Journal of Microbiology, Immunology and Infection (2016) 49, 737—742

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk factors associated with death in patients with severe respiratory syncytial virus infection

Yen-I Lee [a], Chun-Chih Peng [a,b], Nan-Chang Chiu [a,c], Daniel Tsung-Ning Huang [a,d], Fu-Yuan Huang [a], Hsin Chi [a,b,c,d,*]

[a] *Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[c] *Mackay Junior College of Medicine, Nursing and Management, Taipei, Taiwan*
[d] *Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan*

Received 28 April 2014; received in revised form 29 August 2014; accepted 29 August 2014
Available online 31 October 2014

KEYWORDS
Down's syndrome;
mortality;
nosocomial infection;
respiratory syncytial virus;
risk factors

Background: Respiratory syncytial virus (RSV) infection is an important cause of viral respiratory tract infection in children. This retrospective study describes the clinical characteristics of severe RSV infection and determines the risk factors for death.
Methods: Patients were identified through a review of all patients discharged with a diagnosis of RSV lower respiratory tract infection and admitted to hospital in the pediatric intensive care unit (PICU) of a tertiary medical center between July 1, 2001 and June 30, 2010. The medical and demographic variables were recorded and analyzed.
Results: The 186 RSV-positive patients admitted to the PICU had a median age of 5.3 months (interquartile range 2.3—12.4 months) and included 129 boys and 57 girls. Among them, 134 had at least one underlying disease: prematurity in 92, neurological disease in 57, bronchopulmonary dysplasia in 40, congenital heart disease in 26, hematological malignancies in 11, and Down's syndrome in nine patients. The 10 patients who died from RSV-related causes had a median age of 20.8 months (interquartile range 6.6—89.2 months) and all had a comorbidity. In multivariate analysis, the risk factors for death in severe RSV infection were Down's syndrome (odds ratio 7.20, 95% confidence interval 1.13—45.76; $p = 0.036$) and nosocomial RSV infection (odds ratio 4.46, 95% confidence interval 1.09—18.27; $p = 0.038$).
Conclusion: Down's syndrome and nosocomial RSV infection are significantly associated with death in severe RSV infections. Clinicians should be alert to these conditions.

* Corresponding author. Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Zhongshan North Road, Taipei 10449, Taiwan.
E-mail address: chi.4531@mmh.org.tw (H. Chi).

http://dx.doi.org/10.1016/j.jmii.2014.08.020

Introduction

Respiratory syncytial virus (RSV) is an important cause of acute lower respiratory tract infection (LRTI) in children younger than 5 years of age. In 2005, RSV was estimated to be responsible for at least 3.4 million episodes of severe LRTI requiring admission to hospital in children worldwide and caused 66,000—199,000 deaths in children younger than 5 years old.[1] In Switzerland, RSV infections cause intermediate or intensive care unit (ICU) admissions of approximately 1—2% of each annual birth cohort.[2] In a retrospective study in Hong Kong, the rate of RSV-associated ICU admissions was 2.4% among 4912 RSV-positive pediatric patients.[3]

Many studies have shown that patients at high risk of severe RSV disease include premature infants,[4,5] children with hemodynamically significant congenital heart disease (CHD),[4,6,7] patients with bronchopulmonary dysplasia (BPD),[4,5,8] and those who are immunocompromised.[6,9—11] However, data regarding risk factors for death in severe RSV infection remain limited. The aim of this retrospective study was to identify the clinical characteristics of patients admitted to the pediatric intensive care unit (PICU) with RSV infection and the risk factors for death.

Materials and methods

Ethics statement

The Ethics Committee of Mackay Memorial Hospital, Taipei, Taiwan approved this study (Institute Review Board number MMH-I-S- 627, protocol title "Clinical Features of Pediatric Respiratory Syncytial Virus Infections: Risk Factors and Outcome").

Patient inclusion

Patients were identified through a review of medical records from July 1, 2001 to June 30, 2010. This study used data from a 12-bed PICU in a tertiary medical center.

Patients aged $\leq$18 years and discharged with a diagnosis of RSV LRTI were evaluated. The diagnosis was confirmed by an RSV antigen immunofluorescence test and/or culture from specimens taken from nasopharyngeal or throat swabs. Patients who were admitted to the PICU and were labeled as "severe" were enrolled into this study.

The general policy was that patients who required mechanical respiratory support or intensive care were transferred to the PICU. In the PICU, respiratory support included mechanical ventilation (conventional and high frequency), nasal intermittent positive pressure ventilation, nasal continuous positive airway pressure, and supplemental oxygen only.

Virology sampling and investigations

Diagnostic samples, including nasopharyngeal aspirates for the RSV antigen test and throat virus cultures, were obtained by residents, nurses, or PICU staff members. The RSV was identified using IMAGEN Respiratory Syncytial Virus (Oxoid Ely Ltd, Hampshire, UK), a qualitative immunofluorescence test for the direct detection of RSV in clinical specimens. Throat swabs for viral culture used standard cell culture methods.

Treatment with ribavirin

Ribavirin treatment was used for PICU patients younger than 6 years of age who had RSV LRTI and least one of the following: (1) high-risk for RSV infection, including immunocompromised patients, prematurity, or patients with CHD, BPD, or a malignancy being treated with chemotherapy; (2) severe respiratory distress ($Pao_2 \leq 65$ mmHg or $Sao_2 \leq 90\%$); and (3) requiring ventilator support. Ribavirin (20 mg/mL) was given via continuous aerosol administration for 12—18 hours daily for 3 days. However, ribavirin became unavailable in Taiwan from February 2009.

Definitions of variables

Children with gestational age <37 weeks were regarded as preterm. Hemato-oncological diseases included acute lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and lymphoma. Congenital hemodynamically significant heart diseases or cyanotic heart diseases were defined as CHD. Patients with atrial septal defect were excluded from the study. Neurological diseases included cerebral palsy, neuromuscular diseases, or other central nervous system abnormalities. Patients with seizures were excluded from this category. Nosocomial RSV infection was defined as symptoms or signs of RSV infection developing 72 hours or more after admission for other diagnoses.

Statistical analysis

Frequency distribution analysis was used to describe the patients' baseline characteristics. Median and interquartile ranges (IQRs) were used to interpret the demographic distributions. Continuous variables were expressed as a median with IQR and were compared using the Student *t* test or the Mann—Whitney *U* test. Categorical variables were presented as frequencies and percentages and were compared using the χ^2 or Fisher's exact test as appropriate. Univariate analysis was performed to evaluate the relationship between the variables and death. The factors were also analyzed using a multivariate model built by backwards elimination (a significance level of 5%) to assess the

relationship to death. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 17.0 software (IBM Corporation, Somers, NY, USA).

Results

Demographic data and clinical characteristics

A total of 5675 patients proved to have an RSV infection, including 186 who were admitted to the PICU. Severe infections accounted for 3.3% of RSV infections. Of the 186 patients, 129 were boys and 57 were girls (ratio 2.3:1). Their mean age was 5.3 months (range 0.2–168.1 months). Ninety-two (49.5%) patients were born prematurely, 46 (24.7%) patients had a nosocomial RSV infection, and 54 (29.0%) patients received treatment with ribavirin. One hundred and thirty-four (72.0%) patients had at least one underlying disease. Respiratory support included mechanical ventilation (29.5%), nasal intermittent positive pressure ventilation (30.1%), nasal continuous positive airway pressure (10.8%), and oxygen supplement (29.5%). Ten patients died giving a mortality rate of 5.4% (Table 1).

Characteristics of the patients who died

Table 2 lists the characteristics of the patients who died. Patient 1 had a very long stay in hospital as a result of complicated underlying diseases. This patient had a nosocomial RSV infection and *Serratia marcescens* sepsis, which caused his death. Patient 5 had a ventricular septal defect, patent ductus arteriosus, and pulmonary hypertension. His condition deteriorated and he died a few days after surgery. His RSV infection was identified and was posited to have aggravated the burden of pulmonary and cardiac disease in this patient.

Table 1 Characteristics of children admitted to the pediatric intensive care unit for respiratory syncytial virus infection

Variable	*N* (%) of patients ($n = 186$)
Sex	
Male	129 (69.4)
Female	57 (30.6)
Median (IQR) age at diagnosis (mo)	5.3 (2.3–12.4)
Prematurity	92 (49.5)
Pre-existing disease	134 (72.0)
Bronchopulmonary dysplasia	40 (21.5)
Congenital heart disease	26 (14.0)
Down's syndrome	9 (4.8)
Hemato-oncological disease	11 (5.9)
Neurological disease	57 (30.6)
None	52 (28.0)
Nosocomial acquisition	46 (24.7)
Treatment with ribavirin	54 (29.0)
Respiratory support	
Oxygen supplement	55 (29.5)
NCPAP	20 (10.8)
NIPPV	56 (30.1)
Mechanical ventilation	55 (29.5)
Death	10 (5.4)

IQR = interquartile range; NCPAP = nasal continuous positive airway pressure; NIPPV = nasal intermittent positive pressure ventilation.

Analysis of risk factors for death

In univariate analysis (Table 3), hemato-oncological diseases [odds ratio (OR) 9.0, 95% confidence interval (CI) 1.95–41.45; $p = 0.015$], nosocomial infections (OR 5.10, 95% CI 1.37–18.97; $p = 0.016$), and treatment with ribavirin (OR 6.40, 95% CI 1.59–25.79; $p = 0.007$) were associated with death. Among the continuous variables, death was associated with a longer duration of fever and lower platelet counts. The duration of fever among survivors was 4.8 ± 8.3 days and among non-survivors was 8.8 ± 4.7 days ($p = 0.038$). The platelet count among survivors was $364.4 \pm 171.5 \times 10^3/mm^3$ and among non-survivors was $187.8 \pm 110.1 \times 10^3/mm^3$ ($p = 0.001$).

Using multiple logistic regression analysis (Table 4), Down's syndrome (OR 7.20, 95% CI 1.13–45.76; $p = 0.036$) and nosocomial RSV infection (OR 4.46, 95% CI 1.09–18.27; $p = 0.038$) were predictive factors for death. Older children have more risk for death from RSV (OR 1.024, 95% CI 1.01–1.04; $p = 0.002$).

Discussion

In this study, all the children who died from severe RSV disease had pre-existing diseases. This study also showed that Down's syndrome and nosocomial RSV infection are significant risk factor for death in severe RSV infection.

Previous studies have shown that Down's syndrome is a major risk factor for RSV LRTI. There are many possible explanations. Children with Down's syndrome have an increased rate of comorbidities with both CHD and pulmonary hypertension, which are two independent risk factors for RSV LRTI.[12,13] Patients with Down's syndrome, even without coexisting risk factors such as CHD, still have higher risks of being admitted to hospital for RSV LRTI.[14] Other hypothesized mechanisms include hypotonia,[15] more injury-prone lungs,[16] an abnormal upper respiratory anatomy,[15] and altered lung growth.[17] Immunological impairment associated with Down's syndrome is also a potential mechanism, as demonstrated in many aspects including defects in adaptive[18,19] and intrinsic immunity,[20,21] diminished numbers of B and T cells due to abnormal thymus function,[21] decreased lymphocyte numbers and responses to stimulations,[22] reduced phagocytosis by neutrophils,[23] and lower serum immunoglobulin levels.[24]

Nosocomial RSV infection is also a risk factor for death in severe RSV infection.[25] Comorbidity may confound the relationship between nosocomial RSV infection and death. In previous studies, children with BPD, CHD, and impaired immune systems had increased incidences of nosocomial RSV infection.[9,26–29] This may be due to the longer stay in hospital and in the ICU and more exposure to potential cross-infection.

In multivariate analysis, older children have a higher risk for death from RSV infection. Older children often have

Table 2 Characteristics of the ten patients with severe respiratory syncytial virus infections who died

Patient no.	Sex	Age of diagnosis (mo)	Underlying disease	Nosocomial infection	Treatment with ribavirin
1	M	7.0	Prematurity, rickets, short bowel syndrome	Yes	No
2	M	5.2	Prematurity, BPD, Down's syndrome	No	Yes
3	M	11.0	Prematurity, BPD	Yes	Yes
4	F	8.6	Prematurity, bronchopulmonary dysplasia	No	Yes
5	M	54.4	VSD, PDA, pulmonary hypertension	No	No
6	M	86.3	ALL	Yes	Yes
7	F	30.5	Cerebral palsy	No	No
8	F	5.6	Down's syndrome, VSD	Yes	Yes
9	M	168.1	ALL	Yes	Yes
10	M	97.6	ALL	Yes	Yes

ALL = acute lymphoblastic leukemia; BPD = bronchopulmonary dysplasia; F = female; M = male; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

milder symptoms than younger children when they have an RSV infection. However, in older children with severe RSV infection, death may be related to their underlying conditions and they may therefore present with more severe infections and more complications.

In this study, only 12 virus isolates underwent serotyping. Nine were RSV-A and three were RSV-B. A previous study has shown that there is no difference in severity of disease caused by RSV-A or RSV-B.[30] However, the sample size in this study was too small to include this variable in the analysis.

Ribavirin is a guanosine analogue with antiviral activity against a variety of viruses. In 1985, the United States Food and Drug Administration approved its aerosol form for use in infants and children with RSV bronchiolitis.[31] Some previous studies have shown that treatment with ribavirin can reduce the severity of illness, the duration of mechanical ventilation, the length of hospital stay, and viral shedding in RSV bronchiolitis.[32–34] However, other studies have not shown these benefits.[35–37] A 2004 systematic review of randomized trials showed that trials of treatment with nebulized ribavirin lacked sufficient power to provide reliable estimates of the effects.[31] The American Academy of Pediatrics no longer recommends the routine use of ribavirin because of the high costs, concerns for its teratogenic potential in pregnant health care staff, and uncertainty about its effectiveness. Nonetheless, ribavirin may still be considered for selected patients with potentially life-threatening RSV infection. In this study, ribavirin was only given to a few patients. As ribavirin has not been available in Taiwan since February 2009, the effects of treatment with ribavirin are difficult to evaluate in this study.

Palivizumab is a monoclonal antibody produced by recombinant DNA technology used in the prevention of RSV infections. It has been universally used in Taiwan since December 2010 for specific high-risk patients, including

Table 3 Univariate analysis of the risk factors and death in patients with respiratory syncytial virus infection

Variable	Survival (n = 176)	Death (n = 10)	OR (95% CI)	p
Male sex	122 (69.3)	7 (70.0)	1.03 (0.26–4.15)	> 0.99
Age (mo)	12.1 ± 21.9	47.4 ± 54.7		0.072
Preterm birth	88 (50.0)	4 (40.0)	0.67 (0.18–2.44)	0.747
Bronchopulmonary dysplasia	37 (21.0)	3 (30.0)	1.61 (0.40–6.53)	0.450
Congenital heart disease	24 (13.6)	2 (20.0)	1.58 (0.32–7.91)	0.633
Down's syndrome	7 (4.0)	2 (20.0)	6.04 (1.08–33.84)	0.077
Neurological disease	56 (31.8)	1 (10.0)	0.24 (0.03–1.93)	0.288
Hemato-oncological disease	8 (4.5)	3 (30.0)	9.00 (1.95–41.45)	0.015
Nosocomial RSV infection	40 (22.7)	6 (60.0)	5.10 (1.37–18.97)	0.016
Treatment with ribavirin	47 (26.7)	7 (70.0)	6.40 (1.59–25.79)	0.007
Duration of fever (d)	4.8 ± 8.3	8.8 ± 4.7		0.038
Duration of hospitalization (d)	37.6 ± 51.0	80.6 ± 116.3		0.274
Duration of PICU stay (d)	9.5 ± 11.8	14.4 ± 15.6		0.374
Hemoglobin (g/dL)	12.2 ± 10.7	15.6 ± 15.2		0.534
White blood cell count ($\times 10^3/mm^3$)	13.0 ± 8.8	11.2 ± 8.7		0.552
Platelet ($\times 10^3/mm^3$)	364.4 ± 171.5	187.8 ± 110.1		0.001
C reactive protein (mg/dL)	3.1 ± 5.9	8.32 ± 9.5		0.140

Data are presented as n (%) or mean ± SD.
CI = confidence interval; OR = odds ratio; PICU = pediatric intensive care unit; RSV = respiratory syncytial virus.

Table 4 Multivariate analysis of the variables associated with death from respiratory syncytial virus infection

Variable	OR (95% CI)	*p*
Age	1.02 (1.01—1.04)	0.002
Down's syndrome	7.20 (1.13—45.76)	0.036
Nosocomial RSV infection	4.46 (1.09—18.27)	0.038

CI = confidence interval; OR = odds ratio; RSV = respiratory syncytial virus.

those with prematurity with gestational age ≤28 weeks, prematurity with gestational age ≤35 weeks and BPD, and patients with hemodynamically significant heart disease. The patients in this study were recruited before palivizumab was used.

RSV is primarily spread by close contact with aerosols of infectious respiratory secretions and medical staff are often instrumental in its transmission. RSV is a labile virus and is rapidly inactivated by alcohol, dishwashing detergents, and antibacterial hand soaps. Thus hand-washing probably plays the most important part in infection control. Although there are various barrier methods, the isolation of RSV-positive patients in single rooms is recommended.[38]

This study is limited by its retrospective nature and small sample size. Further research is warranted to determine other risks factors for death in RSV infection.

In children with severe RSV disease, nosocomial RSV infection is associated with increased risk of death. Pre-existing diseases and co-morbidities, particularly Down's syndrome, are significant risk factors for death from severe RSV infection.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;**375**:1545—55.
2. Berger TM, Aebi C, Duppenthaler A, Stocker M, Swiss Pediatric Surveillance U. Prospective population-based study of RSV-related intermediate care and intensive care unit admissions in Switzerland over a 4-year period (2001—2005). *Infection* 2009;**37**:109—16.
3. Leung TF, Lam DS, Miu TY, Hon KL, Chau CS, Ku SW, et al. Epidemiology and risk factors for severe respiratory syncytial virus infections requiring pediatric intensive care admission in Hong Kong children. *Infection* 2014;**42**:343—50.
4. Boyce TG, Mellen BG, Mitchel Jr EF, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr* 2000;**137**:865—70.
5. Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, Dobson S, et al. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of admission and management variation in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1996;**129**:390—5.
6. Navas L, Wang E, de Carvalho V, Robinson J. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. Pediatric Investigators Collaborative Network on Infections in Canada. *J Pediatr* 1992;**121**:348—54.
7. Kristensen K, Stensballe LG, Bjerre J, Roth D, Fisker N, Kongstad T, et al. Risk factors for respiratory syncytial virus hospitalisation in children with heart disease. *Arch Dis Child* 2009;**94**:785—9.
8. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009;**360**:588—98.
9. Hall CB, Powell KR, MacDonald NE, Gala CL, Menegus ME, Suffin SC, et al. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med* 1986;**315**:77—81.
10. Milner ME, de la Monte SM, Hutchins GM. Fatal respiratory syncytial virus infection in severe combined immunodeficiency syndrome. *Am J Dis Child* 1985;**139**:1111—4.
11. El Saleeby CM, Somes GW, DeVincenzo JP, Gaur AH. Risk factors for severe respiratory syncytial virus disease in children with cancer: the importance of lymphopenia and young age. *Pediatrics* 2008;**121**:235—43.
12. Shah PS, Hellmann J, Adatia I. Clinical characteristics and follow up of Down syndrome infants without congenital heart disease who presented with persistent pulmonary hypertension of newborn. *J Perinat Med* 2004;**32**:168—70.
13. Freeman SB, Taft LF, Dooley KJ, Allran K, Sherman SL, Hassold TJ, et al. Population-based study of congenital heart defects in Down syndrome. *Am J Med Genet* 1998;**80**:213—7.
14. Zachariah P, Ruttenber M, Simoes EA. Down syndrome and hospitalizations due to respiratory syncytial virus: a population-based study. *J Pediatr* 2012;**160**:827—31.
15. Uong EC, McDonough JM, Tayag-Kier CE, Zhao H, Haselgrove J, Mahboubi S, et al. Magnetic resonance imaging of the upper airway in children with Down syndrome. *Am J Respir Crit Care Med* 2001;**163**:731—6.
16. Bruijn M, van der Aa LB, van Rijn RR, Bos AP, van Woensel JB. High incidence of acute lung injury in children with Down syndrome. *Intensive Care Med* 2007;**33**:2179—82.
17. Schloo BL, Vawter GF, Reid LM. Down syndrome: patterns of disturbed lung growth. *Hum Pathol* 1991;**22**:919—23.
18. Murphy M, Epstein LB. Down syndrome (DS) peripheral blood contains phenotypically mature CD3+TCR alpha, beta+ cells but abnormal proportions of TCR alpha, beta+, TCR gamma, delta+, and CD4+ CD45RA+ cells: evidence for an inefficient release of mature T cells by the DS thymus. *Clin Immunol Immunopathol* 1992;**62**:245—51.
19. Murphy M, Lempert MJ, Epstein LB. Decreased level of T cell receptor expression by Down syndrome (trisomy 21) thymocytes. *Am J Med Genet Suppl* 1990;**7**:234—7.
20. Kusters MA, Verstegen RH, Gemen EF, de Vries E. Intrinsic defect of the immune system in children with Down syndrome: a review. *Clin Exp Immunol* 2009;**156**:189—93.
21. de Hingh YC, van der Vossen PW, Gemen EF, Mulder AB, Hop WC, Brus F, et al. Intrinsic abnormalities of lymphocyte counts in children with Down syndrome. *J Pediatr* 2005;**147**:744—7.
22. Murphy M, Epstein LB. Decreased T cell receptor and CD3 expression by Down syndrome thymocytes: evidence for delayed maturation. *Prog Clin Biol Res* 1990;**360**:117—30.
23. Licastro F, Melotti C, Parente R, Davis LJ, Chiricolo M, Zannotti M, et al. Derangement of non-specific immunity in Down syndrome subjects: low leukocyte chemiluminescence activity after phagocytic activation. *Am J Med Genet Suppl* 1990;**7**:242—6.
24. Loh RK, Harth SC, Thong YH, Ferrante A. Immunoglobulin G subclass deficiency and predisposition to infection in Down's syndrome. *Pediatr Infect Dis J* 1990;**9**:547—51.

25. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. *Arch Dis Child* 2009;**94**:99—103.
26. Buckingham SC, Quasney MW, Bush AJ, DeVincenzo JP. Respiratory syncytial virus infections in the pediatric intensive care unit: clinical characteristics and risk factors for adverse outcomes. *Pediatr Crit Care Med* 2001;**2**:318—23.
27. Thorburn K, Kerr S, Taylor N, van Saene HK. RSV outbreak in a paediatric intensive care unit. *J Hosp Infect* 2004;**57**:194—201.
28. Purcell K, Fergie J. Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatr Infect Dis J* 2004;**23**:418—23.
29. Hall CB, Douglas Jr RG, Geiman JM. Quantitative shedding patterns of respiratory syncytial virus in infants. *J Infect Dis* 1975;**132**:151—6.
30. Katzov-Eckert H, Botosso VF, Neto EA, Zanotto PM, Consortium V. Phylodynamics and dispersal of HRSV entails its permanence in the general population in between yearly outbreaks in children. *PLoS One* 2012;**7**:e41953.
31. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev* 2004:CD000181.
32. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med* 1991;**325**:24—9.
33. Rodriguez WJ, Kim HW, Brandt CD, Fink RJ, Getson PR, Arrobio J, et al. Aerosolized ribavirin in the treatment of patients with respiratory syncytial virus disease. *Pediatr Infect Dis J* 1987;**6**:159—63.
34. Hall CB, McBride JT, Walsh EE, Bell DM, Gala CL, Hildreth S, et al. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. A randomized double-blind study. *N Engl J Med* 1983;**308**:1443—7.
35. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med* 1994;**22**:566—72.
36. Moler FW, Steinhart CM, Ohmit SE, Stidham GL. Effectiveness of ribavirin in otherwise well infants with respiratory syncytial virus-associated respiratory failure. Pediatric Critical Study Group. *J Pediatr* 1996;**128**:422—8.
37. Guerguerian AM, Gauthier M, Lebel MH, Farrell CA, Lacroix J. Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 1999;**160**:829—34.
38. Groothuis J, Bauman J, Malinoski F, Eggleston M. Strategies for prevention of RSV nosocomial infection. *J Perinatol* 2008;**28**:319—23.