A human metapneumovirus outbreak at a community hospital in England, July to September 2010

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We describe an outbreak of human metapneumovirus (hMPV) which occurred in July–September 2010 at a community hospital in the East of England. Based on the medical and nursing records, cases were retrospectively defined as suspected if they had had an influenza-like illness (ILI), and probable if they had had an ILI and an epidemiological link to a laboratory-confirmed case. Of a total of 17 symptomatic inpatients, five were classified as probable cases, five were laboratory confirmed and seven were suspected. The attack rate was 29.4% for confirmed and probable cases combined. The median age of symptomatic inpatients was 85 years-old (range 68–96) and the majority (16/17) of symptomatic inpatients had an underlying medical condition. Control measures introduced appeared to restrict further exposure of susceptible patients to infection although modelling suggested that up to four of 10 confirmed and probable cases (40%) could have been prevented through more timely diagnosis and recognition of an outbreak. These findings suggest that there should be increased awareness of hMPV infection within healthcare settings, particularly when the population at risk has a high prevalence of underlying co-morbidities.

Introduction

Human metapneumovirus (hMPV) is a paramyxovirus discovered in the Netherlands in 2001 [1]. It was first isolated from nasopharyngeal aspirates from children hospitalised with undiagnosed respiratory tract infection (RTI) although it has been identified retrospectively in samples from children with upper respiratory tract illness (URTI) from 1982 [2]. hMPV is part of the same family as parainfluenza, measles and mumps virus. Its genetic organisation is very similar to human respiratory syncytial virus (RSV). There are two main genotypes identified to date (A and B) with two subtypes within each. Circulation of subtypes appears to be temporal, with re-circulation occurring periodically [3,4]. In the United Kingdom (UK), hMPV and RSV co-circulate throughout the winter season both in hospitalised patients and in the community, with peak incidence found between December and March [5-7]. In two studies carried out in Scotland, of over 7,000 and over 9,000 community specimens, hMPV was the fifth and the sixth most frequently detected respiratory virus [3,8].

Studies have shown that, although clinical severity is not clearly associated with hMPV subtype, pathological signs on chest X-ray were observed more often in subtype B [9]. Clinical signs in healthy adults range from mild influenza-like illness (ILI) to severe RTI and are associated to both upper and lower RTI [10]. In adults with underlying conditions, it has been demonstrated that hMPV is a major causative agent of RTI and can be associated with fatal outcomes [11]. Recent studies have shown that hMPV infection may also be subclinical [12] or asymptomatic, especially in healthy and young individuals and sometimes among healthy elderly (≥65 years old) patients [13]. However, asymptomatic infection in frail elderly individuals and people with underlying disease are rare [14]. This has also been observed in animal models [15]. Amongst elderly individuals with confirmed hMPV infection, the most frequent diagnoses are ILI or an upper RTI followed by bronchitis and pneumonia [11]. Only limited studies of hMPV infection of elderly adults or institutionalised elderly adults are available [11,13,16]. In these studies the attack rate varies from 18% to 72% and the case fatality rate among elderly inpatients of a long-term care facility reached 50% of six laboratory-confirmed cases during one outbreak (9% of 96 reported possible cases in the same outbreak) [11]. Nosocomial transmission of hMPV within a healthcare setting has been documented [11,13,16,17]. Studies conducted in

paediatric wards in Korea and Hong Kong suggest that hMPV has an incubation period ranging from five to nine days for a symptomatic nosocomial case [17,18]. In the Netherlands, a seroprevalence study has shown almost 100% seropositivity by five years of age [1,7,19]; but, like RSV, primary infection with hMPV does not seem to induce lifelong immunity and re-infections occur in all age groups [14,19-22]. To date no vaccine or specific antiviral treatment is available which make non-pharmaceutical infection control interventions crucial in preventing the transmission of the virus.

On 3 August 2010, two inpatients from one ward of a community hospital (CH) in the East of England presented with respiratory symptoms. On 9 August 2010, by which time a total of eight inpatients had developed respiratory symptoms, this ward as well as a second ward of the hospital were closed to admissions, visits were restricted, and discharges to nursing homes and locations where there might be immunocompromised individuals were discontinued.

On 12 August 2010 an hMPV outbreak was declared in the two wards of the CH and an Outbreak Control Committee (OCC) convened on 13 August 2010. As recommended by the Health Protection Agency when managing an outbreak of respiratory illness in care homes, the following additional control measures were implemented [23]: patients were cohorted, physiotherapy sessions were suspended, respiratory infection control precautions were instituted including the use of surgical face masks and filtering facepiece (FFP3) masks, gloves and plastic aprons, attention to hand hygiene was intensified along with the use of alcohol hand rub; symptomatic staff were excluded until six days after onset or when well enough to work, whichever was the later; pregnant and immunocompromised staff were sent home until the outbreak was declared over; environmental cleaning using general-purpose detergent was augmented. The OCC defined a suspected case as any person with acute respiratory tract illness of abrupt onset, characterised by two or more of the following symptoms: fever (>38°C), cough, sore throat, runny nose and dyspnoea; and in the seven days prior to the onset of symptoms, who had been in close contact (less than one metre) with a suspect, probable or confirmed case of hMPV. A probable case was a person meeting the definition of a suspected case and with infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (hypoxemia, severe tachypnoea). A confirmed case was a person meeting the definition of a suspected case and with a laboratory testing demonstrating one or more of the following: positive real-time reverse

Table 1

Characteristics of patients hospitalised during an outbreak of human metapneumovirus at a community hospital in the East of England, United Kingdom, July–September 2010 (n=34)

Characteristic		Inpatients n/N[a]	Cases		
			Confirmed cases (n=5) n/N[a]	Confirmed and probable (n=10) n/N[a]	All symptomatic (n=17) n/N[a]
Sex	Male	16/34	3/5	6/10	11/17
	Female	18/34	2/5	4/10	6/17
Residing	On his/her own and alone	13/30	2/4	3/9	6/16
	By his/herself with help	13/30	2/4	6/9	9/16
	With family	4/30	0/4	0/9	1/16
Underlying condition	Respiratory	15/33	2/4	4/9	9/16
	Cardiac	27/33	3/4	7/9	13/16
	Liver	0/33	0/4	0/9	0/16
	Kidney	11/33	1/4	2/9	5/16
	Diabetes	8/33	1/4	2/9	3/16
	Malignancy	7/33	0/4	0/9	2/16
	At least one of the above	30/33	3/4	8/9	13/14
Admitted from	Home	3/31	0/4	0/9	0/15
	General practioner referral	4/31	1/4	2/9	4/15
	Another hospital	24/31	3/4	7/9	11/15
Outcome	Still hospitalised at community hospital	9/33	0/5	1/10	3/17
	Discharged	15/33	4/5	7/10	8/17
	Transferred	2/33	1/5	1/10	2/17
	Dead	7/33	0/5	1/10	4/17

[a] N: Total number of persons of a category, for whom the information was available.

transcription-polymerase chain reaction (rRT-PCR) for hMPV or positive viral culture for hMPV.

On 8 September 2010 the OCC declared the end of the outbreak with no cases having occurred for more than 12 days.

The objectives of our study were: (i) to retrospectively describe the outbreak, (ii) to examine risk factors associated with clinical infection; (iii) to retrospectively determine the number of cases that could have been prevented through earlier implementation of control measures in order to (iv) inform public health guidance for future hMPV outbreaks.

Methods

Our investigation was a retrospective cohort study. The study population for our analytic study included all hospital inpatients who resided at the CH between 31 July 2010 and 9 September 2010. Data on demographics, medical history and admission history were collected from medical and nursing records. Healthcare workers (HCW) with reported ILI during the study period were interviewed by telephone for details of their illness (but were not included in the study population). The study was undertaken as part of a formal outbreak investigation, and in line with National Research Ethics Service guidance and formal ethical approval was not required. More sensitive case definitions were used for the retrospective study than those used by the OCC. Particularly, we removed the requirement of a suspected case to have been in known close contact with a previous case (<1 metre) and the clinical evidence of pneumonia or respiratory failure for a probable case.

Case definitions

A suspected case was defined as a patient presenting with ≥ 1 respiratory symptoms (rhinorrhoea, sore throat, or cough) or ≥1 constitutional symptoms (fever (≥38°C), loss of appetite, fatigue or myalgia) [23]. A probable case was a patient meeting the definition of a suspected case and with an epidemiological link (determined from the transmission model described below) to a symptomatic confirmed or probable case, and whose date of onset occurred within five to nine days prior, or after an exposure day. An exposure day was defined as shared time within a single day in the same room as a confirmed or a probable case. A confirmed case was a patient meeting the definition of a suspected case, with additional positive rRT-PCR for hMPV, on a throat swab.

Analysis

Cumulative incidence (attack rate) among patients was estimated including all confirmed and probable cases and the denominator of all patients admitted during the relevant timeframe. In order to avoid selection bias by counting potential non-hMPV cases, we performed the analysis with only confirmed cases and undertook a separate analysis with both probable and confirmed cases. We compared cases to non-cases, by age, sex and underlying medical conditions. The distribution of quantitative variables was compared using the t-test; associations with qualitative data were tested in a univariable analysis using the Chi-squared statistic. For both tests we used a significance level of 5%.

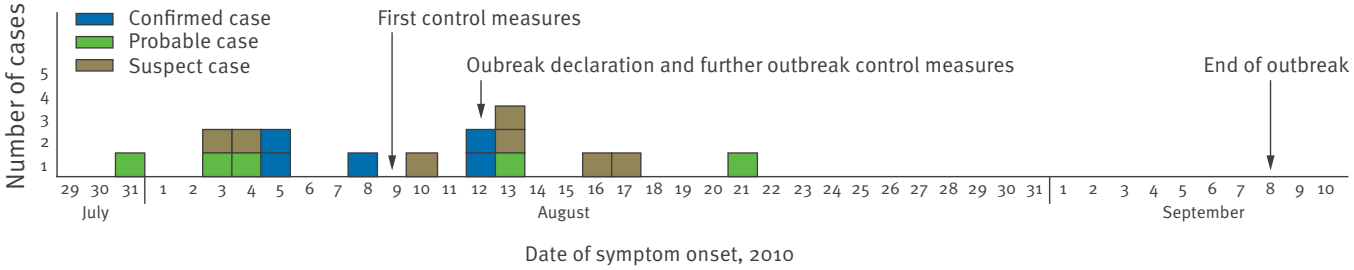
Estimation of possible transmission events among inpatients

Patient locations within the hospital during their infectious period were used to model potential transmission events. In the absence of relevant data from the literature on the infectious period in hMPV cases, the infectious period was defined for this study as the number of days (inclusive) from the date of onset to the end of symptoms. For the four cases where the date of end of symptoms was not known, the average duration of the symptomatic period of confirmed and probable cases in the study was used (eight days).

The model determines possible exposure periods of recipient cases to symptomatic cases (donors) and was written in R [24]. We assumed a minimum incubation period of five days prior to the onset of symptoms and a maximum incubation period of nine days. The model scans all infectious donors for overlap with the assumed incubation period of recipients when both

Figure 1

Distribution of cases from an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)



donor and recipients beds were within the same room in the CH. The model does not produce any measure of the likelihood of individual transmission events and is wholly deterministic; all possible transmission events are reported based on the entire overlapping period between the assumed incubation period and infectious period. Symptomatic HCW were not included in modelling of possible transmission events as they had been working in all the patient rooms within the hospital during their shifts.

Laboratory analyses

Throat swabs and sputum from seven symptomatic patients were tested locally by multiplex rRT-PCR for swine influenza A(H1N1), RSV, enterovirus, parainfluenza virus 1, 2, 3 and 4, rhinovirus, influenza A virus, adenovirus, hMPV, and influenza B virus. Samples from confirmed hMPV cases were sent to the Health Protection Agency Reference Laboratory in Colindale for sequencing of the fusion protein (F) gene.

Table 2

Characteristics of cases during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)

Case number	Duration of Illness[a] (days)	Time of specimen collection (days after symptom onset)	Laboratory confirmed	Case status[b]
1	12	Not collected	Not tested	Probable
2	4	Not collected	Not tested	Suspected
3	16	Not collected	Not tested	Probable
4	21	20	Not tested	Suspected
5	7	Not collected	Not tested	Probable
6	NA	7	Positive	Confirmed
7[c]	NA	7	Positive	Confirmed
8	18	4	Positive	Confirmed
9	10	Not collected	Not tested	Suspected
10	9	Same day	Positive	Confirmed
11	5	Same day	Positive	Confirmed
12	4	Not collected	Not tested	Probable
13	NA	Not collected	Not tested	Suspected
14	NA	Not collected	Not tested	Suspected
15	10	Not collected	Not tested	Suspected
16	2	Not collected	Not tested	Suspected
17	5	3	Negative	Probable

NA: Data not available in the medical records or medical records not available.

[a] The number of days between onset and last date of reported symptoms.

[b] Assessed retrospectively according to the investigation case definition.

[c] The medical records for this patients were not retrieved; however this patient was confirmed by the laboratory as having human metapneumovirus infection.

Table 3

Clinical symptoms of cases during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)

Symptom	Probable and confirmed cases[a] (n=10)	Suspected cases[b] (n=7)
Cough	8	2
Cough and wheezing	4	3
Fever	5	2
Fatigue	2	2
Rhinorrhoea	1	1
Loss of appetite	2	1
Sore throat	1	0
Myalgia	0	0

[a] Clinical information was not available for one case.

[b] Excluding probable and confirmed cases.

Results

Patient characteristics

There were a total of 34 patients hospitalised in the CH during the study period. The demographic and medical characteristics of the patients hospitalised during the time of the outbreak are described in Table 1. There were as many men as women. The hospitalised patients had a median age of 79 years (range: 51–100). Almost all of the inpatients with available information (30 of 33) had at least one underlying condition. The majority (24 of 31) were admitted from an acute hospital. Two cases were admitted to the community hospital for respiratory disease (chronic obstructive pulmonary disease and persistent chest infection). One inpatient was admitted for palliative care. Among the 24 inpatients that were no longer in hospital on 9 September 2010, 15 had been discharged, two had been transferred to an acute hospital, and seven had died.

Human metapneumovirus infection in inpatients

Overall, there were five confirmed cases, five probable cases, and seven suspected cases among the inpatients (Table 2). The median age of the confirmed cases was 78 years (range: 71–94), that of the confirmed and probable 84 years (range: 68–96) and that of all cases 85 years (range: 68–96). Laboratory analyses revealed that all five confirmed cases had been infected, with hMPV genotype A, subtype 2 clade 4 [3]. The earliest case identified during the investigation was a probable case with onset of symptoms on 31 July 2010 (Figure 1). The first two confirmed cases both had onset of symptoms on 5 August 2010.

Specimens were taken from suspected cases for laboratory testing on 12 August 2010 (5 cases) and 24 August (2 cases). The calculated cumulative attack rate (number of confirmed and probable cases/total number of inpatients) during the 37 days study period

was 29.4% (95%CI: 13.3–45.5). Details of clinical symptoms and patient characteristics are shown in Tables 2 and 3.

The mean duration of illness was 7.6 days (range 1–18 days) for the 10 confirmed and probable cases where it could be calculated. Of these, one died, another was transferred to an acute hospital, and seven were discharged. The remaining case was still hospitalised at the time of data collection.

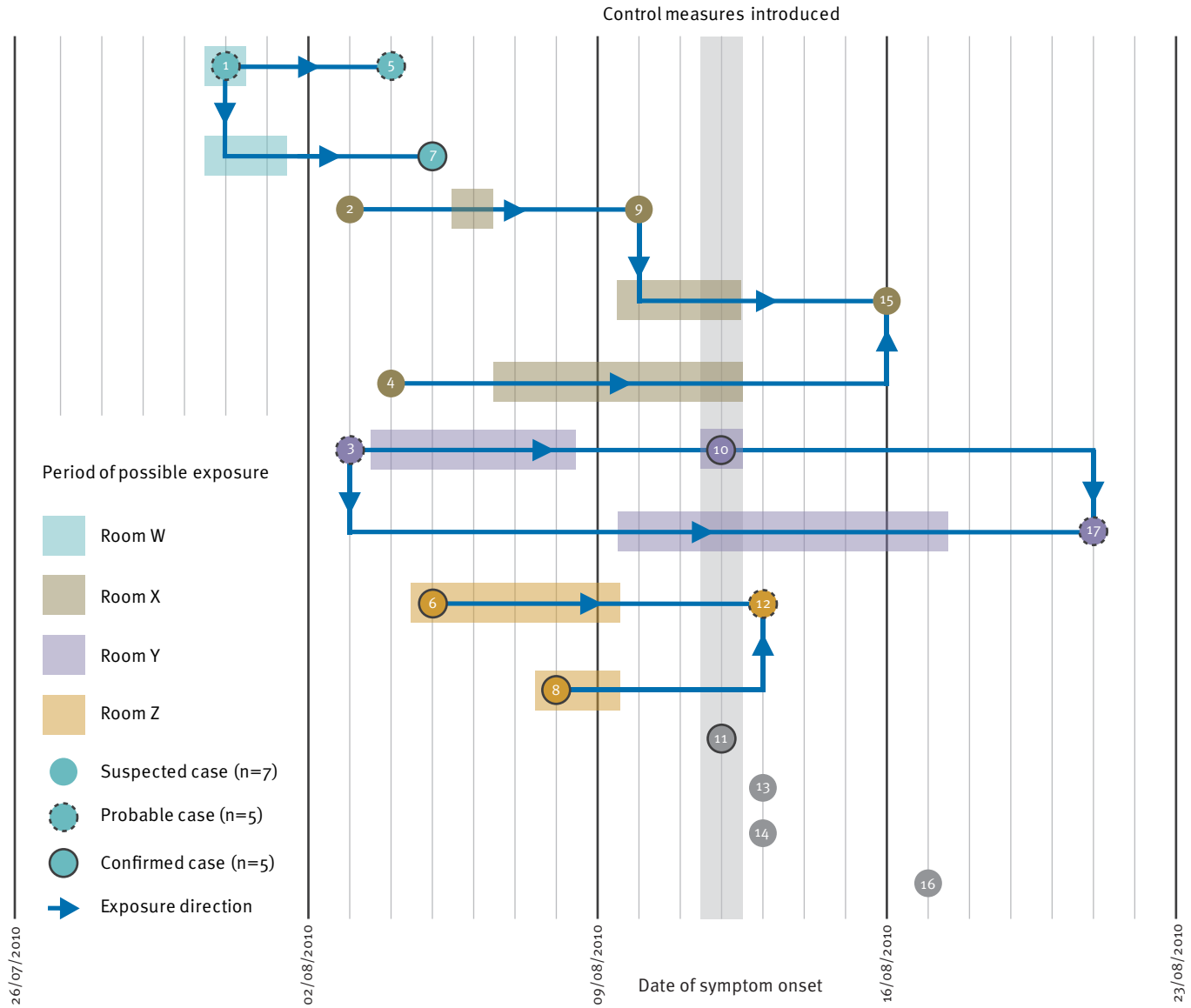
Seven inpatients died over the study period: Four of the 17 hMPV cases and three of the 17 other inpatients. The hMPV cases were not more likely to die than the other inpatients hospitalised during the same period (p=0.324). No common underlying condition, age group or sex was significantly associated with infection in either analyses (results not shown).

Symptomatic healthcare workers

We interviewed three of six HCW who were reported symptomatic during the study period. Of the two who were tested by throat swabs, both were negative for hMPV; however, specimens were taken 18 and 21 days after onset. Assuming an incubation period of five to nine days, the dates of onset of HCW are consistent with exposure on the ward during duty and occurred between 1 and 16 August 2010. Two of the three

Figure 2

Possible transmission networks predicted by a donor–recipient model, during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010 (n=17)



The number within each circle is the study identification number of each patient. Horizontal coloured bars represent possible exposures (in the direction of the underlying arrow) of infectious donors to recipients at the colour-coded locations.

interviewed HCW had onset of symptoms on a day they worked. They were all on night shifts and took care of all inpatients. Symptoms lasted for seven, 10 and 21 days respectively and all recovered. None had a specific underlying condition or relevant travel history outside of the UK.

Modelling predictions of preventable cases among human metapneumovirus inpatient cases

Using dates of onset and end of the symptomatic period we plotted probable periods of exposure for each symptomatic case (Figure 2). Six early cases (identification (ID) number 1, 2, 3, 4, 6, and 8) have no discernable source of infection. According to our model of transmission, a maximum of 10 potential transmission events could have occurred as illustrated in Figure 2 (between cases 1-5, 1-7, 2-9, 9-15, 4-15, 3-10, 3-17, 10-17, 6-12, 8-12). Four later cases (ID number 11, 13, 14, and 16) are not linked to other cases within the proposed transmission networks (Figure 2).

From this schematic depiction of the outbreak we were able to infer the possible number of cases that may have been prevented, had full control measures been implemented earlier (Table 4). Following the control measures implemented on 12 August 2010, our exposure model suggests that only one potential exposure occurred (between case number 3 and 17), indicating that control measures might have been successful in restricting further transmission. The model shows that had control measures been implemented after the first three cases were recognised 40% (4/10) of the total number of probable and confirmed cases could have been prevented.

Table 4. Predicted total outbreak size given hypothetical dates of control measure implementation during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010

Discussion

The outbreak described here is one of the few documented outbreaks of hMPV within a healthcare setting [10,11,16,17,25]. Although the case definitions used in this analytical study differ from those used during the course of the outbreak, incorporation of the modelling data has provided information which has been used to assess aspects of the dynamics of this outbreak which could not have been otherwise studied. We estimated an attack rate of 29.4% based on the retrospective study definition of confirmed and probable hMPV cases. This is within the range of values described in previous outbreak investigation in similar settings [11,13,16]. Our modelling of possible exposure periods together with the laboratory findings are consistent with a degree of nosocomial transmission of hMPV within the CH. The model used in this study was wholly deterministic and was used to detect all possible transmission events that could have occurred given the assumed range of incubation and infectious periods. Although such an approach is suitable for the analysis of this study, the further inclusion of a measure of uncertainty by a full sensitivity analysis would enable specific person-to-person transmission events to be assessed more fully but is beyond the scope of this paper.

Due to the non-specific nature of the symptoms of hMPV infection, and the lack of laboratory confirmed cases, we adopted a conservative approach to our analysis and excluded all symptomatic cases who had neither been laboratory confirmed nor had a possible transmission link with a confirmed case. We also excluded data from the HCW and limited the exposure link to contact with a symptomatic confirmed case within the same room. Of course, we cannot be certain that HCW were not involved in transmission networks of hMPV within the CH but given the available data it was impossible to include HCW in modelling with any level of precision. Nonetheless, inclusion of HCW in the model would only have generated more suggested

Table 4

Predicted total outbreak size given hypothetical dates of control measure implementation during an outbreak of human metapneumovirus among patients of a community hospital in the East of England, United Kingdom, July–September 2010

Date of hypothetical control measure implementation	Number of suspected cases to given date	Number of confirmed or probable cases to given date[a]	Total number of probable and confirmed cases in the outbreak[b]	Number of cases prevented (% reduction)[c]
03/08/2010	3	2	6	4 (40)
04/08/2010	5	3	8	2 (20)
05/08/2010	7	5	9	1 (10)
08/08/2010	8	6	9	1 (10)
09/08/2010	8	6	9	1 (10)
10/08/2010	9	6	10	0
12/08/2010[d]	11	7	10	-

[a] Assessed retrospectively.
[b] Had all exposures prior to the proposed implementation date been prevented.
[c] The percent reduction is calculated using the combined confirmed and probable cases as denominator.
[d] Date control measures were implemented, date of positive result of human metapneumovirus confirmed cases.

transmission events which make the estimates of possible transmission reduction here a likely conservative underestimate.

Separate analyses using just confirmed cases (n=5) and confirmed/probable cases (n=10) found no risk factor to be significantly associated with infection when comparing cases to non-cases; nor did they show evidence of increased mortality associated with the infection. Of course, the power of detecting a statistically significant difference is limited due to the high frequency of co-morbidities in the population at risk. Asymptomatic cases of hMPV infection are not common among a population of frail elderly adults [14]. Therefore we feel confident that we accounted for all suspected cases of hMPV infection among the inpatients. However, asymptomatic cases might have occurred among the HCW.

We could not identify a possible exposure to hMPV infection for five confirmed and probable cases; this was likely related to the restricted definition of exposure used. It is very likely that virus transmission not only occurred when sharing the same room but also during daily activities (e.g. lunch) or healthcare activities (transmission from HCW to patient). Symptomatic HCW were tested long after the onset of symptoms making it problematic to comment on the role of HCW in the possible introduction of hMPV into the CH. Symptoms lasted up to three weeks for both inpatients and HCW. Data on the duration and magnitude of viral shedding following infection with hMPV are limited. In hospitalised children the duration of viral shedding has been documented as five days [26] but may be much longer for the elderly [27]. It may be important for further studies to address this issue in order to provide further insight into the probability of both transmission and laboratory diagnosis following the onset of symptoms.

Early recognition and laboratory confirmation of the causative agent are crucial to restricting the spread of a respiratory pathogen within a healthcare setting and adapting infection control strategies [14]. This is critical in situations where the incidence of respiratory illness in the population is high (as was the case for the outbreak described here) and early detection of an outbreak of respiratory virus infection may often be masked by the underlying level of chronic or sporadic respiratory syndrome. Furthermore, this outbreak occurred towards the end of summer when clinical surveillance may be less focused on respiratory syndromes. These elements may have contributed to making the start of the outbreak difficult to identify.

Admissions and discharges were suspended by the nursing staff after eight symptomatic cases had occurred. Further control measures within the ward were implemented four days later, after 11 patients had presented with ILI, including five who later tested positive for hMPV. The Health Protection Agency defines an Acute Respiratory Illness (ARI) outbreak as "two or more cases arising within the same 48 hour period or three or more cases arising within the same 72 hours period, which meet the same clinical case definition and where an epidemiological link can be established" [23]. Transmission modelling suggests that had control measures been implemented at the time of the occurrence of the third symptomatic case, 40% of the cases could have been prevented; however, any interpretation of this must take into account the difficulty in clinical case ascertainment in a care setting where the prevalence of non-specific hMPV symptoms is high. The occurrence of ARI cases in a vulnerable population should be detected at an early stage in order to implement control measures and prevent further cases, especially within healthcare settings, where the exposed population is particularly vulnerable to increased disease severity, such as the very young, the very old, or those with chronic medical conditions.

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