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Human coronavirus OC43 causes influenza-like illness in residents and staff of aged-care facilities in Melbourne, Australia

C. J. BIRCH[1], H. J. CLOTHIER[2,3]*, A. SECCULL[2], T. TRAN[1], M. C. CATTON[1], S. B. LAMBERT[3,4] AND J. D. DRUCE[1]

[1] *Victorian Infectious Diseases Reference Laboratory, North Melbourne, Victoria, Australia*
[2] *Communicable Diseases Section, Rural and Regional Health and Aged Care Services Division, Department of Human Services, Melbourne, Victoria, Australia*
[3] *Master of Applied Epidemiology Program, National Centre of Epidemiology and Population Health, Australian National University, Canberra, Australia*
[4] *Vaccine and Immunisation Research Group, Murdoch Childrens Research Institute and the School of Population Health, University of Melbourne, Australia*

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SUMMARY

Three outbreaks of respiratory illness associated with human coronavirus HCoV-OC43 infection occurred in geographically unrelated aged-care facilities in Melbourne, Australia during August and September 2002. On clinical and epidemiological grounds the outbreaks were first thought to be caused by influenza virus. HCoV-OC43 was detected by RT–PCR in 16 out of 27 (59%) specimens and was the only virus detected at the time of sampling. Common clinical manifestations were cough (74%), rhinorrhoea (59%) and sore throat (53%). Attack rates and symptoms were similar in residents and staff across the facilities. HCoV-OC43 was also detected in surveillance and diagnostic respiratory samples in the same months. These outbreaks establish this virus as a cause of morbidity in aged-care facilities and add to increasing evidence of the significance of coronavirus infections.

INTRODUCTION

Coronaviruses are large, positive-stranded RNA viruses capable of causing disease in humans and animals [1]. In non-humans they cause a range of syndromes, including respiratory, enteric, hepatic and neurological infection. Until recently, the prototype strains HCoV-OC43 and HCoV-229E were the only coronaviruses known to cause human disease. The respiratory disease with which they are associated mostly involves symptoms typical of the common cold in both adults and children [2]. However, lower respiratory illness has been reported in institutionalized individuals, including military recruits [3], elderly persons attending day-care centres [4] and hospitalized adults with underlying chronic conditions [5–8]. Active surveillance in the community setting has also identified these viruses in up to one third of individuals with lower respiratory symptoms [9]. The recent association of a novel coronavirus with a severe acute respiratory syndrome (SARS) [10–12] and HCoV-NL63 in a 7-month-old child [13] has increased awareness of these viruses as a cause of respiratory illness across all age groups.

Historically, human coronaviruses have been difficult to grow directly from clinical material in cell culture systems. However, molecular technology such as reverse transcriptase–polymerase chain reaction

* Author for correspondence: Ms. H. Clothier, Epidemiology Unit, Victorian Infectious Diseases Reference Laboratory, 10 Wreckyn Street, North Melbourne, Victoria 3051, Australia.
(Email: hazel.clothier@mh.org.au)

(RT–PCR) now enables their routine detection. Several of the RT–PCR strategies used are based on amplification of the nucleocapsid gene, which appears to be more highly conserved than other regions of the genome [1]. This technology is facilitating a greater understanding of the role of these viruses in respiratory diseases.

In Victoria, Australia, laboratory-confirmed influenza is a notifiable disease. Institutional outbreaks of influenza-like illness notified to the Department of Human Services (DHS) are rapidly investigated to ascertain a diagnosis and implement transmission control measures. We describe three outbreaks of influenza-like illness, later determined to be caused by HCoV-OC43, in aged-care facilities in Melbourne, Australia.

METHODS

Outbreak investigations

Three outbreaks of respiratory disease occurred in geographically distinct aged-care facilities in Melbourne during August and September 2002. Notification of each outbreak was made to DHS. For each outbreak a case of respiratory illness was defined as a resident or staff member with at least one symptom of cough, sore throat or rhinorrhoea occurring during the time of the outbreak. Nasopharyngeal swabs collected into viral transport medium were obtained from residents and staff who had onset of symptoms within 72 h of the start of each outbreak investigation. An outbreak was attributed to coronavirus when at least two respiratory specimens tested positive for the virus in the absence of other common respiratory pathogens.

Infection control

The locations of residential rooms on floor plans were mapped to determine whether clustering of cases to particular locations occurred within the three facilities. Infection control measures were implemented within 24 h of outbreak notification and were continued for at least 10 days after the last identified case in each facility. These measures included enhanced general hygiene, restrictions on visitors, confinement of ill residents to their rooms, exclusion of ill staff, and restrictions on new admissions and transfer of residents to other facilities. However, all asymptomatic residents mixed freely for meals and social activities.

Community respiratory virus surveillance

Surveillance for influenza-like illness was ongoing in Victoria at the time of the above outbreaks [14]. This surveillance programme collected clinical data on patients presenting with influenza-like illness to sentinel general practices and was supported by laboratory testing for respiratory viruses. During this time specimens were also received at the laboratory for routine detection of viruses as part of a diagnostic service offered to public hospitals, clinics and general practices. All specimens from the surveillance and diagnostic programmes were tested using the PCR methods described below. During August and September 2002 a total of 378 specimens were tested as part of these programmes.

Laboratory methods

Viral nucleic acid was extracted from specimens using an automated procedure (MagNA Pure LC Total Nucleic Acid Isolation kit, Roche Diagnostics, Mannheim, Germany). A nested, multiplexed RT–PCR based on previously published assays [15–17] was used to detect the following respiratory viruses: influenza A(H1N1), influenza A(H3N2), influenza B, parainfluenza types 1, 2 and 3, adenovirus (all serotypes), respiratory syncytial virus (RSV) and picornaviruses (including enteroviruses and rhinoviruses). A separate, nested RT–PCR assay was used to detect HCoV-229E and HCoV-OC43. The HCoV-OC43 primers were modified from a previously reported method [18] to detect a nucleocapsid gene product of 215 bases. The outer primers were CV43R1-F: 5′-AGGAAGGTCTGCTCCTAATTC-3′ and CV43R1-R: 5′-GCAAGAATGGGGAACTGTGG-3′. The inner primers were CV43R2-F: 5′-CTGGCAATAGAACCCCTACC-3′ and CV43R2-R: 5′-TATTGGGGCTCCTCTTCTGG-3′. During validation of the HCoV-OC43 PCR assay the 215-base product was sequenced to confirm its identity.

RESULTS

Outbreak investigations

The three aged-care facilities accommodated a total of 131 residents, with 85 staff involved in their direct care. The attack rate of respiratory illness for all residents and staff combined was 92/216 (43%). This varied from a minimum of 37% for residents in one facility to a maximum of 56% for residents in a

Table. *Recorded symptoms of cases from each of the three facilities, combined for residents and staff*

Symptom	Number (%)
Cough*	67 (73·6)
Rhinorrhoea	54 (59·3)
Sore throat	49 (53·4)
Malaise	43 (47·3)
Fever	30 (30·0)
Myalgia	21 (23·1)
Chills	20 (22·0)

* Includes productive cough (50·5%) and dry cough (23·1%).

second facility. However there was no significant difference in attack rates between facilities ($P=0{\cdot}13$) or between residents and staff across the three facilities (42% *vs.* 44% respectively, $P=0{\cdot}77$). There was no clustering of cases by wing of residence or location of resident's bedroom. The symptoms observed and their frequency for both residents and carers are shown in the Table. There was no significant difference between facilities for these variables (results not shown). Six residents, all from one facility, were hospitalized. Eight residents died during the time period these outbreaks were occurring, three of them with a documented respiratory illness. However, laboratory testing was not performed on any clinical material obtained from deceased patients.

Outbreak duration from onset of the first case to onset of the last case for each of the three facilities was 19, 29 and 36 days respectively, and all occurred between 14 August and 16 September 2002. Epidemic curves are shown in the Figure. The index cases in two of the three outbreaks were staff members. No links attributable to permanent or casual staff, residents or their visitors were found between the three facilities. At each facility the onset of the last case occurred within 4 days of the outbreak being notified and infection control measures being implemented.

Laboratory investigations

A total of 27 nasopharyngeal swabs were obtained from the 92 symptomatic patients at the three institutions; four (11%) from the 37 symptomatic staff and 23 (42%) from the 55 symptomatic residents. All specimens tested negative by PCR for influenza types A and B, parainfluenza types 1, 2 and 3, adenoviruses, RSV, picornaviruses and HCoV-229E. HCoV-OC43 RNA was detected in 16 of the 27 specimens (59%);

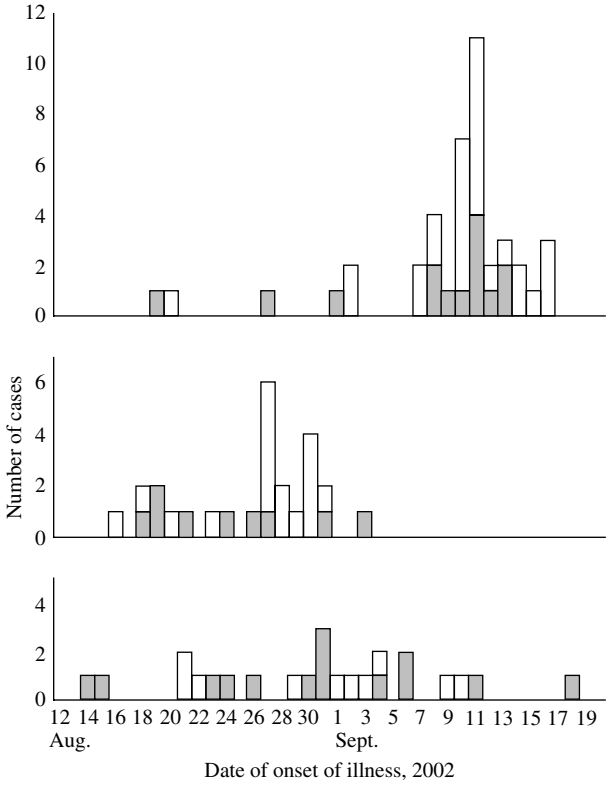

Fig. Epidemic curves showing number of cases by date of onset of illness for residents (□) and staff (▩) for the three aged-care facilities, August to September 2002.

three of these were from staff members. HCoV-OC43 detection rates in these specimens using RT–PCR were 40, 66 and 71% across the facilities. At the time these institutional outbreaks were occurring, each of the respiratory viruses represented in the respiratory virus multiplex assay were circulating in the general community, in particular influenza A viruses, RSV and rhinoviruses [14].

HCoV-OC43 was detected in specimens collected for influenza surveillance and routine virus detection in all months of 2002 (results not shown). In August of that year, 12 out of 210 (5·7%) specimens tested positive for this virus; in September, 21 out of 168 specimens (12·5%) were positive.

DISCUSSION

The presence of HCoV-OC43 in more than half of all specimens tested and the absence of other respiratory pathogens suggest this virus was the causative agent in each of the three outbreaks. Interestingly, no other respiratory pathogens apart from HCoV-OC43 were detected by PCR during these investigations, despite their circulation in the general community. The

relatively short duration of each of the outbreaks and the limited time during which specimens were collected are likely to have contributed to this finding.

The predominant clinical manifestations of cough (74%), rhinorrhoea (59%) and sore throat (53%) are consistent with those previously reported for HCoV-OC43 [2, 15] and HCoV-229E [4]. The outbreaks occurred during early spring, a finding also consistent with previous reports of coronavirus seasonality being predominantly winter to early spring [3, 19]. They also occurred on a background of HCoV-OC43 activity in the general community.

Notification of the outbreak to public health authorities in one facility occurred because of a perceived significant increase in mortality. Death from any cause during the outbreaks occurred in eight residents, three of whom had documented respiratory symptoms. However, as specimens for viral studies were not collected from these individuals, and mortality rates among symptomatic patients were not significantly different to those for non-ill residents, we are unable to conclude that coronavirus infection contributed to mortality.

Once infection control measures were implemented these outbreaks rapidly ceased. Coronaviruses can be spread by fomites and close contact [20]. Because they can survive for several days in suspension and for a few hours dried on surfaces, person-to-person transmission of these viruses via hand contamination of surfaces is also possible [21]. Thus, simple hygiene measures, e.g. using common disinfectants are likely to provide effective infection control.

Staff were identified as the incident cases in two of the three outbreaks. While staff may receive annual influenza vaccination and are encouraged not to attend work if they have influenza-like symptoms, the education of staff that mild respiratory illness in healthy adults may have severe consequences in the frail elderly needs to be reinforced. All respiratory illness in aged-care facilities is deserving of commitment to infection control practices: diligence in simple clean-up practice, stringent hygiene and exclusion of staff from work when unwell are strongly indicated to break transmission and prevent morbidity and mortality.

Prior to the emergence of SARS in 2002, infection of humans with coronaviruses had not been associated with mortality and only occasionally with symptoms consistent with severe lower respiratory tract infection. Recently, determination of the role of coronaviruses in respiratory disease has been facilitated by the availability of molecular testing procedures such as PCR. Indeed, the cause of the outbreaks described here is unlikely to have been established without this technology, which is contributing to a clearer understanding of the natural history and epidemiology of these viruses. Our data suggest that the possible role of the human coronaviruses in severe respiratory illness in the institutionalized elderly, if not the wider community, deserves some reappraisal.

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REFERENCES

1. **Lai MMC, Holmes KV.** *Coronaviridae*: the viruses and their replication. In: Knipe DM, Howley PM, eds. Fields virology, 4th edn, vol 1. Philadelphia: Lippincott Williams & Wilkins, 2001: 1163–1186.
2. **Bradburne AF, Bynoe ML, Tyrrell DA.** Effects of a 'new' human respiratory virus in volunteers. Br Med J 1967; **3**: 767–769.
3. **Wenzel RP, Hendley JO, Davies JA, Gwaltney JM.** Coronavirus infections in military recruits. Three year study with coronavirus strains OC43 and 229E. Am Rev Respir Dis 1974; **109**: 621–624.
4. **Falsey AR, McCann RM, Hall WJ, et al.** The 'common cold' in frail older persons: impact of rhinovirus and coronavirus in a senior daycare center. J Am Geriatr Soc 1997; **45**: 706–711.
5. **El-Sahly HM, Atmar RL, Glezen WP, Greenberg SB.** Spectrum of clinical illness in hospitalized patients with 'common cold' virus infections. Clin Infect Dis 2000; **31**: 96–100.
6. **Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB.** Impact of respiratory virus infection in patients with chronic chest disease. J Am Med Assoc 2000; **283**: 499–505.
7. **Wiselka MJ, Kent J, Cookson JB, Nicholson KG.** Impact of respiratory virus infection in patients with chronic chest disease. Epidemiol Infect 1993; **111**: 337–346.
8. **Falsey AR, Walsh EE, Hayden FG.** Rhinovirus and coronavirus infection-associated hospitalisations among older adults. J Infect Dis 2002; **185**: 1338–1341.

9. **Vabret A, Mourez T, Gouarin S, Petijean J, Freymuth F.** An outbreak of coronavirus OC43 in respiratory infection in Normandy, France. Clin Infect Dis 2003; **36**: 985–989.
10. **Drosten C, Gunther S, Preiser W, et al.** Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl J Med 2003; **348**: 1967–1978.
11. **Peiris JS, Lai ST, Poon LLM, et al.** Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; **361**: 1319–1325.
12. **Ksiazek T, Erdman D, Goldsmith C, et al.** A novel coronavirus associated with severe acute respiratory syndrome. New Engl J Med 2003; **348**: 1953–1966.
13. **Van der Hoek L, Pyrc K, Jebbink MF, et al.** Identification of a new human coronavirus. Nat Med. Published online 21 March 2004; DOI: 10.1038.nm1024. Accessed 24 March 2004.
14. **Watts C, Andrews R, Druce J, Kelly H.** Establishing thresholds for influenza surveillance in Victoria. Aust NZ J Public Health 2003; **27**: 409–412.
15. **Ireland DC, Kent J, Nicholson KG.** Improved detection of rhinoviruses in nasal and throat swabs by seminested RT-PCR. J Med Virol 1993; **40**: 96–101.
16. **Osiowy C.** Direct detection of respiratory syncytial virus, parainfluenza virus, and adenovirus in clinical respiratory specimens by a multiplex reverse transcription-PCR assay. J Clin Microbiol 1998; **36**: 3149–3154.
17. **Zhang WD, Evans DH.** Detection and identification of human influenza viruses by the polymerase chain reaction. J Virol Methods 1991; **33**: 165–189.
18. **Pitkaranta A, Virolainen A, Jerro J, Arrunda E, Hayden FG.** Detection of rhinovirus, respiratory syncytial virus, and coronavirus infections in acute otitis media by reverse transcriptase polymerase chain reaction. Pediatrics 1998; **102**: 291–295.
19. **Hendley JO, Fishburne HB, Gwaltney JM.** Coronavirus infections in working adults. Eight year study with 229E and OC43. Am Rev Respir Dis 1972; **105**: 805–811.
20. **Falsey AR, McCann RM, Hall WJ, et al.** The 'common cold' in frail older persons: impact of rhinovirus and coronavirus in a senior daycare center. J Am Geriatr Soc 1997; **45**: 706–711.
21. **Sizun J, Yu MW, Talbot PJ.** Survival of human coronaviruses 229E and OC43 in suspension and after drying on surfaces: a possible source of hospital-acquired infections. J Hosp Infect 2000; **46**: 55–60.