Microbiological and epidemiological features of respiratory syncytial virus

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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

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.
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-

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**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.
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 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].

RSVs’ 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 $10^{-4}$ nucleotide substitutions/site/year [41–44], depending on the gene and strain. RSV-A viruses appear to have a lower mutation rate (1.48x10$^{-4}$ nucleotide substitutions/site/year) than RSV-B viruses (1.92x10$^{-5}$ 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, SA1, and NA1) [1], but RSV-B has at least 32 genotypes (BA1-14, GB1-GBS, 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.
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The virion nucleocapsid is then released into the host cell membrane, fusing both membranes and initiating in

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RSV reinfections within their first five years of life [51]. RSV

According to certain research, 36-42% of children suffered

Other processes, like as recombination, which can gen

rate 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 ex

perienced this effect, such as the development of the XBB var

iation 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 reinfe

tions are more common and severe in younger children [53].

Viral cycle. RSV infection characteristics are greatly de

pending 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 in

ternalization [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 pol-

ymerase-RNA-dependent complex. The polymerase then starts

transcribing viral mRNAs and replicating the genome, generat

ing 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 pol

ymerase-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 transmis

sion 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 trans

ported 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 vi

ral 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 im

plication 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

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.
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 (lower-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,
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 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].
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 preventative 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.

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**CONFLICT OF INTEREST**

The authors declare no conflicts of interest.

**REFERENCES**


