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# Consecutive yearly outbreaks of respiratory syncytial virus in a haemato-oncology ward and efficacy of infection control measures

T. Inkster<sup>a,\*</sup>, K. Ferguson<sup>a</sup>, A. Edwardson<sup>a</sup>, R. Gunson<sup>b</sup>, R. Soutar<sup>c</sup>

<sup>a</sup> Department of Infection Control, Gartnavel General Hospital, Glasgow, UK

<sup>b</sup> Department of Virology, Glasgow Royal Infirmary, Glasgow, UK

<sup>c</sup> Department of Haematology, West of Scotland Beatson Oncology Centre, Gartnavel Hospital, Glasgow, UK

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## SUMMARY

**Background:** Respiratory syncytial virus (RSV) causes significant respiratory tract infection in immunosuppressed patients.

**Aim:** To describe two consecutive yearly outbreaks of RSV in our haemato-oncology ward.

**Methods:** Haematology patients presenting with respiratory symptoms were screened by polymerase chain reaction for viral respiratory pathogens using a saline gargle.

**Findings:** None of our patients had undergone bone marrow transplant but all had underlying haematological malignancies. Eight patients were affected in the first outbreak (mortality rate: 37.5%) and 12 patients were affected in the second (mortality rate: 8.3%). Extensive infection control measures were implemented in both outbreaks and were successful in preventing further cross-transmission.

**Conclusion:** There was significant learning from both outbreaks and actions implemented with the aim of reducing the likelihood and impact of future outbreaks.

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## Introduction

Respiratory syncytial virus (RSV) is an important cause of viral lower respiratory tract infection in infants and children worldwide and is a significant pathogen in immunocompromised hosts. The incubation period of RSV is typically two to eight days [1]. Route of transmission is person to person via droplets or through direct/indirect contact with contaminated hands or surrounding environment. In patients with underlying haematological conditions RSV may lead to higher mortality

and prolonged viral shedding [2]. Progression to lower respiratory tract infection is estimated to occur in 50% of patients who have had chemotherapy for leukaemia [3]. Prior to 2015 the last outbreak of RSV in haemato-oncology patients in our health board occurred in 1999 [4]. We describe two consecutive winter outbreaks of RSV in a haematology ward occurring in December 2015 and again in December 2016.

## Methods

### Setting

Both outbreaks took place on a 19-bedded haemato-oncology ward in the Beatson West of Scotland Cancer Centre (BWoSICC). The unit opened in 2008 and is the UK's second

\* Corresponding author. Address: Department of Medical Microbiology, Queen Elizabeth University Hospital, Govan Road, Glasgow G52 4ZF, UK. Tel.: +44 (0)141 211 4640.

E-mail address: [Teresa.Inkster@nhs.net](mailto:Teresa.Inkster@nhs.net) (T. Inkster).

largest centre for specialist, non-surgical oncology and Scotland's largest.

The haematology ward cares for patients with haematological malignancies. Allogeneic bone marrow transplant patients are nursed in a neighbouring ward and were unaffected by these outbreaks.

The ward layout comprises five single rooms with *en suite*, one double room with shared *en suite* and the remainder of the accommodation is provided in three four-bedded bays with shared en-suite rooms.

It is standard practice in this ward to screen haematology patients presenting with respiratory symptoms for viral respiratory pathogens using a saline gargle. Patients who are unwell are told to report directly to the haematology unit rather than attend the accident and emergency department.

### Laboratory methods

All samples were extracted on the Siegen Mix using the Siam viral RNA kit (Siegen, Crawley, UK). The samples were pre-lysed and 263  $\mu$ L of the sample extracted, and nucleic acid was eluted into 110  $\mu$ L. Samples were then screened by a well-established and validated in-house real-time respiratory screen used at the West of Scotland Specialist Virology Centre since 2002. The screen consists of five multiplex assays which detect influenza A, influenza B, coronaviruses (229E, OC43, NL63), rhinovirus/enterovirus, human metapneumovirus, RSV A/B, parainfluenza (1–4), adenovirus, and *Mycoplasma pneumoniae*.

One-step reverse transcription–polymerase chain reaction (RT–PCR) was performed on 6  $\mu$ L of nucleic acid extract with Superscript III Platinum One Step Quantitative RT–PCR System (Invitrogen, Thermo Fisher Scientific, Basingstoke, UK) on an ABI Prism 7500 SDS real-time platform (Applied Biosystems, Thermo Fisher Scientific) in a 15  $\mu$ L reaction volume. The following thermal profile was used: a single cycle of reverse transcription for 10 min at 50°C, 2 min at 95°C for DNA polymerase activation followed by 40 amplification cycles of 8 s at 95°C and 34 s at 60°C each (annealing-extension step). For each set of paired samples we compared the cycle threshold values for all pathogens detected.

## Results

### Outbreak descriptions

The case definitions employed were the same for both outbreaks and are listed in [Box 1](#). There is variation in the published literature regarding the definition of nosocomial RSV, the interval between hospital admission and symptom onset varying from two to eight days because of the length of the possible incubation period [1,2]. We applied the lower limit of two days in our outbreak policy, taking account of our high-risk patient group.

### Outbreak 1: December 2015

In December 2015 three patients on the haematology ward with respiratory symptoms tested positive for RSV in a 24 h period. Each of the patients had an underlying haematological malignancy. At the time of initial laboratory referral and subsequent investigation by the infection prevention and control team (IPCT), one patient case had been discharged home with

### Box 1

#### Case definitions of respiratory syncytial virus (RSV)

##### Nosocomial RSV

Any patient with respiratory symptoms and a positive respiratory sample for RSV if patient was hospitalized two or more days before the onset of symptoms.

##### Confirmed case of RSV

Any patient or staff member with respiratory symptoms and a positive respiratory sample for RSV

##### Probable case of RSV

Any patient or staff member with respiratory symptoms

##### Asymptomatic carrier

Any patient or staff member in whom RSV was detected on screening in the absence of respiratory symptoms or fever

two remaining on the ward. One of the two remaining patients, whose symptoms had resolved by the time of referral to the IPCT, was being nursed in a four-bedded bay; the other had respiratory symptoms and was in a single side room with droplet and contact precautions in place.

As there were three confirmed cases (two nosocomial) linked in time, place and person, an outbreak was declared and the ward closed to admissions/transfers. On the day of ward closure a fourth patient with respiratory symptoms tested positive for RSV and was isolated with precautions in place. An outbreak control team (OCT) was established.

The index case was community onset and had been admitted feeling unwell, complaining of cough and green spit, and with an unwell child at home. The patient improved and was discharged home prior to the positive sample result being reported.

Screening of all patients and 28 staff on the ward by PCR on gargles took place over the course of the outbreak, which lasted nine days. In total eight patients and two healthcare workers tested positive for RSV. Of the patients who tested positive for RSV three were asymptomatic. Three of the patient cases who tested positive for RSV required treatment with antiviral (ribavirin) and immunoglobulin.

Three of the confirmed patient cases died over the course of the outbreak with RSV cited on death certification. Although only two staff members tested positive for RSV, a total of seven staff reported symptoms over the course of the outbreak, and this, along with ward closure, led to service disruption in this highly specialist area.

Patient characteristics of this outbreak are listed in [Table 1](#). The majority of patients were male (six out of eight). The average age was 64 years (range: 49–82) and the mortality rate was 37.5% (three of eight patients).

A full list of infection control measures employed in both outbreaks is listed in [Box 2](#). Precautions remained in place for patient cases until two negative viral gargle samples were achieved 48 h apart. Symptomatic staff were advised to remain off duty until 48 h asymptomatic. A patient information leaflet was produced for distribution to all patients on the ward. Over the course of the outbreak the ward was visited twice daily as a minimum by a member of the IPCT and this allowed for observational audit of staff practice, including use of personal protective equipment and informal teaching. The IPCT completed formal infection prevention and control audit,

**Table 1**  
Patient characteristics

Patient no.	Sex	Age (years)	Treatment for respiratory syncytial virus	Lymphocyte count <sup>a</sup> at time of respiratory symptoms ( $\times 10^9/L$ )	Underlying haematological condition	Mortality
<b>Outbreak 1, 2015</b>						
1	M	54	No	1.1	Chronic lymphocytic leukaemia	No
2	M	52	Ribavirin and immunoglobulin	28.9	Chronic lymphocytic leukaemia	Yes
3	M	49	No	0.6	T-cell prolymphocytic leukaemia	No
4	F	72	Ribavirin and immunoglobulin	>600	T-cell prolymphocytic leukaemia	Yes
5	M	82	No	18.4	Chronic lymphocytic leukaemia	No
6	M	66	No	0.6	Multiple myeloma	Yes
7	F	61	No	0.4	Acute myeloid leukaemia	No
8	M	79	Ribavirin and immunoglobulin	0.5	Waldenström's macroglobulinaemia	No
<b>Outbreak 2, 2016</b>						
1	M	23	No	0.1	Acute lymphoblastic leukaemia	No
2	M	52	Ribavirin and immunoglobulin	0.7	Transformed follicular lymphoma	No
3	M	54	Immunoglobulin	0.5	Acute lymphoblastic leukaemia	Yes
4	M	53	No	0.9	Acute lymphoblastic leukaemia	No
5	M	51	Immunoglobulin	0.2	Granulocytic sarcoma	No
6	M	30	No	Undetectable	Acute myeloid leukaemia	No
7	M	34	No	0.2	Acute lymphoblastic leukaemia	No
8	F	55	No	0.4	Diffuse large B-cell lymphoma	No
9	F	84	No	1.4	Diffuse large B-cell lymphoma	No
10	M	52	No	0.9	Multiple myeloma	No
11	M	36	No	0.2	Diffuse large B-cell lymphoma	No
12	M	61	Immunoglobulin	0.4	Acute myeloid leukaemia	No

<sup>a</sup> Normal range:  $1.5\text{--}4.0 \times 10^9/L$ .

## Box 2

### Infection control measures implemented for both outbreaks

- Ward closed to admissions/transfers.
- Isolation of symptomatic cases in single side-room or cohorted with other respiratory syncytial virus-positive patients.
- Increased environmental cleaning: twice daily with chlorine-based detergent (Actichlor™ plus).
- Cough etiquette emphasized.
- Use of personal protective equipment (gloves, aprons, surgical masks, visors) emphasized and adequate supplies obtained.
- Hand hygiene emphasized.
- Screening of all patients.
- Screening of all staff (2015 outbreak only).
- Restriction of patient and staff movement.
- Access to adjoining ward (bone marrow transplant) restricted and entry via alternative route agreed.
- Reduced visiting hours and visitor numbers (no more than two per patient). If possible no child visitors aged <12 years. Media statements released which reinforced this.
- Symptomatic staff to refrain from duty until 48 h symptom-free.
- Enhanced observation of the ward by the infection prevention and control team and education.
- Frequent meetings with infection control, clinical and management staff.
- Written communication, so all staff were aware of situation.
- Psychological and practical support to ward staff dealing with patients and relatives from infection control staff.

measuring both standard and transmission-based infection control precautions at the time of ward reopening, and a training package was put in place for ward staff. The end of the outbreak was declared after nine days.

### Outbreak 2: December 2016

In December 2016 the IPCT was alerted to four patients testing positive for RSV on the haematology ward over a five-day period. Again these were nosocomial infections and linked in time, place, and person; therefore an outbreak was declared and an OCT established.

At the time of referral two patients had been sent home well and the other two cases, both of whom were symptomatic, were cohorted together in a four-bedded bay with the remaining two beds blocked. A fifth patient tested positive prior to the first outbreak meeting and was isolated in a single side-room with precautions in place. Staff recalled a positive patient seven days previously who had been discharged home. This was also determined to be a nosocomial infection and it was likely that this patient was the index case, taking the total numbers at this point to six patients.

Screening of the remaining 13 patients was undertaken and a further three cases were identified, all of whom were asymptomatic. During the course of the outbreak a further three symptomatic cases were detected, taking the total number of patients to 12. One patient died with RSV cited on death certification. One patient was treated with ribavirin and immunoglobulin and a further three patients were given

immunoglobulin alone. The end of the outbreak was declared after 14 days. No staff screening was undertaken but symptomatic staff were excluded from work.

Patient characteristics are displayed in Table I. Male patients were predominantly affected (10 out of 12 patients). The average age of patients was 49 years (range: 23–84), and the mortality rate was 8.3% (one out of 12 patients).

## Discussion

We describe two outbreaks of RSV in our haematology ward, which have occurred in the last two consecutive years during the month of December. All patients in both outbreaks had underlying haematological malignancies but none had had autologous or allogeneic bone marrow transplants. The outbreaks coincided with seasonal outbreaks of RSV in the community and increased admissions in the paediatric setting. From timelines that were created, and particularly during the December 2016 outbreak, there were opportunities for cross-transmission between patients in the same bed bays. However, this did not explain the full picture, as some RSV-positive patients had no contact with other positive cases (Figures 1 and 2). Our hypothesis for both outbreaks is that RSV was introduced from the community by a patient, a staff member or a relative and cross-transmission then occurred in the ward setting between patients themselves, and staff members with mild symptoms. This appeared to be the case in the first outbreak where the index case was admitted symptomatic from the community. This pattern has been demonstrated in other RSV outbreaks. Jensen *et al.* described an RSV outbreak in haematology patients involving 12 patients and one staff member. Sequencing of the isolates was consistent with transmission occurring on the ward and introduction of RSV from the community [5]. In a 2011–12 outbreak involving 57 haematology patients, investigations showed single introduction of the outbreak strain from the community; this strain subsequent spread among patients into the unit [6].

In addition to direct contact with symptomatic patients or staff, asymptomatic patients and prolonged excretion may have contributed to continued transmission within the unit. Viral shedding in this patient group is known to occur for several weeks after the resolution of symptoms, and has been reported to be seven to 84 days in one study [7]. In both outbreaks we detected asymptomatic patients on screening. We also noted patients who continued to be PCR positive following resolution of symptoms and who became positive again after having negative PCR results. Both outbreaks were relatively short, so it was not possible to determine for how long patients were continuing to excrete the virus. Whether these patients could shed virus in sufficient amounts to contribute to further transmission is unknown. Outbreak investigators in the paediatric setting have detected asymptomatic patients and have postulated that these patients may shed RSV and cause onward transmission [8,9]. Due to our high-risk population we employed patient screening to detect those who were asymptomatic in both outbreaks. Further research investigating the efficacy of this measure is required. During a large outbreak of RSV in a German haematology unit, 20% of RSV patients had recurrent positive tests even after two consecutive negative PCR tests. This led the authors to conclude that it might be

appropriate to treat patients as positive for their duration of stay [2].

Mortality rates in haemato-oncology patients as a result of RSV are high. The mortality rate in outbreak 1 was higher at 37.5%. Average age in this outbreak was also higher at 64 years, which might have been a factor in the mortality rate. A retrospective cohort study of 227 adult patients attending the emergency department with RSV identified lower respiratory infection, chronic lung disease and bacterial co-infection as independent predictors of life-threatening infection [10]. Risk factor analysis specific to haematology patients is difficult due to small numbers but sharing a room with a positive patient was identified as a risk factor from one study [2]. One of the larger studies examining risk factors involved 56 haematology patients. Hypogammaglobulinaemia was identified as a significant risk factor for morbidity and mortality and was not reversible by treatment with polyvalent immunoglobulin [11]. Pre-existing lung disease was also thought to be a factor but the finding was not statistically significant [11]. In 181 haematopoietic cell transplant recipients with RSV, lymphopenia was associated with progression to lower respiratory disease [12]. The majority of our patients in both outbreaks were noted to be lymphopenic (Table I) although this is not a rare finding in this patient population.

A range of infection control precautions were employed during both outbreaks. On both occasions the ward was closed to admissions in an attempt to control the outbreak, to prevent exposure of other haematology patients and to limit the re-introduction of virus from the community. The implementation of broad precautions applicable to the entire unit is recommended during RSV outbreaks in preference to those focusing only on specific patients [1]. A recent systematic review of control measures implemented in 40 RSV outbreaks supported the use of multi-component measures. These measures reduced the transmission risk by 50%. It was not possible, however, to assess the effects of individual components [13].

In the first outbreak in 2015 several staff members exhibited symptoms compatible with RSV infection. Screening was therefore undertaken for all groups of staff in the unit. Two were positive, both of whom were displaying symptoms. Staff screening was not performed in the second outbreak. Fewer staff were symptomatic and our experience from the outbreak the preceding year was that only the symptomatic staff tested positive. Similarly, in an outbreak of RSV in adult stem cell recipients 99 asymptomatic healthcare workers were screened and all tested negative [1]. Had the outbreak control measures failed we would have proceeded with staff screening in 2016. During both outbreaks healthcare workers with mild symptoms remained at work and this has been described by others [1]. Human resource policies in relation to sickness absence and concerns about ward staffing may mean that staff are reluctant to take time off when symptoms are mild. When caring for RSV-positive patients our staff wore surgical masks. Implementation of a universal surgical mask policy, whereby all staff in direct contact with patients wore a mask, led to a significant reduction in respiratory viral illness in a haemopoietic stem cell unit [14].

Prophylaxis in paediatric outbreaks of RSV is well described; however, studies into its use in adults are lacking [14]. Prophylactic administration of palivizumab was administered during a nosocomial outbreak involving five stem cell transplant patients in 2010. Sixteen patient contacts were







designated high risk and administered prophylaxis with intravenous palivizumab, none of whom went on to develop RSV [15]. Further studies into the benefits of prophylaxis in this patient group are needed.

Given that the last outbreak of RSV in haematology patients in our health board was in 1999 we were surprised to experience two significant outbreaks two years in succession. Although both outbreaks were relatively short-lived there was significant morbidity, mortality and disruption to our haematology service. A review of both outbreaks has been undertaken and a number of measures implemented as a result. RSV is highly transmissible and rapid detection in this susceptible patient group is essential. We are limited by accommodation with only five single rooms; in addition our virology laboratory is situated off site. Near-patient testing done at ward level for RSV and other respiratory viruses has now been implemented. This will enable prompt detection and isolation or cohorting, depending on results. Human resources have agreed that staff members who are excluded during a confirmed outbreak will not have the sickness absence recorded – it is hoped that this will encourage staff members to refrain from duty when symptomatic. An early warning trigger has been implemented to inform the ward and infection control team when RSV cases in the community start to increase. Consideration is to be given to admitting haematology patients to other areas when presenting with respiratory symptoms, provided specialist haematology care is not required. Our board RSV policy was reviewed and now includes specific information relevant to RSV outbreaks in adults; the previous emphasis had been on the paediatric setting where outbreaks are more frequent. A report was produced following each outbreak and provided summary information as well as recommendations including: staff education, local audits of hand hygiene, and standard infection control precautions. A full staff debrief was undertaken after the first outbreak as there was naturally staff anxiety both in relation to patient outcomes and as to whether staff had been implicated in the outbreak.

Haematology units should be alert to the possibility of RSV outbreaks, especially during periods of high incidence in the community. Both outbreaks were relatively short-lived and the initial infection control measures implemented were effective in preventing further cross-transmission. Infection control measures we felt were key in managing these outbreaks were:

- ward closure
- isolation/cohorting of positive patients
- rapid exclusion of symptomatic staff
- hand hygiene and personal protective equipment.

Infection control measures which may be useful but require further evaluation include:

- isolation of positive patients for their duration of stay
- screening to detect asymptomatic patients with subsequent isolation
- universal application of surgical masks.

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## Conflict of interest statement

None declared.

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