national air quality standards allow for ambient $PM_{2.5}$ concentrations up to an annual mean of 8 $\mu g/m^3$ and 24 hour mean of 25 $\mu g/m^3$, with exemptions to the 24-hour standard allowed when the exceedance is directly related to bushfires, hazard-reduction burning or dust storms (56).

Limitations of our study include the lack of data on primary health care presentations and reliance on coding data. We did not have data for a separate elderly age group and were unable to fractionally attribute ambient $PM_{2.5}$ to particular sources. Some degree of exposure measurement error will have occurred as a result of using pollution and weather data from fixed sites to infer individual exposure, along with reliance on recorded residential address (57). This could be partly addressed by the use of more sophisticated location-based models of exposure (50). However, availability of adequate hourly $PM_{2.5}$ data over the study period was limited to a few closely clustered sites, and sensitivity analyses using alternative exposure assignment methods resulted in only small changes to our estimates.

The validity of our effect estimates depends on the compatibility of our implicit causal and explicit statistical models with reality. In particular, residual confounding remains a concern in studies of environmental exposures (58). Our primary analysis controlled for all major ambient pollutants known to have short-term effects on respiratory health (16), using concentrations averaged over the same period as the $PM_{2.5}$ exposure. Confidently untangling the contribution of individual ambient

pollutants is challenging due to the potential for synergistic effects, and differences in timing of short-term effects between pollutants (16). Grass pollen exposure is associated with asthma hospitalisation in Australian children (59), and several studies have suggested that pollen exposure might weakly confound the effects of $PM_{2.5}$ on asthma (38-40). In our setting, year-round pollen monitoring data were not readily available. However, sensitivity analysis excluding events occurring during the pollen season did not result in substantially different estimates (Supplementary figure S5), indicating that such confounding may cause minimal bias in the current study.

We found that short-term ambient $PM_{2.5}$ levels were associated with increased likelihood of ED visits and hospital admissions for acute respiratory illness during a period when national particulate matter air quality standards were rarely exceeded. Taken together with other research, these findings provide further evidence to consider in assessing improvements to the current Australian national standards, such as to align with new international targets (21).

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Data availability:

Historical air quality data collected by the Environmental Protection Authority Victoria is publicly available through DataVic (https://discover.data.vic.gov.au/dataset/epa-air-watch-all-sites-air-quality-hourly-averages-yearly/historical). Historical Australian weather data is available on request from the Australian Bureau of Meteorology (http://www.bom.gov.au/climate/data-services/data-requests.shtml). Data from the Victorian Admitted Episodes Dataset and Victorian Emergency Minimum Dataset are available on request from the Victorian Agency for Health Information (https://vahi.freshdesk.com/support/home).

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Effect of ambient PM2.5 on healthcare utilisation for acute respiratory illness, Melbourne, Victoria, 2014-2019.

Supplementary material:

S1: Diagnosis groups based on ICD-10-AM primary diagnosis

1. **Acute upper respiratory tract infections (AURI)**

   Including all of:

   J00 Acute nasopharyngitis [common cold]

   J01 Acute sinusitis

   J02 Acute pharyngitis

   J03 Acute tonsillitis

   J04 Acute laryngitis and tracheitis

   J05 Acute obstructive laryngitis [croup] and epiglottitis

   J06 Acute upper respiratory infections of multiple and unspecified sites

2. **Acute lower respiratory tract infections (ALRI)**

   Including all of:

   J10.0 Influenza with pneumonia, seasonal influenza virus identified

   J11.0 Influenza with pneumonia, virus not identified

   J10.1 Influenza with other respiratory manifestations, seasonal influenza virus identified

   J11.1 Influenza with other respiratory manifestations, virus not identified

   J12 Viral pneumonia, not elsewhere classified

   J13 Pneumonia due to Streptococcus pneumoniae

   J14 Pneumonia due to Haemophilus influenza

   J15 Bacterial pneumonia, not elsewhere classified

   J16 Pneumonia due to other infectious organisms, not elsewhere classified

   J17* Pneumonia in diseases classified elsewhere

J18 Pneumonia, organism unspecified

J20 Acute bronchitis

J21 Acute bronchiolitis

J22 Unspecified acute lower respiratory infection

3. Asthma and COPD

Including all of:

J41 Simple and mucopurulent chronic bronchitis

J43 Emphysema

J44 Other chronic obstructive pulmonary disease

J45 Asthma

J46 Status asthmaticus

Table S2. Summary of emergency department presentations and hospital admissions for acute respiratory illness for residents of metropolitan Melbourne 2014-2019, by ICD-10-AM[6] diagnosis, diagnosis group, and age.

Emergency department presentations					
Diagnosis group	**ICD-10-AM diagnosis[7]**	**Number of admissions (% of total for each age and diagnosis group combination)**			
		7 days - 5 years	**5-18 years**	**>=18 years**	**All**
Acute upper respiratory infection (AURI)	J06: Acute upper respiratory infections of multiple and unspecified sites	35430 (40%)	6871 (25.8%)	15138 (30.7%)	57439 (34.9%)
	J05: Acute obstructive laryngitis [croup] and epiglottitis	38480 (43.5%)	8565 (32.2%)	368 (0.7%)	47413 (28.8%)
	J03: Acute tonsillitis	9929 (11.2%)	7682 (28.9%)	17709 (36%)	35320 (21.5%)
	J02: Acute pharyngitis	2073 (2.3%)	2026 (7.6%)	7407 (15%)	11506 (7%)
	J00: Acute nasopharyngitis [common cold]	2424 (2.7%)	630 (2.4%)	2974 (6%)	6028 (3.7%)
	J01: Acute sinusitis	47 (0.1%)	557 (2.1%)	4401 (8.9%)	5005 (3%)
	J04: Acute laryngitis and tracheitis	108 (0.1%)	289 (1.1%)	1257 (2.6%)	1654 (1%)
	Total	**88491**	**26620**	**49254**	**164365**
Acute lower respiratory infection (ALRI)	J22: Unspecified acute lower respiratory infection	7834 (14.9%)	3374 (38.1%)	59328 (48.3%)	70536 (38.3%)
	J18: Pneumonia - organism unspecified	5220 (10%)	3351 (37.8%)	46482 (37.8%)	55053 (29.9%)
	J21: Acute bronchiolitis	37700 (71.9%)	46 (0.5%)	166 (0.1%)	37912 (20.6%)
	J10-J11: Influenza	1212 (2.3%)	1835 (20.7%)	12731 (10.4%)	15778 (8.6%)
	J20: Acute bronchitis	484 (0.9%)	260 (2.9%)	4182 (3.4%)	4926 (2.7%)
	Total	**52450**	**8866**	**122889**	**184205**
Asthma and chronic obstructive pulmonary disease (COPD)	J45: Asthma	28995 (100%)	21867 (100%)	33143 (46.8%)	84005 (69%)
	J44: Other chronic obstructive pulmonary disease	2 (0%)	1 (0%)	36015 (50.8%)	36018 (29.6%)
	J43: Emphysema	0 (0%)	1 (0%)	1690 (2.4%)	1691 (1.4%)
	Total	**28997**	**21869**	**70848**	**121714**
Hospital admissions					
Diagnosis group	**ICD-10-AM diagnosis**	**Number of admissions (% of total for each age and diagnosis group combination)**			
		7 days - 5 years	**5-18 years**	**>=18 years**	**All**
Acute upper respiratory infection (AURI)	J06: Acute upper respiratory infections of multiple and unspecified sites	12038 (50.6%)	2254 (33.6%)	13610 (44.2%)	27902 (45.5%)
	J03: Acute tonsillitis	2547 (10.7%)	2345 (35%)	11458 (37.2%)	16350 (26.7%)
	J05: Acute obstructive laryngitis [croup] and epiglottitis	8355 (35.1%)	1414 (21.1%)	280 (0.9%)	10049 (16.4%)
	J02: Acute pharyngitis	545 (2.3%)	438 (6.5%)	3136 (10.2%)	4119 (6.7%)
	J01: Acute sinusitis	11 (0%)	118 (1.8%)	1105 (3.6%)	1234 (2%)
	J04: Acute laryngitis and tracheitis	46 (0.2%)	83 (1.2%)	695 (2.3%)	824 (1.3%)

[6] International statistical classification of diseases and health related problems, 10th revision, Australian modification.

[7] Rows containing all zero values are not shown. See supplementary material for a full list of queried codes.

	J00: Acute nasopharyngitis [common cold]	246 (1%)	55 (0.8%)	479 (1.6%)	780 (1.3%)
	Total	**23788**	**6707**	**30763**	**61258**
Acute lower respiratory infection (ALRI)	J18: Pneumonia - organism unspecified	3526 (10.7%)	2198 (38.5%)	93649 (55.4%)	99373 (47.9%)
	J22: Unspecified acute lower respiratory infection	3445 (10.5%)	1301 (22.8%)	35863 (21.2%)	40609 (19.6%)
	J10-J11: Influenza	1424 (4.3%)	1112 (19.5%)	18774 (11.1%)	21310 (10.3%)
	J21: Acute bronchiolitis	18811 (57.3%)	20 (0.4%)	224 (0.1%)	19055 (9.2%)
	J15: Bacterial pneumonia - not elsewhere classified	699 (2.1%)	396 (6.9%)	9391 (5.6%)	10486 (5%)
	J12: Viral pneumonia - not elsewhere classified	4651 (14.2%)	563 (9.9%)	4442 (2.6%)	9656 (4.6%)
	J13: Pneumonia due to Streptococcus pneumoniae	74 (0.2%)	36 (0.6%)	2532 (1.5%)	2642 (1.3%)
	J20: Acute bronchitis	169 (0.5%)	54 (0.9%)	1603 (0.9%)	1826 (0.9%)
	J14: Pneumonia due to Haemophilus influenza	26 (0.1%)	13 (0.2%)	1533 (0.9%)	1572 (0.8%)
	J17: Pneumonia in diseases classified elsewhere	13 (0%)	8 (0.1%)	847 (0.5%)	868 (0.4%)
	J16: Pneumonia due to other infectious organisms - not elsewhere classified	7 (0%)	5 (0.1%)	262 (0.2%)	274 (0.1%)
	Total	**32845**	**5706**	**169120**	**207671**
Asthma and chronic obstructive pulmonary disease (COPD)	J44: Other chronic obstructive pulmonary disease	13 (0.1%)	10 (0.1%)	93850 (77.1%)	93873 (63.3%)
	J45: Asthma	15477 (99.3%)	10769 (98.3%)	26601 (21.9%)	52847 (35.7%)
	J43: Emphysema	0 (0%)	24 (0.2%)	823 (0.7%)	847 (0.6%)
	J46: Status asthmaticus	98 (0.6%)	147 (1.3%)	355 (0.3%)	600 (0.4%)
	J41: Simple and mucopurulent chronic bronchitis	0 (0%)	0 (0%)	20 (0%)	20 (0%)
	Total	**15588**	**10950**	**121649**	**148187**

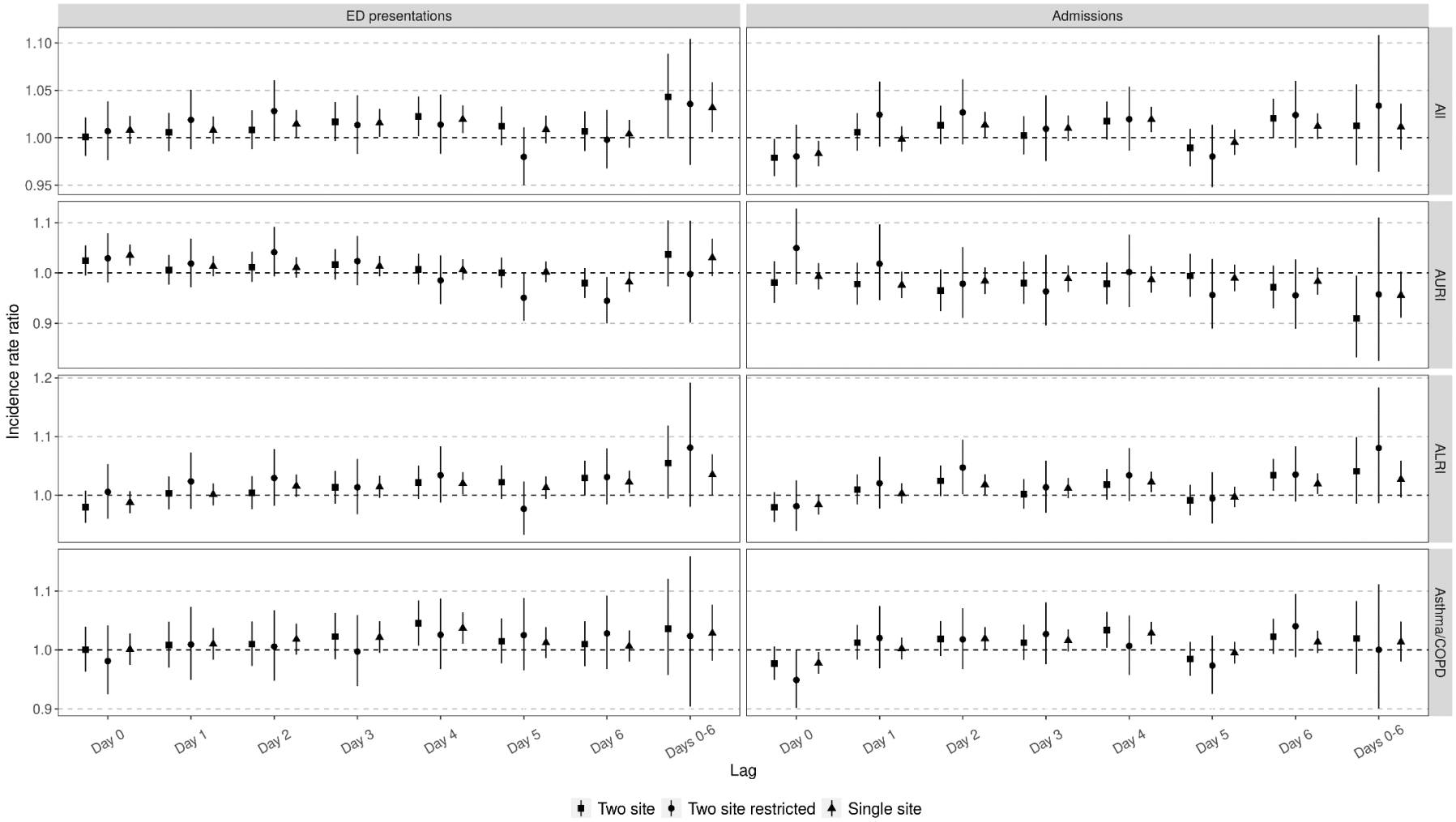

Figure S3. Incidence rate ratios for the estimated short-term effects of for a 10 µg/m³ increase in ambient $PM_{2.5}$ concentration on emergency department (ED) presentations and hospital admissions for acute respiratory illnesses by method of exposure assignment. *"Two site": exposure assigned from closest monitoring site; "Two site restricted": as for "Two site" but only patients residing in a local government area within 10km of one of the two monitoring sites were included; "Single site": exposure for all patients derived from Alphington site. Lags refer to the number of days from exposure/covariate measurement to outcome. Lag "Days 0-6" refers to the effect of exposures averaged across days 0-6 prior to outcome measurement. AURI: acute upper respiratory infection, ALRI: acute lower respiratory infection, COPD: chronic obstructive pulmonary disease. Vertical lines represent 95% confidence intervals.*

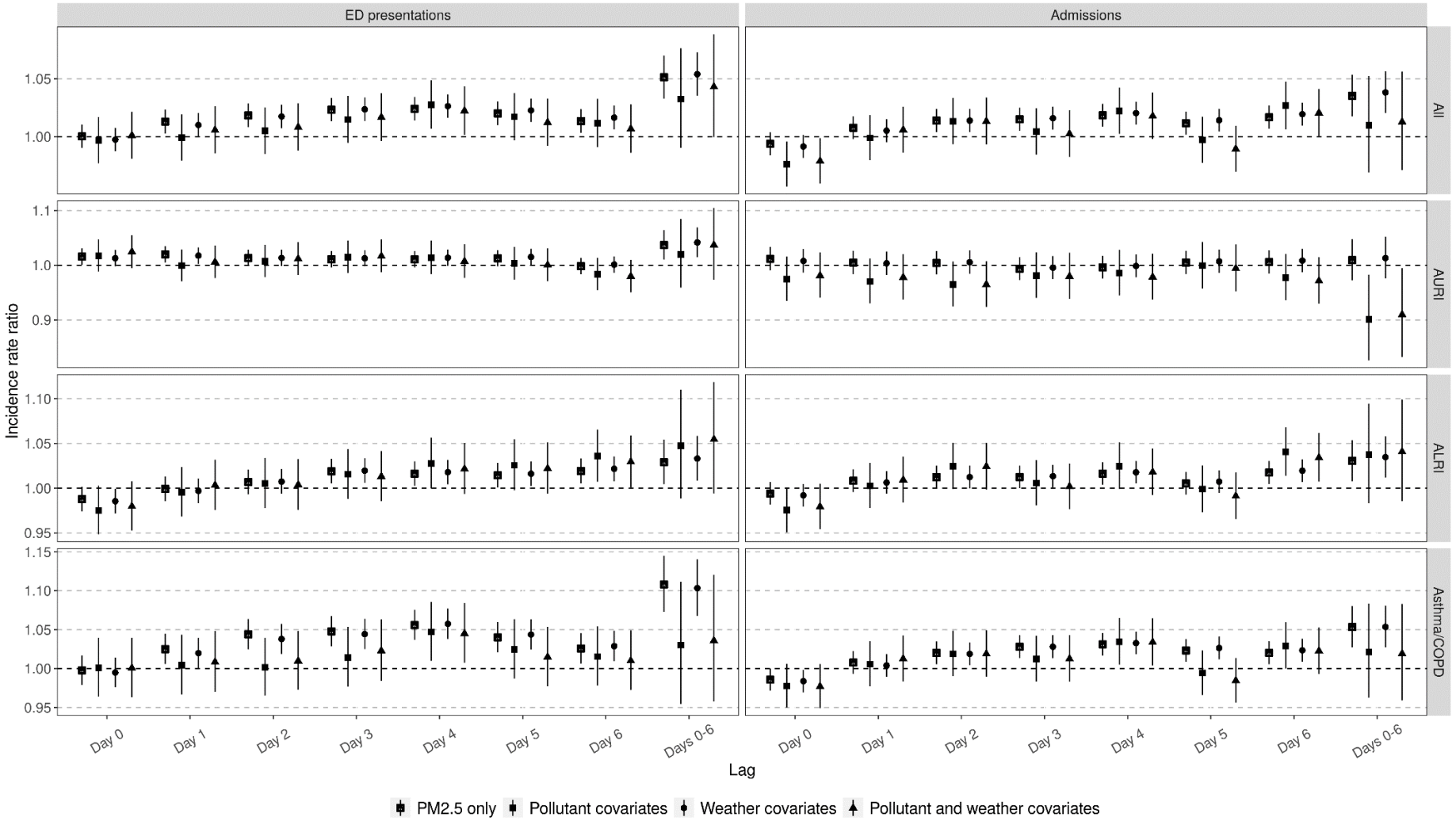

Figure S4. Incidence rate ratios for the estimated short-term effects of for a 10 µg/m³ increase in ambient $PM_{2.5}$ concentration on emergency department (ED) presentations and hospital admissions for acute respiratory illnesses by set of model covariates. *PM2.5: fine particulate matter <=2.5 microns diameter. Lags refer to the number of days from exposure/covariate measurement to outcome. Lag "Days 0-6" refers to the effect of exposures averaged across days 0-6 prior to outcome measurement. AURI: acute upper respiratory infection, ALRI: acute lower respiratory infection, COPD: chronic obstructive pulmonary disease. Vertical lines represent 95% confidence intervals.*

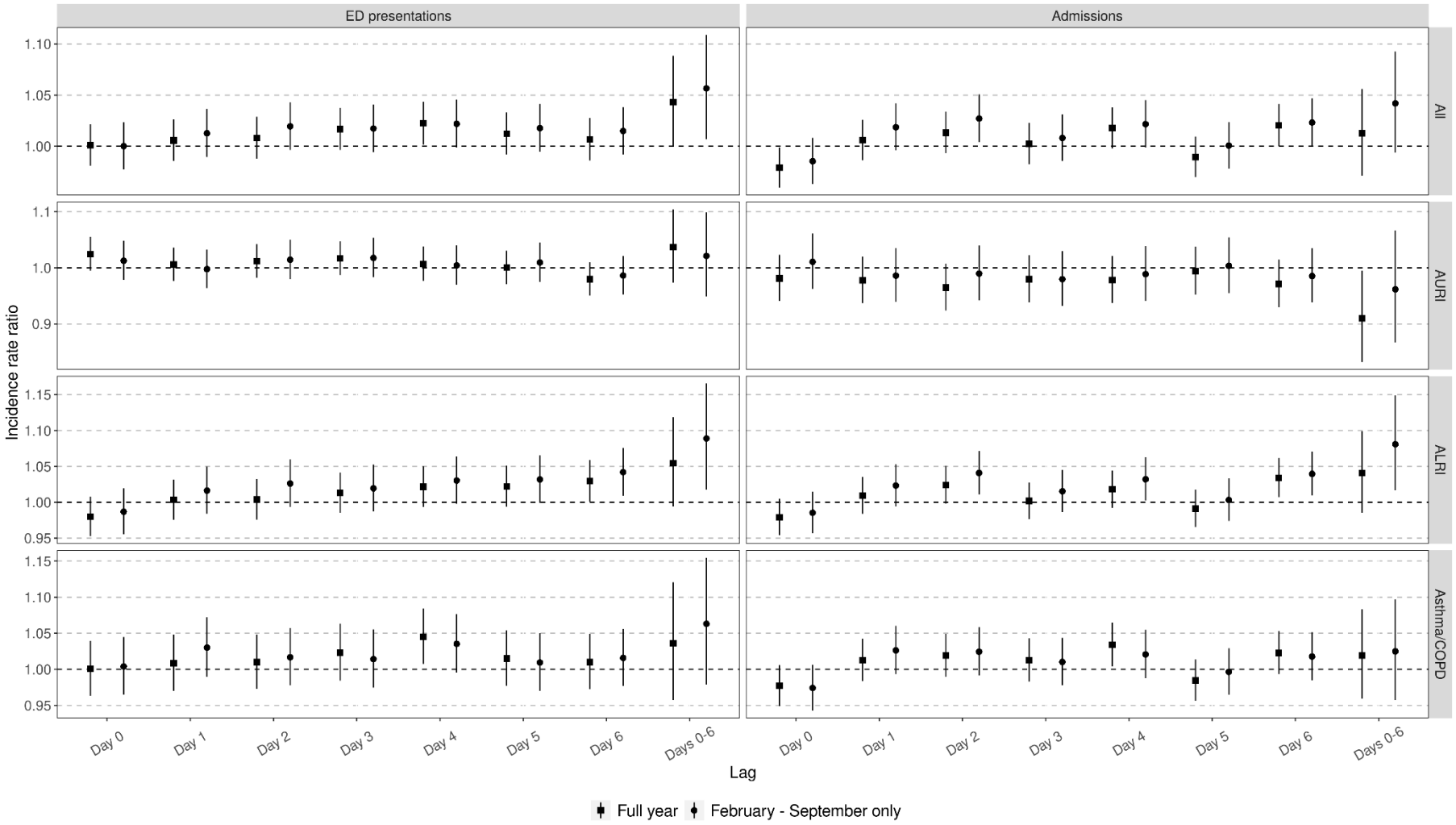

Figure S5. Incidence rate ratios for the estimated short-term effects of for a 10 µg/m³ increase in ambient $PM_{2.5}$ concentration on emergency department (ED) presentations and hospital admissions for acute respiratory illnesses by timing of event*. PM2.5: fine particulate matter <=2.5 microns diameter. Lags refer to the number of days from exposure/covariate measurement to outcome. Lag "Days 0-6" refers to the effect of exposures averaged across days 0-6 prior to outcome measurement. AURI: acute upper respiratory infection, ALRI: acute lower respiratory infection, COPD: chronic obstructive pulmonary disease. Vertical lines represent 95% confidence intervals.*

Chapter 4: Post-pandemic respiratory outbreak surveillance in Victorian residential aged care

Prologue

The second half of 2020 saw severe outbreaks of COVID-19 in Victorian residential aged care facilities. Although respiratory outbreaks in aged care (primarily due to influenza) were an important health problem prior to the pandemic, the disease burden due to COVID-19 was unprecedented. This prompted rapid roll-out of several initiatives to prevent or mitigate outbreaks, including new systems for outbreak surveillance in aged care. I evaluated two such systems for their potential value to ongoing outbreak surveillance in an uncertain post-pandemic future.

My role

With the assistance from my supervisors, I engaged stakeholders from both systems in the evaluation. I reviewed the academic and grey literature and interviewed stakeholders with prior experience in aged care outbreak surveillance to understand the evolving public health challenges involved. I interviewed system stakeholders, reviewed operating documents, and analysed notification data to describe and evaluate each system. Findings from the evaluation will be communicated to stakeholders in a report that forms the bulk of this chapter.

Population health implications

Together with other issues in the aged care sector including underfunding and workforce casualisation, weaknesses in surveillance likely contributed to the scale of COVID-19 outbreaks in residential aged care. In light of shifting respiratory virus epidemiology due to uptake of COVID-19 vaccines, emergence of new SARS-CoV-2 variants, and new patterns in circulation of other respiratory viruses caused by widespread use of non-pharmaceutical interventions, the optimal requirements, priorities, and capacity for ongoing surveillance are still somewhat unclear. At the time of writing, immediate priorities of the public health response to COVID-19 in Victoria include rapid vaccine rollout, maintaining hospital capacity, and mass testing. Hopefully, as these issues are addressed or become less critical, there is more room for focus on sustainable and integrated respiratory outbreak surveillance in higher risk settings such as residential aged care, to which this report might contribute.

Lessons learned

Surveillance evaluation can be a difficult task during a pandemic when resources are stretched. The evaluation would have been strengthened substantially by engagement with aged care service

providers and those delivering care, however I was unable to achieve this due to time constraints as well as the duress placed on stakeholders and the sector by the pandemic. When establishing surveillance in acute public health crises it may be tempting to focus on rapid implementation, however systems may not be successful unless explicit goals are mutually pre-agreed to by those both collecting and acting on the surveillance data.

Evaluation of two surveillance systems for early recognition of respiratory outbreaks in residential aged care, Victoria, 2020.

Summary

Outbreaks caused by respiratory viruses result in substantial morbidity and mortality in residential aged care but are amenable to interventions to reduce severity. The COVID-19 pandemic has highlighted a need for effective surveillance to direct responses by public health authorities in certain instances where there is elevated risk of a severe outbreak. This report evaluates two surveillance systems established in residential aged care in Victoria, with the aim of informing ongoing surveillance efforts for detection of, and response to, outbreaks of COVID-19 and other respiratory viral infections. Experience of stakeholders in both systems and data collected by the systems provide valuable insights to inform future surveillance efforts. Going forward, respiratory outbreak surveillance in residential aged care should continue to focus on achieving rapid testing for important respiratory pathogens in response to broad testing criteria. Novel testing strategies or prioritisation of laboratory notifications for aged care settings may facilitate earlier and more effective public health response. Surveillance must be acceptable to residents and providers, as well as responsive to changes in respiratory virus epidemiology.

List of abbreviations

ACQSC	Aged Care Quality and Safety Commission
ADF	Australian Defence Force
AUS-CAIRS	COVID-19 Aged Care Incident Response System
COVID-19	Coronavirus disease 2019
CDPC	Communicable Disease Prevention and Control unit
EWS	Early Warning System
GP	General practitioner
ILI	Influenza-like illness
IPC	Infection prevention and control
IQR	Interquartile range
NPSRACS	Non-public sector residential aged care services
OBD	Occupied bed day
PCA	Personal care attendant
PCR	Polymerase chain reaction
POCT	Point-of-care testing
PPE	Personal protective equipment
PPV	Positive predictive value
PSRACS	Public sector residential aged care services
VicNISS	The Victorian Coordinating Centre for Healthcare Associated Infections
RACF	Residential aged care facility
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SCV	Safer Care Victoria

Purpose and scope of report

The purpose of this report is to inform planning and implementation of surveillance for respiratory virus outbreaks in residential aged care facilities (RACFs) in Victoria and elsewhere in Australia, based on experiences during the current COVID-19 pandemic. The report is divided into three sections.

The first section provides an overview of respiratory outbreaks in residential aged care in Victoria as a public health problem, both prior to and during the current COVID-19 pandemic. The second section consists of a focused evaluation of two surveillance systems implemented in residential aged care in Victoria in 2020. Although there are distinct purposes to each system, this evaluation will focus on assessing usefulness with regards to early detection of, and response to, respiratory outbreaks in RACFs. This has been recognised as the primary surveillance aim for aged care settings during the COVID-19 pandemic (1). The two surveillance systems evaluated are an Early Warning System (EWS) operated by the Victorian Aged Care Response Centre (VACRC) in 2020, and a system developed by the Victorian Healthcare Associated Infection Surveillance System Coordinating Centre (VicNISS) for collating and reporting on data collected by RACFs using the Safer Care Victoria (SCV) *COVID-19 screening tool for residential aged care services* (referred to from this point on as the SCV/VicNISS system) (2). The final section draws on additional literature and information covered earlier in the report to discuss suggested priorities for respiratory outbreak surveillance in residential aged care, and several potential strategies to address these.

This report is not intended to provide a comprehensive overview of all activities related to respiratory illness surveillance in aged care. In particular, it does not discuss systematic asymptomatic screening for COVID-19, which may be useful during periods of more intense community transmission of COVID-19 (3).

Section 1: Overview of respiratory outbreak in residential aged care in Victoria as a public health problem

Residential aged care in Victoria

In 2015, more than 187,000 Australians lived in RACFs, including 5% of Australians aged 65 or older (4). As of 2020, 812 services provided some form of residential aged care in Victoria, operating a total of about 58,500 places (5). Of Victorian residential aged care services, 21% were public sector (state- or local-government run), 37% were operated by not-for-profit organisations, and the remaining 42% were privately operated. The majority of facilities providing transition care or short-term restorative care were public sector, as were all of the few regional multi-purpose services (5).

Victoria had a higher proportion of public sector and privately-operated facilities, and a lower proportion of not-for-profit facilities than other jurisdictions (5).

As of 2020, in Victoria there was a clear correlation between facility type (public sector, private, not-for-profit) and distribution by facility size and remoteness. Metropolitan facilities tended to have a greater number of operational places than those in regional or remote areas, and relatively few were public sector (6). Conversely, facilities in regional areas tended to be smaller, and almost half were public sector (6). Notably, private and not-for-profit facilities tended to be larger than public sector facilities in both metropolitan and regional areas (6). Overall, 68% of operational places were located in metropolitan areas (6).

Across Australia, approximately two-thirds of aged care residents were female, and more than 75% were aged 80 years or older (7). As of 2016, the workforce providing direct care to residents consisted of 70% personal care attendants (PCAs), 15% registered nurses, 10% enrolled nurses, and various allied health staff (8). PCAs generally held a Certificate III in Aged Care or equivalent qualification (8). In 2016, the median age of workers providing direct resident care was 46, 87% were female, and 1 in 3 were born overseas (8).

Regulation of the residential aged care system is primarily the responsibility of the Australian Government (6). Services are funded by a combination of government contributions (approximately two thirds of revenue in 2018-2019) and consumer fees (6). In order to qualify for commonwealth subsidies, services must be accredited with the Aged Care Quality and Safety Commission (ACQSC). The ACQSC undertakes periodic audits to assess service performance against eight Aged Care Quality Standards which cover all aspects of aged care, including access to a safe living environment (Standard 5) and appropriate clinical care (Standard 3) (9). The Victorian government provides additional funding, and conducts quality indicator monitoring for public sector residential aged care services (10, 11). In addition, public sector facilities are subject to additional state legislation, including mandated minimum staff-resident ratios (12).

Respiratory outbreaks prior to 2020

Many RACF residents experience chronic poor health, putting them at high risk of morbidity and mortality from respiratory infection (13). Shared living arrangements and frequent close contact between staff, residents, and visitors promotes transmission of respiratory pathogens resulting in frequent outbreaks (13, 14). A survey of Australian RACFs during 2017 found that 45% had experienced a potential influenza outbreak, defined as three or more cases of influenza-like illness (ILI) in residents or staff within 72 hours, within the previous 12 months. More than half of all outbreaks affected at least 10 residents (15). Active surveillance in Australia has estimated

respiratory tract infection incidence at around 1 resident case per 1000 occupied bed days (OBDs), a higher rate than for other common infections (16).

Prior to 2020, Influenza viruses were the most commonly-identified causes of respiratory outbreaks in residential aged care both in Australia (17, 18), and internationally (19-23), and were associated with higher attack rates and mortality than most other pathogens (19-21). Respiratory syncytial virus (RSV) was another frequent cause, and is recognised as a common cause of pneumonia requiring hospitalisation in institutionalised elderly people (24). Other causes of outbreaks, of generally lower severity, included human metapneumovirus (hMPV), parainfluenza, seasonal human coronaviruses, and rhinoviruses (19-21).

The mortality and financial costs due to respiratory disease outbreaks in Australian RACF residents have not been well enumerated. However, they are likely to be disproportionate to those experienced by elderly non-residents, and largely preventable. The 2017 survey referred to above found that 12% of facilities had recorded at least one outbreak-associated death in the prior 12 months (15). There are a range of evidence-based interventions, which when implemented early can reduce the severity of outbreaks, including appropriate transmission-based precautions, enhanced surveillance and testing, cohorting of ill residents, and in the case of influenza, antiviral prophylaxis (17-19, 25).

Unfortunately, opportunities to implement these interventions can easily be missed. The vast majority of RACFs self-report having procedures for identifying and managing outbreaks, and notifying all outbreaks to local public health units (15). However, analysis of notifiable disease data prior to the current pandemic suggested that only half of all influenza outbreaks were reported (26). Commonly identified reasons for failure to report outbreaks included misunderstanding of outbreak definitions or reporting requirements, and high workload of RACF staff (26). The Australian Royal Commission into Aged Care Quality and Safety found that the RACF workforce was under-resourced and overworked prior to the current pandemic, and often under-trained in aspects of infection prevention such as the use of personal protective equipment (PPE) (27).

Respiratory outbreaks surveillance

Prior to 2020, the Communicable Disease Prevention and Control Unit (CDPC) within the Victorian Department of Health coordinated surveillance of outbreaks of respiratory infections in Victorian RACFs (28). The system used a common ILI case definition, consisting of sudden onset of at least one respiratory symptom (cough, sore throat, shortness of breath) and at least one systemic symptom (fever, headache, malaise, myalgia) (28). CDPC encouraged RACFs to apply this definition to ill residents or staff. CDPC defined an outbreak as three or more cases of ILI in residents or staff with

onset of symptoms within a 72 hour period (28). CDPC strongly encouraged RACFs to submit reports of outbreaks by telephoning, but reporting was not legally required.

CDPC collected information about the reporting facility, including number of suspected and confirmed cases (28). Response activities included advice on outbreak management and testing, onward notification of the outbreak to the ACQSC or its predecessor (the Australian Aged Care Quality Agency), input to regular reports on influenza epidemiology, and contribution to national surveillance. RACFs were generally expected to self-manage outbreaks, and only to provide further case lists to CDPC if influenza was confirmed as a causative pathogen (28).

COVID-19 outbreaks in Victorian residential aged care, 2020

Disproportionate mortality from COVID-19 in residential aged care has been reported both in Australia, and internationally (29). Australia's ability to control community transmission of COVID-19 in 2020 was undermined by large outbreaks in aged care settings (30). Strikingly, by late 2020, approximately three quarters of all COVID-19 deaths in Australia had occurred in aged care residents, with most occurring during Victoria's second COVID-19 epidemic from June to October 2020 (31).

More than 170 RACFs in Victoria reported COVID-19 outbreaks in 2020 (31, 32), with the vast majority being private or not-for-profit facilities, consistent with the June-October epidemic affecting metropolitan Melbourne most severely (33). Combined, these services reported almost 2000 infected residents, and a similar number of infected staff (31). Approximately 650 resident deaths were attributed to COVID-19 (31). About one quarter of outbreak facilities experienced large outbreaks, reporting at least 20 cases each (31).

The scale of the developing problem of COVID-19 in residential aged care over this period highlighted a need for early and coordinated external assistance. The Victorian Aged Care Response Centre (VACRC) was established in late July 2020 to coordinate rapid state and federal government responses to aged care outbreaks, and to assist providers in preparing for and preventing future outbreaks (34). Assistance included deployment of clinical and support personnel, assistance with surge workforce, provision of PPE, and testing support (35).

Visits by VACRC to non-outbreak facilities revealed that 31% needed assistance with designating areas for cohorting confirmed or suspected cases, 14% did not have an adequate plan in place to support workplace furloughing, and 12% did not have hand hygiene products available in all areas (36). These findings support those of the Royal Commission the many facilities lacked appropriate in-house infection control expertise to prepare for or manage a COVID-19 outbreak (27).

In retrospect, it is interesting to note that almost all aged care services that completed an ACQSC preparedness self-assessment survey in March 2020 rated their readiness for a COVID-19 outbreak as either satisfactory or best-practice (27). This might in part have been due to the development of the survey being based on an incomplete understanding of the risks posed by COVID-19 at the time (27). However, it also highlights a problem in relying solely on self-assessment in assessing preparedness, and supports recent interventions to address preparedness and outbreak prevention (36, 37), as well as more consideration of more intensive external support in the event of an outbreak.

Key challenges to surveillance

The primary objectives of respiratory outbreak surveillance in residential aged care should be early detection and intervention in outbreaks caused by pathogens with substantial risk of morbidity and/or mortality (including influenza A and B, SARS-CoV-2, and RSV). There are several key challenges that must be addressed to achieve these objectives. These include eliciting and recognising signs and symptoms of respiratory virus infection in residents, staff, and visitors, ensuring rapid and appropriate testing and escalation, and minimising the time from sample collection to recognition that a positive result represents an outbreak.

Detecting signs and symptoms of respiratory illness in aged care

Acute respiratory infections with outbreak potential can be difficult to recognise in the aged care resident population because of the prevalence of dementia and other comorbidities that can interfere with communication, as well as a general tendency towards atypical presentations in the elderly (38). This was a recognised barrier to effective surveillance prior to the current pandemic (38). COVID-19 appears to be no easier to identify based on clinical presentation alone, and this problem is compounded by the potential for transmission from cases without symptoms (30).

Data from international surveillance and outbreak investigation suggests that about 30% of aged care residents with COVID-19 are asymptomatic at the time of diagnosis (39, 40). Of symptomatic aged care residents, the most common signs or symptoms are those recognised as “typical” features: fever (~50% of all cases), cough (~20-45%), dyspnoea (~30%), and hypoxia (~30%) (39, 40). Confusion (~20%), loss of appetite (~15%), and weakness (~15%) are more common non-specific features of COVID-19, followed by diarrhoea, nausea/vomiting, and malaise (39). Loss of taste or smell, commonly reported among younger people with COVID-19, are very rare as presenting symptoms among aged care residents (39, 41).

Since many cases of COVID-19 and other respiratory viruses in aged care residents are unlikely to meet traditional ILI case definitions (42), it may be useful to define a suspected case based on the presence of any respiratory symptom. Unfortunately, fever and cough are commonly elicited signs or symptoms in aged care residents, even in the absence of an identified respiratory virus (41, 42). Further, outside of known outbreaks, a minority of ILI cases are actually caused by influenza, with a substantial proportion caused by bacterial infections that pose little or no risk of transmission to other residents or staff (43). Thus, any syndromic criteria for defining a respiratory outbreak in residents will likely have poor positive predictive value (PPV), poor sensitivity, or both. Additionally, because of significant symptom overlap between COVID-19 and other respiratory viruses, performance of syndromic surveillance for monitoring pathogen-specific trends appears to be heavily influenced by the degree to which other respiratory viruses are circulating in the community (22, 44-46).

In the near-term, SARS-CoV-2 is likely to remain the most important respiratory virus for outbreak surveillance, but due to non-specific features and presymptomatic transmission, may be poorly amenable to early detection through syndromic surveillance. Nevertheless, symptom-based risk-stratification remains essential to guide testing, so surveillance activities must consider how respiratory symptoms are elicited. This includes deciding whether to rely on passive self-report of symptoms by residents or elicitation by astute staff, or whether to implement active systematic screening. If screening is instituted, it must address some key questions, namely:

- Which symptoms should be screened for?
- How often should screening occur?
- How should respiratory symptoms in staff and visitors be elicited?

Ensuring timely testing and escalation

Recognition of acute respiratory illness in residents, staff, or visitors needs to be linked to prompt and appropriate escalation. For symptomatic residents, this may be facilitated through staff training and set protocols for escalation, including request for assessment by the resident's general practitioner (GP) to decide if testing is warranted, or immediate testing if initial suspicion is high enough, as well as use of appropriate transmission precautions while test results are pending. Staff and visitors with symptoms should have testing arranged, and be excluded from the facility until any symptoms have resolved. Testing should be targeted towards the detection of pathogens with potential to cause serious outbreaks (i.e. SARS-CoV-2, influenza, RSV), although consideration should be given to estimated prevalence (pre-test probability) and potential for false positive results.

Minimising delays in test processing, availability of results, and notification

A rapid public health and clinical response is recognised as critical in limiting outbreaks in RACFs once they are identified (47), but this in turn requires rapid outbreak detection. Other than delays in symptom recognition and testing described above, delays in outbreak detection may include test processing, reporting of the results to public health authorities, and delay in authorities recognising that a result represents an outbreak in residential aged care.

Pressure on laboratory testing capacity during Victoria's second epidemic meant test turnaround typically took between one and three days, but occasionally longer (48). Despite ongoing efforts to expand laboratory capacity, delays may still occur when there are rapid increases in volumes of tests to be processed, as evidenced in the New South Wales outbreak in July 2021 (49). Prioritisation of tests from high-risk settings has been used to mitigate the effect of these delays on residential aged care. Use of point-of-care testing (POCT) in RACFs provides a potential avenue to bypass these delays, and is currently being trialled (50), but raises another set of challenges (51).

Recognising that a positive test represents a potential outbreak requires linking the laboratory notification to a RACF. This can occur through case investigation by public health authorities, or reporting by facility staff once a result is received. When contact tracing systems are stretched, relying solely on case investigation may result in long delays in identifying an outbreak, hampering management (52). Relying on RACFs to report positive cases in staff or residents may be fraught given existing pressures on the sector. In Victoria, a system has been implemented that allow samples to be labelled as RACF associated at the time of collection, and automate priority alerts. Address matching for notified positive against a list of RACFs can help to identify new cases in residents prior to case investigation, however this will not identify positive staff members (53).

Uncertainty in near term respiratory virus epidemiology

Uncertainties in the near-term respiratory virus epidemiology make it difficult to predict how requirements for respiratory outbreak surveillance will change over the next few years. The focus and intensity of respiratory outbreak surveillance required will depend on a range of as yet difficult-to-predict factors including changing effectiveness of COVID-19 vaccinations, emergence of SARS-CoV-2 variants with differing transmissibility, pathogenicity, and immune evasion, and the re-emergence of other respiratory pathogens such as influenza, which have been suppressed by non-pharmaceutical interventions put in place to limit COVID-19.

Vaccination of residents and staff may lessen the need to absolutely suppress transmission of COVID-19 in RACFs, if there is sufficient uptake and vaccination effectively prevents moderate and

severe disease. A single dose of BNT162b2 or ChAdOx1-S was 80% effective against hospitalisation in the population aged over 70 years in England (54). However protection wanes over time (55, 56), may be slightly further reduced against variants of concern (56, 57), and may be reduced in RACF residents compared with the broader elderly population (58). Reports so far of COVID-19 transmission in nursing homes with reasonable vaccination coverage have generally found that vaccination alone is insufficient to prevent an outbreak, and that ongoing focus on IPC is essential (59-63). This is consistent with previous experience in nursing homes with high influenza vaccination coverage (64).

Influenza activity in Australia has dramatically declined since the onset of the COVID-19 pandemic (65), and has remained below pre-pandemic levels globally (66). It is uncertain what will happen to influenza circulation in Australia as international borders reopen and non-pharmaceutical interventions are relaxed. However, waning population immunity and challenges in development of an effective vaccine due to difficulties in predicting the next dominant strain could make for a worse than usual flu season (67). Circulation of RSV, which typically causes winter epidemics, was suppressed during the 2020 season (65), but caused severe out-of-season outbreaks across multiple Australian jurisdictions in early 2021 (68). Unpredictable changes to patterns of respiratory virus circulation as a result of COVID-19 restrictions reinforce a need for robust surveillance in high-risk settings such as aged care.

Section 2: System evaluations

Methods

The evaluation approach was based on the Centers for Disease Control and Prevention "Updated Guidelines for Evaluating Public Health Surveillance Systems" (2001) (69). Assessment of surveillance attributes was based on notes from one-on-one semi-structured interviews with stakeholders, including seven stakeholders directly involved in implementation and/or operation of the evaluated surveillance systems, and another two involved in routine respiratory outbreak surveillance in residential aged care. Additional information was obtained from operating documents, reports and presentations prepared by staff involved with each system.

Stakeholders supplied notification data for each system. Analysis of these data was limited to an eight week period from 7 August to 2 October 2020, because this was a time when both systems were active, and because previous evaluation of some of the EWS data had already been performed for this period.

Representativeness and coverage were assessed by comparing notifying facilities to a list of 780 RACFs in Victoria (other facilities providing only transition care were excluded to remain consistent

with Department of Health aged care outbreak reporting). Data on remoteness were obtained from the Australian Bureau of Statistics website (70) and linked this to each RACF by postcode. Methods specific to the assessment of each surveillance attribute are given alongside findings in Table 1.

Ethics approval:

The Australian National University Human Research Ethics Committee has granted overarching approval for surveillance evaluations carried out as part of the Masters in Applied Epidemiology program (protocol: 2017/909).

VARCRC Early Warning System

Description

Staff in the VACRC Intelligence Unit implemented and operated an Early Warning System (EWS) from 7 August to 9 October 2020. The purpose of the EWS was "to inform targeted responses that minimise the impact of outbreaks" (71), through identifying RACFs with one or more suspected COVID-19 cases prior to availability of test results, facilitating assessment of outbreak risk and preparedness, and providing necessary referrals according to risk and preparedness. The system was designed and implemented rapidly due to a perceived need for immediate action, so refinement of processes occurred in parallel to operation (71).

The system relied on voluntary case notification data from RACFs, as well as auxiliary RACF level data extracted from several electronic information management systems (Figure 1). The population under surveillance were residents and staff of all Victorian RACFs. The system defined a suspected case as any resident or staff member who had a COVID-19 test requested, for any reason; this was the case definition used to trigger notification.

VACRC informed facilities of the system and asked them to participate via an email sent to all Victorian RACFs. The email asked RACFs to notify when any staff member or resident met the case definition, by email or telephone. Details requested at initial notification included the facility's ID number, the number of suspected cases, and a contact mobile number. All email notifications resulted in an auto-reply acknowledging receipt. Initial notification data were entered manually into a spreadsheet by a VACRC officer.

After receipt of an initial notification, VACRC intelligence unit staff collated information from various sources in order to assess risk of a significant COVID-19 outbreak to the facility. These sources of information changed over the course of the system's operation but variously included:

- Data from the Victorian Department of Health including current RACF outbreaks and geographical “hotspot” areas of higher transmission.
- Details on the outcome of Australian Defence Force (ADF) prevention visits recorded in the COVID-19 Aged Care Incident Response System (AUS-CAIRS).
- Data from ACQSC Sector Intelligence dashboard for risk of and preparedness for COVID-19 outbreaks.

When the system was first implemented, it did not include strict criteria for assessing risk, and assessment was somewhat subjective. Intelligence unit staff later developed a set of criteria to define a high risk facility. These included notifying facilities with more than 3 suspected cases, facilities with suspected cases that were symptomatic, facilities were located in an area with high levels of community transmission, and facilities for which an ADF visit had identified significant issues in outbreak preparedness.

For facilities deemed to be at elevated risk, VACRC staff made a phone call to the notifying facility to confirm details of the suspected case(s), and to assess preparedness for managing an outbreak (e.g. whether residents were in single rooms, whether the facility managers felt they had access to sufficient PPE and workforce).

Based on issues identified by the risk and preparedness assessments, notifying facilities could then be referred via one of several referral pathways. Intelligence unit staff referred facilities identified as high-risk to the VACRC operations team for further follow-up. These referrals were made at 4pm each day based on notifications received in the 24 hours before 12pm, and a response allocated at a 10am meeting the next morning. Other isolated issues in outbreak preparedness were dealt with by Intelligence unit staff on an ad hoc basis, by direct referral to other pathways. For example, facilities struggling to secure PPE through their usual pathways could be referred to the National Medical Stockpile, and facilities with infection prevention and control (IPC) queries referred to the Department of Health hotline.

The team stored EWS data on a Microsoft Excel Spreadsheet online on Microsoft Office 365, accessible to VACRC staff. Staff required access to the AUS-CAIRS information system to retrieve additional information on prevention visits. Data entry, risk and preparedness and assessment took on average about two person-hours per day. Because the system did not exist within a formal legal framework, notification by facilities was voluntary, and the system did not request any personally identifying information on suspected cases.

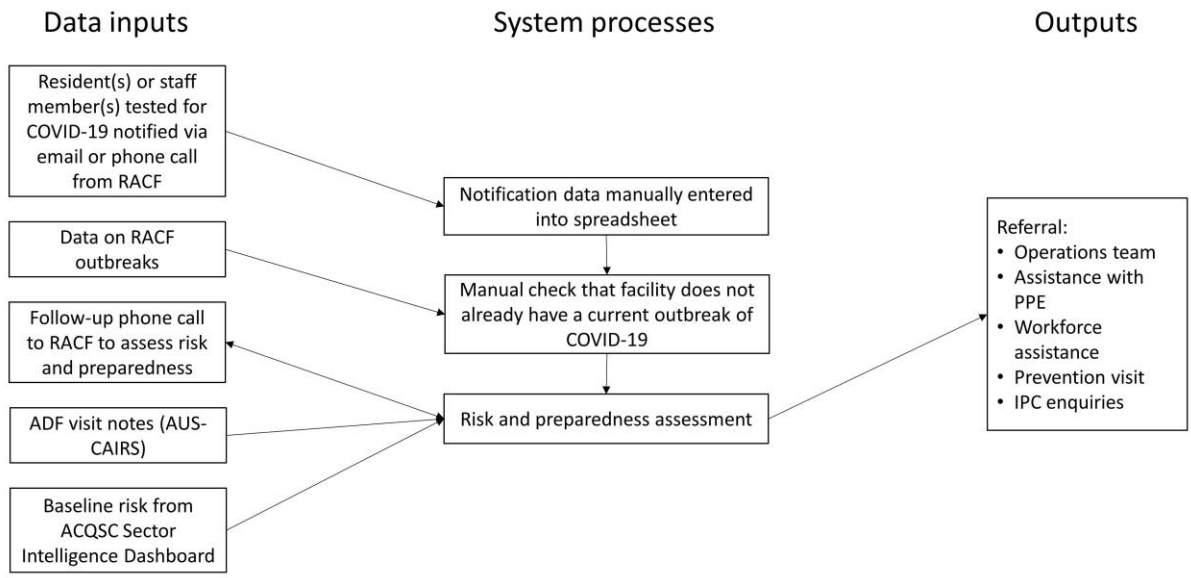

Figure 1. Flowchart showing simplified processes of the Victorian Aged Care Response Centre Early Warning System. *RACF: residential aged care facility; ADF: Australian Defence Force; AUS-CAIRS: COVID-19 Aged Care Incident Response System; ACQSC: Aged Care Quality and Safety Commission; PPE: personal protective equipment; IPC: infection prevention and control.*

Relevance to ongoing surveillance

The main value of the EWS in respiratory outbreak surveillance lay in its ability to provide a pathway for outbreak detection in high-risk settings, which was independent of laboratory notification of a positive PCR result. Such mechanisms are especially important when laboratory testing capacity and systems for case and contact management are strained.

The system achieved reasonable coverage, with 48% of facilities notifying at least once. Notifying facilities were representative of the spectrum of Victorian RACFs in terms of facility type, size, and remoteness (Figure 2). The inclusion of staff members in the population under surveillance substantially improved coverage and would have contributed to the sensitivity of the system; 1225/2629 (47%) suspected cases reported were staff.

However, performance of the system for the early detection of outbreaks was limited. In 12/36 outbreaks (33%) occurring between 7 August and 2 October 2020, the EWS received a notification from the facility prior to diagnosis of the first outbreak case, representing reasonable sensitivity for a newly implemented system. These 12 outbreaks were detected from a total of 1815 notifications, giving a PPV for each notification of 1%. A low PPV should be expected given the broad case definition that encompassed SARS-CoV-2 testing for any reason, including asymptomatic testing, and it is worth noting that the system had a mechanism for prioritising notifications for symptomatic or multiple suspected cases. Further, operating on 2 person-hours per day, the cost of detection per

outbreak over the analysis period was a reasonable 9.3 person-hours, noting that this does not include time associated with providing on-site intervention, or reporting by RACFs.

The direct effects of the system on outbreak management and preparedness are difficult to assess. Analysis by VACRC staff found that outbreaks preceded by a notification were smaller and shorter than non-notified outbreaks. However this association might as easily be explained by confounding via difficult to measure RACF factors that promote both outbreak preparedness and system participation, as by a direct effect of the system itself.

Several stakeholders emphasised the importance of "soft" benefits of the system, citing feedback from RACF staff that they valued the opportunity for engagement and support. Evaluation by VACRC staff found that between 27 August and 30 September 2020, 77/309 (25%) of reporting facilities had some sort of follow-up, including delivery of IPC advice, assistance arranging extra PPE, prioritisation of on-site prevention visits undertaken by the ADF, or provision of general support and reassurance. While the importance of such engagement for outbreak preparedness should not be understated, at face value it seems unlikely that a passive disease surveillance system would be the most effective method to achieve this.

Changing the way data were collected, integrated and reviewed might have improved system usefulness. Some stakeholders raised the complexity of the system as an issue. The system relied on manual integration of data from multiple sources, which was labour intensive, and could have had implications for flexibility and robustness in a longer-running surveillance system. Further, previous notifications were not routinely considered in risk assessment, so a facility reporting suspected cases on multiple consecutive days would not necessarily be prioritised for referral. These limitations might have been partially addressed by designing or altering the system to use more sophisticated data management software. However, given the perceived need for rapid implementation and the short lifespan of the system it is easy to understand why this was not attempted. Additionally, the lack of collection of personal identifying information or use of another method to link notification of suspected cases and their test results, while avoiding potential privacy issues, somewhat undermined the ability to monitor and evaluate system performance.

Finally, better clarity of the agreed role and purpose of the EWS may have improved usefulness of the data. Stakeholders saw this as a key issue in determining the success of the system. Senior staff within VACRC did not perceive the system as being useful due to its low specificity for detecting outbreaks. Stakeholders involved in operating the system felt that despite its poor predictive value, the EWS could be used to prioritise the delivery of outbreak preparedness and prevention interventions to RACFs in most urgent need. However, they reported that the teams responsible for

implementing these interventions struggled to effectively integrate referrals from the EWS into their existing workflows, due to competing priorities such as dealing with existing outbreaks. These difficulties illustrate the importance of effective engagement with users of the data in design and implementation of surveillance.

SCV/VicNISS system

System description

Development of the Safer Care Victoria screening tool was prompted by concerns raised early in the pandemic that the aged care sector was likely to encounter challenges in responding to COVID-19 outbreaks. The purpose of the tool was to facilitate structured assessment of residents for signs and symptoms of COVID-19, and to encourage appropriate early escalation, such as testing or isolation. Developers hoped that uptake of the tool in residential aged care would help to prevent larger outbreaks and reduce impact on the aged care workforce through furlough. The tool was developed by Safer Care Victoria in collaboration with aged care sector experts, clinicians, the Victorian Department of Health, VicNISS, and participating pilot facilities (72). The tool was based on "Stop and Watch" early warning tools and designed to be used to assess residents daily by personal care assistants (PCAs) with limited clinical training, in collaboration with the nurse in charge. The tool and implementation kit are available on the Safer Care Victoria website (2). The tool was piloted with approximately 1000 residents across 17 facilities (72), prior to being rolled out more widely from June 2020 onwards via a series of webinars.

The first section of the tool was designed to be completed by a PCA and consisted of a checklist of several clinical signs including fever and falls. If none were identified the screen was complete and no action was required. Otherwise, a nurse was required to assess the resident and complete the second section. This included prompts to refer the resident for assessment by a GP or Residential In-Reach service if signs or symptoms of respiratory illness were identified, and to record whether the resident was tested for COVID-19 or influenza, as well as the reason for not testing, if not performed. The tool was designed to be used daily with all residents.

The Safer Care Victoria tool was not developed to be used for surveillance; however due to its pre-existing relationship with public sector residential aged care services (PSRACS), VicNISS became involved in collecting data from facilities using the tool in order to monitor uptake and performance. As a system involving regular, systematic collection of data on a health-related event, use of the tool and associated data collection can therefore be assessed for potential usefulness for surveillance (Figure 3).

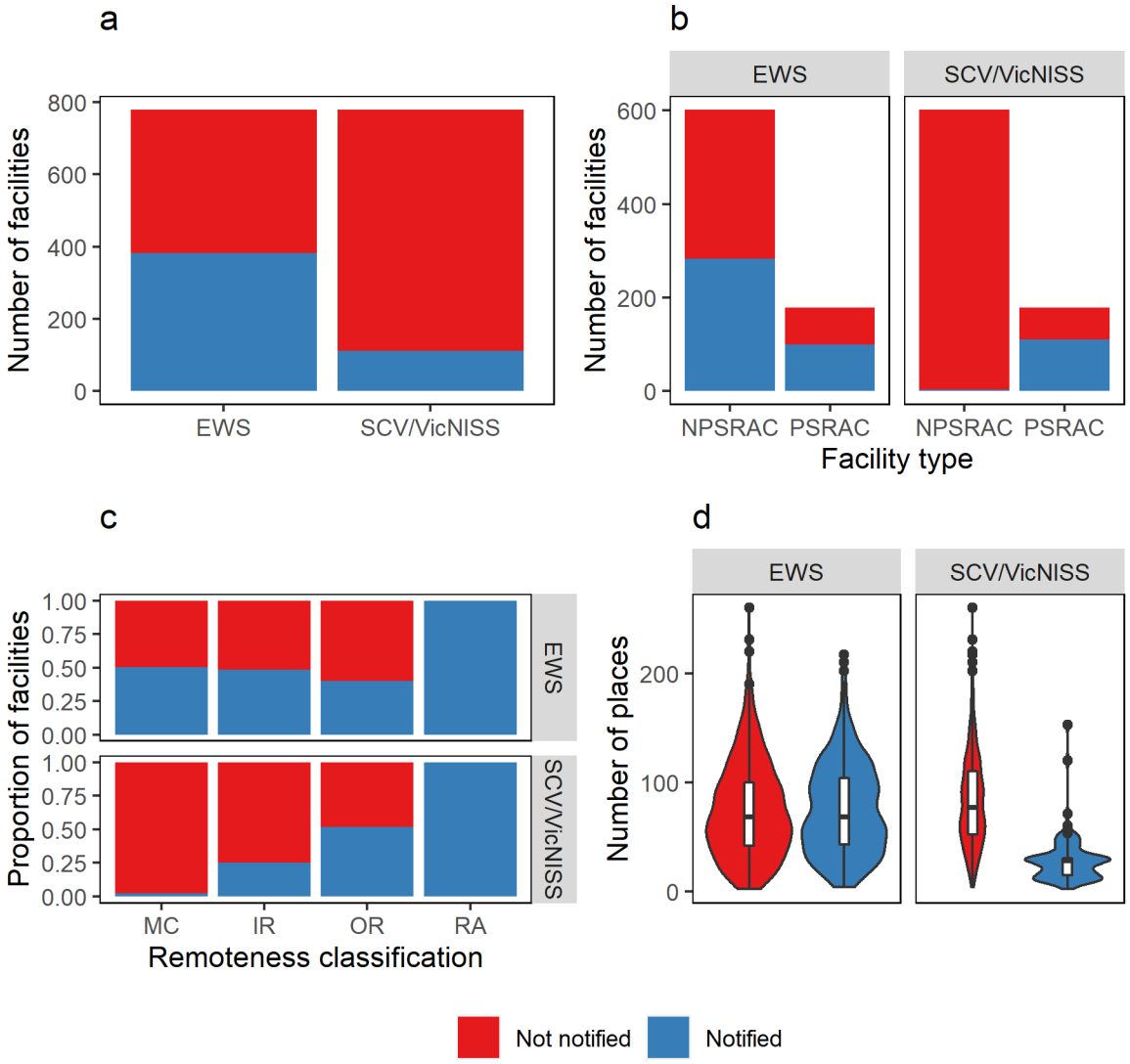

Figure 2. Comparative coverage and representativeness of data received through the Victorian Aged Care Response Centre Early Warning System (EWS) and reporting on use of the Safer Care Victoria Screening Tool (SCV/VicNISS). *(a) Number of facilities that notified. (b) Number that notified by facility type; either public sector residential aged care (PSRAC) or private/not-for-profit (NPSRAC). (c) Proportion of facilities that notified by remoteness area; either major city (MC), inner regional (IR), outer regional (OR), or remote (RA). (d) Notifying and non-notifying facilities by number of operational places. The time period for all data is 7 August to 2 October 2020.*

Data requested by VicNISS included aggregate data on the number of residents screened, number of positive screens, number of care escalations, number of COVID-19 and influenza tests performed, and the results of testing once available. Facilities were encouraged to record these data in a spreadsheet, optionally using a provided template. Facilities could submit data weekly or on an ad-hoc basis throughout the week. Data submission was done using an online portal, which was used regularly by PSRACS to submit data for other surveillance coordinated by VicNISS, for example monitoring of staff and resident vaccinations. Reporting by facilities was voluntary. Reporting facilities received an auto-generated report summarising weekly data on the proportion of residents screened, and summary of escalation and testing. *Relevance to ongoing surveillance*

The value of the Safer Care Victoria screening tool for respiratory outbreak surveillance in residential aged care lay in providing a structured framework for active assessment of residents for respiratory illness. The system implemented by VicNISS to record and report on use of the tool provided a mechanism for monitoring screening for respiratory illness, the occurrence of symptoms, and testing behaviours. These are relevant metrics for respiratory outbreak surveillance in residential aged care settings.

The system was strengthened by use of an existing web portal already familiar to PSRACS participating in other surveillance activities, increasing acceptability. The portal was capable of producing RACF-specific summary reports on submission of data, providing a method for RACFs to self-monitor performance and providing an incentive to participate in the reporting process. Once established, there were minimal ongoing maintenance costs of the system to VicNISS and Safer Care Victoria.

The primary limitation of this system was that there was no agreement for how the data should be used for surveillance. Consequently, while use of the tool may have improved screening, reporting did not serve a useful surveillance purpose, such as early outbreak detection. VicNISS produced a report based on the submitted data for the Department of Health in October 2020, which summarised uptake, screening, and testing. The report suggested that VicNISS could provide ongoing regular summary data, however an explicit purpose for such data provision was not stated.

Were the data to be used for surveillance, one challenge would be extending coverage to include more facilities at higher risk of outbreaks. VicNISS had strong pre-existing relationships with public sector RACFs, but less engagement with private and not-for-profit facilities, and these facilities were not proactively recruited to participate in reporting. This was reflected in data reported to the system, with 109/178 (61%) public sector services participating over the period 7 August to 2 October 2020, compared to only 2/602 (<1%) private or not-for-profit facilities. However, perhaps because they accounted for the majority of beds and were more likely to be located in urban areas (33), the vast majority of cases in residential aged care occurred in private or not-for-profit facilities. Consequently, overall coverage and sensitivity of the system was affected. Over the analysis period 386 COVID-19 tests were reported compared to 1370 resident tests notified to the EWS. One report was linked to one of the 36 outbreaks (sensitivity of 3%). As there was no requirement for facilities using the tool to report, this may not reflect performance of the tool in practice.

Apart from improvements in coverage and representativeness, usefulness of the data for outbreak surveillance could be improved by asking facilities to enter reports on a daily basis, allowing more timely analysis and response. As with the EWS, linkage of laboratory notifications to individual

resident data reported through the system would likely result in greater ability to monitor and refine system performance.

Although piloting facilities assessed the useability of the screening tool as good (72), stakeholders received subsequent feedback from facilities using the tool on a regular basis that screening could be resource intensive. Indeed, assuming the average time required to complete a screen is between 3-5 minutes (72), the time requirements for a facility caring for 60 residents would be 3-5 person-hours per day. It is possible the tool could be further refined to shorten time requirements, for example by removing an item asking about change in taste or smell, which is uncommon in RACF residents with COVID-19 (39), and is not a common feature of other respiratory viral infections. Screening for respiratory illness could also be integrated into other daily resident activities, for example by integrating into clinical deterioration screening, if this is being performed.

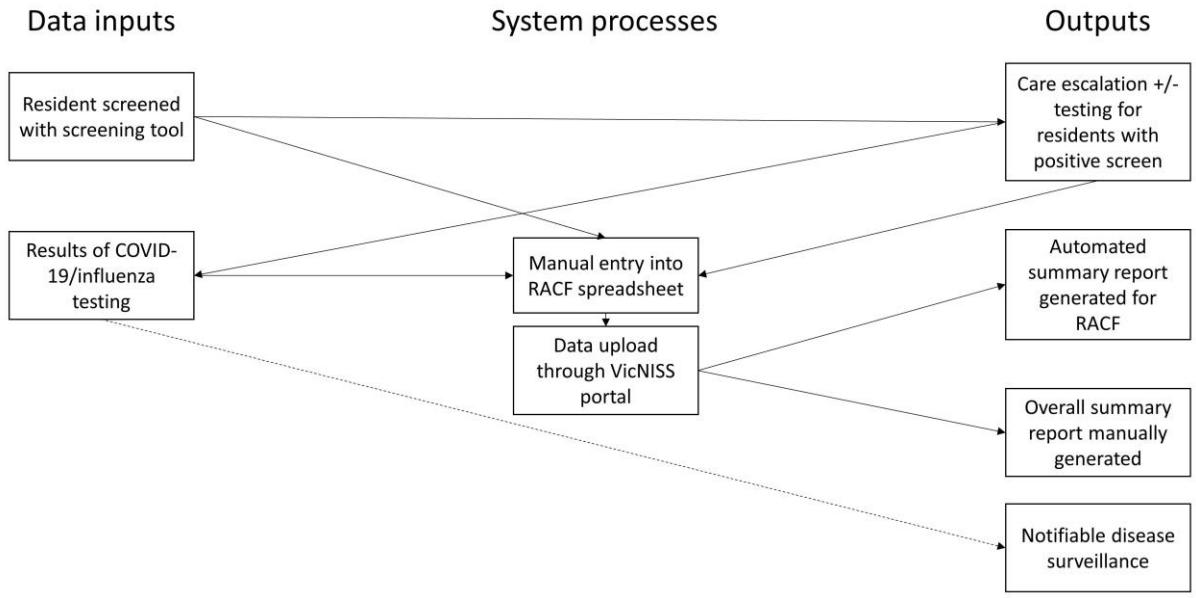

Figure 3. Flowchart showing process for collecting and reporting data collected using the Safer Care Victoria COVID-19 screening tool for residential aged care service. *RACF: residential aged care facility; VicNISS: The Victorian Coordinating Centre for Healthcare Associated Infections.*

Table 1. Assessment of surveillance attributes against the Centers for Disease Control and Prevention criteria.

Attribute	Methods	Findings	
		Early Warning System (EWS)	**SCV/VicNISS system**
Usefulness	Stakeholder interviews, operating documents, assessment of other attributes.	Poor accuracy for identifying facilities which would have a confirmed outbreak, perhaps in part due to the broad case definition. Does appear to have been effective in identifying and addressing preparedness gaps in some notifying facilities. However, operational capacity was prioritised to address existing outbreaks, so referral generated by the system were often not prioritised.	Appears to have been successful in encouraging systematic screening for respiratory symptoms, at least in public facilities. Difficult to assess usefulness for outbreak detection, as most outbreaks occurred in private or not-for-profit facilities. Summary data has been used to monitor uptake but did not serve a surveillance purpose.
Simplicity	Stakeholder interviews, operating documents.	Easy-to-apply case definition. Simple process for notification and initial data entry. Processes for risk-assessment and referral required staff to have familiarity with system and integrate data from multiple information systems.	Fairly simple and easy to use tool. Streamlined data entry process.
Flexibility	Stakeholder interviews, operating documents.	Simple notification process adaptable to changing information requirements.	Given the bespoke nature of the system, should be reasonably flexible and easy to change.

Data quality	Proportion of notification dataset missing or incomplete.	Less than 1% of core notification data missing (date of notification, notifying facility, contact details, number or suspected cases).	Complete for all reporting facilities.
Acceptability	Proportion of Victorian RACFs that notified.	381/780 RACFs (48%) notified at least once with median of 3 notifications per facility (IQR 1-7).	111/780 RACFs (14%) submitted data over the period, including 109/178 PSRACS (61%). The median number of weekly reports submitted per facility was 7 (IQR: 5-7, of a maximum of 7).
	Stakeholder interviews, operating documents.	Process of performing risk assessment was labour intensive for staff, however could be streamlined. Although the reporting requirements for the system were simple, they placed additional strain on RACFs already dealing with demands for information from multiple different sources.	Minimal running costs for data storage or reporting using existing system. Piloting RACFs rated useability of the tool as 4 out of 5, reported the time taken to complete it was less than 5 minutes per resident. (72).
Sensitivity	Proportion of confirmed outbreaks possibly detected by surveillance.	In 12/36 outbreaks (33%) the EWS received a notification from the facility prior to diagnosis of the first outbreak case (in another 6, notifications were received some time after the outbreak was identified).	One of 36 outbreaks (3%) was associated with a facility reporting at least one positive screen.
Positive predictive value	Proportion of notifications possibly associated	Twelve outbreaks from 1815 notifications (1%).	One outbreak detected from 275 weekly reports with at least one positive screen (<1%).

	with an outbreak detected by surveillance.		
Representativeness	Comparison between notifying and non-notifying facilities.	99/178 (56%) of PSRACS vs 282/602 (47%) of NPSRACS notified at least once. Notifying facilities had similar sizes to non-notifying facilities (median of 68 operational places each), and similar remoteness distribution (Figure 2).	109/178 (61%) of PSRACS vs 2/602 (<1%) of NPSRACS. Notifying facilities tended to be smaller compared with non-notifying facilities (median 77 vs 28 operational places, respectively), and facilities in regional locations were more likely to notify (Figure 2).
Timeliness	Stakeholder interviews, operating documents.	Notifications deemed to require action were generally dealt with within 24 hours.	Reporting from RACFs usually done weekly, limiting timeliness of a potential response. However VicNISS has capacity to manage daily reporting.
Stability	Stakeholder interviews, operating documents.	No significant outages or delays.	No significant outages or delays.

Section 3: Discussion

Key considerations and potential strategies for aged care respiratory outbreak surveillance:

Based on a review of the literature and recent surveillance efforts, the following requirements and strategies for effective respiratory outbreak surveillance in residential aged care are tentatively proposed.

1. The system should sensitively and rapidly detect outbreaks that pose a significant risk of harm to residents or staff.

Presentation of respiratory viral infections in aged care residents, encompass a range of atypical signs and symptoms, and are poorly captured by traditional ILI definitions. Sensitivity therefore depends on broad criteria for notification and testing. Sensitive surveillance should include staff and visitors as they are the "vectors" for incursion of respiratory viruses into RACFs (39, 73). Although active surveillance is resource intensive, it may facilitate more timely and complete detection, and has been implemented on limited scales both in Australia and overseas (17, 22, 73). Daily screening of residents, staff, and visitors for symptoms of acute respiratory illness is supported by Communicable Disease Network Australia guidelines (35).

Sensitivity depends also on coverage of the system, and especially on inclusion of facilities at higher risk of large respiratory outbreaks, which is linked to acceptability to RACFs. Therefore processes for screening should be as straightforward as possible. Given evidence for historical underreporting of outbreaks (26), consideration should be given to simplifying testing and notification criteria, even if this results in some loss of specificity. Reporting may be facilitated through the use of online systems which allow the collection of all relevant data without the need for exchange of multiple emails or phone calls, and provide a central point of contact for dialogue between aged care services and public health authorities (74). Periodic active engagement by external IPC staff may help to reinforce good screening and reporting practice (17, 18, 22).

Acceptability might also be improved by demonstrating the direct benefit to participating facilities. Benefit could be demonstrated by: 1). Showing that participation improves outbreak management or outcomes, or; 2) Showing how participation could be used to help demonstrate compliance with accreditation standards, current public health directions, and ACQSC guidance around systematic monitoring of staff/residents for signs/symptoms of COVID-19 and notification (75).

Even so, voluntary systems are unlikely to have complete coverage, and are probably more likely to attract services with greater capacity and resources to participate, which may be those least in need of surveillance. Compulsory participation in surveillance for all RACFs would probably need to be

mandated by the ACQSC or through state public health directions, although public sector facilities could have participation linked to receipt of state funding. Regardless, the potential consequences of any legally enforceable changes would need to be carefully considered, and changes would need to be accompanied by active engagement with and support of less well performing facilities.

2. The system should allow rapid confirmation of causative pathogens

Any syndromic criteria that sensitively detects respiratory outbreaks is likely to lack specificity. Efforts to improve specificity by defining an outbreak based on the presence of multiple ill residents or staff will impede potential for early (and thus more effective) intervention, especially in outbreaks caused by SARS-CoV-2 where a substantial fraction of transmission occurs prior to symptom onset. Therefore, broad criteria should be used to define a suspected respiratory outbreak, but should be accompanied by rapid testing and test processing to provide confirmation and justify intervention. This can be achieved through prioritisation of sample processing through existing mechanisms i.e. laboratory based PCR testing, coupled with priority notification of positive results (as is now done in Victoria for SARS-CoV-2 testing). Alternative options include outreach testing with mobile or point-of-care PCR (17, 76), and roll-out of rapid antigen tests to RACFs (51, 77), although more work is needed to determine the most effective combination of strategies and to evaluate their performance in practice.

3. Confirmation of an outbreak should be linked to effective intervention

Since response is critical to the impact of disease surveillance, protocols to respond to a suspected or confirmed outbreak should be agreed on as part of surveillance implementation. This should ensure that stakeholders, including users of the data agree on the purpose of the surveillance and have sufficient resources and motivation to participate. Since surveillance is likely to incur substantial costs to facilities including time for screening, testing, and reporting, it should involve a demonstrable benefit to participating facilities in order to appear acceptable.

4. Surveillance should be responsive to changing behaviour and respiratory virus epidemiology

Ideally, surveillance should incorporate reported symptoms, volume of testing, and test-positivity for important respiratory viral pathogens. This will allow performance of the system to be monitored, allowing the cost of detecting outbreaks to be more easily estimated, and assisting in evaluation and refinement. The system should incorporate surveillance for SARS-CoV-2, influenza, and RSV but should be flexible to adapt to unexpected fluctuations in circulating respiratory viruses associated with disruptions in travel patterns and population immunity caused by the current pandemic.

Limitations and scope for further work

Limitations of this report include lack of consultation with RACFs, residents, and healthcare providers caring for residents, due to time constraints. Further work is needed to explore the acceptability of surveillance activities to these stakeholders, which will be critical to the success of future implementation. Assessments of system timeliness, and therefore usefulness, were somewhat limited by the data collected by each system, for example dates of symptom onset and testing were not routinely recorded. Further, because of differences in the way data were collected, estimates of coverage, sensitivity, and predictive value are not directly comparable across systems. Given the wide heterogeneity in ways in which respiratory outbreaks in aged care have been defined and identified internationally (18, 22, 45, 74), it would be useful to assess the comparative performance of various methods in identifying and/or preventing severe outbreaks. However this would require prospective data collection.

Conclusions

Respiratory virus outbreaks in Victorian aged care facilities were an important public health problem prior to the current pandemic. Experience with COVID-19 has highlighted potential areas for improvement in outbreak surveillance and prevention. Given ongoing uncertainty in near-term respiratory virus epidemiology, there is a need for sustainable and integrated surveillance for outbreaks caused by important respiratory viruses in residential aged care settings. Surveillance should continue to focus on achieving rapid testing and notification in response to broad testing criteria, in order to inform early targeted intervention. Surveillance implementation should actively seek to include those facilities at highest risk of severe outbreaks.

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Chapter 5: Teaching and additional population health experience

Lessons from the field

MAE students are required to deliver a peer-to-peer teaching session or "Lesson from the field" (LFF) to their classmates. Session topics should relate to something students have encountered as part of their field placement, or one of their projects, that other students might find useful in their own practice. Each lesson consists of some pre-reading and questions, then a one hour group video-conference to discuss the topic. Our cohort was divided into two LFF groups. I volunteered to coordinate one of these groups, which involved ensuring all group members had access to the pre-reading documents and meeting details.

I presented an LFF on "a brief introduction to causal directed acyclic graphs in epidemiological research". Causal diagrams were adopted into epidemiology in the late 20th century as a way to graphically represent the assumptions underlying studies seeking to estimate causal effects, and thus identify and communicate potential sources of bias. They are especially useful in communicating between disciplines such as epidemiology, economics, and social sciences, where there are differences in technical jargon used to describe some types of biases. We didn't get a chance to cover the use of causal diagrams in our MAE course blocks, but I found them very useful in trying to think clearly about my own projects, and hoped that other students would as well.

The pre-reading focussed on the basic interpretation of causal diagrams, and understanding structural definitions of confounding, mediation and selection bias. During the session we discussed the application of causal diagrams to some of our own MAE projects. The pre-reading for my LFF is included as Appendix 3.

First year teaching

In March 2021, our MAE cohort delivered a day of teaching to the new first year students via Zoom. As part of this, Steph Curtis, Fran Sheehan and I lead a session on antimicrobial resistance (AMR) and healthcare acquired infections (HAI), with a focus on surveillance. We began with an online poll to gauge the audience's previous experience with AMR and HAI, then gave a brief presentation to provide some background and context, including a short video. After discussing some of the challenges in carrying out surveillance for healthcare acquired infections, we asked the first years to divide into small groups and come up with a plan for implementing national healthcare acquired infection surveillance in Australia. One member from each group then provided a summary to the class before a wrap-up with reference to the session learning objectives.

We felt that this mix of interactive and didactic learning, utilising multiple types of media was fairly effective at maintaining engagement over Zoom. Most first year students agreed, with 18 out of 20 who provided anonymous feedback either agreeing or strongly agreeing with the statement "Overall, I am very satisfied with the session". Those who provided feedback reacted positively to the interactive aspects of the session but noted the overall quality was impacted by some technical glitches.

Secondment to the Victorian Department of Health

Between March and July 2020, I went on secondment to the Victorian Department of Health to assist with the state-wide pandemic response. During this time I worked as part of a team responsible for surveillance and reporting. Our main aim was to understand the distribution of SARS-CoV-2 infection in Victoria by person, place, and time, in order to inform focussed population health interventions. Responsibilities of the team included the production of daily situation reports, summarising and reporting on outbreaks, reporting on cases in particular priority groups such healthcare and aged care workers, and keeping abreast of the evolving COVID-19 literature.

The work was interesting because the team needed to adapt to meet dynamic information requirements that arose both from efforts to inform the immediate public health response, and from political demands. Further, both these requirements, and our ability to fulfil them, shifted with caseload. This meant that we often had similar workloads on days with just a few new cases as those with dozens, but that priorities shifted from understanding the fine details of each case, to providing a coherent "big picture" of the current epidemiologic situation.

Royal Melbourne Hospital healthcare worker infection working group

In July 2020, while working on the COVID-19 response at the Royal Melbourne Hospital (RMH), I had the opportunity to join a new working group investigating health care worker SARS-CoV-2 infections. The group was broadly tasked with identifying how healthcare workers at RMH were catching COVID-19, and coming up with a list of recommendations to prevent further staff infections.

As a group, we developed a case questionnaire to obtain detailed information on possible exposures to SARS-CoV-2 both within, and outside the workplace, and to understand any environmental or behavioural factors that may have contributed to acquisition within the workplace. Due to the volume of cases and limited personnel, this questionnaire was self-administered via a REDcap survey. Although as a tool to define risk factors, this study was limited by the lack of a comparison group, it did identify some important hypothesis-generating findings with impact for control measures. These included that few cases had known exposure to COVID-19 outside the workplace, that only a minority were involved in performing aerosol generating procedures, but that many had

had contact with COVID-19 patients exhibiting difficult to manage behaviours associated with delirium or dementia.

Another aspect of the project involved combining epidemiologic and genomic data to help understand transmission within the hospital. I helped to integrate location-time data for infected healthcare workers (obtained from rostering software and line managers) with location-time data for infected patients (from the patient administration system) to generate hypotheses about transmission events that could be tested with the use of genomic data. This analysis helped to address important issues such as the contribution to transmission from staff working across multiple wards, and risk of transmission from admitted aged care residents.

Other activities

In March 2021 I co-wrote an article for *The Conversation* with Sheena Sullivan and Kanta Subbarao on the relevance of experience with global influenza surveillance to tackling new SARS-CoV-2 variants[1]. A copy of the article is included as Appendix 1.

Over the course of the MAE I had the privilege of peer-reviewing epidemiology articles for several international journals. Apart from the satisfaction associated with participating in the scientific process, I found this process of actively critically evaluating papers and making suggestions for improvement positively contributed to my own writing and research skills.

Being based in a centre that forms an integral part of the Global Influenza Surveillance and Response System provided excellent day-to-day opportunities for exposure to aspects of influenza surveillance activities from sample processing through virus culture, sequencing, antigenic characterisation, and the formulation of vaccine composition recommendations. I also valued being able to attend a number of excellent clinical, laboratory, and public health seminars and meetings organised through the Doherty Institute.

[1] *The Conversation* does not publish articles from Masters students (see: https://theconversation.com/au/pitches), so I am not listed as an author on the online version.

Appendices

Appendix 1: Public communication piece

Flu vaccines are updated every year. We can learn from this process as we respond to COVID variants

The Conversation, March 18, 2021

While the future of the pandemic remains uncertain, we'll probably have to live with COVID-19 for some time.

We face a range of possible scenarios. At the most optimistic end of the spectrum, new vaccines will protect against all current and future variants of concern. At the other extreme, we'll see the frequent emergence and spread of new variants, against which existing vaccines will have limited effect.

It's likely we'll land somewhere in the middle.

Notably, although new variants do threaten the effectiveness of COVID-19 vaccines, decades of experience updating influenza vaccines can inform our global response.

Evolving variants

We're still learning about how new viral variants affect vaccine effectiveness.

The B.1.1.7 variant, which emerged in the United Kingdom in late 2020, is more infectious and deadlier than the original strain of SARS-CoV-2 (the virus that causes COVID-19). Fortunately, though, preliminary data indicates COVID vaccines still work well against it (although this research hasn't yet been peer-reviewed).

Meanwhile, a study published yesterday found the Oxford/AstraZeneca vaccine is ineffective against mild or moderate COVID-19 caused by the B.1.351 variant. This study was done in South Africa, where this variant emerged and is currently dominant.

Results of clinical trials of the Novavax and Johnson & Johnson vaccines indicated about 60% overall effectiveness in South Africa, according to the vaccine manufacturers. This is lower than the 70-90% reported in the United States and the UK.

Notwithstanding differences in each country's health systems and health status of their populations, which may explain some of the differences, this is a concerning trend.

Reassuringly, Johnson & Johnson reported 85% effectiveness against severe disease, regardless of country or variant. This suggests while some existing vaccines may not entirely prevent infection and

mild illness caused by certain variants, they may still protect from severe illness and reduce the load on hospitals.

But if new variants continue to emerge, COVID vaccines may need to be reformulated regularly.

Several manufacturers have announced they're already working on boosters designed to be more effective against the B.1.351 variant, which has now been detected in 48 countries.

Understanding the global spread of new variants

To develop updated vaccines that best respond to new variants, we need to understand the spread of the variants around the world. This is a big challenge.

To know which variant a person is infected with we need to sequence the viral genome (the genetic material of the virus), which can be expensive and time-consuming. While global access to diagnostic tests is improving, huge disparities in access to sequencing technology remain.

These disparities are reflected in information we have about currently circulating variants. Another variant of concern, P.1, shares some of the key mutations present in the B.1.351 variant. So it may present similar problems with vaccine effectiveness, although clinical trial data are lacking.

The P.1 variant was first identified in Tokyo in travellers from Brazil in January 2021. However, we now understand it's been circulating in Brazil since early December 2020.

Around the world there have only been about 700 shared P.1 sequences, compared with more than 150,000 sequences of the B.1.1.7 variant. There are certainly far more than 700 cases of P.1, but resource constraints mean we're not getting the full picture of how different variants are spreading.

Further, while sequencing capacity has been massively scaled up during the pandemic, it cannot determine whether a mutation will change how the SARS-CoV-2 virus interacts with our immune system. This requires more lab work, called "antigenic characterisation", with limited global capacity to undertake this specialised testing.

Patchy understanding of the nature and spread of new variants may lead manufacturers to focus on modifying their vaccines towards better-known variants, which at the moment are those found in more developed countries. These vaccines may be less effective in developing countries where less well-understood variants may predominate.

So we need ongoing, coordinated and global sharing of sequencing information and virus samples to track virus evolution and vaccine effectiveness.

Lessons from influenza surveillance

We've encountered similar challenges in the development of influenza vaccines, which are updated annually to ensure they remain effective against new strains.

Existing 'flu surveillance has already been adapted to some degree for COVID. The Global Initiative on Sharing All Influenza Data, an online platform set up in 2008, has become the main tool used to share SARS-CoV-2 sequences.

In the case of influenza, we've seen a coordinated global response. The Global Influenza Surveillance and Response System, established in 1952, includes more than 140 laboratories across 114 countries. These labs share information on influenza viruses with five WHO Collaborating Centres, including genomic sequences, antigenic characterisation, and epidemiological data.

The WHO collaborating centres are then responsible for conducting further analysis to guide vaccine composition, inform regular global updates on circulating strains, and provide training and support to national laboratories.

Twice a year, WHO makes recommendations on vaccine composition for the following influenza season. These recommendations are not binding, but national regulatory agencies and manufacturers have consistently used them to develop 'flu vaccines for more than 40 years.

A similar approach may prove useful for COVID-19. So far, manufacturers have made decisions about COVID-19 vaccine composition in consultation with national regulatory agencies. Developing a global framework to identify variants that warrant a vaccine update will allow manufacturers to focus on the technical aspects of vaccine development.

In turn, this will facilitate more rapid rollout of vaccines — and importantly, vaccines that are effective against variants circulating around the world, rather than only those affecting developed countries.

Some positives

Despite these challenges, current COVID-19 vaccines appear to provide strong protection against moderate to severe illness caused by most variants, and are likely to provide at least reasonable protection against others.

Also, SARS-CoV-2 mutates more slowly than influenza, meaning vaccines may need to be updated less frequently.

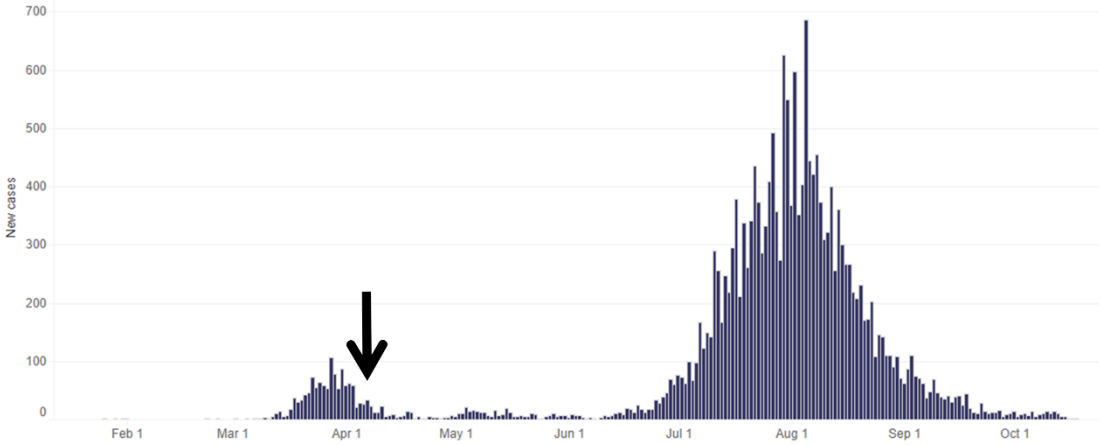
And finally, it will be easier and faster to modify new mRNA and vectored SARS-CoV-2 vaccines than traditional influenza vaccines.

Appendix 2: Presentation slides: Special Edition - Australasian COVID-19 Virtual Conference, 8-10 December 2020

Learning points

- Cruise ships were excellent models for studying COVID-19
- Serology is an important tool for understanding the spectrum of COVID-19

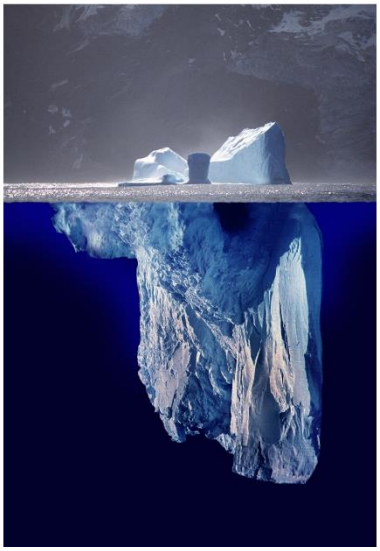
Victoria – April 2020. Tail end of "first wave" driven largely by imported cases



DHHS Victoria. Victorian coronavirus (COVID-19) data. Accessed 19/10/2020.
Available from: https://www.dhhs.vic.gov.au/victorian-coronavirus-covid-19-data

Cruise ships – canaries in the coal mine

- Closed environments
- "Captive" populations
- High attack rates



Diamond Princess – February 2020

- 3,711 on board, 3,063 tests, 634 infected[1]
- 28 PubMed results with "Diamond Princess" in title
- "True" asymptomatic proportion estimated at 0.35[1]
- Data used to estimate China's IFR at 0.6%[2]
- Impact of quarantine on reducing transmission[3]

1. Mizumoto K et al. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Euro Surveill 2020 Mar;25(10):2000180
2. Russell TW et al. Estimating the infection and case fatality ratio for coronavirus disease (COVID-19) using age-adjusted data from the outbreak on the Diamond Princess cruise ship February 2020. Euro Surveill. 2020 Mar;25(12):2000256.
3. Mizumoto K, Chowell G. Transmission potential of the novel coronavirus (COVID-19) onboard the diamond Princess Cruises Ship, 2020. Infect Dis Model. 2020 Feb 29;5:264-270.

Greg Mortimer – departed Ushuaia 16 March[4]

- 217 on board, screened prior to departure[4]
- Decision to terminate cruise early on D3 due to border closures[4].
- Febrile passenger D8. Passengers confined to cabins. Ship barred from disembarking in Uruguay pending testing[4]
- More than half PCR+ on 3 April, most asymptomatic. 8 needing medical evacuation[4].
- 99 Australians repatriated to Melbourne on 12 April
- Limited information available to authorities
- All required to isolate/quarantine in hotel

4. Ing AJ, Cocks C, Green JP. COVID-19: in the footsteps of Ernest Shackleton. Thorax. 2020 Aug;75(8):693-694

Aims

1. Describe symptoms, patterns of viral shedding, symptomatic and asymptomatic attack rates
2. Examine differences in antibody response between symptomatic and asymptomatic cases

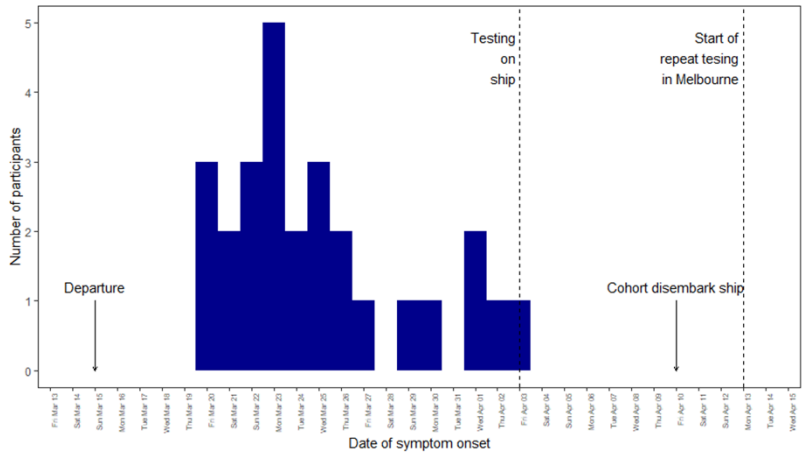
Data collected in hotel quarantine

- 49/99 participated
- Symptom and health data extracted from baseline interviews and daily follow-up performed as part of public health response.
- Respiratory (48/49) and rectal (37/49) swabs for PCR, live virus isolation.
- Serology: 2 sets of samples collected at 1 week interval (7/49 provided only one sample).
  - ELISA for IgA, IgG
  - Microneutralisation assay

Demographics, comorbidities, hospitalisation, presence of symptoms, and previous SARS-CoV-2 PCR results for study participants (n = 49)

Age in years – median (range)	67 (36-81)
Sex	
Female – n (% of total)	31 (63.3%)
Male – n (% of total)	18 (36.7%)
Comorbidities	
None – n (% of total)	26 (53.1%)
Any – n (% of total)	23 (46.9%)
Chronic respiratory disease – n (% of total)	6 (12.2%)
Cardiac disease (excluding uncomplicated hypertension) – n (% of total)	5 (10.2%)
Other – n (% of total)	19 (38.8%)
Symptoms	
Present – n (% of total)	27 (55.1%)
Absent – n (% of total)	22 (44.9%)
Hospitalised	
Yes – n (% of total)	1 (2.0%)
No – n (% of total)	48 (98.0%)
Respiratory PCR result on ship (3 April 2020)	
Positive – n (% of total)	36 (73.5%)
Negative – n (% of total)	12 (24.5%)
Not available – n (% of total)	1 (2.0%)

Delay from disease onset to testing on board



Only 15% PCR+ in Melbourne (Ct 31-45). No live virus isolated

Based on IgG and/or PCR 92% had been infected.

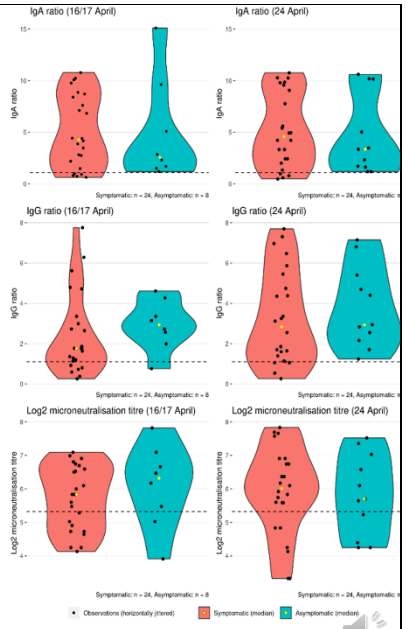
- 42% of cases asymptomatic
- Only 15% of symptomatic cases reported fever
- Similar antibody response in symptomatic and asymptomatic PCR+ individuals at 3 and 4 weeks after median symptom onset

Assay	Positive	%
IgG and/or IgA	46	94%
IgA	44	90%
IgG	41	84%
Both IgA and IgG	39	80%
Microneutralisation	30	71%

IgA

IgG

MN



symptomatic asymptomatic

Summary

- High attack rate, many pauci-symptomatic
- Serology was useful for confirming prior infection in this largely convalescent cohort.
  - May have a role in aiding risk assessment in future overseas arrivals
- Similar antibody response in asymptomatic and mildly symptomatic cases
  - Implications for screening, sero-surveys
  - Longevity still unclear

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Appendix 3: Lesson from the field pre-reading

Lesson from the field: A brief introduction to causal DAGs in epidemiological research

Directed acyclic graphs (DAGs) are an intuitive way to visually represent your assumptions when conducting research involving causal relationships. They are a useful way to identify and avoid bias, to plan data collection and analysis, and to communicate across disciplines that traditionally use different terminology to describe bias.

In this lesson you will learn how to interpret and draw DAGs and use them to identify, and correct for, confounding, "colliding", and selection bias.

Learning objectives:

1. Be able to interpret a DAG
2. Understand structural definitions of confounding, colliders, and mediation.
3. Represent selection bias in a DAG
4. Be able to draw a DAG applicable to your own research

What is a DAG?

A DAG is a way to visually represent your assumptions about causal relationships between variables.

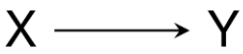

Figure 1: A DAG: X causes Y

Causal relationships are represented by single-headed arrows. This makes DAGs *DIRECTED.*

No cycles are allowed. This makes DAGs *ACYCLIC.*

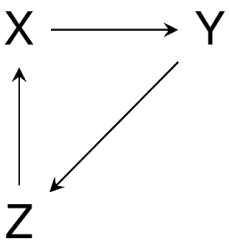

Figure 2: NOT A DAG

DAGs tell you about the direction of a causal relationship but they don't tell you anything about the strength or importance of that relationship, or its statistical nature (linear, exponential etc.). They also don't tell you whether the causal relationship is positive or negative.

DAGs are representations of your "expert" understanding of underlying causal structures. If the causal structure represented in a DAG does not reflect reality, it will probably lead to incorrect conclusions.

Common examples relate to chronic disease or cancer epidemiology but DAGs can easily be applied in other fields. As an example, we will imagine we want to study the effect of socioeconomic status on disease severity in people infected with COVID-19 (Figure 3).

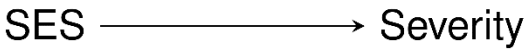

Figure 3

Confounding

A confounder is a variable that has a causal effect on both the exposure and outcome of interest. In Figure 4, age confounds the causal effect of SES on disease severity and should be conditioned on (controlled/adjusted for) in analysis (e.g. by stratification, or inclusion as a covariate in a regression). Conditioning on age can also be thought of as blocking the path SES -> Age -> Severity, leaving the causal effect of interest, SES -> Severity, as the only open path from exposure to outcome.

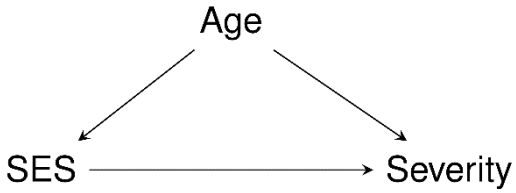

Figure 4

When discussing DAGs, it often makes more sense to think of "confounding", via a path, rather than "confounder" variables. For example, in Figure 5, age is a confounder but frailty is not, according to the above definition. However we can completely address the confounding by conditioning on frailty without having to conditioning on age, thus blocking the path SES -> Age -> Frailty -> Severity (Note we could achieve the same outcome by conditioning on age only, or both age and frailty, although the latter is unnecessary).

Figure 5

Mediation

Mediation occurs when a third variable is causally influenced by the exposure and then has a causal effect on the outcome. Mediator variables can be responsible for some of the effect of the exposure on outcome (Figure 6) or all of it (Figure 7). Conditioning on smoking in Figure 6 gives us the effect of SES on disease severity that is not mediated by smoking. If we condition on smoking in Figure 7 we will block the association of SES and severity. However, if we are interested in the overall effect of SES on disease severity in either case we should not condition on smoking status.

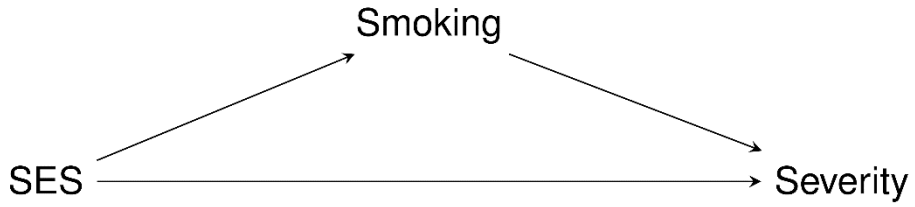

Figure 6

Figure 7

Colliders

Colliders are variables causally influenced by two or more other variables in a DAG. They are called "colliders" because incoming arrow heads appear to collide (Figure 8). Paths through colliders are blocked by default, and do not allow the flow of causal information. However conditioning on a collider will open this path.

There is often a temptation to control for every measured variable other than the exposure and outcome, in an attempt to prevent confounding. However, conditioning on ICU admission in Figure 8 would be an error, as it is not a confounder but a collider.

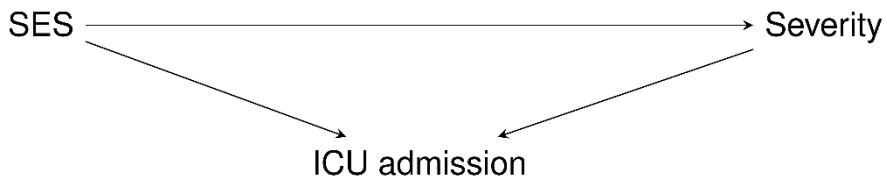

Figure 8

Imagine for the sake of this example that people of lower SES are less likely to be admitted to ICU (hopefully this is not the case in reality). In this case you either need to be of higher SES, or very, very sick to be admitted to ICU. If we condition on ICU admission, for example by stratifying analysis based on ICU status, we will make a biased estimate of the effect of SES on disease severity because the ICU contains people of higher SES with varying disease severity but only people of low SES with very severe disease. If the DAG in Figure 8 is correct, then the right approach is to ignore ICU admission in our analysis.

Selection bias

In the language of DAGs, selection bias occurs when selection of participants opens an otherwise blocked path between exposure and outcome. Usually this occurs when a collider is conditioned on during selection.

We are interested in the population effect of SES on severity. However we will probably only be able to recruit participants who seek care. If SES and disease severity both have causal effects on health seeking behaviour, as illustrated in Figure 9, then collider bias is introduced through selection.

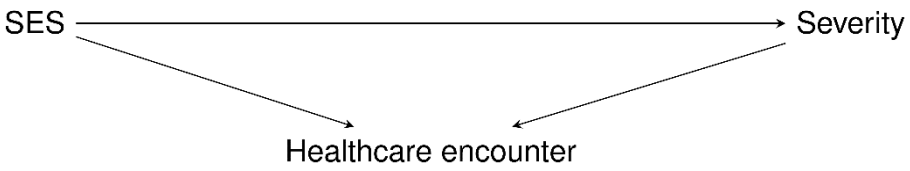

Figure 9

Note that conditioning on the "descendant" of a collider has the same effect as conditioning on a collider itself. In our study we will probably only recruit people who have had a positive test result (Figure 10), but this leads to the same bias as discussed above.

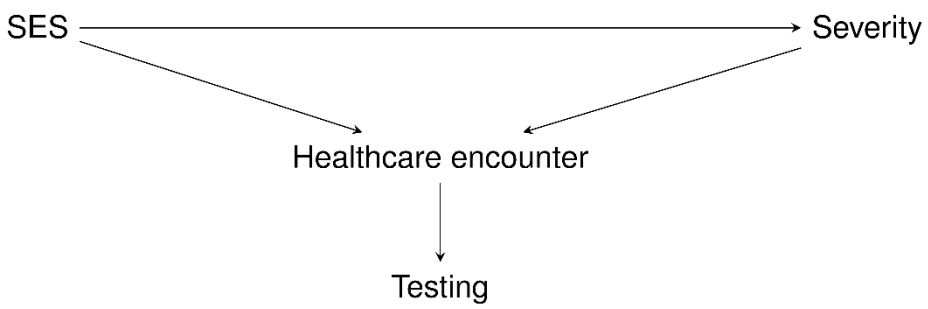

Figure 10

In this case it is impossible, or at least highly impractical, to recruit participants who have COVID-19 but who have not sought care or been tested. Thus we can't avoid conditioning on a collider. However if we have a causal model, and can make assumptions about the possible effects of SES and severity on health seeking behaviour, then we can conduct a sensitivity analysis to estimate the likely effect of selection bias in this case (which is beyond the scope of this lesson).

How to draw a DAG

DAGs look simple but drawing them can be challenging. Our internal understanding of causal relationships are usually very complex but may appear crowded and confusing on paper. How do we know which variables to include in the DAG and which to leave out?

It's helpful to keep in mind that DAGs are not intended to represent everything we know about a causal structure, but only the minimum information needed to identify and resolve bias.

Here are a few basic rules of thumb for drawing DAGs

1. They should include your exposure and outcome variables
2. They should generally include variables you are adjusting for (e.g. by selection)
3. They should include any other variables which have a causal effect on two or more variables already included in your DAG.
4. Mediators along the causal path of interest generally don't need to be included unless they are also part of another pathway or they are being conditioned on.
5. If in doubt about whether to draw an arrow between two variables, the safest option is to do so. Assuming there is no causal relationship between variables should take more confidence than acknowledging the possibility of one.

Recap

Hopefully you can now interpret DAGs, with reference to confounding, mediation, colliders, and selection bias, and are able to draw a DAG relevant to your own research.

Exercise

Please try to draw a DAG applicable to one of your own MAE projects, and have it ready to share for the LFF session. During the session we will review a few examples, and discuss strategies for dealing with identified bias.

Further reading

A nice introductory article:

https://journals.sagepub.com/doi/full/10.1177/2515245917745629

A great free edX course "Draw your assumptions before your conclusions":

https://www.edx.org/course/causal-diagrams-draw-your-assumptions-before-your

A worked example involving colliders (including R script):

https://academic.oup.com/ije/article/48/2/640/5248195

More discussion of collider bias in COVID-19 research:

https://www.nature.com/articles/s41467-020-19478-2

shinyDAG: a browser based app for drawing DAGs:

https://apps.gerkelab.com/shinyDAG/