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ORIGINAL ARTICLE

Respiratory syncytial virus infections requiring hospitalization in patients with primary immunodeficiency☆,☆☆

Luis Ignacio González-Granado[a], Andrea Martín-Nalda[b], Laia Alsina[c], Olaf Neth[d], Manuel Santamaría[e], Pere Soler-Palacín[b,*], grupo SENTIR[1]

[a] *Unidad de Inmunodeficiencias, Pediatría, Instituto de Investigación Hospital 12 de Octubre, Facultad de Medicina, Universidad Complutense, Madrid, Spain*
[b] *Grupo de Investigación de Infección en el Paciente Pediátrico Inmunodeprimido, Vall d'Hebron Institut de Recerca (VHIR); Unidad de Patología Infecciosa e Inmunodeficiencias de Pediatría, Hospital Universitari Vall d'Hebron; Centro Jeffrey Modell para Diagnóstico e Investigación en Inmunodeficiencias Primarias, Barcelona, Catalonia, Spain*
[c] *Unidad de Inmunología Clínica e Inmunodeficiencias Primarias, Servicio de Alergología e Inmunología Clínica, Hospital Sant Joan de Déu; Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain*
[d] *Sección de Enfermedades Infecciosas, Reumatología e Inmunología Pediátrica, Hospital Infantil Universitario Virgen del Rocío; Instituto de Biomedicina de Sevilla (IBiS), Sevilla, Spain*
[e] *Servicio de Inmunología, Hospital Universitario Reina Sofía; Facultad de Medicina, Universidad de Córdoba, Córdoba, Spain*

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KEYWORDS
Acute respiratory infection;
Combined immunodeficiency;
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Abstract
Introduction: The aim of the study was to assess the incidence of hospital admission due to severe acute respiratory infection by respiratory syncytial virus (RSV-ARI) in children with primary immunodeficiencies (PIDs) and the severity of RSV-ARI in these patients.
Methods: We conducted a nationwide cross-sectional retrospective and prospective multicentre study in the 2011–2017 period. The study was performed in 15 Spanish hospitals and included children with PID who required hospital admission due to RSV-ARI.
Results: Out of 439 patients with PID followed up at participating hospitals, 13 (3%) required hospital admission due to RSV-ARI. The median age of admitted patients was 1.6 years (interquartile range, 0.5—2.2), and 7 were male. The types of PID most frequently associated

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* Corresponding author.
E-mail address: psoler@vhebron.net (P. Soler-Palacín).
[1] The members of the SENTIR Group are presented in Appendix A.

with admission due to RSV-ARI were combined immunodeficiency (CID; 4/71; 6%) and CID with associated or syndromic features (CIDwASF; 6/147; 4%). Two of the 13 patients were receiving palivizumab for RSV prophylaxis, and 3 received potentially active therapies against RSV during the hospital stay. Viral coinfection was detected in 6 patients, 5 (39%) developed complications, and 4 (31%) required admission to the paediatric intensive care unit. There were no documented RSV-related deaths.
Conclusions: In the group of patients with PID, severe RSV infection requiring hospitalization is more frequent in patients with CID and CIDwASF, in whom special efforts should be made to prevent RSV infection. Further studies are needed to confirm these results.

PALABRAS CLAVE
Infección respiratoria aguda;
Inmunodeficiencia combinada;
Inmunodeficiencia primaria;
Virus respiratorio sincitial

Infecciones por virus respiratorio sincitial que requieren hospitalización en pacientes con inmunodeficiencias primarias

Resumen
Introducción: El objetivo del estudio fue evaluar la incidencia de la hospitalización por infección respiratoria aguda (IRA) grave por virus respiratorio sincitial (VRS) en niños con inmunodeficiencia primaria (IDP) y la gravedad de la IRA causada por VRS (IRA-VRS) en estos pacientes.
Métodos: Estudio transversal ambispectivo multicéntrico a nivel nacional realizado en el período 2011–2017. El estudio se llevó a cabo en 15 hospitales españoles incluyendo a niños que requirieron hospitalización por IRA-VRS.
Resultados: De los 439 pacientes con IDP seguidos en los centros participantes, 13 (3%) fueron ingresados por IRA-VRS. La mediana de edad de los pacientes fue de 1,6 años (rango intercuartílico: 0,5—2,2), y 7 eran varones. Los tipos de IDP asociados con mayor frecuencia a la hospitalización por IRA-VRS fueron la inmunodeficiencia combinada (IDC; 4/71 [6%]) y la IDC con características sindrómicas (IDCCS; 6/147 [4%]). Dos de los 13 pacientes recibían palivizumab para profilaxis frente al VRS, y 3 recibieron terapias potencialmente activas frente al VRS durante la estancia hospitalaria. Se detectó coinfección viral en 6 pacientes, 5 (39%) desarrollaron complicaciones y 4 (31%) requirieron ingreso en la unidad de cuidados intensivos. No se registraron muertes relacionadas con el VRS.
Conclusiones: Dentro de los pacientes con IDP, la necesidad de hospitalización por infección grave por VRS es más frecuente en los pacientes con IDC y IDCC, en los que ha de prestarse una atención especial a la prevención de infección por VRS. Se requieren estudios adicionales para confirmar estos resultados.

Introduction

Respiratory syncytial virus (RSV) is the most common cause of serious respiratory disease in infants and children worldwide. Specific RSV antibodies are detected in 87% of children under 18 months and virtually all children by age 3 years.[1,2] In regions with temperate climate there are annual outbreaks of RSV infection, which is the most common reason for hospital admission in children in the winter months in developed countries.[1–3]

Each year, RSV causes 3.4 million cases of disease severe enough to require hospital admission. Its clinical spectrum encompasses acute respiratory infections (ARIs) of the upper or lower respiratory tract; the lower respiratory tract infections (LRTIs), which include pneumonia and bronchiolitis, are associated with greater morbidity and mortality.[2–4] Furthermore, children that experience severe LRTIs caused by RSV are at greater risk of asthma and recurrent wheezing throughout the lifespan.[5]

Patients with primary immunodeficiencies (PIDs) - currently named as inborn errors of immunity - are very vulnerable to serious and possibly life-threatening ARIs. Respiratory syncytial virus infections tend to be more severe in immunocompromised infants compared to healthy infants, characterised by prolonged viral shedding and development of potentially lethal LRTI.[6] The literature describes severe courses of disease following infection by RSV infections in infants and children with primary and acquired immunodeficiencies, and in-depth studies have been conducted in patients with acquired immunodeficiency due to human immunodeficiency virus (HIV) infection, treated with antineoplastic drugs or under immunosuppressive therapy after solid organ transplantation.[2,7–10] In the case of PIDs, there is a higher risk of hospitalization and an increased mortality

due to RSV in affected patients compared to children with normal immune function.[11,12]

Environmental infection control measures are essential to reduce the spread of RSV during the epidemic season in hospitalized immunocompromised infants. Prophylaxis with palivizumab is recommended in high-risk infants born preterm and in children aged less than 2 years with bronchopulmonary dysplasia or haemodynamically significant congenital heart disease. Although some authors have proposed extending prophylaxis to infants with PID, routine prophylaxis is not recommended at present in this high-risk group.[2,13] In some countries, like Japan, palivizumab is indicated for prophylaxis during the RSV season in immunocompromised children and in children with Down syndrome, and new guidelines on the use of palivizumab in children with acquired immunodeficiency have been published.[14]

Given the potential repercussions of community-acquired infection by RSV in very young children with PIDs, these patients could especially benefit from preventive strategies. However, to estimate the real burden of infection by RSV in patients with PIDs, we need to identify which patients are at high risk of increased morbidity and mortality in association with these infections.

Therefore, the aim of our non-interventional study was to evaluate the frequency of hospital admission due to RSV-related ARI (RSV-ARI admission) in children with PIDs in Spain, and to identify clinical predictors of severity.

Methods

Study design and patients

We conducted a nationwide, multicentre, cross-sectional prospective and retrospective observational study in children with PIDs that required RSV-ARI admission. The study was conducted in 15 hospitals that manage children with PIDs throughout Spain. We obtained authorization from participating institutions and written consent from the parents or legal guardians of the children with PID hospitalized due to RSV infection included in the study. The study was exempted from the need of informed consent in case of deceased patients or patients lost to follow-up before the study started. The study protocol was approved by the competent ethics committees and was classified by the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, Spanish Agency of Medicines and Medical Devices) as non-post-marketing observational study.

The inclusion criteria were age less than 5 years at the time of RSV-ARI admission and previous diagnosis of any of the following PIDs: combined immunodeficiency (CID), combined immunodeficiency with associated or syndromic features (CIDwASF), immune dysregulation, congenital defects of phagocyte number, function, or both (CDPNFs), innate immune defects, or PID under investigation. The rationale for the age criterion was to ensure recruitment of a sample of susceptible patients with PID with immune cell deficiency that had undergone few pharmacological interventions.

We excluded patients with other types of PID based on the International Union of Immunological Societies (IUIS) classification, as these forms are not associated with a higher risk of RSV-ARI admission. Patients with HIV infection, clinically significant congenital heart disease other than DiGeorge syndrome (22q11 deletion) and/or who had participated in a clinical trial or experimental study with drugs in the 3 preceding months were not considered eligible for the study.

Recruitment for the prospective study period started in November 2015, and the last patient visit took place in May 2017. The retrospective study period ranged from October 2011 to April 2015, and the prospective period covered from November 2015 to May 2017. The study protocol adhered to the principles of the Declaration of Helsinki and good clinical practice guidelines.

Objectives

The primary objective of the study was to determine the incidence of RSV-ARI admission. We calculated it as follows: number of children with PID in any of the study groups with at least one RSV-ARI admission/ number of children with PID followed up in participating hospitals in the period under study (October 2011–May 2017).

The secondary objective was to assess the severity of RSV-ARI in every group of patients based on the following variables: length of stay in hospital (days), admission to the paediatric intensive care unit (PICU) and length of stay in the PICU (days), need and duration (days) of oxygen therapy, need and duration (days) of mechanical ventilation, need and duration (days) of life support, associated complications and mortality.

Statistical analysis

We performed a descriptive statistical analysis. We have expressed categorical variables as absolute and relative frequencies (%) unless noted otherwise, and continuous variables are represented as the median and interquartile range (IQR). The statistical analysis was performed with the software SAS® version 9.4.

Sample size calculation

Since we conducted an observational study, we did not establish a null hypothesis for determination of statistical significance or correlations, and therefore it was not necessary to carry out a sample size calculation to achieve a specific statistical power.

Results

Incidence of RSV-ARI admission and patient characteristics

Of the 439 patients with PID followed up at the participating hospitals, 13 (3%) required admission due to RSV-related ARI during the study period (Table 1). One patient was admitted twice due to RSV-related ARI. Infection by RSV was confirmed by indirect immunofluorescence in 8 patients and by reverse transcription polymerase chain reaction (RT-PCR) in the other 5.

Table 1 Rate of hospital admission due to RSV-related acute respiratory infection by primary immunodeficiency type.

PID type	Total patients (*N* = 439)	Hospitalization due to RSV-ARI (*n* = 13)	Total patients with RSV-ARI during stay (*n* = 16[a])
CID	71	4 (6%)	6 (9%)
CIDwASF	147	6 (4%)	6 (4%)
Immune dysregulation	59	1 (2%)	1 (2%)
CDPNF	61	1 (2%)	1 (2%)
Innate immune defects	41	0 (0%)	0 (0%)
PID under study	60	1 (2%)	2 (3%)

ARI, acute respiratory infection; CDP, congenital defects of phagocyte number or function; CID, combined immunodeficiency; CIDwASF, combined immunodeficiency with associated or syndromic features; PID, primary immunodeficiency; RSV, respiratory syncytial virus.

[a] In 3 patients, RSV infection was confirmed during the hospital stay but was not the reason for admission. These 3 patients had nosocomial infections.

Tables 2 and 3 summarise the main characteristics of the patients. The median age was 1.6 years (IQR, 0.5—2.2), and 54% (7/13) were male. Except for 2 children born preterm at 35^{+6} weeks and 36 weeks, respectively, all children were born at term. The median birth weight was 3.2 kg (IQR, 2.7—3.4). Most of children were breastfed (9/13; 69%) and fed formula (10/13; 77%). Only 3 patients (23%) had siblings attending school or a childcare centre.

The types of PID associated with the highest frequency of RSV-ARI admission were CID (4/71; 5.6%) and CIDwASF (6/147; 4%). The incidence of RSV-ARI admission was very similar in the patients with immune dysregulation (1/59; 2%), CDPNF (1/61; 2%) and PID under investigation (1/60; 2%). None of the patients with innate immune defects (0/41) required admission due to RSV-related ARI.

There were also 3 patients with nosocomial infection confirmed by detection of RSV during the hospital stay, but RSV was not the primary reason for admission in these cases (Table 1).

Table 2 Patient characteristics.

Variable	*n* = 13
Age (years), median [IQR]	1.6 [0.5—2.2]
Male sex, *n* (%)	7 (54%)
Birth weight (kg), median [IQR]	3.2 [2.7—3.4]
Weeks of gestation, median [IQR]	39.1 [38.0—40.5]
Breastfeeding, *n* (%)	9 (69%)
Formula feeding, *n* (%)	10 (77%)
Immunodeficiency	
CID, *n* (%)	4 (31%)
CIDwASF, *n* (%)	6 (46%)
Immune dysregulation, *n* (%)	1 (8%)
CDPNF, *n* (%)	1 (8%)
Innate immune defect, *n* (%)	0 (0%)
PID under evaluation, *n* (%)	1 (8%)
Immunoglobulin replacement therapy, *n* (%)	5 (39%)
IgG trough levels (mg/dL), median [IQR]	701.0 [500.3—1284.0]
RSV prophylaxis[a], *n* (%)	2 (15%)
Antibiotic prophylaxis, *n* (%)	7 (54%)
Antiviral prophylaxis, *n* (%)	3 (23%)
Antifungal prophylaxis, *n* (%)	4 (31%)
Immunosuppressive therapy, *n* (%)	4 (31%)
History of respiratory infection, *n* (%)	8 (62%)
Respiratory comorbidities	
Wheezing, *n* (%)	3 (23%)
Anatomical anomalies[b], *n* (%)	1 (8%)
Other comorbidities, *n* (%)	8 (62%)

ARI, Acute respiratory infections; CDPNF, congenital defect of phagocyte number or function; CID, combined immunodeficiency; CIDwASF, combined immunodeficiency with associated or syndromic features; IQR, interquartile range; PID, primary immunodeficiency; RSV, respiratory syncytial virus.

[a] Two patients received prophylaxis with palivizumab.

[b] Tracheomalacia (main bronchus stenosis) and chronic lung disease in a patient with corrected tetralogy of Fallot and pulmonary atresia.

Immunoglobulin replacement therapy and RSV prophylaxis

Five patients (38.5%) received immunoglobulin replacement therapy (IRT) for treatment of PID, 2 during the episode of RSV infection (IgG trough levels, 500.3 mg/dL and 1056 mg/dL, respectively). In the group patients for who this information was available (11/13; 85%), the median IgG trough level was 701.0 mg/dL (IQR, 500.3—1284.0).

Two patients (15.4%) received prophylaxis with palivizumab during the RSV-ARI hospitalization. Three other patients (23.1%) received prophylaxis with palivizumab only in other RSV seasons. The median number of administered doses of palivizumab was 6.0 per patient (IQR, 4.0–12.0). The number of doses to be administered was determined based on the judgment of the clinician: fewer doses were given to patients receiving prophylaxis close to the end of RSV season, and the greatest numbers corresponded to patients that received prophylaxis for 2 consecutive RSV seasons (mainly patients with other comorbidities, such as congenital heart disease and/or pulmonary dysplasia).

Four of the 5 patients that received prophylaxis with palivizumab had a diagnosis of CIDwASF including a congenital heart disease, and 1 patient had PID that was still being evaluated. Overall, 6 patients had congenital heart disease: pulmonary atresia with ventricular septal defect (*n* = 1), tetralogy of Fallot (*n* = 1), corrected tetralogy of Fallot with residual ventricular septal defect (*n* = 1), corrected ventricular septal defect (*n* = 1) and other congenital heart defects (*n* = 2).

Of the 13 patients, 7 (54%) were receiving antibiotic prophylaxis, 3 (23%) antiviral prophylaxis, 4 (31%) antifungal

Table 3 Demographic and clinical characteristics of patients admitted to hospital due to RSV infection.

Patient	Age	Sex	Weeks of gestation	PID	Treatment for PID	Prophylaxis with palivizumab	Hospital LOS	Mechanical ventilation	PICU admission and LOS	Complications during hospitalization	Viral coinfection
1	6 m	M	39	CID	IRT	No	23 d	Yes	Yes, 11 d	Pneumonia	Cytomegalovirus
2	2 y 3 m	F	41	Immune dysregulation	No	No	10 d	No	No	–	Adenovirus
3	7 m	F	41	CIDwASF	No	Yes	6 d	No	No	Bacterial superinfection	–
4	3 m	F	41^{+6}	CIDwASF	No	No	7 d	No	No	–	–
5	2y 2 m	F	35^{+6}	CIDwASF	No	Yes	23 d	Yes	Yes, 5 d	Bacterial superinfection	–
6	1 y 5 m	F	40	CDPNF	No	No	7 d	No	No	–	–
7	1 y 6 m	M	–	CIDwASF	No	No	4 d	No	No	–	Influenza A
8	5 y 1 m	M	38	CIDwASF	No	No	4 d	No	No	–	–
9	1 y 8 m	M	40	CIDwASF	No	No	5 d	No	No	–	–
10	2 y 3 m	M	38	CID	IRTI	No	14 d	No	No	–	Adenovirus
11	4 m	M	39	CID	IRTI	No	101 d	Yes	Yes, 20 d	Pneumonia, apnoea, bacterial superinfection	–
12	4 m	F	39	CID	IRTI	No	57 d	Yes	Yes. -	Pneumonia	Cytomegalovirus, parainfluenza type 3
13	3 y 10 m	M	36	PID under study	IRTI	No	6 d	No	No	–	–

ARI, acute respiratory infection; CDPNF, congenital defects of phagocyte number or function; CID, combined immunodeficiency; CIDwASF, combined immunodeficiency with associated or syndromic features; d, days; F, female; IRT, immunoglobulin replacement therapy; LOS, length of stay; M, male; m, months; PICU, paediatric intensive care unit; PID, primary immunodeficiency; RSV, respiratory syncytial virus; y, years.

prophylaxis and 4 (31%) immunosuppressive drugs during their hospital stay for RSV-related ARI.

Length of stay and treatment

The median length of stay was 8.5 days (IQR, 6.0–23.0). Four patients (30.8%) admitted due to RSV-related ARI were admitted to the PICU during their stay for a median of 11.0 days (IQR, 5.0–20.0).

Of the 13 patients, 9 (69.2%) required oxygen therapy for a median of 5.0 days (IQR, 4.0–15.0), 4 (31%) required mechanical ventilation for a median of 15.0 days (IQR, 10.0–42.0) and 2 (15%) required continuous positive airway pressure. In one patient, there were no records regarding treatment during the hospital stay. One patient (8%) required inotropic support, and none required extracorporeal membrane oxygenation, surfactant therapy or cardiopulmonary resuscitation.

Although the use of ribavirin remains controversial,[15,16] 2 patients (15%) received it: 1 (8%) as monotherapy, and 1 (8%) in combination with palivizumab.

Complications and coinfection

Of the 13 patients, 5 (39%) developed complications during the hospital stay. Pneumonia and bacterial/fungal superinfection each developed in 3 patients (23%). The pathogens isolated in these patients were *Haemophilus influenzae* (*n* = 1; 8%), *Klebsiella* spp, *Staphylococcus aureus* (*n* = 1; 8%), and *Pneumocystis jirovecii* (*n* = 1; 8%). The patient with infection by *Pneumocystis jirovecii* infection had a CID.

Cytomegalovirus coinfection was detected in 2 patients (15%), both with a CID. Other viral coinfections were diagnosed in 4 patients (31%): adenovirus (*n* = 2), influenza A virus (*n* = 1) and parainfluenza virus type 3 (*n* = 1).

One patient that had undergone stem cell transplantation died of sepsis caused by *Pseudomonas aeruginosa*. There were no other deaths.

Discussion

Globally, ARIs remain one of the leading causes of morbidity and mortality in children under 5 years, and human RSV is the viral pathogen identified most frequently in children with ARI. It is estimated that 10% of episodes of RSV infection require hospital admission. Shi et al. estimated an annual rate of hospital admission due to RSV-related ARI of 0.16% (95% confidence interval, 0.1—0.25) in developed countries.[17] In a nationwide survey conducted in Japan, children with PID were 10 times as likely to require admission due to RSV-related ARI (1.6% over a 10-year period, 15 patients out of 910).[18] In our study, the overall incidence of RSV-ARI admission in children with one of the PIDs considered to carry a high-risk of hospitalization was 3.0% in a 5-year period. This was very similar to the frequency reported in other studies, including the one by Domínguez-Pinilla et al., who found an incidence of 6.5% in children under 15 years with acquired or primary immunodeficiency in a 5-year single centre retrospective study in Spain. However, only 1 of those children had a PID (SCID). The remaining 8 children had solid cancer (*n* = 3) or blood cancer (*n* = 5). Although roughly one third of patients in that study received palivizumab, which was consistent with our findings, half of the patients in the study had congenital heart defects.[19]

In our study, the median length of stay was 8.5 days, much lower compared to the median hospital stay in the study from Domínguez-Pinilla et al. (20 days)[17] and in the Japanese nationwide survey of PID patients (10.5 days),[16] but greater than the median length of stay described in children in the general population admitted to hospital due to RSV (3–6.9 days).[20,21]

In a cohort of 406 children hospitalized for RSV infection in the 1999–2007 period, Thorburn et al. observed that pre-existing diseases and comorbidities, including primary immunodeficiencies, were associated with an increased frequency of PICU admission and higher mortality.[9] In a cohort study that included 117 immunocompromised paediatric patients with primary or acquired immunodeficiency and RSV infection carried out between 2006 and 2011, Asner et al. found a frequency of ICU admission greater than 20% and a mortality of 5%.[22] Our findings were similar, as 4 of the patients admitted due to RSV-related ARI in our study (30.8%) required admission to the PICU during their stay, although there were no RSV-related deaths.

Cell-mediated immunity plays a more critical role in the control of most viral infections than antibody-mediated immunity. In this regard, there is evidence that deficiencies in systemic CD4+ and CD8 + T-cell responses may contribute to RSV susceptibility in the elderly, who have lower levels of RSV-specific CD4+ and CD8 + T cells compared to younger adults.[23,24] Immunosuppressive drugs prescribed to solid organ transplant recipients may also have an inhibitory effect on T cells, thus impairing the ability of these patients to clear opportunistic RSV infections, which results in more severe disease.[25] Similarly, haematopoietic stem cell transplant recipients are also at increased risk of severe RSV infection, and peripheral blood lymphopaenia has been identified as a specific risk factor for LRTI by RSV.[26–28] In addition, conventional CD4 + T cells from infants infected by RSV produce low amounts of IL-2, which is required for the effective generation of effector and memory CD8 + T cells.[29,30] In our study, nearly 80% of the patients hospitalized due to RSV-ARI had CID or CIDwASF, both classifications that include cellular immunodeficiencies.

One of the limitations of the study is its design, as we did not collect data on patients with PID that were not hospitalized.

The low incidence of RSV-ARI admission in children with PID also posed a barrier to learning about the risk factors for RSV-ARI. As a result, we were unable to properly pursue the secondary objective of the study, which was to assess RSV-related ARI severity in relation to risk factors previously found to be significantly associated with this disease, such as such as prematurity and low birth weight.[31]

The low admission rate was comparable to the rate observed in late preterm infants, but comorbidities in PID children are quite different.[32,33] In addition, the incidence of RSV-ARI admission in children with PID could be even higher, as children with antibody deficiencies, who were not eligible for this study, could add to the number of RSV-related hospital admissions. However, it should also be taken into account that comorbidities can also contribute to hospitalization and

to development of severe RSV-ARI and, therefore, increased risk of severe disease.

In conclusion, in the group of paediatric patients with PIDs, RSV infection requiring hospital admission is more frequent in patients with CID or CIDwASF. Special attention should be devoted to the prevention of RSV infection in patients with these disorders.

The results of this study suggest that the implementation of measures to prevent nosocomial RSV infections in paediatric patients with PID should be mandatory during epidemic seasons. Further studies are needed to confirm these results.

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Pere Soler-Palacín has no financial relationships relevant to this article to disclose.

Conflicts of interest

AbbVie participated in the study design and implementation, interpretation of the data, and manuscript revision and approval for publication.

Author contributions

Doctors Luis Ignacio González-Granado, Andrea Martin-Nalda and Pere Soler-Palacín conceived and designed the study, participated in data collection, conducted the initial analysis, drafted the initial manuscript and revised the manuscript.

Doctors Laia Alsina, Olaf Neth, Manuel Santamaría and the SENTIR group participated in data collection and in the revision of the manuscript.

All authors approved the final article for submission and agreed to be accountable for all aspects of the work.

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Appendix A. SENTIR group

Luis Ignacio González-Granado, Paediatric Immunodeficiencies Unit, Instituto de Investigación 12 de Octubre, School of Medicine, Universidad Complutense, Madrid, Spain; Andrea Martín-Nalda and Pere Soler-Palacín, Research Group on Infection in Immunocompromised Paediatric Patients, Vall d'Hebron Institut de Recerca (VHIR), Hospital Universitari Vall d'Hebron, Barcelona, Spain; Paediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain; Jeffrey Modell Centre for Primary Immunodeficiencies, Barcelona, Spain; Laia Alsina, Clinical Immunology and Primary Inmunodeficiencies Unit, Department of Paediatric Allergy and Clinical Inmunology, Hospital Sant Joan de Déu, Barcelona, Spain; Universitat de Barcelona, Barcelona, Spain; Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Barcelona, Spain; Olaf Neth, Section of Paediatric Infectious Diseases, Rheumatology and Immunodeficiency, Hospital Infantil Universitario Virgen del Rocío, Seville, Spain; Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain; Manuel Santamaría, Department of Clinical Immunology, Hospital Universitario Reina Sofía, Cordoba, Spain; School of Medicine, Universidad de Córdoba, Cordoba, Spain; María Carmen Carreras Gil de Santivañes, Department of Paediatric Infectious Disease, Hospital Universitario y Politecnico La Fe, Valencia, Spain; Teresa del Rosal, Department of Inpatient Paediatric Care, Infectious and Tropical Diseases, Hospital Universitario La Paz, Madrid, Spain; Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain; María Elena Seoane Reula, Paediatric Immunology and Allergy, Hospital General Universitario Gregorio Marañón, Madrid, Spain; Pilar Llobet Agulló, Paediatrics Unit, Fundació Privada Hospital Asil de Granollers, Barcelona, Spain; Sonia de Arriba, Paediatrics Unit, Hospital Universitario de Salamanca, Salamanca, Spain; Juan Luis Santos, Paediatric Infectious Diseases and Inmunodeficiencies Unit, Hospital Materno-Infantil Virgen de las Nieves, Granada, Spain; José Domingo Moure González, Paediatric Pulmonology and Allergology Unit, Hospital Clínico Universitario de Santiago, A Coruña, Spain; José Tomás Ramos, Department of Public Health and Obstetrics, Universidad Complutense, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain; Joaquín Dueñas Morales, General Pediatrics, Infectious Diseases and Inmunodeficiencies Unit, Department of Paediatrics, Hospital Universitario Son Espases,

Palma de Mallorca, Spain; Instituto de Investigación Sanitaria Illes Balears (IdISBa), Palma de Mallorca, Spain

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