Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
doi:10.37201/req/006.2024

Iván Sanz-Muñoz[1,2,3]
Laura Sánchez-de Prada[1]
Javier Castrodeza-Sanz[1,4]
José M Eiros[1,3,5,6]

Microbiological and epidemiological features of respiratory syncytial virus

[1]National Influenza Centre, Valladolid, Spain
[2]Instituto de Estudios de Ciencias de la Salud de Castilla y León, ICSCYL, Soria, Spain
[3]Centro de Investigación Biomédica en Red de Enfermedades Infecciosas (CIBERINFECC), Spain
[4]Preventive Medicine and Public Health Unit, Hospital Clínico Universitario de Valladolid, Spain
[5]Microbiology Unit, Hospital Universitario Río Hortega, Valladolid, Spain
[6]Microbiology Unit, Hospital Clínico Universitario de Valladolid, Spain

Article history
Received: 10 January 2024; Revision Requested: 8 February 2024; Revision Received: 9 February 2024; Accepted: 23 February 2024; Published: 21 March 2024

ABSTRACT

The properties of the main surface proteins and the viral cycle of the respiratory syncytial virus (RSV) make it an attractive pathogen from the perspective of microbiology. The virus gets its name from the manner it infects cells, which enables it to produce syncytia, which allow the virus' genetic material to move across cells without having to release viral offspring to the cellular exterior, reducing immune system identification. This causes a disease with a high impact in both children and adults over 60, which has sparked the development of several preventive interventions based on vaccines and monoclonal antibodies for both age groups. The epidemiological characteristics of this virus, which circulates in epidemics throughout the coldest months of the year and exhibits a marked genetic and antigenic drift due to its high mutation capability, must be taken into consideration while using these preventive methods. The most important microbiological and epidemiological elements of RSV are covered in this study, along with how they have affected the creation of preventive medications and their use in the future.

Keywords: Respiratory syncytial virus; F protein; microbiology; epidemiology

Características microbiológicas y epidemiológicas del virus respiratorio sincitial

RESUMEN

Las características de las principales proteínas de superficie y el ciclo vírico del virus respiratorio sincitial (VRS) lo convierten en un patógeno atractivo desde el punto de vista de la microbiología. El virus debe su nombre a la forma en que infecta las células, lo que le permite producir sincicios, que permiten que el material genético del virus se desplace a través de las células sin tener que liberar descendientes virales al exterior celular, lo que reduce la identificación por parte del sistema inmunitario. Esto provoca una enfermedad con un alto impacto tanto en niños como en adultos mayores de 60 años, lo que ha motivado el desarrollo de diversas intervenciones preventivas basadas en vacunas y anticuerpos monoclonales para ambos grupos de edad. Las características epidemiológicas de este virus, que circula en epidemias durante los meses más fríos del año y presenta una marcada deriva genética y antigénica debido a su alta capacidad de mutación, deben ser tenidas en cuenta a la hora de utilizar y diseñar estos métodos preventivos. En esta revisión se abordan los elementos microbiológicos y epidemiológicos más importantes del VRS, así como la forma en que han afectado a la creación de medicamentos preventivos y a su uso en el futuro.

Palabras clave: Virus respiratorio sincitial; proteína F; microbiología; epidemiología

INTRODUCTION

After COVID-19 pandemic, there has been a surge of interest in virology, particularly in microbes that have a significant impact on human health but have previously gone unnoticed. One of these is respiratory syncytial virus (RSV), which generates annual epidemics primarily in infants but also has a significant influence on the elderly's health.

Before pandemic, multiple product concepts for RSV prevention in various age groups were in development. Among the prophylactic approaches available were monoclonal antibodies for passive immunization and vaccinations for children and people >60 years. This, combined with the inclusion of this virus in most surveillance systems globally, particularly in Europe, illustrates the high level of interest in this pathogen and the burden of disease it causes.

Correspondence:
Dr. Iván Sanz-Muñoz
National Influenza Centre, Valladolid, Spain
Calle Rondilla de Santa Teresa s/n, Edificio Rondilla, Hospital Clínico Universitario de Valladolid, Valladolid, Spain
E-mail: isanzm@saludcastillayleon.es

It is vital to have quality knowledge on the microbiological features of RSV, as well as the aspects involved in its seasonality and form of circulation, in order to understand the details of their use and the reasons for their use. As a result, we propose this narrative review focused on the virological features and an examination of the available RSV epidemiology data.

VIROLOGICAL FEATURES OF RSV

History of their discovery. RSV was first described in 1956 [1], but it was not until much later that it was linked to the respiratory disease it produces in humans [2]. In fact, the virus was discovered in a group of 14 chimps suffering from the common cold, and a virus was isolated from them that the researchers termed CCA, or "Chimpanze Coryza Agent" [3,4]. Antibodies were found in all convalescent animals, implying that the attack rate was 100% [5]. Furthermore, one of the animal caregivers had an acute respiratory infection and a detectable antibody response to this novel virus, but unlike the animals, the etiologic agent could not be identified in the respiratory samples. The pathogenicity of the CCA virus was demonstrated by re-inoculating the isolated virus in healthy chimps, who acquired the sickness three days later.

Subsequently, it was revealed that this same infectious agent caused respiratory illness in children, and that many of them had neutralizing antibodies against it, therefore the virus was named Respiratory Syncytial Virus [2] owing to the behavior it displayed in cell cultures. As 80% of 4-year-olds had antibodies against RSV, this led to the conclusion that CCA was a human virus that infrequently affected other primates [6]. The researchers Chanock and Finberg [6] found two distinct viruses in respiratory samples from children with bronchopneumonia and laryngotracheobronchitis, designating them "Long strain" and "Snyder strain," respectively. When it was discovered that the Long strain, as well as the Snyder and CCA strains, exhibited a very similar respiratory pathology, they were merged into a single group, Respiratory Syncytial Virus, as further papers describing this disease arose.

Classification and virological features of RSV. RSV is a virus belonging to the genus *Orthopneumovirus*, family *Pneumoviridae*, order Mononegavirales [7,8], and their species denomination is *Human orthopneumovirus* or *Orthopneumovirus hominis*. This family contains RSV as well as other viruses that affect various animals, such as bovine and murine RSV [7,9–11]. The other genus in the family *Pneumoviridae* that affects also human being is *Metapneumovirus*, which has only one representative, the human Metapneumovirus (hMPV) [2], which was initially reported in the Netherlands in 2001 [12].

RSV has a dual morphology, sometimes spherical with a diameter of roughly 100-350 nm and occasionally filamentous with a diameter of 60-200 nm [13]. In reality, when cultivated in cells, its filamentous form is common, with many of the virions remaining attached to the infected cell and not being released until certain procedures are used.

The genetic material is made up of single-stranded, unsegmented, negatively polarized RNA [14], which is made up of 15,000 nucleotides. The RSV genome is organized into 10 genes and 11 ORFs (Open Reading Frames) encoding 11 structural and non-structural proteins, NS1, NS2, N, P, M, SH, G, F, M2-1 & M2-2 (encoded by two ORFs) and L [15,16] (Figure 1) (Table 1). The genetic material is surrounded by many proteins, includ-

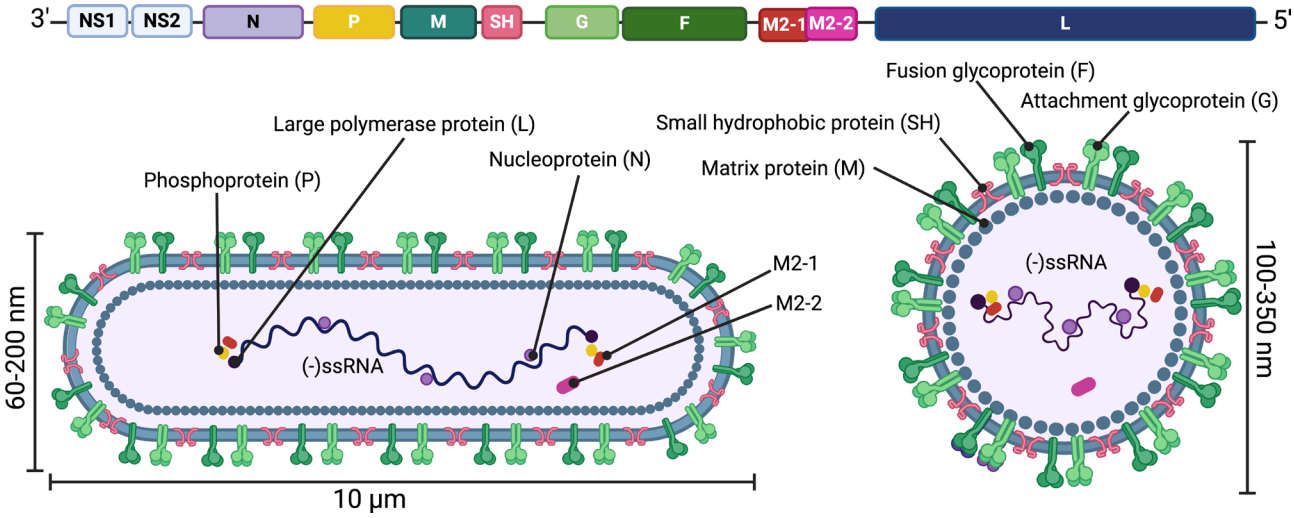

Figure 1 Morphological features of the Respiratory Syncytial Virus and genomic organization and structure of genes. On the left site, filamentous form and on the right site spherical form. M2-1 and M2-2 are represented inside the virion but are not present in nature because they are non-structural proteins. M2-1 and M2-2 genes are overlapped because they pertain to the same gene but are translated by different ORFs (Open Reading Frames). Created with BioRender.com.

Tabla 1 **Features of the genes and proteins composing the RSV genome. Modified from Collins *et al.* [17].**

Protein	Length nucleotides	Length aminoacids	Type	Location	Function
G	923	298	Structural	Lipid envelope	Attachment
F	1903	574	Structural	Lipid envelope	Fusion/attachment
SH	410	64	Structural	Lipid envelope	Viroporin/ion channel
M	958	256	Structural	Inner envelope face	Assembly
N	1203	391	Structural	Ribonucleocapsid	RNA-binding
P	914	241	Structural	Ribonucleocapsid	Phosphoprotein
L	6578	2165	Structural	Ribonucleocapsid	Polymerase
M2-1	961	194	Nonstructural	Ribonucleocapsid	Transcription processivity factor
M2-2	961	90	Nonstructural	Not present in virion	Transcription RNA replication
NS1	532	139	Nonstructural	Not present in virion	Inhibit type I IFN induction and signaling, inhibit apoptosis
NS2	503	124	Nonstructural	Not present in virion	Inhibit type I IFN induction and signaling, inhibit apoptosis

ing nucleoprotein (N), phosphoprotein (P), and RNA-dependent polymerase (L), which are involved in the encapsulation of the virion RNA to create the ribonucleoprotein (RNP) complex, which is part of the viral replication machinery. Furthermore, M2-1 and M2-2 proteins proceed from the same gene expressing two different proteins by two different ORFs. M2-1 protein is an enzyme that increases RNA transcription processivity, and M2-2 has regulatory activities in RNA replication and transcription [17]. The M, or matrix protein, is found beneath the virus membrane and is in charge of viral structural integrity, as well as mechanisms associated to virion production and virus outward "budding."

RSV contains three distinct membrane glycoproteins. Protein G is a cell adhesion protein with the primary function of anchoring to the host cell membrane. The F protein is involved in the fusion of the cytoplasmic membrane of the host cell and the viral membrane. The SH (Short Hydrophobic) protein generates an ion channel that is required for virion internalization into the cell. RSV contains two extra proteins that are not found in other paramyxoviruses. These are the non-structural NS1 and NS2 proteins, which have roles linked to interferon production inhibition, cell signaling limiting, and apoptosis inhibition [17].

To protect themselves from enzymatic destruction, to be recognized by cellular translation mechanisms [18], and to escape identification by certain immune system elements [19], the mRNAs that give rise to these proteins are methylated at the 5' end and have polyA tails at the 3' end. Except for the M2 gene, which has two separate ORFs producing M2-1 and M2-2 proteins, the genetic material is arranged from 3' to 5', and each gene expresses its matching mRNA. The genome starts at 3' with an extragenic area of 44 nucleotides before the NS1 gene and ends with another extragenic region of 155 nucleotides after the L gene. The first nine genes are separated by a brief spacer of 1-58 nucleotides that has no known function and varies between virus genotypes.

Functions of G, F and SH proteins. Antigenic sites and their importance for disease prevention. RSV surface glycoproteins G and F are the most important. These two proteins are responsible for virus adherence to the host cell and virion internalization within the cell, and therefore for the virus's infectious process.

Protein G is an approximately 80 kDa heavily glycosylated protein. Depending on the serotype, it has approximately 298 amino acids. It has so many carbohydrate groups connected to the protein that the glycosylated portion accounts for 60% of the total protein weight [20]. Its primary purpose is to keep RSV attached to the host cell. The action of this protein is known from trials in which RSV adherence to HeLa cells was reduced using specific antibodies against the G protein, demonstrating that the function of this protein was cell adhesion [21]. However, this protein serves other purposes. It plays a role in both the inflammatory response and immunological evasion. G protein may mimic some cellular receptors and be responsible for some inhibitory effects, such as those caused by TNF-α [22]. As a result, future vaccines directed against this immunogenic protein should help to minimize illness by lowering virus-induced inflammation as well as viral replication [23,24].

The F protein (fusion protein) is a 574-amino acid transmembrane protein [25]. It is synthesized in its inactive state (F0) and is surrounded by strain-dependent glycans. F protein is made up of three F0 monomers (trimer). This inactive protein is cleaved by furin-like proteases [26], resulting in the formation of two protein subunits, F1 and F2, which are covalently connected by disulfide bridges [27], activating the F protein to its post-fusion state [20]. The hydrophobic fusion peptide is buried in a central cavity of the protein in the pre-fusion state

(F0), and the protein undergoes a conformational change that results in a new folding of the protein that allows insertion of the fusion peptide into the host cell membrane by a currently unknown mechanism [28]. This permits the viral and host cell membranes to gradually approach each other [29], resulting in membrane fusion and internalization of the virion and its genetic material for starting of the viral replication cycle. Specific antibodies against the F protein have been found to impede membrane fusion and thereby prevent infection and its severity [30]. Furthermore, some researchers believe that the F protein can facilitate cell adhesion and fusion in the absence of G and SH proteins, making it one of the most important targets for vaccination [31].

The F protein's membrane-fusion function is responsible not only for virion internalization but also for syncytium formation, which is characteristic of RSV disease and pathogenesis. During the viral replication cycle, the F protein is produced in infected cells and subsequently localized in the cell membrane, where it binds to other neighboring cells and causes them to fuse [32]. As a result, syncytia form, which are multicellular and multinucleated formations without continuity dissolution, allowing the passage of the virus's genetic material from one cell to another without the need to leave the cell [33], favoring transmission and avoiding, at some extent, immune system activity. This pathway is required for RSV pathogenesis and cytotoxicity. This syncytium-forming impact is also seen in other viral diseases such as measles [34], HIV, herpes simplex virus, and, in rare circumstances, SARS-CoV-2 [35,36].

The virus interacts with the host cell via a variety of receptors. The G protein, for example, binds to CX3CR1 and HSPG (heparan sulfate proteoglycans) receptors, whereas the F protein interacts with nucleolin receptors, EGFR (Epidermal growth factor), IGF1R (Insulin-like growth factor-1 receptor), and ICAM-1 (Intercellular molecular adhesion-1) [14,20].

Finally, the SH protein is an integral membrane protein of 64-65 amino acids that is very phylogenetically conserved [37]. The SH protein acts as an ion channel to permeabilize the membrane of the infected cell. It is also involved in the prevention of apoptosis in infected cells.

Evolution/mutation rate. Genetic variability, viral evolution, immune escape and impact on reinfections. RSV is formed by two distinct subtypes, A and B, that differ fundamentally by antigenic and genetic drift of the virus, which happens mostly through the G protein but also in the other viral proteins at less extent [10]. These two subtypes were initially described based on reactivity to monoclonal antibodies [38], but it was later discovered that the differences between them were more complex, and were based, as previously noted, on the existing variety in the sequence of their different genes. There are several genotypes within subtypes A and B in this sense, but there is no agreement on their nomenclature and characterization [39,40]. In fact, this evolutionary process, which involves the introduction of new genotypes into populations where others were previously circulating and the extinction of the latter [40], is very similar to the seasonal dynamics of other respiratory viruses such as influenza and, more recently, SARS-CoV-2, which involves the continuous emergence of new variants, the introduction of the same and new populations, and the extinction of the previous ones [41].

RSV's mutation rate, like that of other RNA viruses, is significant, resulting in constant genetic and antigenic drift with repercussions for humans. RSV, like influenza viruses, is very variable, and the lack of a proof-reading exonuclease (which exists in SARS-CoV-2) results in a mutation rate of roughly $10^{-3}/10^{-4}$ nucleotide substitutions/site/year [41–44], depending on the gene and strain. RSV-A viruses appear to have a lower mutation rate ($1.48x10^{-3}$ nucleotide substitutions/site/year) than RSV-B viruses ($1.92x10^{-3}$ nucleotide substitutions/site/year) [41]. This high mutation rate results in the continuous selection of new strains or variants as a result of immune system pressure, among other mechanisms [39], which has a clear impact on the medium/long term development of effective vaccines, antivirals, and monoclonal antibody treatments [1].

The aforementioned genetic and antigenic diversity resulted in a full genotype classification [45,46]. RSV-A has 9 genotypes (GA1-GA7, SAA1 and NA1) [1], but RSV-B has at least 32 genotypes (BA1-14, GB1-GB5, SAB1-4, URU1-2, NZB1-2, BA-CCA, BA-CCB, BA-C, CBB and CB1) [41]. These distinct genotypes of both groups can co-circulate in the same RSV season in consecutive years, but the predominant genotype often changes each year [47]. This rapid divergence and evolution is a problem for vaccines in development or near to be approved, since they must create a broad response against all genotypes while maintaining a distinct response against each genotype.

Within the two RSV proteins with the highest antigenic capability (G and F), the G protein exhibits a 10-fold stronger antigenic drift than F and other internal virus genes [48]. RSV-A viruses (NA1 genotype) have a 72-nucleotide duplication in the G protein, while RSV-B viruses (BA genotype) have a 60-nucleotide duplication [1]. These duplications in the G protein's genetic material have resulted in an increase in viral fitness, causing these two genotypes to spread fast around the world [49]. The F protein, on the other hand, is far more conserved, thus while both proteins are of relevance for vaccine and monoclonal antibody creation, the F protein has a greater interest since it may have higher long-term utility. Nonetheless, there are genetic and antigenic changes in the F protein (particularly in RSV-B viruses), so its genetic drift will have to be taken into account in the future for the adaptation of these preventive treatments, as is done with influenza viruses and will most likely be done with SARS-CoV-2 infections.

The immune system's pressure is substantially responsible for RSV's genetic and antigenic drift [39]. The high variability of the G protein indicates positive selection, allowing the virus immune escape to the host, whereas the lower variability of other proteins, including F, indicates that they are genes that specialize and optimize over time and have important functions in the cell cycle related to genetic material replication and viral transmission.

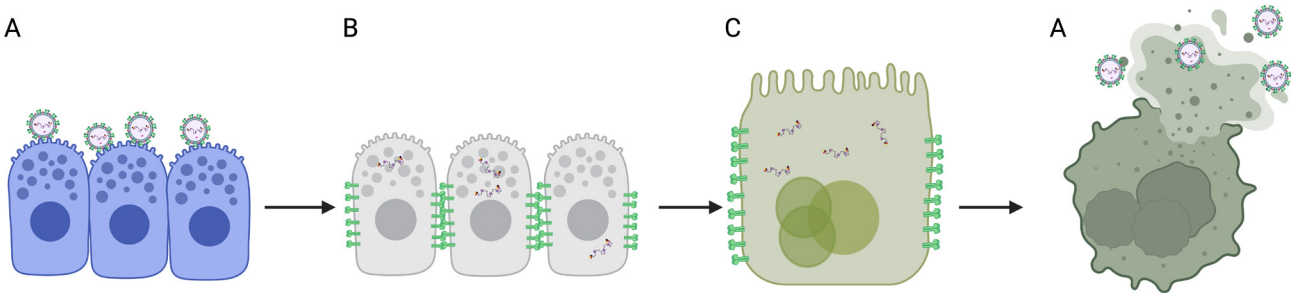

Figure 2 **Mechanism of infection and syncytia formation of respiratory syncytial virus. First the virus attach to the cell through G protein (A) and insert their genetic material after fusion of viral/cell membranes via activation of F protein. After that, the genetic material starts their replication and mRNA translation for protein formation. The F protein is then produced and located into the cell host membrane (B), attaching the infected cell to the next one and forming syncytia (C), a superstructure formed by several cells with only one cytoplasm but with several nuclei, where the genetic material of the virus can travel from one cell to another. When the virus produces damage into the syncytia, this triggers the death of several cells at the same time. Created with BioRender.com.**

Other processes, like as recombination, which can generate new genotypes, allow the virus to evolve. According to some authors, these recombination can only occur between genotypes of the same group (A or B), not between groups [41]. However, there is limited data indicating co-infections of many genotypes in the same individual, which could allow for this form of recombination, thus further research is needed in this area. Despite this, the recombination hypothesis may be realistic because other viruses, such as SARS-CoV-2, have experienced this effect, such as the development of the XBB variation as a result of BA.2.10.1 and BA.2.75 recombination [50].

The aforementioned RSV variability, mediated by the aforementioned processes, results in recurrent reinfections. According to certain research, 36-42% of children suffered RSV reinfections within their first five years of life [51]. RSV infections do not elicit a long-lasting immune response, but reinfections are typically milder than the original episode [52]. Antibodies produced during the first infection do not vanish, but the antibody titer tends to diminish over time, resulting in the recurrence of similar episodes, albeit with reduced clinical signs. One of the most critical determinants in reinfection is age, particularly for reinfections that occur during the same RSV season in which the kid was first infected. These reinfections are more common and severe in younger children [53].

Viral cycle. RSV infection characteristics are greatly depending on cell type. When RSV enters the respiratory system by inhalation, it attaches via the G protein to the ciliated cells of the respiratory epithelium via the receptors indicated above, most notably CX3CR1. Following this interaction, the F protein is activated in its post-fusion state and the virion binds to the host cell membrane, fusing both membranes and initiating internalization [17]. The virion nucleocapsid is then released into the cell cytoplasm, where the viral genome, along with the N protein, forms a helical structure and associates with the polymerase-RNA-dependent complex. The polymerase then starts transcribing viral mRNAs and replicating the genome, generating positive polarity RNA sequences (antigenome) that serve as a template for the synthesis of negative polarity RNA that will be part of the viral offspring [54]. The "de novo" synthesized genomes bind to the structural proteins that comprise the polymerase-RNA-dependent complex and the N protein to form new nucleocapsids, which are then transported to the infected cell's plasma membrane to bind to the rest of the structural proteins and produce the new virions that are released from the infected cell.

Pathogenic effect of the virus through the creation of syncytia. Although the virus can continue its infectious cycle by releasing virions into the extracellular space, the formation of syncytia is another prevalent method of intercellular transmission in RSV, which also lends the virus its name. As previously stated, syncytia are cellular clusters that share the same area within a single lipid membrane but contain several cell nuclei. This superstructure permits viral genetic material to be transported between cells without being released into the cellular space, resulting in a very efficient transmission system that also hides the virus from immune system action [55] (Figure 2).

One implication of syncytia formation is that the peak viral load occurs later than in other viral infections that do not induce syncytia [56,57]. Another difference is that this type of virus progression appears to be a viral evasion strategy, with a direct impact on the severity of infection [55]. Another implication of syncytium formation is that, unlike in the case of an influenza infection, where cell death occurs one at a time, cell death occurs abruptly in the case of RSV and syncytia, in which many cells die at the same time because they are part of the same syncytium, which has been dubbed the "burst model" [58]. This huge cell death appears to be linked to significant lung injury, which has a direct impact on the progression of

the disease and consequently the severity of the clinical process [59]. Although syncytia development impacts other disorders, such as COVID-19, the exact processes by which it worsens the condition in these patients remain unknown.

Antigenic sites in the F protein and the possible impact on vaccine effectiveness and protection. Six distinct antigenic regions in the F protein have been identified as being of particular significance for the production of vaccines and monoclonal antibodies. These antigenic sites were discovered both before and after fusion. Neutralizing antibodies were developed in the following sequence of potency: site Ø, site V, site III, site IV, site II, and site I [60]. Sites Ø and V are exclusively present in the F protein's pre-fusion conformation, but the others are present in both, with considerable differences in the effectiveness of neutralizing antibodies produced against them (up to 80-fold in some circumstances) [60].

Given that the Ø and V sites are the most potent inducers of neutralizing antibodies, and that these are only present in the pre-fusion state of the protein, the great majority of vaccine and monoclonal antibody designs will target the pre-fusion form of this protein. Sixty percent of the neutralizing antibodies found against the F protein target the Ø and V sites. The most likely explanation for these large differences is that the Ø and V sites on the F protein are much more topologically accessible than the rest, in addition to the angle of approach of the antibodies, which interacts with other annexin structures less than other antigenic sites on the same protein [61].

In terms of the technique to be taken to avoid infection or minimize its severity, the two preventative strategies available at present time are drastically different. Vaccines formulated against the F protein in its pre-fusion condition generate a broad polyclonal antibody response when manufactured using the complete protein. In other words, antibodies are made preferentially towards the most accessible antigenic sites Ø and V, although antibodies against other sections of the protein are also formed [62]. However, antibody treatments such as nirsevimab and palivizumab are directed against specific epitopes (in the case of nirsevimab Ø and II in the case of palivizumab) [63], implying that we are dealing with monoclonal antibodies [64]. This results in significant discrepancies in active and passive immunization techniques, despite the fact that both paradigms examine different areas of protection and are, of course, complementary.

Several Spanish hospitals conducted the first global estimate of nirsevimab's effectiveness using real-world evidence, which was published in February 2024 [65]. According to this trial, in infants under 9 months old who were candidates for this vaccine, nirsevimab was found to be effective in preventing laboratory-confirmed RSV LRTI (low-respiratory tract infections) by 70% to 84%, with coverages exceeding 90%.

EPIDEMIOLOGICAL FEATURES OF THE RSV

Features of the transmission of RSV. RSV is transmitted by infected people's secretions via the respiratory pathway [66]. Furthermore, children with bronchiolitis produce aerosols that might transport the virus via extremely small droplets that are easily spread [67]. On the other hand, other authors suggest that aerosol transmission is inefficient, since investigations in pediatric primary care found that just 2.3% of aerosol samples collected had detectable RSV [68]. As a result, the process of respiratory transmission necessitates, above all, closeness between two people. Furthermore, some authors argue that fomite contamination may be an additional pathway for virus transmission [69], albeit of lesser consequence than respiratory transmission. RSV has a basic reproductive number of roughly 3.0 (SD=0.6) [65]. However, as with all respiratory diseases, this number varies based on the features of the individual source of infection (behavior, age, etc.), as well as the preventive measures implemented throughout the virus's circulation months.

This fast transmission rate has an impact on more than just the process by which the virus spreads from an infected individual to a vulnerable one. Other elements, like as coexistence and interpersonal interactions, also have a role. The characteristics of families and persons living together in the family setting are highly linked to RSV transmission. Some authors, for example, show that infections in younger children frequently develop when the virus enters the home via an older sibling's infection [70,71]. Younger children who are not in school have a very restricted contact regimen, but older children who are already in day care/school are more likely to become infected, developing a milder condition but having a significant influence on younger children who are cohabitants due to their age. Children, on the other hand, can transmit RSV to older caregivers, which can be harmful if they have risk diseases [72,73]. Vaccination measures for older children may thus be beneficial in preventing sickness in younger children.

Features of epidemic circulation and lasting of epidemics. During the coldest months of the year, RSV spreads like wildfire. It is typically diagnosed in the northern hemisphere between the months of October and March, with the epidemic peak recorded in several European nations around week 48-50 of the year, about at the end of December [68,69] (Figure 3). Epidemics in these countries last from 12-32 weeks, depending on the territory and the characteristics of the surveillance system (a total of 5-6 months). RSV epidemics often spread from the southern hemisphere to the northern hemisphere. They begin in the southern hemisphere in March and June and conclude in the northern hemisphere in September and December [74,75]. However, in tropical climatic areas, the RSV season might last up to ten months [76].

The seasonal prevalence of RSV in temperate regions may reflect one of two previously proposed ideas for influenza viruses. The first theory holds that epidemics during the cold months of the year are caused by new virus introductions from countries with widespread virus circulation, either from the opposite hemisphere or from tropical or subtropical climates where the virus adopts a type of endemic circulation [78]. These reintroductions would occur on a regular basis,

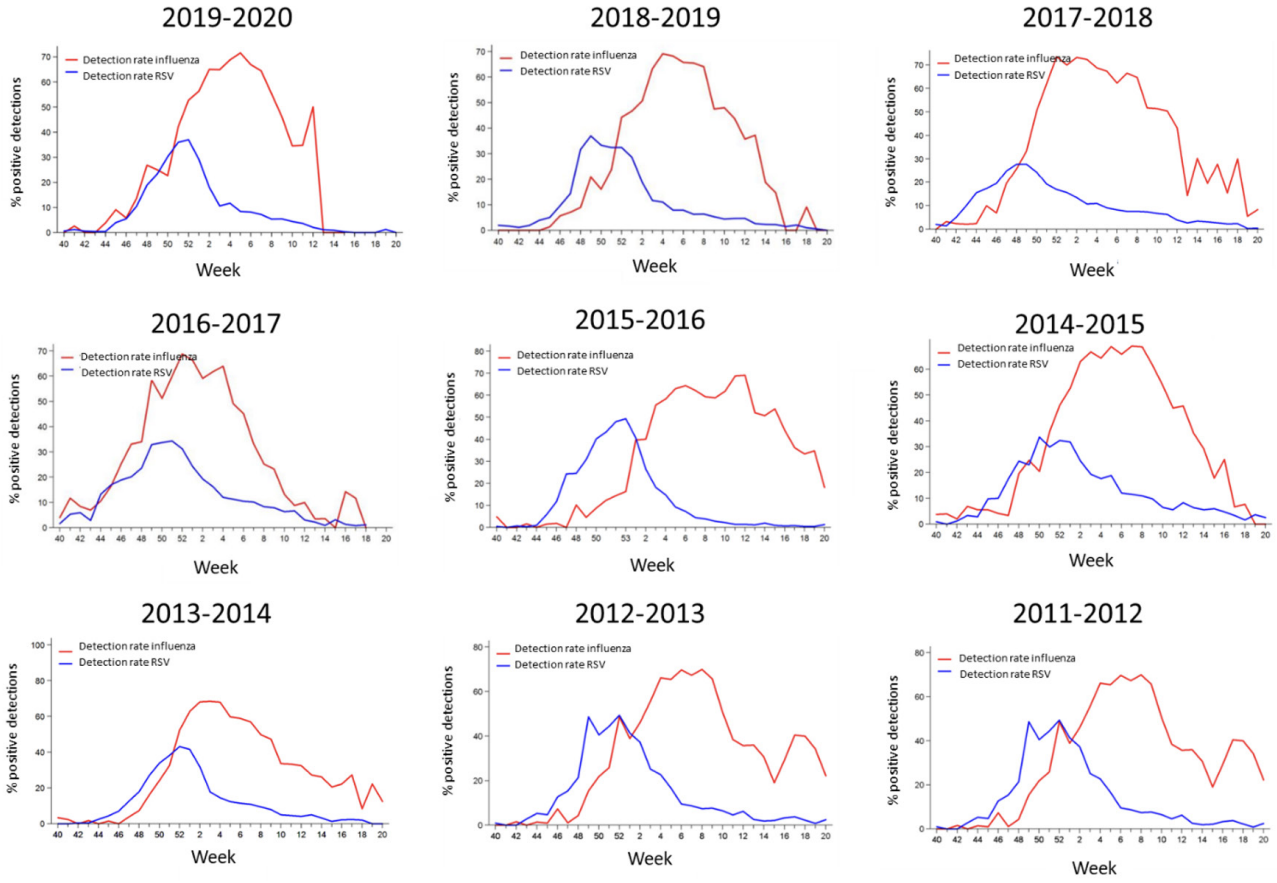

Figure 3 | **Circulation of RSV and influenza viruses during the last 9 epidemic seasons before the COVID-19 pandemic in Spain. Modified from Instituto de Salud Carlos III [77].**

but in unfavorable times due to an unfavorable climate for the virus in temperate climes, brief chains of transmission would occur, which would not result in epidemics. On the contrary, once the cold months arrive and the above-mentioned environmental conditions (low temperatures, low absolute humidity, overcrowding, etc.) favor virus persistence, reintroductions from other parts of the world lead to longer chains of transmission, eventually leading to epidemics, as seen with influenza [79].

Alternatively, the second hypothesis proposes that the virus will remain dormant in select populations, such as immunocompromised persons such as HIV/AIDS patients and even children, until the following season [40]. These people are generally long-term virus excretors, even weeks or months [80,81], since they are unable to clear the infection or reduce the viral load, but they are often asymptomatic or pauci-symptomatic. However, until the appearance of COVID-19, current surveillance systems focused their efforts on influenza and exclusively on the epidemiological surveillance period (week 40 of one year to week 20 of the following year), making it difficult to discover this sort of case.

For example, in the case of influenza, one of the most widely accepted explanations for the annual occurrence of epidemics is that reintroductions are the primary driver of this seasonality. Indeed, the "East-Southeast Asian epicenter model" hypothesis, proposed by Smith *et al.* in 2008, demonstrated the existence of a continuous reservoir of influenza in East and Southeast Asia, which could be the epicenter of strains that were then distributed globally in each epidemic, both in the northern and southern hemispheres [82]. These scientists even claimed that dispersions out of this part of the world had little effect on the evolutionary divergence of influenza viruses, implying that this epicenter was responsible for the majority of the virus's antigenic alterations. Similar patterns have been seen by other researchers from several tropical climatic reservoirs [78]. However, as previously discussed, the possibility that RSV could survive for a long time in non-immunocompromised populations should not be discounted. According to some authors, the mixed hypothesis is the most correct. Indeed, due to nitric oxide activity, RSV may remain latent in monocyte-derived dendritic cells for lengthy periods of time [83,84], which could be significant to the occurrence of epidemics or non-periodic seasonal outbreaks in temperate regions.

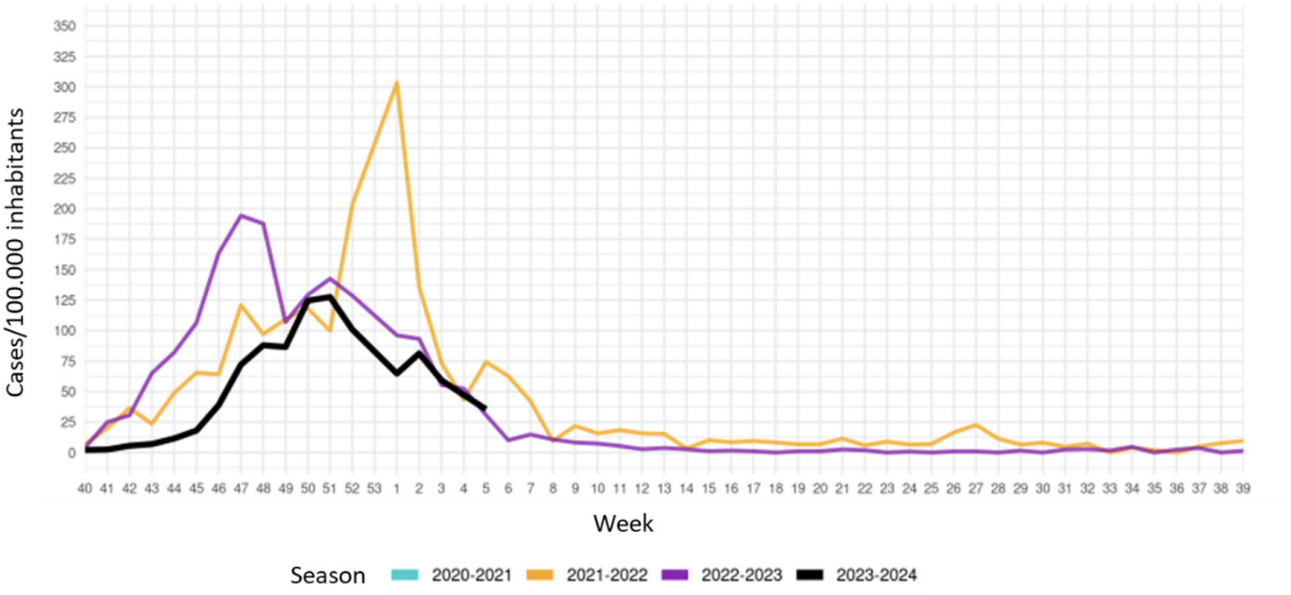

Figure 4 | **Incidence rate (cases/100.000 inhabitants) of RSV in Spain during the last five seasons since the emergence of COVID-19 pandemic. Modified from SIVIRA [96].**

RSV has been described as having two subtypes (RSV-A and RSV-B) and various genotypes, as previously stated. Historical divergence statistics indicate that the two RSV groups may have separated in the year 1681 [41]. The two RSV subtypes frequently co-circulate in the same epidemic [38,85], however one subtype predominates over the other depending on the year [86]. Which subtype is more widespread is highly dependent on the season, the affected population, the territory, and the people's immunological background. However, numerous reports claim that subtype A is more common than subtype B in around 60% of outbreaks [87,88]. Both RSV subtypes have similar pathologic characteristics in illness manifestation. However, there appears to be a larger prevalence of ICU hospitalizations in pediatric RSV-A patients than in RSV-B patients [89].

Impact of the COVID-19 pandemic on the RSV circulation. The COVID-19 pandemic changed the way all respiratory viruses behaved. Mask use, social isolation, travel bans to other countries, and isolation all abruptly halted the spread of SARS-CoV-2 and other respiratory-transmitted viruses [90]. However, the relaxation of these measures beginning in 2021 caused some respiratory viruses to partially resurface, albeit with epidemiological characteristics in terms of timing of presentation that were not normal compared to before the pandemic (higher intensity, longer months of circulation, localization of epidemics in unusual months of the year, and so on).

In Japan, for example, the 2021 RSV outbreak began in July, significantly earlier than usual [91]. This was due not only to the relaxation of the aforementioned measures, but also to the fact that many countries adopted strict measures to keep children away from the virus, closing daycare centers, schools, and even parks to prevent transmission [88], effectively keeping them in a bubble in which only adults were responsible for the virus's entry into the home environment. In 2021, an unseasonalized RSV outbreak occurred in France as well, beginning in February and lasting until about May of that year [92]. Pinquier *et al.* found a 3-4 month disparity between what happens in this country and what happens in other countries. Other studies have found similar shifts in various countries, primarily during the off-season and notably in late RSV epidemics [93].

RSV behavior in 2022 was more similar to that observed prior to the pandemic, with the virus emerging in several nations in the fall months, albeit significantly earlier. The majority of cases (91%) in the United States were caused by different genotypes of the RSV-A subtype. This revival was severe, with detection and hospitalization rates higher than before the pandemic [94]. Other countries, such as Spain, have also reported a more severe RSV outbreak in 2022 compared to previous years, particularly among younger children [95]. The national reports produced by the SiVIRA tool (ARI Surveillance System) at the state level demonstrate this anomalous behavior. They indicate a delocalized epidemic peak in comparison to other post COVID-19 epidemics, with the epidemic peak occurring in week 1/2023, and a very high incidence, approaching 300 cases/100,000 inhabitants [96]. Following that, both the incidence and the pattern that accompanied the epidemic peak in the 2023–2024 season were comparable to those of prior years (Figure 4).

CONCLUSIONS

RSV has a significant influence on human health, particu-

larly in youngsters and the elderly. The virological and genetic properties of this virus constitute a barrier for the development of appropriate preventative strategies to avoid the disease from a microbiological standpoint. Among these obstacles is the high variability of the G protein, which is primarily responsible for reinfections in the initial years of life, as well as an etiopathogenesis of the disease that inhibits the immune system's ability to eradicate the virus. However, the characteristics of the RSV F protein in the prefusion state have made viable the appearance of different preventive treatments, which have already seen or will see the light of day in the coming years.

It is desirable to improve existing knowledge on the epidemiological realities of RSV, particularly the disease's influence on human health, not only in infants but also in older age groups. This may allow us to assess who will gain the most from the advent of this sort of preventative medicine, allowing us to prioritize its usage in these populations. Robust surveillance mechanisms, in addition to those already in place for influenza and COVID-19, are required to properly track the virus's activities. The breakthroughs in RSV treatment and prevention that are now being achieved will likely allow for progress in many aspects of its treatment and prevention during the coming decade.

FUNDING

None to declare.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Muñoz-Escalante JC, Comas-García A, Bernal-Silva S, Robles-Espinoza CD, Gómez-Leal G, Noyola DE. Respiratory syncytial virus A genotype classification based on systematic intergenotypic and intragenotypic sequence analysis. Sci Rep 2019;9:20097. https://doi.org/10.1038/s41598-019-56552-2.
2. Walsh EE, Hall CB. Respiratory Syncytial Virus (RSV). Mand Douglas Bennetts Princ Pract Infect Dis 2015:1948-1960.e3. https://doi.org/10.1016/B978-1-4557-4801-3.00160-0.
3. Blount RE, Morris JA, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med Soc Exp Biol Med N Y N 1956;92:544–9. https://doi.org/10.3181/00379727-92-22538.
4. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999;282:1440–6. https://doi.org/10.1001/jama.282.15.1440.
5. Caroline B Hall, Edward E Walsh. Respiratory Syncytial Virus. Feigin Cherrys Textb. Pediatr. Infect. Dis., vol. 3, 2012. https://doi.org/10.1016/B978-1-4557-4801-3.00160-0.
6. Chanock R, Roizman B, Myers R. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization. Am J Hyg 1957;66:281–90. https://doi.org/10.1093/oxfordjournals.aje.a119901.
7. ICTV. Virus taxonomy. The ICTV Report on virus classification and taxon nomenclature. Pneumoviridae Chapter. 2017 cited on 11th of December 2023.. Available: http://taxonomy.cvr.gla.ac.uk/PDF/Pneumoviridae.pdf
8. Susana Payne. Family Pneumoviridae. En: Viruses From understanding to investigation. 2.ª ed. Elsevier; 2023. p. 233-7.
9. Hao M, Li Y, Wang Y, Zhang S. A Classification Study of Respiratory Syncytial Virus (RSV) Inhibitors by Variable Selection with Random Forest. Int J Mol Sci 2011;12:1259–80. https://doi.org/10.3390/ijms12021259.
10. WHO. Respiratory Syncytial Virus (RSV) disease. 2023 cited on 11th of December 2023. Available: https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/vaccine-standardization/respiratory-syncytial-virus-disease
11. ICTV. Family: Pneumoviridae 2023.
12. van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 2001;7:719–24. https://doi.org/10.1038/89098.
13. Jeffree CE, Rixon HWM, Brown G, Aitken J, Sugrue RJ. Distribution of the attachment (G) glycoprotein and GM1 within the envelope of mature respiratory syncytial virus filaments revealed using field emission scanning electron microscopy. Virology 2003;306:254–67. https://doi.org/10.1016/s0042-6822(02)00016-8.
14. Feng Z, Xu L, Xie Z. Receptors for Respiratory Syncytial Virus Infection and Host Factors Regulating the Life Cycle of Respiratory Syncytial Virus. Front Cell Infect Microbiol 2022;12:858629. https://doi.org/10.3389/fcimb.2022.858629.
15. McNamara PS, Smyth RL. The pathogenesis of respiratory syncytial virus disease in childhood. Br Med Bull 2002;61:13–28. https://doi.org/10.1093/bmb/61.1.13.
16. Huang YT, Collins PL, Wertz GW. Characterization of the 10 proteins of human respiratory syncytial virus: identification of a fourth envelope-associated protein. Virus Res 1985;2:157–73. https://doi.org/10.1016/0168-1702(85)90246-1.
17. Collins PL, Fearns R, Graham BS. Respiratory Syncytial Virus: Virology, Reverse Genetics, and Pathogenesis of Disease. Curr Top Microbiol Immunol 2013;372:3–38. https://doi.org/10.1007/978-3-642-38919-1_1.
18. Lodish HF, Rose JK. Relative importance of 7-methylguanosine in ribosome binding and translation of vesicular stomatitis virus mRNA in wheat germ and reticulocyte cell-free systems. J Biol Chem 1977;252:1181–8.
19. Hyde JL, Diamond MS. Innate immune restriction and antagonism of viral RNA lacking 2′-O methylation. Virology 2015;479–480:66–74. https://doi.org/10.1016/j.virol.2015.01.019.
20. McLellan JS, Ray WC, Peeples ME. Structure and Function of RSV Surface Glycoproteins. Curr Top Microbiol Immunol 2013;372:83–104. https://doi.org/10.1007/978-3-642-38919-1_4.

21. Levine S, Klaiber-Franco R, Paradiso PR. Demonstration that glycoprotein G is the attachment protein of respiratory syncytial virus. J Gen Virol 1987;68 (Pt 9):2521–4. https://doi.org/10.1099/0022-1317-68-9-2521.
22. Langedijk JP, de Groot BL, Berendsen HJ, van Oirschot JT. Structural homology of the central conserved region of the attachment protein G of respiratory syncytial virus with the fourth subdomain of 55-kDa tumor necrosis factor receptor. Virology 1998;243:293–302. https://doi.org/10.1006/viro.1998.9066.
23. Miao C, Radu GU, Caidi H, Tripp RA, Anderson LJ, Haynes LM. Treatment with respiratory syncytial virus G glycoprotein monoclonal antibody or F(ab')2 components mediates reduced pulmonary inflammation in mice. J Gen Virol 2009;90:1119–23. https://doi.org/10.1099/vir.0.009308-0.
24. Tripp RA, Power UF, Openshaw PJM, Kauvar LM. Respiratory Syncytial Virus: Targeting the G Protein Provides a New Approach for an Old Problem. J Virol 2018;92:e01302-17. https://doi.org/10.1128/JVI.01302-17.
25. Collins PL, Huang YT, Wertz GW. Nucleotide sequence of the gene encoding the fusion (F) glycoprotein of human respiratory syncytial virus. Proc Natl Acad Sci U S A 1984;81:7683–7.
26. Bolt G, Pedersen LO, Birkeslund HH. Cleavage of the respiratory syncytial virus fusion protein is required for its surface expression: role of furin. Virus Res 2000;68:25–33. https://doi.org/10.1016/s0168-1702(00)00149-0.
27. Day ND, Branigan PJ, Liu C, Gutshall LL, Luo J, Melero JA, et al. Contribution of cysteine residues in the extracellular domain of the F protein of human respiratory syncytial virus to its function. Virol J 2006;3:34. https://doi.org/10.1186/1743-422X-3-34.
28. McLellan JS, Chen M, Leung S, Graepel KW, Du X, Yang Y, et al. Structure of RSV Fusion Glycoprotein Trimer Bound to a Prefusion-Specific Neutralizing Antibody. Science 2013;340:1113–7. https://doi.org/10.1126/science.1234914.
29. McLellan JS, Yang Y, Graham BS, Kwong PD. Structure of respiratory syncytial virus fusion glycoprotein in the postfusion conformation reveals preservation of neutralizing epitopes. J Virol 2011;85:7788–96. https://doi.org/10.1128/JVI.00555-11.
30. Swanson KA, Settembre EC, Shaw CA, Dey AK, Rappuoli R, Mandl CW, et al. Structural basis for immunization with postfusion respiratory syncytial virus fusion F glycoprotein (RSV F) to elicit high neutralizing antibody titers. Proc Natl Acad Sci U S A 2011;108:9619–24. https://doi.org/10.1073/pnas.1106536108.
31. Techaarpornkul S, Barretto N, Peeples ME. Functional Analysis of Recombinant Respiratory Syncytial Virus Deletion Mutants Lacking the Small Hydrophobic and/or Attachment Glycoprotein Gene. J Virol 2001;75:6825–34. https://doi.org/10.1128/JVI.75.15.6825-6834.2001.
32. König P, Giesow K, Schuldt K, Buchholz UJ, Keil GM. A novel protein expression strategy using recombinant bovine respiratory syncytial virus (BRSV): modifications of the peptide sequence between the two furin cleavage sites of the BRSV fusion protein yield secreted proteins, but affect processing and function of the BRSV fusion protein. J Gen Virol 2004;85:1815–24. https://doi.org/10.1099/vir.0.80010-0.
33. Domachowske JB, Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. Clin Microbiol Rev 1999;12:298–309. https://doi.org/10.1128/CMR.12.2.298.
34. Herschke F, Plumet S, Duhen T, Azocar O, Druelle J, Laine D, et al. Cell-Cell Fusion Induced by Measles Virus Amplifies the Type I Interferon Response. J Virol 2007;81:12859–71. https://doi.org/10.1128/JVI.00078-07.
35. Lin L, Li Q, Wang Y, Shi Y. Syncytia formation during SARS-CoV-2 lung infection: a disastrous unity to eliminate lymphocytes. Cell Death Differ 2021;28:2019–21. https://doi.org/10.1038/s41418-021-00795-y.
36. Leroy H, Han M, Woottum M, Bracq L, Bouchet J, Xie M, et al. Virus-Mediated Cell-Cell Fusion. Int J Mol Sci 2020;21:9644. https://doi.org/10.3390/ijms21249644.
37. Gan S-W, Tan E, Lin X, Yu D, Wang J, Tan GM-Y, et al. The Small Hydrophobic Protein of the Human Respiratory Syncytial Virus Forms Pentameric Ion Channels. J Biol Chem 2012;287:24671–89. https://doi.org/10.1074/jbc.M111.332791.
38. Mufson MA, Örvell C, Rafnar B, Norrby E. Two Distinct Subtypes of Human Respiratory Syncytial Virus. J Gen Virol 1985;66:2111–24. https://doi.org/10.1099/0022-1317-66-10-2111.
39. Trento A, Ábrego L, Rodriguez-Fernandez R, González-Sánchez MI, González-Martínez F, Delfraro A, et al. Conservation of G-Protein Epitopes in Respiratory Syncytial Virus (Group A) Despite Broad Genetic Diversity: Is Antibody Selection Involved in Virus Evolution? J Virol 2015;89:7776–85. https://doi.org/10.1128/JVI.00467-15.
40. Agoti CN, Otieno JR, Ngama M, Mwihuri AG, Medley GF, Cane PA, et al. Successive Respiratory Syncytial Virus Epidemics in Local Populations Arise from Multiple Variant Introductions, Providing Insights into Virus Persistence. J Virol 2015;89:11630–42. https://doi.org/10.1128/JVI.01972-15.
41. Yu J-M, Fu Y-H, Peng X-L, Zheng Y-P, He J-S. Genetic diversity and molecular evolution of human respiratory syncytial virus A and B. Sci Rep 2021;11:12941. https://doi.org/10.1038/s41598-021-92435-1.
42. Haider MSH, Khan WH, Deeba F, Ali S, Ahmed A, Naqvi IH, et al. BA9 lineage of respiratory syncytial virus from across the globe and its evolutionary dynamics. PloS One 2018;13:e0193525. https://doi.org/10.1371/journal.pone.0193525.
43. Zlateva KT, Lemey P, Vandamme A-M, Van Ranst M. Molecular evolution and circulation patterns of human respiratory syncytial virus subgroup a: positively selected sites in the attachment g glycoprotein. J Virol 2004;78:4675–83. https://doi.org/10.1128/jvi.78.9.4675-4683.2004.
44. Pandya MC, Callahan SM, Savchenko KG, Stobart CC. A Contemporary View of Respiratory Syncytial Virus (RSV) Biology and Strain-Specific Differences. Pathogens 2019;8:67. https://doi.org/10.3390/pathogens8020067.
45. Salimi V, Viegas M, Trento A, Agoti CN, Anderson LJ, Avadhanula V, et al. Proposal for Human Respiratory Syncytial Virus Nomenclature below the Species Level. Emerg Infect Dis 2021;27:e204608.

https://doi.org/10.3201/eid2706.204608.

46. Goya S, Galiano M, Nauwelaers I, Trento A, Openshaw PJ, Mistchenko AS, et al. Toward unified molecular surveillance of RSV: A proposal for genotype definition. Influenza Other Respir Viruses 2020;14:274–85. https://doi.org/10.1111/irv.12715.
47. Peret TC, Hall CB, Schnabel KC, Golub JA, Anderson LJ. Circulation patterns of genetically distinct group A and B strains of human respiratory syncytial virus in a community. J Gen Virol 1998;79 (Pt 9):2221–9. https://doi.org/10.1099/0022-1317-79-9-2221.
48. Tan L, Lemey P, Houspie L, Viveen MC, Jansen NJG, van Loon AM, et al. Genetic variability among complete human respiratory syncytial virus subgroup A genomes: bridging molecular evolutionary dynamics and epidemiology. PloS One 2012;7:e51439. https://doi.org/10.1371/journal.pone.0051439.
49. Bin Lu, Liu H, Tabor DE, Tovchigrechko A, Qi Y, Ruzin A, et al. Emergence of new antigenic epitopes in the glycoproteins of human respiratory syncytial virus collected from a US surveillance study, 2015–17. Sci Rep 2019;9:3898. https://doi.org/10.1038/s41598-019-40387-y.
50. Scarpa F, Sanna D, Azzena I, Casu M, Cossu P, Fiori PL, et al. Genome-based comparison between the recombinant SARS-CoV-2 XBB and its parental lineages. J Med Virol 2023;95:e28625. https://doi.org/10.1002/jmv.28625.
51. Bont L, Versteegh J, Swelsen WTN, Heijnen CJ, Kavelaars A, Brus F, et al. Natural reinfection with respiratory syncytial virus does not boost virus-specific T-cell immunity. Pediatr Res 2002;52:363–7. https://doi.org/10.1203/00006450-200209000-00009.
52. Henderson FW, Collier AM, Clyde WA, Denny FW. Respiratory-syncytial-virus infections, reinfections and immunity. A prospective, longitudinal study in young children. N Engl J Med 1979;300:530–4. https://doi.org/10.1056/NEJM197903083001004.
53. Winterstein AG, Hampp C, Saidi A. Effectiveness of palivizumab prophylaxis in infants and children in Florida. Pharmacoepidemiol Drug Saf 2012;21:53–60. https://doi.org/10.1002/pds.2246.
54. Collins PL, Huang YT, Wertz GW. Identification of a tenth mRNA of respiratory syncytial virus and assignment of polypeptides to the 10 viral genes. J Virol 1984;49:572–8. https://doi.org/10.1128/JVI.49.2.572-578.1984.
55. Cifuentes-Muñoz N, Ellis Dutch R. To assemble or not to assemble: The changing rules of pneumovirus transmission. Virus Res 2019;265:68–73. https://doi.org/10.1016/j.virusres.2019.03.002.
56. Jessie B, Dobrovolny HM. The role of syncytia during viral infections. J Theor Biol 2021;525:110749. https://doi.org/10.1016/j.jtbi.2021.110749.
57. Gonzàlez-Parra G, De Ridder F, Huntjens D, Roymans D, Ispas G, Dobrovolny HM. A comparison of RSV and influenza in vitro kinetic parameters reveals differences in infecting time. PLoS ONE 2018;13:e0192645. https://doi.org/10.1371/journal.pone.0192645.
58. Chen HY, Di Mascio M, Perelson AS, Ho DD, Zhang L. Determination of virus burst size in vivo using a single-cycle SIV in rhesus macaques. Proc Natl Acad Sci U S A 2007;104:19079–84. https://doi.org/10.1073/pnas.0707449104.
59. Buchrieser J, Dufloo J, Hubert M, Monel B, Planas D, Rajah MM, et al. Syncytia formation by SARS-CoV-2-infected cells. EMBO J 2020;39:e106267. https://doi.org/10.15252/embj.2020106267.
60. Taleb SA, Al Thani AA, Al Ansari K, Yassine HM. Human respiratory syncytial virus: pathogenesis, immune responses, and current vaccine approaches. Eur J Clin Microbiol Infect Dis 2018;37:1817–27. https://doi.org/10.1007/s10096-018-3289-4.
61. Gilman MSA, Castellanos CA, Chen M, Ngwuta JO, Goodwin E, Moin SM, et al. Rapid profiling of RSV antibody repertoires from the memory B cells of naturally infected adult donors. Sci Immunol 2016;1:eaaj1879. https://doi.org/10.1126/sciimmunol.aaj1879.
62. Mukhamedova M, Wrapp D, Shen C-H, Gilman MSA, Ruckwardt TJ, Schramm CA, et al. Vaccination with prefusion-stabilized respiratory syncytial virus fusion protein induces genetically and antigenically diverse antibody responses. Immunity 2021;54:769-780.e6. https://doi.org/10.1016/j.immuni.2021.03.004.
63. Ye X, Iwuchukwu OP, Avadhanula V, Aideyan LO, McBride TJ, Ferlic-Stark LL, et al. Antigenic Site-Specific Competitive Antibody Responses to the Fusion Protein of Respiratory Syncytial Virus Were Associated With Viral Clearance in Hematopoietic Cell Transplantation Adults. Front Immunol 2019;10:706. https://doi.org/10.3389/fimmu.2019.00706.
64. Pantaleo G, Correia B, Fenwick C, Joo VS, Perez L. Antibodies to combat viral infections: development strategies and progress. Nat Rev Drug Discov 2022;21:676–96. https://doi.org/10.1038/s41573-022-00495-3.
65. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, López-Labrador FX, Mengual-Chuliá B, Fernández-García C, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Eurosurveillance 2024;29:2400046. https://doi.org/10.2807/1560-7917.ES.2024.29.6.2400046.
66. Kulkarni H, Smith C, Hirst R, Baker N, Easton A, O'Callaghan C. Airborne transmission of respiratory syncytial virus (RSV) infection. Eur Respir J 2011;38. https://doi.org/10.1126/science.abd9149
67. Kulkarni H, Smith CM, Lee DDH, Hirst RA, Easton AJ, O'Callaghan C. Evidence of Respiratory Syncytial Virus Spread by Aerosol. Time to Revisit Infection Control Strategies? Am J Respir Crit Care Med 2016;194:308–16. https://doi.org/10.1164/rccm.201509-1833OC.
68. Grayson SA, Griffiths PS, Perez MK, Piedimonte G. Detection of airborne respiratory syncytial virus in a pediatric acute care clinic. Pediatr Pulmonol 2017;52:684–8. https://doi.org/10.1002/ppul.23630.
69. Hall CB, Douglas RG, Geiman JM. Possible transmission by fomites of respiratory syncytial virus. J Infect Dis 1980;141:98–102. https://doi.org/10.1093/infdis/141.1.98.
70. Colosia AD, Masaquel A, Hall CB, Barrett AM, Mahadevia PJ, Yogev R. Residential crowding and severe respiratory syncytial virus disease among infants and young children: A systematic literature review. BMC Infect Dis 2012;12:95. https://doi.org/10.1186/1471-2334-12-95.
71. Heikkinen T, Valkonen H, Waris M, Ruuskanen O. Transmission of Respiratory Syncytial Virus Infection Within Families. Open Forum Infect Dis 2014;2:ofu118. https://doi.org/10.1093/ofid/ofu118.

72. Coultas JA, Smyth R, Openshaw PJ. Respiratory syncytial virus (RSV): a scourge from infancy to old age. Thorax 2019;74:986–93. https://doi.org/10.1136/thoraxjnl-2018-212212.

73. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults. N Engl J Med 2005;352:1749–59. https://doi.org/10.1056/NEJMoa043951.

74. Bloom-Feshbach K, Alonso WJ, Charu V, Tamerius J, Simonsen L, Miller MA, et al. Latitudinal variations in seasonal activity of influenza and respiratory syncytial virus (RSV): a global comparative review. PloS One 2013;8:e54445. https://doi.org/10.1371/journal.pone.0054445.

75. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003;22:S21-32. https://doi.org/10.1097/01.inf.0000053882.70365.c9.

76. Robertson SE, Roca A, Alonso P, Simoes EAF, Kartasasmita CB, Olaleye DO, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 2004;82:914–22.

77. Instituto de Salud Carlos III (ISCIII). Sistema de vigilancia de la gripe en España 2020 cited 16th of May 2023.. Available: https://vgripe.isciii.es/inicio.do

78. Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature 2008;453:615–9. https://doi.org/10.1038/nature06945.

79. Lowen A, Palese P. Transmission of influenza virus in temperate zones is predominantly by aerosol, in the tropics by contact. PLoS Curr 2009;1:RRN1002. https://doi.org/10.1371/currents.RRN1002.

80. Munywoki PK, Koech DC, Agoti CN, Kibirige N, Kipkoech J, Cane PA, et al. Influence of age, severity of infection, and co-infection on the duration of respiratory syncytial virus (RSV) shedding. Epidemiol Infect 2015;143:804–12. https://doi.org/10.1017/S0950268814001393.

81. Madhi SA, Venter M, Madhi A, Petersen MK, Klugman KP. Differing manifestations of respiratory syncytial virus-associated severe lower respiratory tract infections in human immunodeficiency virus type 1-infected and uninfected children. Pediatr Infect Dis J 2001;20:164–70. https://doi.org/10.1097/00006454-200102000-00010.

82. Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, et al. The global circulation of seasonal influenza A (H3N2) viruses. Science 2008;320:340–6. https://doi.org/10.1126/science.1154137.

83. Hobson L, Everard ML. Persistent of respiratory syncytial virus in human dendritic cells and influence of nitric oxide. Clin Exp Immunol 2008;151:359–66. https://doi.org/10.1111/j.1365-2249.2007.03560.x.

84. Martinón-Torres F, González-Barcala F-J. Where does Respiratory Syncytial Virus Hide? Arch Bronconeumol 2022;58:T298–9. https://doi.org/10.1016/j.arbres.2021.06.022.

85. Johnson PR, Spriggs MK, Olmsted RA, Collins PL. The G glycoprotein of human respiratory syncytial viruses of subgroups A and B: extensive sequence divergence between antigenically related proteins. Proc Natl Acad Sci U S A 1987;84:5625–9. https://doi.org/10.1073/pnas.84.16.5625.

86. Mufson MA, Belshe RB, Orvell C, Norrby E. Respiratory syncytial virus epidemics: variable dominance of subgroups A and B strains among children, 1981-1986. J Infect Dis 1988;157:143–8. https://doi.org/10.1093/infdis/157.1.143.

87. Ciarlitto C, Vittucci AC, Antilici L, Concato C, Di Camillo C, Zangari P, et al. Respiratory Syncityal Virus A and B: three bronchiolitis seasons in a third level hospital in Italy. Ital J Pediatr 2019;45:115. https://doi.org/10.1186/s13052-019-0704-0.

88. Song J, Zhu Z, Song J, Mao N, Cui A, Xu W, et al. Circulation pattern and genetic variation of human respiratory syncytial virus in China during 2008–2021. J Med Virol 2023;95:e28611. https://doi.org/10.1002/jmv.28611.

89. Laham FR, Mansbach JM, Piedra PA, Hasegawa K, Sullivan AF, Espinola JA, et al. Clinical Profiles of Respiratory Syncytial Virus Subtypes A and B among Children Hospitalized with Bronchiolitis. Pediatr Infect Dis J 2017;36:808–10. https://doi.org/10.1097/INF.0000000000001596.

90. Sanz-Muñoz I, Tamames-Gómez S, Castrodeza-Sanz J, Eiros-Bouza JM, de Lejarazu-Leonardo RO. Social Distancing, Lockdown and the Wide Use of Mask; A Magic Solution or a Double-Edged Sword for Respiratory Viruses Epidemiology? Vaccines 2021;9:595. https://doi.org/10.3390/vaccines9060595.

91. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N. Resurgence of Respiratory Syncytial Virus Infections during COVID-19 Pandemic, Tokyo, Japan. Emerg Infect Dis 2021;27:2969–70. https://doi.org/10.3201/eid2711.211565.

92. Pinquier D, Crépey P, Tissières P, Vabret A, Roze J-C, Dubos F, et al. Preventing Respiratory Syncytial Virus in Children in France: A Narrative Review of the Importance of a Reinforced Partnership Between Parents, Healthcare Professionals, and Public Health Authorities. Infect Dis Ther 2023;12:317–32. https://doi.org/10.1007/s40121-022-00737-2.

93. Chuang Y-C, Lin K-P, Wang L-A, Yeh T-K, Liu P-Y. The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus Infection: A Narrative Review. Infect Drug Resist 2023;16:661–75. https://doi.org/10.2147/IDR.S396434.

94. Adams G, Moreno GK, Petros BA, Uddin R, Levine Z, Kotzen B, et al. The 2022 RSV surge was driven by multiple viral lineages. medRxiv 2023:2023.01.04.23284195. https://doi.org/10.1101/2023.01.04.23284195.

95. IISCIII. Vigilancia centinela de Infección Respiratoria Aguda en Atención Primaria (IRAs) y en Hospitales (IRAG) Gripe, COVID-19 y otros virus respiratorios. Semana 14/2023. 2023 cited 14th of April 2023.. Available: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/GRIPE/Informes%20semanales/Temporada_2022-23/Informe%20semanal_SiVIRA_142023.pdf

96. SIVIRA, ISCIII. Vigilancia centinela de Infección Respiratoria Aguda en Atención Primaria (IRAs) y en Hospitales (IRAG): Gripe, COVID-19 y VRS CNE-CNM. ISCIII. Informe nº 168. Semana 05/2024 (del 29 de enero al 4 de febrero del 2024) 2024. cited 9th of February 2024] Available: https://docsivira.isciii.es/Informe_semanal_SiVIRA_202405_n168.html