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Respiratory syncytial virus: A new era

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ABSTRACT

Respiratory syncytial virus (RSV) is a major public health problem that has undergone significant changes in recent years. First of all, it has become easier to diagnose with highly reliable and rapidly available confirmatory tests. This has led to a better understanding of its epidemiology and RSV has gone from being a disease of the pediatric age group, severe only in infants and immunosuppressed children, to being a common disease in people of all ages, particularly important in patients of advanced age or with immunosuppressive diseases. Recent therapeutic and prophylactic advances, both with long-lasting monoclonal antibodies and vaccines, are another reason for satisfaction. For these reasons, the COVID and Emerging Pathogens Committee of the Illustrious Official College of Physicians of Madrid (ICOMEM) has considered it pertinent to review this subject in the light of new knowledge and new resources for dealing with this infection. We have formulated a series of questions that we believe will be of interest not only to members of the College but also to any non-expert in this subject, with a particular focus on the situation of RSV infection in Spain.

Keywords: RSV, Respiratory Syncytial Virus, Respiratory Infection, Virus, Pneumonia, Vaccines, Monoclonal Antibodies, Ribavirin, Nirsevimab

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Virus respiratorio sincitial: un nuevo tiempo

RESUMEN

El Virus Respiratorio Sincitial (VRS), es un problema de salud pública de primera magnitud que en años recientes ha experimentado cambios muy importantes. En primer lugar, se ha producido una mayor facilidad diagnóstica con pruebas confirmatorias altamente fiables y rápidamente disponibles. Esto ha permitido conocer mejor su epidemiología y VRS ha pasado de ser una enfermedad de la edad pediátrica, grave sólo en lactantes y niños inmunodeprimidos, a ser una enfermedad común en personas de toda edad, particularmente importante en pacientes de edades avanzadas o con enfermedades que inmunodeprimen. Los avances terapéuticos y profilácticos, recientes, tanto con anticuerpos monoclonales de larga duración como con vacunas, constituyen otro motivo de satisfacción. Por estos motivos, el Comité de COVID y de patógenos emergentes del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) ha considerado pertinente revisar este tema, a la luz de los nuevos conocimientos y de los nuevos recursos para afrontar esta infección. Hemos formulado una serie de preguntas que creemos de interés no sólo para los colegiados si no para cualquier persona no experta en este tema, con una vista particular en la situación de la infección por VRS en España.

Palabras clave: VRS, Virus Respiratorio Sincitial, Infección Respiratoria, Virus, Neumonía, Vacunas, Anticuerpos monoclonales, Ribavirina, Nirsevimab

INTRODUCTION

Respiratory Syncytial Virus (RSV) infection has entered a new era, mainly due to new diagnostic tests, highly reliable and easy to perform. The disease has abandoned the paradigm of being a potentially serious disease only in children under 2 years of age and in immunocompromised patients, to become a disease of any age, potentially more serious in elderly patients, immunocompromised patients and transplanted patients. It is a disease that competes as a cause of hospitalization and death with influenza itself and is a well-recognized cause of admission to Intensive Care Units.

RSV disease can not only be diagnosed but can also be treated specifically in severe patients and, above all, can and should be prevented both with vaccines and with long half-life monoclonal antibodies.

All these changes require a new awareness on the part of physicians and health care professionals in general, as well as a decisive attitudes on the part of the health care authorities, involving significant financial resources.

In view of the above, the COVID and Emerging Pathogens Committee of the Illustrious College of Physicians of Madrid (ICOMEM) has decided to address the issue, asking some questions both to the Committee members and also to experts on the subject from outside the Committee. We offer below the result of these deliberations with a particular focus on the situation in Spain and the position of the Health Authorities.

WHAT ARE THE CHARACTERISTICS OF RESPIRATORY SYNCYTIAL VIRUS? WHAT IS THE SIGNIFICANCE OF ITS DIFFERENT LINEAGES AND ANTIGENIC VARIANTS?

Respiratory syncytial virus (RSV) belongs to the genus Orthopneumovirus of the family Pneumoviridae [1]. It owes its name to its ability to produce syncytia from adjacent cells in the host following infection with the virus. It is an RNA virus with a linear single-stranded genome surrounded by a helical nucleocapsid and this in turn by a lipoprotein envelope giving it a spherical or filamentous appearance. Its genome is relatively simple with 10 genes encoding 11 proteins including non-structural (NS1 and NS2) and structural proteins. Prominent among the latter are the membrane glycoproteins G and F which mediate, respectively, adhesion and fusion to the host respiratory tract epithelial cell surface. Glycoprotein F is also involved in the formation of the characteristic syncytia. Structural proteins are also the matrix protein (M), involved in virus assembly, two nucleocapsid proteins (N and P) and M2-1 and M2-2 proteins, responsible for transcriptional activity and regulation. RSV also presents an RNA-dependent RNA polymerase (L) that regulates transcription and replication of the virus in the cytoplasm of the host cell once penetration has occurred.

The non-structural proteins NS1 and NS2 are the first to be transcribed during infection, interfering with the interferon (TNF) response and other elements of the immune system. They determine immunosuppression and are partly responsible for possible bacterial infections secondary to RSV infection [2]. Both proteins are quite conserved in their amino acid sequence with variations not exceeding 4% and are responsible for host specificity of infection. Glycoprotein G, whose sequence is less conserved, is not [3].

Although there are different genotypes of RSV, from an antigenic point of view, only one type has been described, divided into two subgroups, A and B, which predominate indistinctly during epidemics, with A being the majority in recent years [4]. Although the results are not sufficiently conclusive, subgroup A is associated with more severe disease. However, they are of interest in the knowledge of their epidemiology and possible diagnostic strategies. The advent of whole genome sequencing and sequence alignment has made it possible to discriminate between different genotypes of RSV, with at least 37 genotypes of type B and 13 genotypes of type A [5].

WHAT ARE THE MAIN MECHANISMS OF PATHOGENICITY AND IMMUNITY OF RSV?

After entering the organism through the nasopharyngeal and conjunctival mucosa, the virus descends to the tracheo-bronchial mucosa and bronchioles and finally by extension to the alveolar epithelium. In the bronchial mucosa it has a tropism for the apical cell lines and greater respect for the basal layer and the virions are detected in this location. In the bronchioles is where it induces greater damage, generating a necrotizing bronchiolitis that occludes the bronchiolar lumen with the detritus of necrotized epithelial cells, lymphocytes, and interstitial space compromise. There is alveolar necrosis. Multinucleated epithelial cells with intracytoplasmic eosinophilic inclusion bodies (giant cells or syncytia), as seen in other paramyxovirus infections, are frequently seen.

Necrosis of the larger caliber bronchi is not as radical as that produced by influenza virus, but the involvement of the small airway is the determinant of severity and ventilatory failure. In the bronchial mucosa, RSV has a tropism for apical cells and usually preserves the basal layer. Ulceration may occur and epithelial hyperplasia is seen.

The lung becomes firm and heavy and hyperexpanded or atelectasis areas may be seen [6,7]. This anatomic response correlates radiologically with the finding of multifocal pulmonary infiltrates; multiple interstitial opacities and peribronchial thickening. Although infrequent, RSV can be isolated from other affected organs such as the brain, heart and liver [8].

Bacterial superinfection adds inflammatory components and variations in morphologic and radiologic expression.

RSV conditions a first natural immune response and a specific one generating blocking antibodies against the pre-F (fusion) protein that although they do not prevent reinfections, sometimes even in the same seasonal outbreak, they attenuate them [9].

It appears that the formation of these antibodies is lackluster and the need for repeated infections to achieve pro-

tective levels is postulated [10,11]. Other non-protective antibodies are produced that could serve as a misguided decoy in defense [12].

The protective character of blocking Ac. is demonstrated by the lower severity of primoinfection in the first months of life in those infants with higher antibody levels in cord blood of maternal origin [13,14] although very preterm infants do not achieve protection as maternal antibodies only reach levels in the third trimester [15]. Also protective is a high level of blocking antibodies after primary and subsequent reinfections in both children and adults [16] and finally the increased protection demonstrated by recent monoclonal antibodies in use and assay for prophylaxis, which recognize antigens expressed in the pre-fusion conformation of the F-protein, as well as those induced by already approved vaccines [17-22].

The role of cellular immunity seems transcendent for viral clearance and its effector arm is the IFN-Y-producing CD4+ and CD8+ differentiated T cells that also modulate the inflammatory response and tissue damage [23].

Their role is intuited by the severity of infection in patients with this type of immunosuppression, both genetically acquired [24] and that induced by various disorders. In HIV-infected patients, RSV replication is prolonged for up to months [25], as occurs in the experimental mouse model lacking CD4+ and CD8+ cells [26]. RSV conditions functional alterations of the immune response; it can desensitize macrophages for Toll receptor ligands [21], facilitating for months other infections; it can also hyper-express, in infected epithelial cells, inhibitory molecules such as PD-L1, which decrease T-cell activation [27]. RSV can also alter T-cell differentiation and shift the balance from beneficial Th1 cell stimulation to a proliferative Th2 cell response that enhances the severity of the inflammatory process. It is a finding that was used to try to justify the symptom potentiation seen in previously uninfected children vaccinated with an inactivated virus in the 1960s [25]. The interaction with dendritic cells and their modulatory role in the immune response is another line of study in RSV [28,29]. There are more and more references to genetic polymorphisms of the interaction receptors between the virus and the stimulation target cells and of the proinflammatory molecules involved in and conditioning the response [30].

WHAT DO WE KNOW ABOUT THE EPIDEMIOLOGY OF RSV INFECTION?

RSV leads to seasonal infections that traditionally occur 2 to 8 weeks before the peak of the influenza epidemic. Although during the first year of the COVID-19 pandemic there were virtually no cases of RSV infection, and subsequently there was an atypical peak during the summer of 2021, in the last two seasons (2021-2022 and 2022-2023) seasonal peaks have again occurred during the fall.

Globally, RSV is the leading cause of lower respiratory tract infections in children under one year of age, especially bronchiolitis and pneumonia, and one of the most important in adults over 65 years of age and in people with at-risk conditions. It is also the second leading cause of death worldwide in children under one year of age [31].

In Spain, epidemiological information on RSV comes mainly from the sentinel surveillance system for acute respiratory diseases (SiVIRA), which records especially cases of COVID-9, influenza and RSV. Cases recorded in primary care report the extent of infection, while cases admitted to hospitals and the percentage of them requiring ICU care report their severity. Since there is considerable variability in RSV infection rates between epidemic seasons, the figures presented below should be considered rough estimates, as in the current 2023-2024 season they may change.

According to the latest annual SiVIRA report [32] available at the time of writing, which corresponds to the 2021-2022 season, cumulative RSV infection rates in primary care in children under 5 years of age (approx. 12/1,000 persons) were more than 10 times higher than in adults aged 65 years and older (1/1,000 persons). In total, RSV infections produced approximately one million primary care consultations, of which almost 25% were in children under 5 years of age and almost 10% in those over 65 years of age (thus generating a higher frequency in the latter than the corresponding rate of infection).

Regarding RSV infections in hospitals, weekly RSV hospitalization rates have shown peaks of up to 10 cases/ 100,000 people in recent seasons. Weekly peaks and cumulative hospitalization rates tend to be highest in children under 5 years of age followed by persons 80 years and older. Overall, there were 23,000 hospitalizations for RSV in the 2021-2022 season. Eight to 15% of those hospitalized are admitted to the ICU. Information on case fatality corresponds mainly to older adults, and in those aged 80 and over, case fatality among those hospitalized is 5 to 10% [32].

All of the above indicates that RSV infection is very frequent and translates into a high health care burden in Spain.

Lastly, according to the latest weekly surveillance report on acute respiratory infections (ARI) [33], corresponding to week 46/2023 (November 13-19, 2023), only 1.7% of the 4,207 ARI samples analyzed in primary care since the start of the 2023-2024 season have been positive for RSV; however, in children under one year of age, positivity has been 5% and the percentage of positivity is gradually increasing since the start of the season. As for hospitals, 1,234 samples have been tested for RSV since the beginning of the season, and of these 67 (5.4%) have been positive.

WHAT ARE THE MAIN CLINICAL MANIFESTATIONS OF RSV INFECTION IN CHILDREN?

RSV infection is very common in pediatrics. Almost all children become infected in the first 24 months of life and can also be reinfected [34,35].

The clinical manifestations, complications, sequelae and prognosis of RSV infection depend on the age of the

child at the time of first infection (newborns, infants, children) and whether or not they have associated underlying diseases that conditions greater severity (prematurity, congenital heart disease, pulmonary malformations, hypotonic syndromes, etc). RSV in infancy has three typical forms of presentation: common cold, acute bronchiolitis and apnea pauses [35,36].

In healthy children, after the first 8-12 months of life, acute RSV infection is usually mild, like a common cold affecting the upper respiratory tract (rhinorrhea, cough and fever) and is cured in a few days with symptomatic treatment.

In young children (under 12 months) and infants, the typical presentation is bronchiolitis. The initial RSV infection progresses, affecting the lower respiratory tract and in 2-3 days 25-30% of children develop acute bronchiolitis. The initial picture of rhinitis and cough evolves to continuous cough, progressive increase of respiratory work, intense decay and refusal of food. Clinical signs (tachypnea, tugging, nasal flaring, disseminated wheezing, thoracic hyperinflation, generalized hypoventilation, hypoxemia and cyanosis) and radiological signs (air trapping, areas of consolidation or major complications such as pneumonia and atelectasis) characteristic of severe bronchopulmonary involvement stand out in the examination. The evolution of acute bronchiolitis is unpredictable when the disease begins: most children with acute RSV bronchiolitis, previously healthy and without pulmonary complications, improve in 3-4 days without requiring hospitalization; of those hospitalized, many improve with symptomatic treatment, oxygen therapy, and can be discharged in 2-3 days. On the other hand, 1-3% of the youngest infants (under 6 months, especially under 2 months) and children with underlying conditions usually develop pulmonary complications. They require longer hospitalization, often admission to the pediatric or neonatal ICU for respiratory support and treatment of the respiratory complications they develop (pneumonia, pneumothorax, atelectasis [37] .

In premature infants and infants less than one month old, acute infection may present with minimal respiratory involvement, which makes identification and diagnosis difficult. Neurological involvement predominates, with phases of intense irritability, decay, refusal of food and episodes of apnea and cyanosis, which can be repeated and lethal [37]. Neurologic recovery without sequelae will depend on early diagnosis and specialized medical care.

The highest rates of hospitalization for RSV occur in children 1-2 months of age, although the course of acute RSV infection can be unpredictable, so prevention is important.

Immaturity of the functional component of the respiratory tree and immune system is evident in RSV mortality figures that decline from the first year of life to four years [38]. Immunodeficiencies and comorbidity are very determinant in the severity of infection [35,39,40], although from the clinician's point of view in a large percentage of children the risk factor that has conditioned severe or fatal disease is not evident.

IS CHILDHOOD INFECTION A PREDISPOSING CAUSE OF CHRONIC RESPIRATORY DISEASE IN ADULTS?

In recent years the concept of "exposome" has emerged, understood as the factors that, accompanying the genome from the prenatal period, contribute to the development of chronic lung diseases. RSV, due to its high incidence and functional repercussions in the first months of life, has been related to an increased risk of asthma in children and young people, and with the same conditioning factors, in addition to its infection in adults, to chronic obstructive pulmonary disease (COPD) [41].

The relationship between RSV disease in childhood and asthma is relatively well documented up to adolescence and early adulthood. Some authors report up to a two- to twelvefold higher incidence of asthma in children who have suffered RSV infection in their first months of life [42]. A meta-analysis published in 2014, including 74 studies shows that RSV infection in the first months of life is associated with impaired lung function, recurrent wheezing and asthma into adolescence with greater uncertainty as to what may occur in adulthood [43,44].

The mechanisms by which RSV infection may potentiate the immediate hypersensitivity response characteristic of asthma are multifactorial. First, epithelial damage would increase [45] the absorption of airborne allergens favoring subsequent sensitization. Secondly, the production of specific IgE against RSV may condition an increase in the release of inflammatory mediators by eosinophils and plasma cells in response to subsequent stimuli. In addition, the persistence of inflammatory cells generating cytokines, leukotrienes and intercellular adhesion molecules may induce a persistent inflammatory response characteristic of asthma: a chronic variable inflammatory disease. Finally, presentation of RSV antigens to T lymphocyte subpopulations may elicit a Th2 response in those predisposed subjects [45]. The most recent meta-analysis published in Lancet in 2020, does not confirm an increase in wheezing and asthma episodes during adolescence in those subjects who presented RSV bronchiolitis in the first months of life, and does report a protective effect against this complication in those who underwent immunoprophylaxis [46]. In summary, although there are more studies that support a possible relationship between RSV bronchiolitis in infancy and the subsequent development of asthma, we cannot currently speak of evidence and further research will be necessary.

In relation to COPD, the finding of persistent virus in subjects with COPD without a history of infection and in a clinically stable situation, higher than that found in the general population, has led to a growing interest in the possible relationship between RSV infection in childhood and the development of COPD in adults. There is no doubt that patients with COPD have a higher incidence of infection with higher morbidity and mortality than the population without COPD and with other similar risk factors [47,48]. In these subjects, persistence of RSV is associated with increased inflammato-

ry activity in the small airways with increased IL6, IL 8 and metalloprotease activity which is associated with a greater deterioration of lung function, with a loss of FEV1 around 100 cc/year, much higher than the physiological 30 cc/year [49]. On the other hand, the participation of viral infections and specifically RSV in the first months of life in the origin of COPD has been recognized since the end of the 20th century [50] and has gained momentum over the last few decades, to the extent that very recently a group of experts has proposed a change in the nomenclature and definition of COPD as an inflammatory process of the airway related not only to exposure to tobacco smoke, but also to host factors such as reduced lung development. This structural alteration secondary to bronchiolitis is currently considered the mechanism by which RSV infection in the first months will influence the development of COPD, enhancing the exposure risk factors [51]. Epidemiological studies have been published showing the relationship between childhood infection and COPD or at least altered respiratory function and premature death from chronic respiratory disease, probably the two most important studies have been published this year. The BAMES study, conducted in a population-based cohort of more than 4,000 children born in Sweden, showed very reduced lung function at 26 years of age in those children diagnosed with RSV infection in the first months of life. The study was replicated with the same findings in a second cohort, PIAMA [52]. A second study conducted in Great Britain also with a population-based cohort of 5,362 children recruited at birth in 1946 and from which 3,589 who had reached 26 years of age and had all data available were included for analysis. In this group it was found that the 913 with a history of confirmed lower respiratory tract infection in the first years of age the risk of death from early respiratory disease up to 73 years of age was significantly higher than in those who had not suffered infections [53]. A study has now been initiated from Utrecht, the CLARITY study [54], focused on analyzing the link between RSV and chronic respiratory tract disease to find out why children who had RSV in early childhood would have a higher risk of developing asthma and COPD in the future.

WHAT IS THE IMPORTANCE AND CHARACTERISTICS OF RSV INFECTION IN ADULTS?

Only in the 1980's did the medical community begin to pay attention to the relevance of RSV in the nursing home population [55,56]; since then, interest has also arisen in its prevalence in the community and its risk of complications [57].

Lately, more attention has been paid to RSV in older adults (>65years), highlighting how the impact of this disease is similar to non-pandemic influenza, both in the community and in institutions for the elderly [58], especially the risk is high in patients with congestive heart failure (CHF) and COPD [57]. It has been estimated that RSV infection in the elderly accounts for 10,000 to 14,000 deaths annually in the USA alone [59].

Spanish data [60], have found that a high proportion of non-immunocompromised adult patients, presenting with flu-like symptoms, were RSV positive (8% vs 9% for influenza) with a high rate of elderly patients (>65 years) involved and with significantly higher mortality than influenza A patients (14.7% vrs 6.1%).

A 2017 American review [61] supports these data, stating that RSV could be implicated in 12% of acute respiratory illnesses in older adults requiring medical care, with an admission of 3-6 days and a mortality of 6-8%.

In conclusion, only in recent years, with the advancement of molecular diagnostic systems, has a real picture of the epidemiological situation of RSV in older adults begun to emerge, whereas in the past many cases were considered as influenza, based on clinical suspicion. Currently, RSV morbidity and mortality in older adults in many cases exceeds that of non-pandemic influenza.

Recognition of RSV in the older population as a potential agent of severe disease will likely lead to more diagnostic testing, which will reflect positively on the pursuit of targeted therapy, improved antibiotic stewardship (antibiotic discontinuation when necessary) and appropriate isolation measures in nursing home [62] or hospital settings.

In the young and healthy adult in general RSV disease behaves like a coryza and becomes more transcendent again with immunosenescence that together with cardiopulmonary comorbidity and of course other immunodeficiencies [16,57], brings mortality in elderly admitted for RSV back to percentages of up to 8% [63].

WHAT CHARACTERIZES RSV INFECTION IN THE IMMUNOCOMPROMISED?

RSV is a common infection in transplant patients, with an incidence of 12% in hematopoietic cell transplantation and 16% in adult lung transplantation. Compared to immunocompetent patients, both solid organ and bone marrow transplant patients with RSV infection have a higher morbidity and mortality compared to the general population. In bone marrow transplant patients the mortality of RSV pneumonia can reach 100%, especially when treatment is delayed and in lung transplants, although mortality is lower (10-20%), it can lead to graft dysfunction or bronchiolitis obliterans [64]. The FLUVAC trial showed an increased risk of RSV infection in patients with cancer or immunosuppressive treatment [65].

Signs and symptoms may be different in immunosuppressed patients such as absence of fever or by increased progression to lower respiratory tract infections in patients with hematopoietic cell transplantation, lung transplantation or lymphopenia [66,67].

Since management options for RSV infection are limited, or lack strong clinical evidence, the main measure is its prevention by strict adherence to infection control measures to avoid nosocomial outbreaks, frequent in immunocompromised patients.

WHAT IS THE RISK OF COINFECTIONS IN RSV-INFECTED PATIENTS AND WHICH ARE THE MAIN ONES?

Viral respiratory infections can favor bacterial superinfection due to the damage they cause on respiratory epithelial cells and the increased susceptibility of the host, due to an abnormal innate and adaptive response that increases the expression of cellular molecules that act as bacterial receptors [68]. RSV is no exception and polymicrobial infections are common, especially when pneumonia develops. Therefore, when faced with a poor evolution of the patient with RSV infection, the possibility of bacterial superinfection should be kept in mind in order to initiate specific antibiotic treatment.

In general, the rate of coinfection in hospitalized patients can reach 68% [69]. The most frequently associated pathogens are *Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis* and *Klebsiella pneumoniae* [70] These are associated with increased severity of illness by causing increased risk of pneumonia, increased oxygen requirements, longer lasting mechanical ventilation and increased mortality [71].

In recent years, the use of molecular amplification techniques has made it possible to verify the non-negligible percentage of mixed infections between virus [72]. Harada *et al.* [73] reported that 18% of RSV infections are mixed, while a Spanish study raised them to 40% [72]. The viruses most frequently involved in the literature are rhinoviruses (40%), adenoviruses (20%) and influenza A and B viruses (15%). In general, these viral coinfections do not result in increased severity of the respiratory process. However, some study shows increased severity, need for ICU and mortality in coinfection with influenza viruses [74,75]. On the other hand, viral coinfections with metapneumoviruses showed in a meta-analysis an increased risk of ICU admission and mean length of stay, but no increased need for oxygen, mechanical ventilation or death [76]. Regarding SARS-CoV-2 viral coinfection, especially in children, data from studies differ greatly, giving RSV coinfection rates of between 2%-20% [77,78]. In general, studies show that there is no worse prognosis in these cases of coinfection, although some report a longer hospital stay [79].

WHAT LABORATORY METHODS CAN CONFIRM THE PRESENCE OF RSV?

Laboratory diagnosis of RSV, like that of other respiratory viruses, has changed drastically in recent years. Cell line culture has been abandoned, being maintained only in some reference laboratories or for research purposes. The use of fluorescence microscopy techniques, previously used to confirm the presence of RSV in cell cultures or for direct detection in respiratory samples, is not frequent either. The detection of antibodies has also lost interest. The present routine diagnosis of RSV is based on the application of molecular techniques or on the use of immunochromatography based on the detection of conserved RSV antigens, essentially membrane glycoproteins. The latter have the advantage of being simple to perform and rapid to obtain results (15-20 minutes), but have the limitation of low sensitivity [80].

Currently we have automated molecular techniques or in point-of-care format with a single target or with several targets that also detect other respiratory viruses [81]. Prior to the pandemic it was common to detect in epidemic season of acute respiratory infection simultaneous detection of RSV and influenza [82]. Currently, SARS-CoV-2 has been added, with the study of the three viruses being performed, even if there is suspicion of only one of them based on clinical and epidemiological criteria. The so-called syndromic panels based on molecular techniques and oriented to respiratory infection also often include RSV.

As with SARS-CoV-2 and influenza, the best specimen for RSV detection is nosopharyngeal, although lower respiratory tract specimens can also be used in hospitalized patients, including tracheal aspirates and bronchoalveolar lavage samples [80].

Whole genome sequencing with next-generation platforms are also applied in reference laboratories to gain insight into the dispersion of different RSV genotypes. Phylogeny studies are usually based on the analysis of the gene corresponding to glycoprotein G [83]. From an epidemiological point of view, some authors advocate the use of Sanger sequencing of G-glycoprotein G genes, or SH and M2 proteins.

WHAT IS THE ANTIVIRAL TREATMENT FOR RSV?

The self-limiting nature of RSV infection in previously healthy children makes supportive measures the mainstay of disease management. There is no unanimity regarding the benefits of using specific antiviral drugs. The aim of this treatment would be to alleviate symptoms, decrease the duration and severity of the disease, as well as decrease the risk of transmission [84].

Ribavirin is the most researched and widely used drug for the treatment of RSV infection. It is a broad-spectrum guanosine analogue that inhibits DNA and RNA virus replication. It is marketed in aerosol, oral and intravenous formulations. Clinical trials in children without other health problems have not shown clear benefits. A Cochrane review of placebo-controlled clinical trials of ribavirin concluded that there were no statistically significant differences in mortality, severity of illness, improvement in oxygenation or duration of hospitalization with the use of the drug [85]. These results together with the potential side effects (bronchospams, shortness of breath, rash, headache, vomiting) and inconvenience in administering the aerosol formulation, with the risk of inhalation of the drug by patients and healthcare personnel [86], have led to ribavirin not currently being recommended in previously healthy children acquiring RSV infection.

However, clinical trials with ribavirin in selected populations of children have shown potential benefit. In children undergoing bone marrow transplantation with RSV infection, a randomized trial comparing aerosolized ribavirin (2 g, three

times daily, for 10 days) along with supportive therapy versus supportive therapy alone [87] was conducted. The study showed that ribavirin treatment was associated with a reduction in viral load and in the development of pneumonia.

In patients undergoing lung transplantation, the effect of oral ribavirin has been tested [88], following a loading dose with intravenous ribavirin (52 patients) or an equivalent oral dose (2 patients). Of these, 21 children received oral ribavirin for a median of 11 days. The authors concluded that oral ribavirin was a good alternative to intravenous ribavirin in the treatment of RSV infection after lung transplantation. Similar conclusions were obtained in a meta-analysis and systematic review in patients with hematologic diseases, showing a decrease in mortality [89]. Based on these data, the use of ribavirin should be considered in severely immunosuppressed children with RSV infection. All studies show that early administration improves outcomes.

In addition to ribavirin, other options have been tested as specific treatment for RSV infection, including palivizumab [90], motavizumab [91] and RSV-specific immunoglobulin [92]. In no case have any of these drugs been shown to have benefit.

Clinical trials are currently underway with other antivirals, replication inhibitors or virus fusion inhibitors, such as RV521 and AK0529 (ziresovir), among others. Only ALN-RSV01 and presatovir have completed their study in transplanted populations without favorable results. The guidelines for the management of patients with hematopoietic and solid organ transplants do not establish specific recommendations in these populations.

WHAT IS THE ROLE OF LONG HALF-LIFE MONOCLONAL ANTIBODIES? NIRSEVIMAB

In recent years, new prevention strategies against RSV have been developed. In the case of infants, due to the limitations of active immunization (vaccines), new passive immunization alternatives have been developed to prevent RSV infection: Long half-life monoclonal antibodies and maternal vaccination.

Monoclonal antibodies. In the 1990s, the first monoclonal antibody against RSV, palivizumab, was developed and demonstrated that high titers of monoclonal antibodies reduced the severity of RSV infection. This monoclonal antibody was successfully administered for decades, but only to high-risk groups for this infection (premature infants, infants with congenital heart disease and infants with bronchopulmonary dysplasia). Its selective administration to certain groups, intramuscularly in five consecutive doses during the months of the epidemic, and its high cost, have limited its availability for administration to all infants [93,94].

We now have a new generation of monoclonal antibodies with a prolonged half-life due to the introduction of a YTE mutation in the FC region of the antibody. Their potency is higher than palivizumab because they are directed against epitopes located in the pre-fusion region of the RSV surface F protein [93].

Nirsevimab is an extended half-life monoclonal antibody directed against the Ø site on the pre-fusion form of the F-protein that has been shown to be safe and effective in the prevention of RSV infection in infants. This prolonged half-life provides adequate serum concentrations for at least 150 days, allowing a single dose of this antibody to be able to protect throughout the RSV season [93].

This monoclonal antibody would be indicated in all infants less than 6 months of age, all infants born during the RSV season, and all at-risk children in the first 24 months of life. Efficacy and safety results of nirsevimab demonstrate in the Melody study, conducted in late preterm (>35 weeks gestational age) and term infants, that a single dose of nirsevimab is associated with a 76.4% reduction in RSV lower respiratory tract infection requiring medical attention and a 76.8% reduction in RSV hospitalizations during the 150-day follow-up period [18,19]. Subsequently, a real-life study (Harmonie study) enrolling over 8,000 infants both term and preterm infants older than 29 weeks gestational age has been conducted comparing a no intervention group with a group receiving a dose of nirsevimab and demonstrating an 83.2% decrease in RSV hospitalizations and a 75.7% decrease in very severe forms of infection [95]. Regarding the safety profile of this antibody, few side effects have been documented and generally local at the injection site. Nirsevimab is currently authorized by the EMA and its administration has been initiated in Spain since the end of September 2023.

Clesrovimab is another monoclonal antibody with a prolonged half-life, targeting the IV site present in both configurational forms of RSV F protein, this antibody is currently in phase III research with very preliminary efficacy results but similar to nirsevimab [93].

Maternal vaccination. Maternal vaccination to protect newborns and infants against infectious diseases from birth is a safe and well-established strategy, especially in cases of whooping cough, influenza and COVID-19. Recently, the European Medicines Agency (EMA) has licensed the bivalent pre-fusion A and B vaccine in pregnant women to prevent RSV infection in newborns and up to 6 months of age, although it is not yet available this season [96,97]. This vaccine has shown good immunogenicity results and good transplacental passage of antibodies. Recently, the results of the Matisse study conducted in pregnant women between 18 and 49 years of age, who received RSV vaccine or placebo in the second or third trimester of gestation, have been published, showing a reduction of 81.8% of severe RSV infections in infants during the first 90 days of life, and 69.4% during the 6 months of follow-up, as well as a reduction of hospital admissions due to RSV of 67.7% in infants in the first three months of life and 56.8% at 6 months after birth. The safety profile of this vaccine is good with few side effects and no increase in prematurity according to results published so far [22,96-98].

WHAT IS THE OUTLOOK FOR AN RSV VACCINE FOR CHILDREN?

Efforts to develop a vaccine or immunoprophylaxis against RSV remain very active [98]. As mentioned above, Nirsevimab (Beyfortus® AstraZeneca/Sanofi) and Abrysvo® (bivalent PreF-VRS, Pfizer), are the first immunizing agents available to prevent pediatric RSV infection; although it should be noted that Abrysvo® is indicated for passive immunization of infants by maternal administration, at women who are 32-36 weeks pregnant during RSV season [99].

We will now focus on the different types of vaccines in development against RSV, including: mRNA-based vaccines, subunit and particulate vaccines, live attenuated or chimeric vaccines, and recombinant vector-based vaccines.

During the period of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, mRNA vaccines were manufactured and licensed for commercial use within a short period of time, which was a source of adverse event (AE) information through large-scale pharmacovigilance; moreover, high levels of immunity induction can be achieved without invading the recipient genome, providing a good safety profile [100].

Subunit vaccines are manufactured with the addition of adjuvants to enhance antigen presentation to host cells and enhance host responses. This category is not preferred for RSV vaccine development in the pediatric population due to the potential for development of severe respiratory disease (RDE). Several subunit vaccine candidates are based on the F protein [101].

Live attenuated vaccines represent an appropriate candidate for the pediatric population not exposed to RSV because the association with the development of GERD is weak, and they provide a painless method of vaccination, due to administration.

Chimeric vaccines include attenuated viruses of a related pathogen modified to express specific genes of the virus of interest. Two chimeric vaccines under development for RSV are the rBCG-N-hRSV and SeV/RSV [98] vaccines. Subunit vaccines consist of purified fragments of the desired pathogen, which can be peptides, proteins or polysaccharides, lacking the entire pathogen genome, resulting in a non-virulent vaccine with a higher level of vaccine safety, but have been ruled out for development in the pediatric population [102].

In recombinant vector-based vaccines, their production mechanism consists of modifying viruses by adding the desired genetic information to them. As a result, the gene is expressed and the protein is produced using the virus as a transport system [103]; unfortunately, in March 2023, Jansen announced the suspension of his phase III clinical trial (EVERGREEN). There are currently two clinical trials in pediatric population (NCT03303625 and NCT03606512) Phase I/II with Ad26.RSV.preF, a vaccine using replication-defective Adenovirus26 as a vector, modified to express the RSV F protein of RSV-A2 strain.

In conclusion, we do not yet have a specific vaccine for commercial use in the pediatric population.

WHAT IS THE STATUS OF RSV VACCINES IN ADULTS?

The population aged 60 years or older, adults with chronic heart or lung disease, diabetes mellitus, chronic kidney disease, immunocompromised, frail persons, or those residing in nursing homes are at increased risk of hospitalization and severe RSV disease [104-106].

There are currently four phase 3 studies of vaccines against RSV in the adult population, all of which are based on the F protein in its prefusion (preF) conformation. The evidence of efficacy of these vaccines comes from randomized, double-blind, placebo-controlled clinical trials in immunocompetent patients aged ≥60 years. So far three of them have already published results:

1. RSVPreF3 OA vaccine (Arexvy®) is a combination of an RSVPreF3 antigen (120 µg) of RSV F protein and an AS01E adjuvant system. The Arexvy® vaccine significantly reduced by 82.6 % (96.95% CI: 57.9- 94.1%) the risk of developing RSV-associated lower respiratory tract disease (LRTD) diagnosed by PCR and by 94.1 % (95 % CI: 62.4 to 99.9) against severe RSV-associated LRTD over one season (median follow-up 6.7 months) [107]. Vaccine efficacy was similar against RSV subtypes A and B and was consistently high among participants aged 70-79 years (93.8%), pre-fragile persons (92.9%), and those with coexisting conditions (94.6%) [107]. This study will remain active for 2 seasons to test the effect of revaccination.

2. RSVpreF vaccine (Abrysvo®) is an adjuvant-free bivalent vaccine with 60 µg of RSV A strain and 60 µg of RSV B strain. Efficacy in preventing RSV-confirmed LRTD with at least two symptoms was 66.7% and 85.7% in LRTD with at least three signs or symptoms, over one season (mean duration of surveillance was 7 months) [108]. The study was not powered to estimate efficacy against severe forms of infection.

3. The mRNA-1345 vaccine is based on mRNA encoding a stabilized pre-F. In January 2023 the manufacturing company reported the results of the pivotal trial (NCT05127434). The vaccine achieved efficacy against the risk of developing RSV-associated LRT) defined by two or more symptoms of 83.7% and 82.4% when defined by three or more symptoms [109]. The trial is ongoing and additional efficacy analyses are planned as the caseload increases, including for severe RSV.

In all studies the profile of a reactogenicity and safety profile were acceptable, with no apparent severe safety issues [108,109].

In May 2023 the FDA approved the first vaccines for the prevention of RSV-associated lower respiratory tract disease in adults ≥60 years (RSVPreF3 and RSVpreF) [110]. Subsequently, the CDC's Advisory Committee on Immunization Practices (ACIP) issued a report in favor of recommending vaccination for adults ≥60 years, through shared clinical decision making [110].

The European Medicines Agency (EMA) authorized EU-wide marketing for prescription use of RSVPreF3 vaccine on June 6, 2023 [111] and on August 23, 2023 RSVpreF vaccine [112].

On April 26, 2023 the EMA recommended marketing authorization for Arexvy vaccine for the prevention of RSV infections in persons ≥ 60 years [111].

Despite the positive clinical results of RSV vaccines for older adults, the cost-effectiveness of implementing an RSV vaccination program in this population group has not yet been examined. In a study designed to evaluate the potential cost-effectiveness of a single dose of two RSV 8 vaccines (RSVPreF3 and RSVpreF) in adults ≥ 60 years in Hong Kong over a 2-year period, this strategy appears to increase quality-adjusted life-years (QALYs) by reducing RSV-associated events [112]. In an economic analysis of the potential cost-effectiveness of RSV vaccines in adults, conducted by the Institute for Healthcare Policy and Innovation (IHPI) at the University of Michigan and presented to the CDC's Advisory Committee on Immunization Practices (ACIP), estimated that if 20% of US adults ≥ 65 years were vaccinated with one of the 2 FDA-licensed vaccines (RSVPreF3 and RSVpreF), more than 220. 000 outpatient visits, 26,000 emergency department visits, 22,000 hospitalizations, and 1,100 RSV-related deaths over a 1-year span and would mean spending between $100,000 and $150,000 per QALY [113]. However, although this study suggests that vaccines could potentially be cost-effective, this cost-effectiveness depends on a variety of factors such as vaccine price, RSV attack rate, and vaccine efficacy and duration. At this time, we do not have an analysis of the health and economic impact of these vaccines in the Spanish population.

WHAT ARE THE PLANS OF THE SPANISH HEALTH ADMINISTRATION TO COMBAT RSV IN CHILDREN AND ADULTS? WHAT IS THE SITUATION IN THE DIFFERENT AUTONOMOUS COMMUNITIES?

As of November 2013, the Spanish health administration does not have a defined strategy to combat RSV for the entire population, and RSV is not included in the list of preventable infectious diseases [114]. The latest update on RSV on the Carlos III Institute of Health website is July 2022 [115], in a link that lacks content related to this virus, although it provides access to the reports of the surveillance system for influenza and other respiratory viruses for the 2020-21 season.

In July 2023, the Vaccination Program and Registry Committee issued a report on recommendations for the use of nirsevimab against respiratory syncytial virus for the 2023-2024 season [116]. This document indicates a passive immunization plan limited to the 2023-24 campaign, in which, in order of priority, immunization is recommended for the following population groups:

Infant population at high risk of severe RSV disease:

(a) preterm infants with a gestational age <35 weeks (administration of a single dose before 12 months of age.

(b) patients with cyanosing or non-cyanosing congenital heart disease with significant hemodynamic involvement

(c) patients with bronchopulmonary dysplasia

(d) patients with other underlying pathologies that pose a high risk for severe RSV bronchiolitis.

In patients with risk conditions b, c and d, nirsevimab will be administered prior to each RSV season before reaching 24 months of age at the time of immunization.

Children younger than 6 months of age at the start of or during the RSV season, born on or after April 1, 2023, through March 31, 2024. Those born during the season will be prioritized for immunization and those born previously will be immunized as soon as possible (October).

The document indicates that efforts should be made to immunize the majority of the target population in October, at the beginning of the RSV season. Those born during the season (October - March) should receive nirsevimab very early, preferably within 48 hours of birth, due to the increased severity of RSV disease in the first days of life.

The document indicates the desire to be able to establish other prevention strategies shortly, citing in particular vaccines for pregnant women.

This recommendation has been transcribed in the different autonomous communities, with minor variations in the calendars.

WHAT DO WE KNOW ABOUT THE CONSUMPTION OF RESOURCES MOTIVATED BY RSV OUTSIDE AND INSIDE SPAIN?

Globally, based on modeling by the RESCEU project (REspiratory Syncytial virus Consortium in EUrope) [34], it was estimated that in 2019, there were 33·0 million RSV-associated acute lower respiratory infection episodes, 3·6 million RSV-associated acute lower respiratory infection hospital admissions, 26 300 RSV-associated acute lower respiratory infection in-hospital deaths, and 101,400 RSV-attributable overall deaths in children aged 0-60 months.

Within this population, both hospitalizations and deaths were more frequent in children under 6 months of age. In this regard, the elderly are the other age group associated with a higher risk of severe RSV disease (immunosenescence, comorbidities, institutionalization). Thus, each year RSV causes more than 5.2 million cases, 470,000 hospitalizations and 33,000 deaths in those over 65 years of age in industrialized countries worldwide [117,118].

The US Centers for Disease Control and Prevention (CDC) [119] estimates that in children under 5 years of age, RSV results in 2.1 million outpatient (non-hospital) visits, 58,000-80,000 hospitalizations, and 100-300 deaths, with a direct healthcare cost of all RSV-related cases estimated at $652 million per year and an associated hospitalization cost per child of $4,584. In elderly people living in the community, RSV infection affects 2-10%, rising to 5-10% of those living in resi-

dences, with some 60,000-160,000 hospitalizations and 6,000-10,000 deaths, figures already higher than in children.

In Spain, the data show the significant burden of care and the cost of RSV infection in both primary care and hospitals [33,116,120]:

- The highest number of hospitalizations due to RSV was observed in children under 1 year of age followed by the 80 and over age group, with 38% (12,422 hospitalizations) and 23% (7,618 hospitalizations) with respect to total hospitalizations in both age groups, respectively. This resulted in an estimated average annual cost of 87.1 million euros.
- On average, children under 1 year of age requiring a health visit had an average of 9.4 visits to primary care, 1.4 to specialty care, 2.4 to the emergency department and one hospitalization. Each specific case of RSV would thus have a direct health care cost of 3,362 euros in the first year of life (72.9% for hospitalizations) and 3,252 euros in the second year (72.1%) [120].
- Although the hospital burden is responsible for the greatest economic expenditure, the specific care burden of primary care is responsible for causing its "collapse" in seasonal periods. As previously stated [33] RSV produced in the 2022-23 season approximately one million primary care consultations, of which almost 25% were in children under 5 years of age and almost 10% in those over 65 years of age (higher than the corresponding figure for the influenza virus). In costs [121] among children born prematurely, this translates into an average calculated expenditure of 525 € per PC visit, 300 € per visit to the Emergency Department and 102 € per visit to a specialist. Among children with risk factors, the calculated costs were 430 € per PC visit, 409 € per visit to the emergency department and 108 € per visit to the specialist.

In summary, according to the parameters established by the WHO in terms of frequency, rate of spread, ICU patients, case fatality, burden of disease and cost, RSV infection should be considered a priority public health problem based on current resource consumption data [121-123] in two extreme populations of life, children under 5 years of age, especially those under 1 year of age, and adults over 65 years of age, especially those over 80 years of age.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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