Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biol Blood Marrow Transplant 20 (2014) 844–851

Nosocomial Transmission of Respiratory Syncytial Virus in an Outpatient Cancer Center

Helen Y. Chu [1,*], Janet A. Englund [2,3], Sara Podczervinski [4], Jane Kuypers [5], Angela P. Campbell [2,3,†], Michael Boeckh [1,2,6], Steven A. Pergam [1,2,4,6], Corey Casper [1,2,4,6]

[1] *Division of Allergy & Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington*
[2] *Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[3] *Department of Pediatrics, Section of Infectious Diseases, Seattle Children's Hospital, University of Washington, Seattle, Washington*
[4] *Infection Control and Prevention Program, Seattle Cancer Care Alliance, Seattle, Washington*
[5] *Department of Laboratory Medicine, University of Washington, Seattle, Washington*
[6] *Public Health Sciences Divisions, Fred Hutchinson Cancer Research Center, Seattle, Washington*

Article history:
Received 15 January 2014
Accepted 27 February 2014

Key Words:
Molecular epidemiology
Infection control
Health care worker
Respiratory syncytial virus
Outpatient clinic

A B S T R A C T

Respiratory syncytial virus (RSV) outbreaks in inpatient settings are associated with poor outcomes in cancer patients. The use of molecular epidemiology to document RSV transmission in the outpatient setting has not been well described. We performed a retrospective cohort study of 2 nosocomial outbreaks of RSV at the Seattle Cancer Care Alliance. Subjects included patients seen at the Seattle Cancer Care Alliance with RSV detected in 2 outbreaks in 2007-2008 and 2012 and all employees with respiratory viruses detected in the 2007-2008 outbreak. A subset of samples was sequenced using semi-nested PCR targeting the RSV attachment glycoprotein coding region. Fifty-one cases of RSV were identified in 2007-2008. Clustering of identical viral strains was detected in 10 of 15 patients (67%) with RSV sequenced from 2007 to 2008. As part of a multimodal infection control strategy implemented as a response to the outbreak, symptomatic employees had nasal washes collected. Of 254 employee samples, 91 (34%) tested positive for a respiratory virus, including 14 with RSV. In another RSV outbreak in 2012, 24 cases of RSV were identified; 9 of 10 patients (90%) had the same viral strain, and 1 (10%) had another viral strain. We document spread of clonal strains within an outpatient cancer care setting. Infection control interventions should be implemented in outpatient, as well as inpatient, settings to reduce person-to-person transmission and limit progression of RSV outbreaks.

INTRODUCTION

Respiratory syncytial virus (RSV) causes substantial morbidity and mortality among hematopoietic stem cell transplantation (HSCT) and oncology patients who are at high risk for progression to lower respiratory tract infection (LRTI)-associated respiratory failure and death [1]. Mortality rates for RSV-associated LRTI range from 15% to 70% [2,3]. Treatment regimens for RSV-associated LRTI include aerosolized ribavirin, often in combination with palivizumab or intravenous immunoglobulin; supplemental oxygen; and respiratory support [4-6]. However, antiviral therapies are expensive, difficult to administer, and have not reliably prevented progression to LRTI [7,8]. With no available vaccine or prophylaxis measures available for adults, infection control practices remain the only effective method to limit RSV outbreaks among adult cancer patients.

RSV may be acquired in a health care setting and has been implicated in outbreaks in inpatient hematology-oncology and transplant wards [9]. Hospital-based outbreaks of RSV infection in HSCT recipients occur through introduction of circulating community strains as well as nosocomial transmission of identical viral strains [10]. The molecular epidemiology of RSV is characterized by sequencing a hypervariable region of the attachment (G) glycoprotein gene [11,12]. Evidence of acquisition of the same viral strain in inpatient cancer care settings has demonstrated the importance of specific infection control policies to prevent nosocomial RSV transmission, although data describing this in the outpatient setting are not available [13]. Studies have shown outpatient transmission of parainfluenza, a respiratory virus also associated with high mortality in immunocompromised cancer patients [14].

Efforts to enhance infection control to prevent RSV spread include strict hand hygiene, use of droplet precautions, cohorting of nursing staff, and symptom screening of employees and visitors [15,16]. Previous studies in inpatient settings have shown that the number of RSV-positive cases decreased after implementation of these infection control interventions [17]. However, most cancer care is now delivered in the outpatient setting. The routine use of antibiotic prophylaxis and hematopoietic growth factors has reduced many risks associated with prolonged neutropenia and prolonged hospital stays [18]. It has been assumed that outpatients generally acquire their respiratory infections in the community through routine daily activities, such as work and exposure to children, and not through contact within the health care setting. Few data are currently available on transmission of RSV infection in

Financial disclosure: See Acknowledgments on page 850.
* Correspondence and reprint requests: Helen Y. Chu, MD MPH, Division of Allergy & Infectious Diseases/Department of Medicine, University of Washington Molecular Virology Laboratory, 1616 Eastlake Ave E. Suite 320, Box 358115, Seattle, WA 98102.
E-mail address: helenchu@uw.edu (H.Y. Chu).
† Current address: Angela P. Campbell, Centers for Disease Control and Prevention, Atlanta, Georgia.

1083-8791/$ – see front matter
http://dx.doi.org/10.1016/j.bbmt.2014.02.024

the outpatient cancer care setting. In this study molecular virologic methods were used to demonstrate nosocomial transmission of RSV during 2 RSV outbreaks at a large outpatient cancer care center.

METHODS

The Seattle Cancer Care Alliance (SCCA) is an inpatient and outpatient cancer care center based in Seattle, Washington. In 2012, 5599 patients were treated for cancer at the SCCA over the course of 72,300 visits. Patients at the SCCA are seen by teams of providers in different physical locations at a single site, divided by type of cancer or therapy, designated as Teams A through F. Allogeneic stem cell transplant recipients were seen by Teams A and B, autologous stem cell transplants were seen by Team C, pediatric patients were seen by Team D, patients in long-term follow-up were seen by Team E, and hematology-oncology patients were seen by Team F providers. The SCCA infection control team tracks incident RSV cases using an electronic system that identifies patients by provider team and location.

Electronic medical records were used to abstract sociodemographic and clinical data for patients with RSV detected during the 2 outbreak periods. Lymphopenia was defined as $\leq$500 cells/μL and severe lymphopenia as $\leq$300 cells/μL. Respiratory specimens were obtained in patients for testing by nasal washes or from bronchoalveolar lavage fluid when clinically indicated by the primary treatment team [19]. Direct fluorescent antibody detection was performed using RSV-specific mouse monoclonal antibodies (Chemicon, Temecula, CA) on all nasal wash samples before January 21, 2008, and reverse transcriptase PCR was performed afterward at the University of Washington Virology Laboratories using previously published methods [19,20]. All bronchoalveolar lavage samples undergo routine direct testing for RSV using direct fluorescent antibody, shell vial culture, and/or reverse transcriptase PCR testing.

During the 2007-2008 outbreak, all employees at the SCCA were administered a daily 12-symptom respiratory screening paper questionnaire for presence of runny nose, sinus congestion/stuffy nose, postnasal drip, shortness of breath, cough, wheezing or chest tightness, sputum production, sore throat, sneezing, watery eyes, ear pain, or fever (temperature >100.4°F) and had a nasal wash collected for respiratory viral testing per institutional policy at the time. Testing for RSV and 11 other respiratory viruses, including influenza A and B, human metapneumovirus, parainfluenza 1-4, rhinovirus, human coronavirus groups 1 and 2, and bocavirus were performed on employee samples using previously published methods [19,21]. Employees who had a positive nasal wash for any respiratory virus were not permitted to return to work until complete resolution of all symptoms and clearance by Occupational Health. To compare the outbreak with community data, rates of RSV detected in community samples from the Seattle and Pacific Northwest region were obtained from the University of Washington Diagnostic Virology Laboratory database (http://depts.washington.edu/rspvirus/respiratory.htm).

Sequencing was attempted from residual RSV-positive samples from the 2 respiratory seasons using a semi-nested PCR protocol targeting the second hypervariable region of the attachment glycoprotein coding region [22]. Random residual de-identified RSV-positive community samples collected from subjects seeking medical care during the same respiratory seasons were also sequenced to serve as control subjects. Sequences were submitted to GenBank with accession numbers KC565494 to KC565526. Sociodemographic, clinical, and virologic data were analyzed using Stata 12.0 (STATA Corp, College Station, TX). Nucleotide sequences for 233 and 212 base pair regions of the second hypervariable region of the RSV attachment glycoprotein coding region were aligned using ClustalX2 [23].

Phylogenetic trees were constructed separately for the 2007-2008 and 2012 outbreaks using MEGA5 with evolutionary distances calculated using the maximum likelihood method with 1000 bootstrap replicates [24]. This was performed using the Tamura-Nei model. The tree with the highest log likelihood is shown. When the number of common sites was 100 or less than one-fourth of the total number of sites, the maximum parsimony method was used; otherwise, the BioNJ method with MCL distance matrix was used. The trees were drawn to scale, with branch lengths measured in the number of substitutions per site.

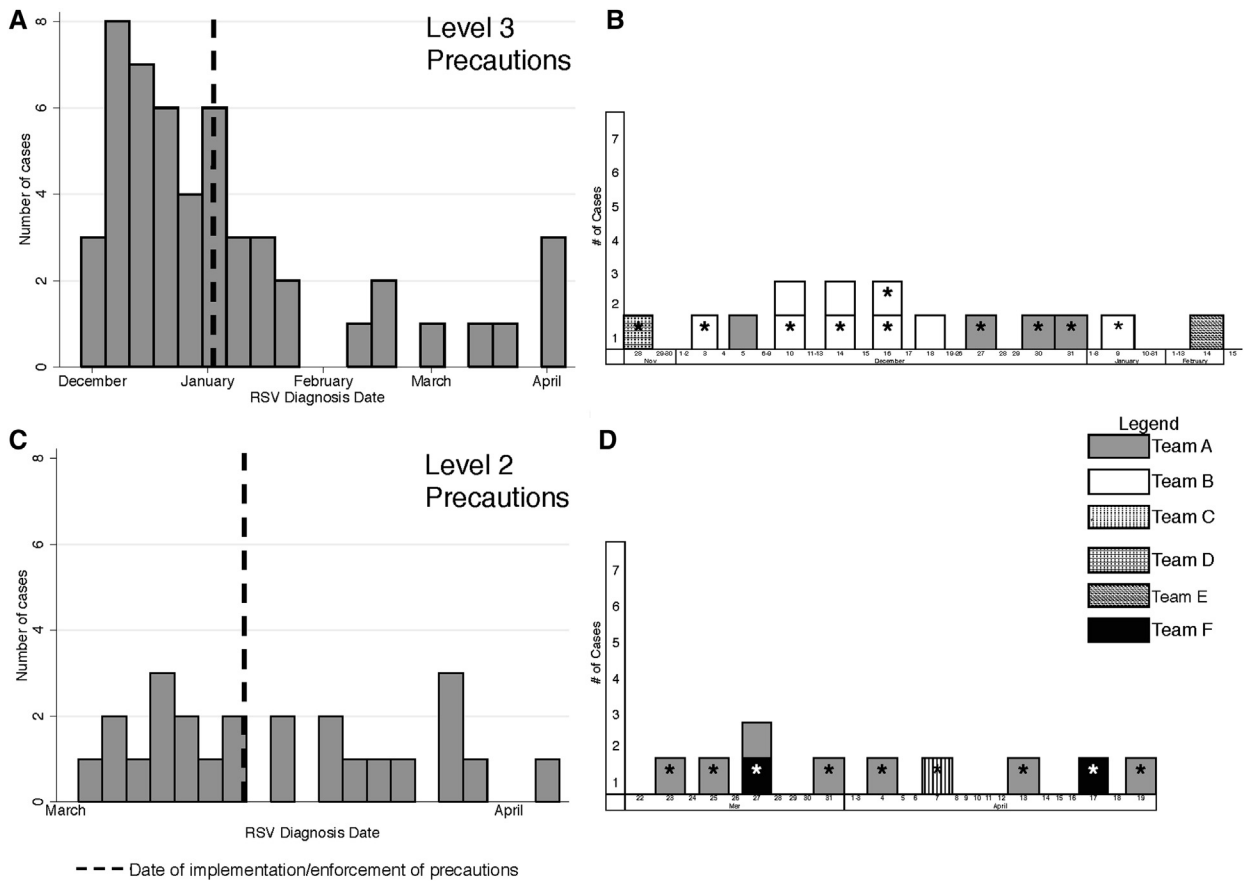


Figure 1. Histogram of all RSV cases at the SCCA per day in the 2007-2008 outbreak (A) and only cases where the viral strain was sequenced (B). Histogram of all RSV cases at the SCCA per day in the 2012 outbreak (C) and only cases where the viral strain was sequenced (D). The asterisk represents an identical viral strain for that season. The pattern of the box represents the team of providers seen by the patient.

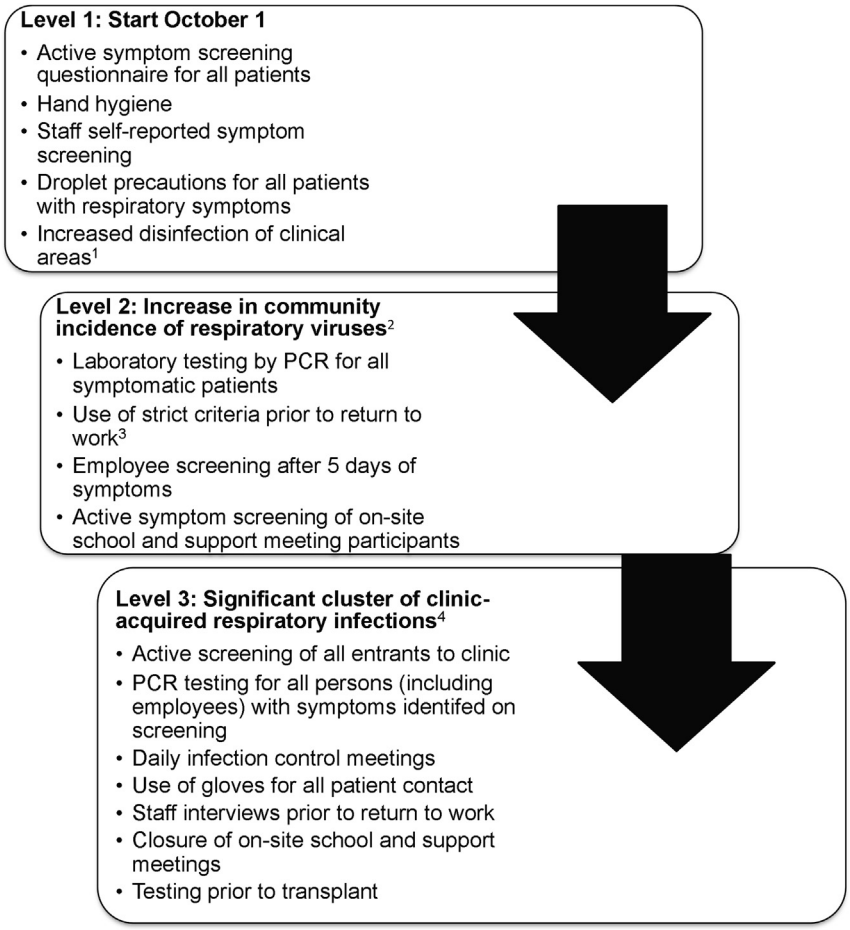
The analysis involved 32 nucleotide sequences. All positions containing gaps and missing data were eliminated. A total of 233 positions was included in the data set for the 2007 tree and 212 positions in the data set for the 2012 tree. Reference and community sequences were included in the comparison. Community samples included were sequences obtained from community childcare attendees from November 2006 to March 2009 and from random residual de-identified samples collected from adult and pediatric inpatients at the University of Washington and Seattle Children's Hospital form November to March of each RSV season in the Pacific Northwest from 2006 to 2009 and 2011 to 2012. Ethical approval for the study was obtained from the Fred Hutchinson Cancer Research Center Institutional Review Board.

RESULTS

RSV Outbreak 2007-2008

In November 2007, a cluster of 3 RSV cases at the SCCA prompted the implementation of an active respiratory virus surveillance system (Figure 1A). This plan designated 3 levels of infection control measures (Figure 2), with the immediate enforcement of Level 3 precautions starting January 1, 2008 (Figure 1A). As part of this plan, all patients, staff, and visitors to the clinic were screened for the presence of respiratory symptoms in the prior week using the 12-symptom respiratory screening questionnaire. Symptomatic persons were placed in respiratory isolation and a nasal wash for respiratory virus testing was collected. Of 51 cases of RSV identified in patients, 42 (82%) patients were HSCT recipients and 9 (18%) had hematologic or solid organ malignancies (Table 1). In the week before RSV detection, 33 patients (65%) were seen only in the outpatient clinic, whereas 7 (14%) were hospitalized and 11 (22%) had no associated health care visits. One of 11 subjects with no associated health care visits attended childcare; the others did not indicate recent sick contacts.

Our institutional policy for RSV treatment during this time included the administration of inhaled ribavirin to prevent progression of RSV upper respiratory tract infection to LRTI in patients with severe lymphopenia and the use of palivizumab or intravenous immunoglobulin for documented RSV-associated LRTI. Lymphocyte counts were measured within 1 week of RSV detection in 47 patients; 14 (30%) were lymphopenic and 8 (17%) had severe lymphopenia. Only 4 (8%) were diagnosed with LRTI. Fifteen patients (29%) received ribavirin alone or in combination with intravenous



[1]Increased disinfection of clinical areas was performed with additional emphasis on disinfecting the elevator buttons, elevator rails, counter tops, table tops, chairs, phones, and door knobs in the reception areas and Play Room.
[2]Level 2 precautions are initiated when there is more than one case of RSV per week.
[3]Return to work criteria included in person screening at Occupational Health after complete resolution of symptoms
[4]Observation of multiple cases at the SCCA with evidence of epidemiologic linkage by dates or location

Figure 2. Our Respiratory Virus Management Plan was implemented January 1, 2008 and included designation of 3 tiers of heightened respiratory viral surveillance and infection control strategies.

Table 1
Sociodemographic and Clinical Characteristics of Patients with RSV Detected in the 2007-2008 and 2012 Outbreaks

Characteristics	2007-2008 Outbreak [n (%)]	2012 Outbreak [n (%)]
Patients	51 (68%)	24 (32%)
Median age, yr (range)	53 (2-75)	58 (8-69)
Women	25 (49)	14 (58)
Underlying condition		
Malignancy	9 (18)	5 (21)
HSCT recipient	42 (82)	19 (79)
Lymphopenia (≤500 cells/μL)*	14 (30)	10 (59)
Severe lymphopenia (≤300 cells/μL)*	8 (17)	6 (35)
Health care location		
Hospital	7 (14)	3 (13)
Clinic	33 (65)	15 (63)
No associated health care visits	11 (22)	6 (25)
Specimen type		
Nasal wash	48 (94)	24 (100)
Bronchoalveolar lavage	3 (6)	0 (0)
Ribavirin treatment	15 (29)	3 (13)
LRTI diagnosis	4 (8)	1 (4)
Follow-up testing performed	23 (45)	19 (79)
Repeat testing positive	7 (30)	7 (37)
Clinical outcome		
Survival	47 (92)	24 (100)
Death due to other causes	3 (6)	0 (0)
Death attributed to RSV	1 (2)	0 (0)

HSCT indicates hematopoietic stem cell transplant recipient; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus.

* Lymphocyte count available within 1 week of RSV detection for 47 patients in the 2007-2008 outbreak and 17 patients in the 2012 outbreak.

immunoglobulin, including 11 with LRTI. Twenty-three patients (45%) had repeat testing performed a median of 13 days later (range, 4 to 32 days) with 7 (30%) having detectable virus. One patient (2%) died due to RSV pneumonia, 3 (6%) died of other causes, and 47 (92%) survived.

Fifty-one cases of RSV were observed over 131 days in the 2007-2008 outbreak (0.39 RSV cases per day; Figure 1A). Residual samples from 19 of 51 patients (37%) in the 2007-2008 outbreak were available for sequencing; 15 outbreak samples (29%) were successfully sequenced, as well as an additional 13 community samples. These included 14 subtype A strains and 1 subtype B strain. During the 2007-2008 outbreak, illness episodes with sequenced samples did not differ by patient age ($P = .28$) or location of care ($P = .43$) from those unable to be sequenced, although sequenced samples were collected later in the epidemic ($P = .01$).

Of the 15 illness episodes sequenced, 10 (67%) were identical, spanning a 43-day period from November 28, 2007 to January 9, 2008 (Figure 1B). Nine of these patients were hospitalized or seen in the clinic in the 7 days before RSV detection, whereas 1 patient had no associated prior health care visits. The first patient with this strain was a pediatric outpatient seen by Team D providers, and the next was seen by Team B providers 5 days later. Of the 10 cases with identical viral strains, only the index case was seen by Team D providers, whereas 3 patients were seen by Team A and 5 by Team B providers. Two of these patients subsequently died with RSV pneumonia as a contributing, although not the primary, cause of their death.

Three other distinct viral strains co-circulated during the outbreak period. One cluster of 2 patients was seen by Team B providers in a 4-day period. In another cluster of 2 patients, 1 was seen in December 2007 by Team B providers and another was seen in February 2008 by Team E providers. No clear epidemiologic link was noted for these 2 patients. One patient seen by Team A providers in December 2007 had a distinct viral strain, similar to circulating community strains from 2009.

Employees with RSV detected included 1 Team D and 1 Team A provider and 2 who provided care across multiple teams. Employee samples were not saved and therefore not available for sequencing from the 2007-2008 outbreak. The volume of patients seen in the clinic remained constant during the outbreak period, with an average of 1909 patient-days during weekdays and 341 patient-days during weekends (Figure 3A).

RSV Outbreak 2012

In March 2012, a cluster of 24 RSV cases was observed in the outpatient clinic (Figure 1C). Baseline sociodemographic and clinical data were similar to those of the patients in the 2007-2008 outbreak (Table 1). One patient (4%) had a diagnosis of LRTI; 3 patients (13%), all with URTI, received ribavirin to prevent progression to LRTI. Eleven of 24 patients (46%) were epidemiologically linked to a single outpatient care team (Team A) over 4 weeks. Although Level 2 precautions had been implemented since January, the Infection Control Team noted they had not been strictly enforced. Specifically, staff with active respiratory symptoms continued to work in the clinic, visitors/staff were not using the screening stickers consistently, and patients with documented respiratory virus symptoms were not tested immediately. On April 3, 2012, the Infection Control Team strictly enforced Level 2 precautions by sending a bulletin to all staff members detailing concerns regarding RSV, increasing outpatient rounds to occur on a daily basis during the week, and implemented education to re-engage staff. Level 3 precautions were not implemented in the 2012 outbreak.

Samples from 21 of 24 patients (88%) in the 2012 outbreak were available for sequencing; 10 of these outbreak samples (48%) were successfully sequenced, as well as 8 community samples from the same time period. An identical RSV subtype A strain was detected in 9 of 10 patients (90%) during a 27-day period between March 23, 2012 and April 19, 2012 (Figure 1D), whereas a distinct subtype B viral strain was detected in 1 patient (10%). Seven of these patients with identical strains were seen in the clinic or hospitalized, whereas 2 had no associated health care visits. Six were seen by Team A, 2 by Team F, and 1 by Team C providers. A patient with a unique viral strain was seen by Team A providers on March 27, 2012. Phylogenetic analysis of the viral strains demonstrated clustering of samples within each outbreak distinct from community samples from the same season (Figures 4 and 5).

In 2012, the numbers of patients seen in the clinic averaged 3128 patient-days during weekdays and 659 patient-days during weekends (Figure 3B). Overall, 1015 employees worked in the outpatient oncology clinic during the 2007-2008 outbreak compared with 1459 employees during the 2012 outbreak. The number of community-acquired RSV cases in the Pacific Northwest region as detected at the University of Washington Clinical Virology Laboratory during the 5-season period from 2007 to 2012 remained stable (median, 713 RSV cases per season; range, 610 to 804 cases; http://depts.washington.edu/rspvirus/respiratory.htm), although no RSV outbreaks were observed in the SCCA in the intervening years.

Employee Testing Results

Of the daily symptom screenings conducted in 1015 employees who worked during the 2007-2008 outbreak, 254

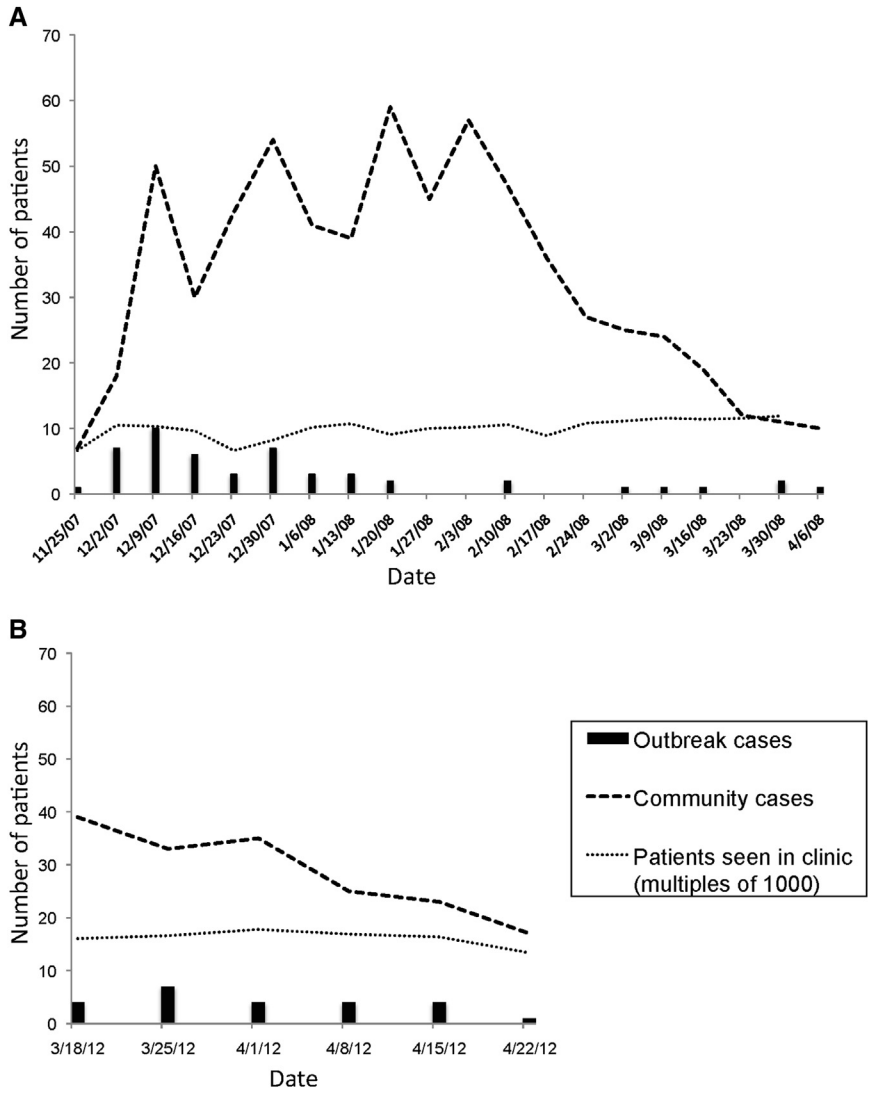


Figure 3. Chart of RSV cases per day during the outbreak as compared with numbers of patients seen and numbers of community RSV cases in the Pacific Northwest Region for the (A) 2007-2008 season and (B) 2011-2012 season. The bars represent the numbers of RSV-positive cases at the SCCA clinic. The dotted line represents the number of patients (in multiples of 1000) seen at the SCCA clinic. The dashed line represents the numbers of community cases in the Pacific Northwest.

had respiratory symptoms prompting the collection of a nasal wash. Ninety-one nasal wash samples (34%) had at least 1 respiratory virus detected, including 14 samples (15%) with RSV. Multiple other respiratory viruses detected in employees included human metapneumovirus (n = 12; 13%), influenza A (n = 14; 15%), influenza B (n = 13; 14%), coronavirus (n = 18; 20%), parainfluenza type 1 (n = 2; 2%), and parainfluenza type 3 (n = 2; 2%). Twelve employees had RSV detected from December 20, 2007 to March 13, 2008, with 2 employees positive on repeat testing. Ten (83%) had direct patient contact; 4 of these worked in the transplant or oncology departments. The first employee with RSV detected had no direct contact with patients with documented RSV, although she had been symptomatic since early December with an upper respiratory illness. Of the 12 employees with RSV, only 1 had contact with a patient with documented RSV. However, transmission between the employee and patient seemed unlikely because the timing of symptom onset and diagnosis dates did not indicate an epidemiologic link between the 2 cases.

DISCUSSION

Molecular sequencing of RSV strains detected during 2 distinct outbreaks from patients attending a large outpatient cancer care center demonstrated circulation of identical viral strains, suggesting the outpatient clinic can serve as a source of nosocomially acquired respiratory infections. In our center, outpatients are seen by multiple providers in common locations, engage in on-site meetings with other patients, providers, and families, and continue to work and interact with others outside of the medical setting. Traditional infection control interventions shown to be effective in hospital settings, such as the use of strict respiratory isolation and limitation of visitors and staff, may not be as effective as in the inpatient setting due to multiple potential sources to introduce infection [17]. Contact tracing is also more difficult in outpatient environments, making it harder to identify patterns of transmission.

Traditionally, cancer care has been delivered to inpatients until neutrophil recovery and clinical improvement. However, early discharge followed by continued outpatient

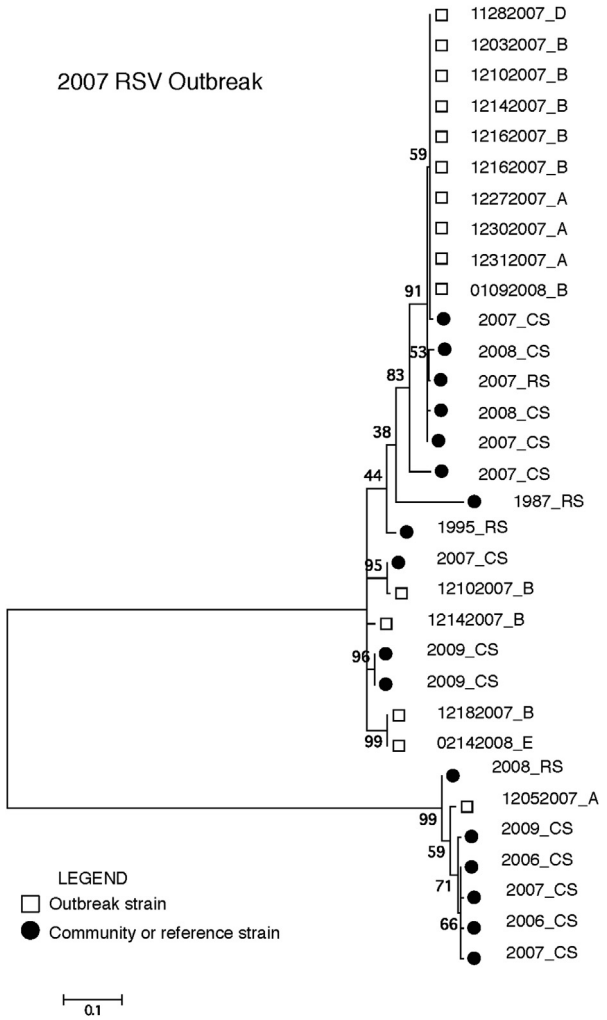


Figure 4. Phylogenetic trees were constructed using sequenced samples from the 2 outbreaks. The outbreak strains are identified by year followed by provider team. The reference and community strains are labeled with year followed by reference strain (RS) or community strain (CS). The numbers at the nodes are the bootstrap values. This phylogenetic tree shows the sequenced samples from the 2007-2008 outbreak. Of the 15 outbreak strains, 14 were subtype A and 1 was subtype B. The tree with the highest log likelihood (−1047.02) is shown. Community samples were collected during RSV season in the Seattle region from November to April from inpatients at Seattle Children's Hospital and the University of Washington, as well as community childcare attendees.

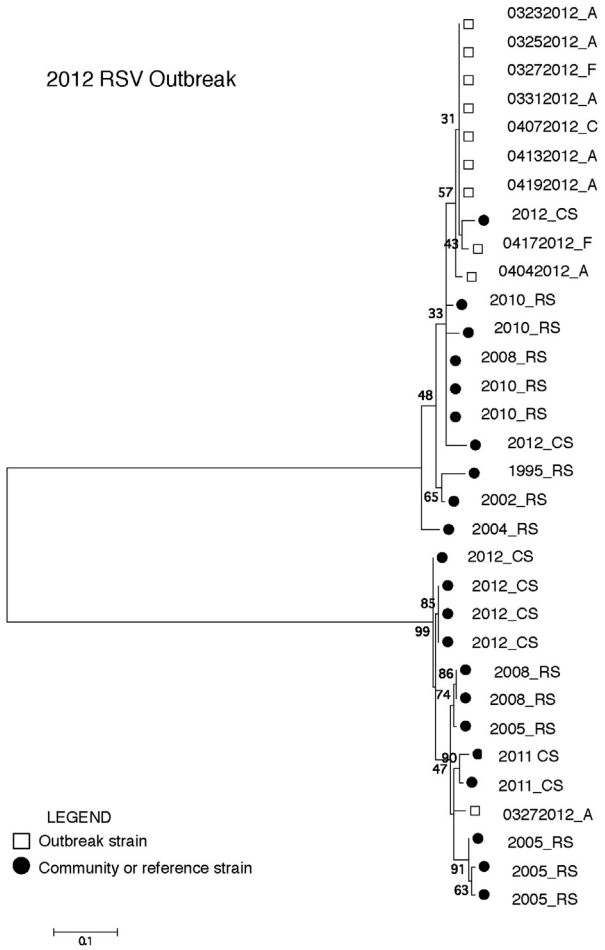


Figure 5. Phylogenetic trees were constructed using sequenced samples from the 2 outbreaks. The outbreak strains are identified by year followed by provider team. The reference and community strains are labeled with year followed by reference strain (RS) or community strain (CS). The numbers at the nodes are the bootstrap values. This phylogenetic tree shows the sequenced samples from the 2012 outbreak. Of the 10 outbreak strains, 9 were subtype A and 1 was subtype B. The tree with the highest log likelihood (−905.54) outbreak is shown. Community samples were collected during RSV season in the Seattle region from November to April from inpatients at Seattle Children's Hospital and the University of Washington, as well as community childcare attendees.

treatment has become more standard in recent years. Delivering care as an outpatient has multiple advantages, including cost savings, improved quality of life, and potentially reduction of nosocomial infections [25,26]. However, many of these patients are seen routinely in outpatient clinics such as ours, where they continue to interact with health care providers and other patients on a regular basis. Few prior studies have examined nosocomial transmission of respiratory viral infections in the outpatient setting. A study by Nichols et al. [27] conducted at our institution documented outpatient transmission of parainfluenza virus, and a small study by Machado et al. [10] documented clusters of identical RSV strains in an HSCT inpatient and outpatient treatment center in Sao Paolo, Brazil. The Brazilian study used direct fluorescent antibody for RSV diagnosis, a much less sensitive technique that likely limited the sensitivity of detection of RSV among the patients.

In response to the RSV outbreak in 2007-2008, we implemented intervention strategies based on Centers for Disease Control and Prevention guidelines for inpatient infection control settings, with interventions including staff cohorting, employee screening, and hand hygiene [28-30]. In an inpatient study by Lavergne et al. [17], measures that included restriction of visitors with respiratory symptoms, droplet isolation precautions, and use of gowns, gloves, and masks by all patients, staff, and visitors were associated with a .09 relative risk of RSV as compared with a more traditional infection control policy. The interventions we implemented in an outpatient setting including heightened symptom surveillance of employees, visitors, and patients at every entry point to the clinic and the strict restriction from access to the clinic based on a positive symptom screen, use of gowns and gloves, and droplet isolation precautions of all clinic patients with respiratory symptoms. We observed that the number of new cases decreased after the intervention in 2008 despite continued high levels of community RSV

activity as well as steady numbers of patient visits at the SCCA, suggesting that implementation of our strategy was effective in reducing the magnitude of the outbreak. In 2012, the magnitude of the outbreak was limited due to strict reinforcement of Level 2 precautions rather than escalation to Level 3 precautions. It is possible that Level 3 precautions would not have been necessary in 2008 if heightened enforcement of Level 2 precautions had been strictly enforced at that time as well.

In the 2007-2008 outbreak, a respiratory virus was identified in one third of employees with respiratory symptoms, including 12 with RSV. Detection of respiratory viruses in symptomatic staff, including high-risk pathogens such as RSV, influenza, parainfluenza, and metapneumovirus, indicates multiple opportunities for staff to introduce community respiratory viruses into an outpatient clinic. All these respiratory viruses have been associated with inpatient nosocomial outbreaks and have the potential to cause severe disease in immunocompromised patients [31-33]. Strict policies restricting symptomatic staff from working may mitigate the potential impact of provider transmission as the source of nosocomial outbreaks.

A study limitation is that we were unable to sequence most samples from the 2 outbreaks. Many samples were inadvertently discarded at the end of the RSV season and were not available for sequencing, including all employee samples. Possibilities for the inability to sequence the remainder of the samples include low viral loads and sample degradation. In the 2007-2008 outbreak in particular, only samples early in the outbreak were sequenced. It is therefore not possible to know whether the cases later in the season were due to continued transmission of the outbreak strain or to sporadic community cases. Additionally, no samples were collected from visitors or family members. These data may have provided additional information regarding the degree of clonal transmission by health care providers and family members in the outbreaks. We also acknowledge no clear epidemiologic data linking outbreak cases. However, in our center, there are multiple sites of potential interaction between patients and care providers, including radiology, phlebotomy, and waiting areas for clinics. Although not documented, we believe these interactions may provide potential exposures of patients to sick employees, and vice versa. It is also possible that the clustering of the RSV strains during the 2 outbreaks was a reflection of the dominant strain circulating during the season in the region. The molecular epidemiology of RSV usually involves 1 dominant strain that circulates over the course of a season [34,35]. However, we found clustering of samples from both outbreaks distinct from co-circulating community strains collected during the same period, making this less likely. Increased sampling and detection during periods of the RSV outbreak may have been partially due to heightened awareness among providers, leading to potential sampling bias. Further, although we observed decreases in numbers of new cases after implementation of our infection control plan, we were unable to document efficacy of the intervention due to the retrospective observational nature of the study.

Molecular sequencing was useful in identifying potential modes of nosocomial spread of RSV in an outpatient cancer care center during 2 separate RSV outbreaks. Infection control interventions used traditionally in inpatient settings should be considered for implementation in outpatient cancer settings to reduce person-to-person transmission and limit progression of RSV outbreaks.

ACKNOWLEDGMENTS

The authors acknowledge the patients at the SCCA as well as members of the Infection Control staff who assisted during the outbreaks.

Financial disclosure: This work was partially supported by National Institutes of Health grants K23-AI103105 (to H.Y.C.), K23HL091059 (to A.P.C.), L40AI071572 (to A.P.C.), CA18029 (to M.B.), HL081595 (to M.B.), HL9329 (to M.B.), and K23HL096831 (to S.A.P.). All other authors declare no sources of financial support.

Conflict of interest statement: J.A.E. has received research support from Gilead, Chimerix, and Roche and serves as a consultant for GlaxoSmithKline. M.B. served as a consultant for Gilead Sciences and GlaxoSmithKline. S.A.P. served as a consult for Merck, Optimer, and Chimerix and has received research support from Merck, Optimer, Viropharma, and Chimerix. All other authors declare no conflicts of interest.

REFERENCES

1. Englund JA, Sullivan CJ, Jordan MC, et al. Respiratory syncytial virus infection in immunocompromised adults. *Ann Intern Med*. 1988;109:203-208.
2. Shah DP, Ghantoji SS, Shah JN, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. *J Antimicrob Chemother*. 2013;68:1872-1880.
3. Waghmare A, Campbell AP, Xie H, et al. Respiratory syncytial virus lower respiratory disease in hematopoietic cell transplant recipients: viral RNA detection in blood, antiviral treatment, and clinical outcomes. *Clin Infect Dis*. 2013;57:1731-1741.
4. Renaud C, Campbell AP. Changing epidemiology of respiratory viral infections in hematopoietic cell transplant recipients and solid organ transplant recipients. *Curr Opin Infect Dis*. 2011;24:333-343.
5. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients. *Clin Infect Dis*. 2007;44:245-249.
6. Seo S, Campbell AP, Xie H, et al. Outcome of respiratory syncytial virus lower respiratory tract disease in hematopoietic cell transplant recipients receiving aerosolized ribavirin: significance of stem cell source and oxygen requirement. *Biol Blood Marrow Transplant*. 2013;19:589-596.
7. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. *Blood*. 2011;117:2755-2763.
8. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. *J Pediatr*. 2003;143:S127-S132.
9. Englund JA, Anderson LJ, Rhame FS. Nosocomial transmission of respiratory syncytial virus in immunocompromised adults. *J Clin Microbiol*. 1991;29:115-119.
10. Machado AF, Sallum MA, Vilas Boas LS, et al. Molecular characterization of strains of respiratory syncytial virus identified in a hematopoietic stem cell transplant outpatient unit over 2 years: community or nosocomial infection? *Biol Blood Marrow Transplant*. 2008;14:1348-1355.
11. Mazzulli T, Peret TC, McGeer A, et al. Molecular characterization of a nosocomial outbreak of human respiratory syncytial virus on an adult leukemia/lymphoma ward. *J Infect Dis*. 1999;180:1686-1689.
12. Peret TC, Hall CB, Schnabel KC, et al. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. *J Gen Virol*. 1998;79(Pt 9):2221-2229.
13. Geis S, Prifert C, Weissbrich B, et al. Molecular characterization of a respiratory syncytial virus (RSV) outbreak in a hematology unit, Heidelberg, Germany. *J Clin Microbiol*. 2012;51:155-162.
14. Sydnor ER, Greer A, Budd AP, et al. An outbreak of human parainfluenza virus 3 infection in an outpatient hematopoietic stem cell transplantation clinic. *Am J Infect Control*. 2012;40:601-605.
15. Garcia R, Raad I, Abi-Said D, et al. Nosocomial respiratory syncytial virus infections: prevention and control in bone marrow transplant patients. *Infect Control Hosp Epidemiol*. 1997;18:412-416.
16. Kassis C, Champlin RE, Hachem RY, et al. Detection and control of a nosocomial respiratory syncytial virus outbreak in a stem cell transplantation unit: the role of palivizumab. *Biol Blood Marrow Transplant*. 2010;16:1265-1271.
17. Lavergne V, Ghannoum M, Weiss K, et al. Successful prevention of respiratory syncytial virus nosocomial transmission following an enhanced seasonal infection control program. *Bone Marrow Transplant*. 2011;46:137-142.

18. McDiarmid S, Hutton B, Atkins H, et al. Performing allogeneic and autologous hematopoietic SCT in the outpatient setting: effects on infectious complications and early transplant outcomes. *Bone Marrow Transplant*. 2010;45:1220-1226.
19. Kuypers J, Campbell AP, Cent A, et al. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. *Transplant Infect Dis*. 2009;11:298-303.
20. Kuypers J, Wright N, Morrow R. Evaluation of quantitative and type-specific real-time RT-PCR assays for detection of respiratory syncytial virus in respiratory specimens from children. *J Clin Virol*. 2004;31: 123-129.
21. Kuypers J, Wright N, Ferrenberg J, et al. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. *J Clin Microbiol*. 2006;44:2382-2388.
22. Chu HY, Kuypers J, Renaud C, et al. Molecular epidemiology of respiratory syncytial virus transmission in childcare. *J Clin Virol*. 2013;57: 343-350.
23. Larkin MA, Blackshields G, Brown NP, Chenna R, McGettigan PA, McWilliam H, Valentin F, Wallace IM, Wilm A, Lopez R, Thompson JD, Gibson TJ, Higgins DG. Clustal W and Clustal X version 2.0. *Bioinformatics*. 2007;23:2947-2948.
24. Tamura K, Peterson D, Peterson N, et al. MEGA5: molecular evolutionary genetics analysis using maximum likelihood, evolutionary distance, and maximum parsimony methods. *Mol Biol Evol*. 2011;28: 2731-2739.
25. Seropian S, Nadkarni R, Jillella AP, et al. Neutropenic infections in 100 patients with non-Hodgkin's lymphoma or Hodgkin's disease treated with high-dose BEAM chemotherapy and peripheral blood progenitor cell transplant: out-patient treatment is a viable option. *Bone Marrow Transplant*. 1999;23:599-605.
26. Russell JA, Chaudhry A, Booth K, et al. Early outcomes after allogeneic stem cell transplantation for leukemia and myelodysplasia without protective isolation: a 10-year experience. *Biol Blood Marrow Transplant*. 2000;6:109-114.
27. Nichols WG, Erdman DD, Han A, et al. Prolonged outbreak of human parainfluenza virus 3 infection in a stem cell transplant outpatient department: insights from molecular epidemiologic analysis. *Biol Blood Marrow Transplant*. 2004;10:58-64.
28. Karanfil LV, Conlon M, Lykens K, et al. Reducing the rate of nosocomially transmitted respiratory syncytial virus. *Am J Infect Control*. 1999; 27:91-96.
29. Snydman DR, Greer C, Meissner HC, McIntosh K. Prevention of nosocomial transmission of respiratory syncytial virus in a newborn nursery. *Infect Control Hosp Epidemiol*. 1988;9:105-108.
30. Hall CB, Douglas RG Jr, Schnabel KC, Geiman JM. Infectivity of respiratory syncytial virus by various routes of inoculation. *Infect Immun*. 1981;33:779-783.
31. Piralla A, Percivalle E, Di Cesare-Merlone A, et al. Multicluster nosocomial outbreak of parainfluenza virus type 3 infection in a pediatric oncohematology unit: a phylogenetic study. *Haematologica*. 2009;94:833-839.
32. Degail MA, Hughes GJ, Maule C, et al. A human metapneumovirus outbreak at a community hospital in England, July to September 2010. *Bull Eur Mal Transm*. 2012;17:1-8.
33. Oguma T, Saito R, Masaki H, et al. Molecular characteristics of outbreaks of nosocomial infection with influenza A/H3N2 virus variants. *Infect Control Hosp Epidemiol*. 2011;32:267-275.
34. Pretorius MA, van Niekerk S, Tempia S, et al. Replacement and positive evolution of subtype A and B respiratory syncytial virus G-protein genotypes from 1997-2012 in South Africa. *J Infect Dis*. 2013; 208(Suppl. 3):S227-S237.
35. Yoshida A, Kiyota N, Kobayashi M, et al. Molecular epidemiology of the attachment glycoprotein (G) gene in respiratory syncytial virus in children with acute respiratory infection in Japan in 2009/2010. *J Med Microbiol*. 2012;61:820-829.