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Navigating the Challenges of Respiratory Syncytial Virus (RSV): Insights into Pathogenesis, Epidemiology and Vaccine Development

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ABSTRACT

Respiratory Syncytial Virus (RSV) is a significant global health concern, particularly affecting paediatric and elderly populations. Despite its non-segmented genome, which mitigates large-scale pandemics, RSV's high mutation rate presents challenges in vaccine development. RSV causes millions of infections annually, with substantial morbidity and mortality, especially among high-risk groups such as infants, the elderly, and individuals with comorbidities. The seasonal transmission of RSV varies geographically and has been influenced by the COVID-19 pandemic. Understanding RSV's transmission dynamics, clinical manifestations, risk factors, and diagnostic methods is crucial for effective management and prevention. While supportive care remains the mainstay of treatment, antiviral therapies like ribavirin and monoclonal antibodies are utilized in specific cases. Vaccines targeting RSV are under development, utilizing various platforms such as inactivated, live-attenuated, viral-vector-based, protein-based, nucleic acid-based, and subunit/VLP-based approaches. Recent advancements include FDA-approved vaccines and promising candidates in late-stage clinical trials, providing hope for mitigating RSV-related disease burden across diverse populations.

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Introduction

RSV represents a substantial burden on global health, particularly affecting paediatric respiratory health. It is a prevalent cause of respiratory tract infections in children and poses health risks to older adults as well, with morbidity and mortality rates comparable to those of influenza [1]. RSV infection impacts more than 30 million children aged five years or younger worldwide, with hospitalization needed in fewer than 10% of cases [2]. In the United Kingdom, respiratory diseases attributed to RSV are estimated to cause an average of 83 paediatric deaths per season [3]. This figure rises significantly to 8,482 deaths per year among adults aged 18 years and older, with 93% of these cases occurring in older adults aged 65 years and above [4].

A recent meta-analysis found that in 2019, there were an estimated 5.2 million cases of RSV among adults aged 60 years and older in high-income countries. This led to approximately 470,000 hospitalizations and 33,000 in-hospital deaths [5]. Epidemiological data are scarce concerning RSV infections in developing countries [5,6]. RSV infects nearly all children by the age of 2 years, with infants under 6 months being at a particularly high risk of severe infection due to their immature immune systems [7]. In older adults, the risk of severe outcomes following RSV infection is heightened due to underlying comorbidities and age-related progressive decline in immune function, a phenomenon known as immunosenescence [8]. The precise mechanism underlying the heightened severity of RSV infection in older adults has yet to be fully understood. Hospitals have observed an uptick in RSV cases in recent years, especially during peak transmission periods. However, the pattern of RSV transmission differs across various regions globally. In regions with temperate climates, RSV rates typically rise in late autumn, winter, and occasionally spring. Conversely, areas with tropical or arctic climates may encounter

RSV cases throughout the year [2].

Methodology

For this review, publications were obtained from open-access repositories such as Elsevier, PubMed, Scopus, and Google Scholar, employing the search criteria: Epidemiology, Respiratory Syncytial Virus, Structural insight, Diagnosis, Prophylaxis, Types of Vaccine were used. Along with Transmission, Spread and approved vaccine We exclusively incorporated original research papers, case studies, and reports from the CDC portal about RSV worldwide, published between 2000 and January 2024, available in English with unrestricted full-text access.

After initially screening over 300 articles, 45 were evaluated for eligibility. Seven articles meeting the inclusion criteria were included in this review. Published reports, research articles, case studies, and disease management information, along with implementation strategies, were sourced from the official websites.

Results

History and Epidemiology

In 1956, researchers discovered RSV in a colony of chimpanzees through throat swabs, observing symptoms like sneezing, coughing, and nasal discharge among the primates, indicating its highly contagious nature Initially named Chimp Coryza Agent, it was later renamed RSV in 1957 when a similar virus was isolated from infants with pneumonia and croup [9,10]. Today, RSV remains the leading viral cause of severe respiratory illness in children under five and a major contributor to infantile bronchiolitis [11]. It was later found also to affect the elderly, exhibiting a seasonal pattern of activity varying by region and year, with peaks typically occurring during winter in temperate climates and the rainy season in tropical regions [12].

However, the COVID-19 pandemic disrupted these patterns, with RSV circulation increasing in the southern United States in spring 2021 and peaking in July 2021. Due to its widespread distribution, a significant proportion of infants in the US contract RSV, with nearly all children infected by age two [11,12].

Structure of RSV

Respiratory Syncytial Virus (RSV) possesses a negative sense, single-stranded RNA genome enveloped within its structure, spanning approximately 15,222 nucleotides, and containing 10 genes that encode 11 proteins. RSV is classified within the Mononegavirales order, specifically in the Pneumoviridae family under the Orthopneumovirus genus. It is characterized as a filamentous enveloped [13]. Unlike influenza, RSV's genome is non-segmented, meaning it cannot undergo reassortment of genome segments, thereby avoiding antigenic shifts that could potentially trigger large-scale pandemics. However, like other RNA viruses, RSV exhibits a high mutation rate due to its reliance on an RNA polymerase lacking proofreading and editing capabilities. Consequently, various strains of RSV exist due to its mutable genome, despite limited antigenic variability. (CDC Respiratory Syncytial Virus, 2016) The RSV genome comprises 10 open reading frames (ORFs), encoding a total of 11 structural and non-structural proteins [14]. Among all paramyxoviruses, the initial seven genes are responsible for encoding structural proteins. These include the nucleoprotein (N), phosphoprotein (P), and RNA-dependent RNA polymerase (L), which together encapsulate the viral RNA, forming a helical assembly known as the ribonucleoprotein complex (RNP). This complex serves to protect the RNA and constitutes the minimal replication machinery. The ribonucleocapsid is encased by a structural framework created by the envelope-associated matrix (M) protein. This lattice of M protein facilitates the formation of a densely packed viral envelope adorned with three integral membrane proteins: the fusion protein (F), receptor attachment glycoprotein (G), and a short hydrophobic (SH) protein [15].

The G protein plays a role in viral attachment to the host cell, while the F protein is responsible for fusion. The SH protein functions by forming a pentameric ion channel [16]. The M2 gene contains two overlapping ORFs, giving rise to two distinct proteins: M2-1, which acts as a transcription processivity factor, and M2-2, which regulates the transition from transcription to genome replication. Following these, the initial transcribed genes are NS1 and NS2, non-structural proteins that collectively suppress apoptosis and interfere with interferon responses [13].

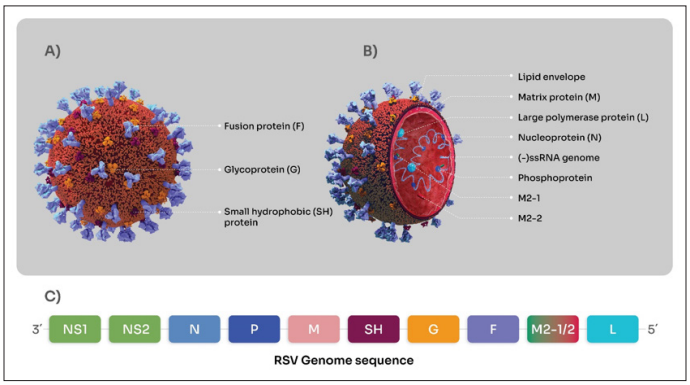

Figure 1: Schematic representation of RSV structure A. Integral Membrane Protein, B. RSV virion structure: Matrix proteins (M) are found at the inner side of the viral envelope. Four nucleocapsid and regulatory proteins function as viral transcription factors: nucleoprotein (N), phosphoprotein (P), large polymerase protein (L), and M2-1 and M2-2 proteins. NS1 and NS2 are the two non-structural proteins. C. RSV genomic RNA sequence [17].

Transmission of RSV

In tropical regions, the seasonal nature of RSV is often associated with fluctuations in temperature and rainfall. In contrast, areas with tropical climates may witness annual outbreaks during warm and rainy seasons [2,18]. The Centers for Disease Control and Prevention (CDC) notes that RSV transmission usually starts in the autumn and reaches its peak during the winter season (CDC, RSV transmission, 2023).

The increase in RSV cases during colder temperatures is linked to factors such as increased indoor crowding, which facilitates viral transmission, as well as enhanced viral stability and host susceptibility in lower temperatures [19]. Recent research suggests a potential correlation between COVID-19 and changes in RSV seasonality. Measures implemented to control the spread of SARS-CoV-2, along with changes in individual behaviours and potential viral interference, may have contributed to a delayed RSV outbreak in the summer of 2021 [2,18,19].

RSV spreads through various means like a. Inhalation of virus droplets expelled when an infected person coughs or sneezes. b. Contact with virus droplets entering the eyes, nose, or mouth, c. Direct contact with the virus, such as kissing the face of an individual with RSV, d. Touching surfaces contaminated with the virus, like doorknobs, and then touching the face before washing hands. Most initial RSV infections occur during infancy or toddlerhood, with nearly all children contracting the virus before their second birthday. However, repeat infections are possible

throughout life, and individuals of any age can become infected. (CDC RSV Transmission, 2023).

When examining the transmission dynamics of RSV, the concept of R0, or the reproductive ratio, becomes crucial. R0 signifies the virus's transmissibility, indicating the number of individuals one infected person can transmit the virus to. For RSV, R0 ranges from one to five, typically estimated at three [20].

This variability stems from various factors, including environmental, biological, and behavioral elements. The annual and seasonal variation in R0 may relate to the antigenicity of circulating strains. (Black CP, 2003) While not definitive, RSVA is suggested to have higher transmissibility, potentially resulting in a higher R0 compared to RSVB. Understanding R0 is vital for implementing effective strategies to mitigate virus transmission.

Symptoms

Natural RSV infection often leads to incomplete immunity, allowing for recurrent symptomatic infections throughout an individual's life [21,22]. As CDC published RSV typically manifests symptoms within 4 to 6 days post-infection. Common symptoms include coughing, decreased appetite, runny nose, fever, sneezing, and wheezing. These symptoms may appear progressively rather than all at once. In infants, symptoms may manifest as irritability, decreased activity, and breathing difficulties. Nearly all children will have experienced an RSV infection by their second birthday. (Symptoms and Care for RSV, CDC, 2023) Even RSV can lead to more severe respiratory infections, including bronchiolitis, characterized by inflammation of the small airways in the lungs, and pneumonia, an infection of the lung tissue itself. It is noteworthy that RSV is the primary cause of both bronchiolitis and pneumonia in infants under the age of 1. (Symptoms and Care for RSV, CDC, 2023). In infants at higher risk, such as those born prematurely, with underdeveloped or damaged airways, males deficient in vitamin D at birth, bronchopulmonary dysplasia (BPD), congenital heart disease (CHD), neuromuscular disorders, immunodeficiency, or Down syndrome, RSV is recognized as a prominent cause of lower respiratory tract infections [23].

Preventive Measures

Basic preventive measures, akin to those for other respiratory viruses, are fundamental in curbing RSV spread. These measures include avoiding close contact, regular disinfection of surfaces, thorough handwashing with soap and water for at least 20 seconds and practicing proper respiratory etiquette by covering the mouth while sneezing and coughing [24,25].

Vulnerabilities to RSV among Elderly and Infants: Factors Amplifying Risk

Elderly individuals, like transplant recipients, are susceptible to RSV due to compromised immune responses [26]. Aging leads to decreased levels of RSV-specific antibodies, increasing vulnerability. Infants, particularly those born prematurely or with underlying conditions like chronic lung disease, cyanotic heart disease, or hematologic malignancies, face a heightened risk of severe illness or mortality. Male infants, with narrower airways, are predisposed to more severe RSV illness, compounded by diminished respiratory capacity. Preterm birth exacerbates the risk due to premature immune system development and the absence of maternal antibodies. Malnutrition, especially vitamin D deficiency, further increases susceptibility. Age remains the primary risk factor [27].

Advancements in RSV Diagnostic Methods and Challenges

The classic method of diagnosing RSV was through viral culture, but it has largely been superseded by newer, more sensitive techniques. Current laboratory methods include identifying viral antigens using immunofluorescent staining or enzyme-linked immunosorbent assays, rapid LFA tests, and amplification assays focusing on viral nucleic acids, primarily RT-PCR and LAMP. Although nasopharyngeal swabs are preferred over nasal washes or nasopharyngeal aspirates in adults due to better tolerance, they often yield lower levels of the virus, leading to an underestimation of RSV infections. Studies combining sputum and paired serology with nasopharyngeal swabs have highlighted the limitations of relying solely on nasopharyngeal swabs for diagnosis [17].

The need for a rapid, point-of-care test for RSV detection is emphasized by various challenges such as sample collection, the necessity for laboratory facilities and trained personnel, high costs, expensive equipment, lengthy procedures, protocol complexity, and concerns regarding sensitivity, specificity, and potential misdiagnosis in cases of coinfections.

Approaches to RSV Clinical Care and Treatment

Supportive care remains pivotal in the clinical management of RSV, mirroring approaches to other viral infections. While options for antiviral therapy are restricted, they are increasingly considered in specific scenarios such as lung transplants, immunocompromised states, and hematopoietic stem cell transplantation (HSCT) [25]. Ribavirin is advocated for severe pediatric cases. Antipyretic medications may be utilized to mitigate fever in individuals of all age groups affected by RSV. Infants frequently encounter challenges associated with nasal congestion and rhinorrhea, leading to compromised respiratory function due to nasal obstruction. Given their reliance on nasal breathing, interventions like nasal suction and lubrication are employed to alleviate congestion, particularly in this population, to enhance respiratory performance [26].

Antiviral Therapies for RSV: Ribavirin and beyond

Ribavirin, a synthetic nucleoside analogy with broad-spectrum activity against RNA and DNA viruses, gained support from the American Academy of Pediatrics (AAP) Committee on Infectious Diseases in 1993 as the sole licensed antiviral agent for severe RSV infections. RSV immunoglobulin (RSV-IVIG, RespiGam) is a pooled hyperimmune polyclonal immunoglobulin purified from donors with high RSV-neutralizing antibody titers, initially licensed in 1996 but discontinued in 2004 due to logistical challenges and safety concerns [28,29].

Palivizumab (Synagis), a humanized monoclonal IgG1 antibody targeting RSV's F protein, has been the only approved prophylactic measure for high-risk infants since its development in 1998, albeit its use is restricted due to cost considerations [30].

Motavizumab (MEDI-524, Numax), a modified version of palivizumab, exhibited enhanced efficacy but was not approved by the FDA due to adverse reactions. Emerging treatments include ALX-0171, an inhaled nanobody, and REGN2222, a monoclonal antibody against RSV-F, currently undergoing clinical trials [31].

RSV Vaccine Types: An Exploration of Approved Options

The objective of a vaccine is to trigger an immune response that safeguards against RSV while mitigating vaccine-enhanced disease (VED) risks. Target populations for vaccine research include infants, children, the elderly, and pregnant women.

Inactivate Vaccine

Inactivated vaccines are produced by deactivating pathogens to prevent severe illness. In 1966, a formalin-inactivated RSV (FIRSV) vaccine was developed but experienced a major failure during that year's RSV season. Shockingly, 80% of vaccinated infants developed severe bronchiolitis or pneumonia, compared to 5% in the placebo group, with two fatalities. The cause of vaccine-enhanced disease (VED) remains debated [32].

Live-Attenuated Vaccines

Live-attenuated vaccines (LAVs) are engineered by gradually reducing the temperature during virus passaging and deleting portions of the genome to maintain sufficient viral RNA replication for eliciting an adequate antibody response [29,33]. These vaccines induce robust immune responses akin to natural infection without the need for adjuvants, often requiring only a single dose for long-term immunity [34]. However, LAVs are generally avoided in immunocompromised individuals and pregnant women due to risks of severe infection or congenital transmission, respectively. Several live-attenuated RSV vaccine candidates, including BLB-201, CodaVax-RSV, RSV-ΔG, rBCG-N-hRSV, SeVRSV, MV-012-968, VAD00001, RSV ΔNS2/Δ1313/I1314L, RSV LID/ΔM2–2/1030s, RSV 6120/ΔNS2/1030s, RSV 6120/F1/G2/ΔNS1/RSV 6120/ΔNS1, are undergoing or have completed clinical trials [34, 35]. Some candidates target the deletion of the M2-2 gene, which mediates the transition from transcription to RNA replication, potentially enhancing neutralizing antibody responses [36].

Additionally, deletion of the SH gene, which may inhibit cell apoptosis or be involved in viral fusion, and the NS2 gene, known to promote epithelial cell shedding and inhibit host antiviral responses, are being explored as potential targets for live-attenuated vaccine development [29,37].

Recombinant Viral-Vector-Based Vaccines

Recombinant viral-vector-based vaccines utilize modified viruses as delivery systems for desired genetic information, inducing a targeted immune response in the host organism. These vaccines harness the vector's ability to efficiently produce proteins, accelerating production timelines significantly [34,38]. Viral vectors, such as adenoviruses, activate both cellular and humoral immunity, with replication-competent vectors mimicking natural infection to enhance vaccine efficacy. Adenoviral-vector-based RSV vaccine candidates, like GlaxoSmithKline's ChAd155-RSV and GSK3003891A, demonstrate promising immune responses in Phase II trials. Additionally, oral vaccine candidates, such as VXA-RSV-f, are being explored for their ability to elicit mucosal IgA and cellular immunity. Modified Vaccinia Ankara (MVA), a non-replicating vector, shows potential in eliciting both cellular and humoral responses, exemplified by candidates like PanAd3-RSV and MVA-RSV, which have shown safety and efficacy in preclinical models [29,39].

Protein-Based Vaccines

Protein-based vaccine candidates encompass whole-inactivated viruses, subunit antigens, and particle-based formulations. Several protein-based vaccine candidates are currently undergoing clinical trials. Particle-based vaccines vary in size and serve as adjuvants, facilitating gradual antigen release [40]. Clinical trials evaluating Novavax's RSV F-protein nanoparticle vaccine, comprising nearly the entire F glycoprotein, have been completed and are ongoing. These trials assess the vaccine both with and without an aluminum hydroxide adjuvant [29].

Nucleic Acid-Based Vaccine

mRNA serves as a vaccine platform, delivering genetic instructions solely for targeted proteins, thereby enhancing safety by minimizing the risk of interference or alteration of the host's genetic materia [41]. However, the necessity for multiple doses to maintain immunity poses challenges related to lipid aggregation, which can impact both safety and efficacy. Examples of vaccine candidates utilizing this platform include mRNA-1345, RSV mRNA LNP CL-0059, and RSV mRNA LNP CL-0137 [34].

Subunit/Virus-Like-Particle (VLP)-Based Vaccines

Subunit vaccines target older populations and children with pulmonary conditions or compromised immunity. Trials primarily evaluate humoral responses, effectively boosting antibody levels, particularly in those with low pre-vaccination titers. Maternal immunization aims to enhance neutralizing antibody levels in infants through transplacental transfer, offering protection in their early months. This approach may mitigate RSV disease burden in healthy near-term infants without passive prophylaxis, though concerns about vaccinating pregnant women could impede evaluation, despite evidence of safety and enhanced protection in infants (Sales & Wang, 2003) Subunit vaccines contain purified fragments of the target pathogen, such as peptides, proteins, or polysaccharides, devoid of the pathogen's entire genome, resulting in a non-virulent vaccine with enhanced safety. IVX-A12, V-306, DPX-RSV(A), VN-0200, BARS13 (ADV110), DS-Cav1 (VRC-RSVRGP084-00-VP), Arexvy/RSVPreF3 OA (GSK3844766A), and Abrysvo/RSVpreF represent subunit vaccines developed for RSV [34].

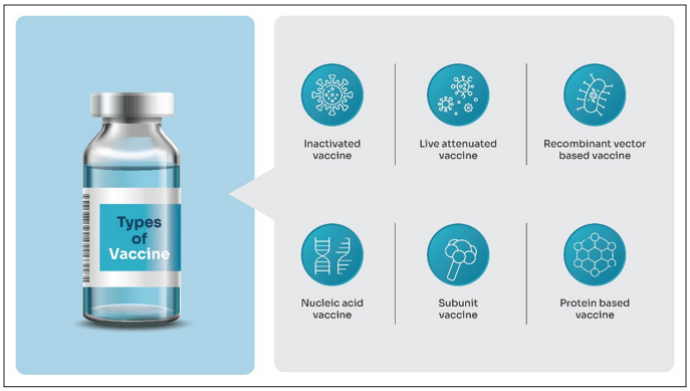

Figure 2: Types of RSV Vaccine

Approved and Investigational RSV Vaccines: Current Landscape

Arexvy, the first FDA-approved drug for active immunization against RSV, is indicated for adults aged 60 years and older, with post-marketing surveillance studies underway to assess potential risks such as atrial fibrillation, Guillain–Barré syndrome, and acute disseminated encephalomyelitis. Pfizer's Abrysvo, also approved for older adults, shows promise as a maternal candidate to reduce RSV disease in infants, based on completed and ongoing clinical trials [34]. Currently, two vaccines are nearing market approval, undergoing Phase III clinical development for the older adult population. MVA-BN-RSV by Bavarian Nordic received a Breakthrough Therapy Designation from the FDA in February 2022 for inducing immunity against RSV-induced lower respiratory tract disease in adults aged ≥60 years. It is also part of the EMA's priority medicines (PRIME) scheme for the same indication. The Phase III VANIR study is expected to conclude in December 2024. Moderna's mRNA-1345 is also in Phase III development and obtained Fast Track designation from the FDA

for adults in August 2021 [15, 34].

Discussion/ Conclusion

In conclusion, Respiratory Syncytial Virus (RSV) continues to pose a significant threat to global health, particularly impacting vulnerable populations such as infants, the elderly, and individuals with underlying health conditions. Despite decades of research, challenges remain in developing effective vaccines and treatments against RSV. However, recent advancements in vaccine development, along with an improved understanding of RSV transmission dynamics and clinical management, offer hope for better control of RSV-related morbidity and mortality. It is imperative to continue investing in research efforts to accelerate the development of safe and efficacious RSV vaccines and therapeutics, ultimately reducing the burden of RSV-associated respiratory illness worldwide. Additionally, public health measures such as improved hygiene practices and vaccination strategies will play a crucial role in mitigating the spread of RSV and protecting vulnerable populations. Collaboration between researchers, healthcare professionals, policymakers, and communities are essential to effectively combatting RSV and improving global respiratory health [42-45].

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