

RSV Burden of Disease in Adults - a new threat

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Abstract

English:

Respiratory syncytial virus (RSV) is responsible for lower respiratory tract infections across all age groups worldwide. Initial exposure to RSV in infants and young children can lead to severe bronchiolitis, which has the potential to be life-threatening. Among older children and healthy adults, recurrent upper respiratory tract infections caused by RSV are frequent, varying in intensity from asymptomatic infection to symptomatic upper respiratory tract disease. The presence of specific comorbidities (cardiopulmonary conditions, including COPD and CHF, and immunocompromising conditions) increases the likelihood of severe disease in adults (1).

This editorial provides a review of the burden of RSV disease among adults, population groups at increased risk of developing severe RSV disease, the current status of surveillance systems and RSV prevention strategies in adults, including the use of RSV vaccines in adults, recently licensed for use.

Keywords

respiratory syncytial virus • RSV • RSVpreF

Virusul Sincițial Respirator la adulți - o nouă amenințare

Rezumat

Romanian:

Virusul sincițial respirator (VSR) determină apariția infecțiilor tractului respirator inferior la toate grupele de vârstă din întreaga lume. Expunerea inițială la VSR la sugari și copii mici poate duce la bronșiolită severă, care poate pune viața în pericol. Printre copiii mai mari și adulții sănătoși, infecțiile recurente ale tractului respirator superior cauzate de VSR sunt frecvente, variind în intensitate de la infecție asimptomatică la boală simptomatică a tractului respirator superior. Prezența unor comorbidități specifice (afecțiuni cardiopulmonare, inclusiv bronhopneumopatie obstructivă cronică și insuficiență cardiacă și afecțiuni imunosupresoare) crește probabilitatea apariției unei boli severe la adulți (1).

Acest editorial oferă o revizuire a poverii bolii cauzate de VSR în rândul adulților, grupele de populație aflate la risc crescut de a dezvolta forme severe ale bolii cauzate de VSR, situația actuală a sistemelor de supraveghere și a strategiilor de prevenție a infecției cu VSR în rândul adulților, inclusiv utilizarea vaccinurilor pentru prevenția VSR la adulți, licențiate recent pentru utilizare.

Cuvinte-cheie

virus sincițial respirator • VSR • RSVpreF

Introduction

Respiratory syncytial virus (RSV) is an enveloped negative-sense, single-stranded ribonucleic acid (RNA) virus belonging to the *Orthopneumovirus* genus of the *Pneumoviridae* family, which also includes the human parainfluenza, metapneumovirus, and measles virus (2-5). Two subtypes of

RSV have been identified, RSV A and RSV B, and circulate simultaneously during respiratory virus season (6).

In Europe, RSV seasons begins in October and lasts until March. The RSV epidemic in Europe progresses rapidly at the beginning of October and the median start of the RSV

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season is at beginning of December. The median length of the RSV season is about 16–18 weeks, and the peak is around end of January (7). RSV is very infectious, and it can be spread through direct oral contact, respiratory droplets, or indirect exposure to the respiratory secretions of individuals who are infected (8). Although the risks of this virus were recognized in previous decades, they are now being reassessed and emphasized.

Burden of disease

Clinical symptoms of RSV infection may vary from mild, cold-like symptoms (runny nose, coughing, sneezing, fever, wheezing and/or decrease in appetite), to severe respiratory disease (e.g., pneumonia or bronchitis) (9,10).

In older adults and in adults at high risk, RSV infection can cause serious respiratory illnesses and complications (including secondary bacterial pneumonia and influenza-like diseases) that significantly affect patient morbidity and mortality (2,12,13) and can worsen a patient's underlying condition like congestive heart failure, chronic obstructive pulmonary disease (COPD) or asthma (15). Children and older adults and adults with certain underlying comorbidities that put them at high risk, such as immunocompromising conditions, chronic cardiopulmonary disease, renal and liver disease, and diabetes are at a higher risk of experiencing severe illness (2,11,12,17).

RSV is one of the leading causes of respiratory illness in older adults, next to influenza and COVID-19 (14). Contrary to children, who will often develop a recognizable bronchiolitis because of an RSV infection, RSV infection in adults is underrecognized.

Besides the presence of underlying comorbidities, the main factors leading to the increased burden of RSV and severe forms of disease in elderly population are ageing and immunosenescence. Pulmonary function is declining with age, compromising the natural ability to overcome infections caused by respiratory pathogens. Immunosenescence is another contributing factor, which describes the progressive dysregulation and decline of the immune system, that leads to increased susceptibility to pathogens (18,19).

RSV is associated with increased morbidity and mortality in elderly population. It is estimated that in United States of America, each year RSV causes 60,000-160,000 hospitalizations and between 6,000-10,000 deaths among adults 65 years and older (20). According to European Centre for Disease Prevention and Control (ECDC) in the EU, Norway and the United Kingdom, RSV is responsible for on average of 158 000 hospitalizations per year (21), in adult population. The rate of RSV-associated acute respiratory illness (ARI) depends on the virus seasonality, age, and comorbidities. Based on a systematic literature review, in 2015 the annual rate RSV-ARI (acute respiratory infections) in the community was

estimated to be 6.7 per 1,000 persons per year (95% confidence interval [CI]: 1.4-31.5) in the older adults in industrialized countries (22). Another meta-analysis from 2022, concluded that when analyzing adult populations with comorbidities, from high-income/industrialized countries, the overall incidence of RSV-ARI was 30.3 (95%CI:15.3-59.9) per 1,000 persons per year/season, indicating a substantial burden of disease (23).

Although the burden of RSV is significant, it still remains an underdiagnosed and underreported condition in adults. Testing for RSV infection in adults is not routinely performed. The lack of specific guidelines for the diagnosis and management of RSV in adults, the low clinical awareness of RSV due to similar presentation to other respiratory illnesses, and lack of sensitivity and reporting delay of some testing modalities are the main reasons for this situation (24). Most existing RSV surveillance is conducted within the context of existing influenza surveillance systems, which may contribute to underreporting of RSV cases.

In the future we could face a continuously increasing burden of RSV, with increasingly pressure on healthcare systems, due to the ageing of the population at global level and overlapping in respiratory viruses season (RSV, influenza, COVID-19), with similar clinical symptoms and manifestations.

Populations at risk for severe RSV

According to Center of Disease Control and Prevention (CDC), adults at highest risk for severe RSV infection are (25):

1. Older adults
2. Adults with chronic heart or lung disease
3. Adults with weakened immune systems

ECDC describes as high-risk groups the adults aged 65 years old and above and individuals with specific comorbidities (26). Among the comorbid conditions that are significantly associated with worse outcomes (hospital admission or readmission, emergency department (ED) visits, ICU admission, mortality, etc.) are cardiopulmonary conditions (including COPD and CHF) and immunocompromising conditions (12, 23,27-30).

Adults living in long-term care facilities (LTCFs), nursing homes, and residential living facilities are at greater risk for influenza and RSV infections compared with their counterparts residing in the community in part due to their decreased functional capacity as well as the institutional nature of LTCFs, where exposure to coresidents, visitors, volunteers, and staff is more common (31-33).

RSV Management – Surveillance systems

Due to the fact that RSV is an important pathogen in older adults, with significant burden of disease, the implementation

of preventive measures, confirmed diagnosis, reporting/surveillance systems and clinical RSV guidelines are a priority. According to ECDC, RSV is not a mandatory reportable disease in European Union (EU), but some countries are performing surveillance of RSV as part of surveillance initiatives for influenza virus and SARS-CoV2. There is large variation regarding the cases definitions that are utilized, types of collected data, the laboratory tests used and the objectives of the surveillance systems.

Due to increasing circulation of respiratory viruses, in December 2022, ECDC made the following recommendations for public health authorities in the EU (26):

1. *implement risk communication activities for the public including active promotion of vaccinations against seasonal influenza and COVID-19;*
2. *increase healthcare professionals' awareness and enhance hospital preparedness;*
3. *provide RSV prophylaxis to high-risk infants in accordance with national guidelines;*
4. *implement appropriate infection prevention and control (IPC) measures based on the local epidemiological situation, particularly for vulnerable groups within healthcare facilities, including long-term care facilities;*
5. *promote good hygiene practices in the community and consider non-pharmaceutical interventions (NPIs), including targeted guidance for risk groups and caregivers of vulnerable groups;*
6. *where possible, implement and improve surveillance of RSV and testing for respiratory pathogens.*

Regarding surveillance of RSV, ECDC recommends the inclusion of RSV in the sentinel surveillance systems for acute respiratory infections (ARI) and severe acute respiratory infections, in order to collect sufficient data to monitor the intensity of circulation and spread of respiratory viruses. Upper respiratory specimens from patients with respiratory symptoms should be tested, when possible, using multiplex PCR assays to detect relevant respiratory viruses. Another aspect that should be taken into consideration is implementation of genomic surveillance, RSV typing (A and B), and partial (F and G proteins) or whole genome sequencing.

Current strategies for prevention and management of RSV infection in the adults.

Until recently, due to the absence of an existing RSV vaccine, preventive measures depended on implementing standard infection control practices that aim to stop the transmission of the virus. These practices include regular handwashing, covering coughs or sneezes with a tissue or one's arm, using face masks when exhibiting symptoms of the disease, and appropriately disinfecting objects and surfaces as required.

At present, there are no specific antiviral therapies available for the treatment of RSV (34). In older adults, supportive care for RSV infection involves administering fluids, oxygen, and

antipyretics to alleviate symptoms. Antivirals, such as ribavirin are sometimes used with the management of severe illness; however, its effectiveness has not been established (35).

Vaccination may provide the best option for prevention of RSV in older adults and adults at high risk. Recently, during the first months of 2023, 2 RSV vaccines for older adults were licensed (36,37).

Since older adults are at a higher risk for more severe outcomes of RSV infection that may result in hampering public health services, the introduction of RSV vaccines, which had proven to be safe and effective, will help substantially reduce this burden by preventing hospitalization and related morbidity after an RSV infection, which could also impact quality of life in this vulnerable population. Furthermore, by reducing public health load, healthcare resources could continue to support all patients during critical respiratory virus season.

Vaccination an important action to protect adult

There are some licensed vaccines in this moment for people over 60 years and above like:

1. **RSV preF vaccine** - Respiratory syncytial virus vaccine (bivalent, recombinant) (37)

It is indicated for active immunisation of individuals 60 years of age and older for the prevention of acute respiratory disease and lower respiratory tract disease caused by RSV. A single dose of 0.5 mL should be administered. It is recommended an intramuscular injection into the deltoid region of the upper arm and RSVpreF can be administered concomitantly with seasonal influenza vaccine (QIV, surface antigen, inactivated, adjuvanted).

The mechanism of action started from the two recombinant stabilised RSV prefusion F antigens representing subgroups RSV A and RSV B. Prefusion F is the primary target of neutralizing antibodies that block RSV infection. Following intramuscular administration, the prefusion F antigens elicit an immune response, which protects against RSV-associated lower respiratory tract disease. Efficacy and safety of RSVpreF vaccine in adults were evaluated in *Efficacy study in Older adults Immunized against RSV disease (RENOIR)* (38) trial. This is an ongoing phase III, multicenter, randomized, double-blind, placebo-controlled study started for evaluating the efficacy, immunogenicity, and safety of RSVpreF in adults aged ≥ 60 years during the first RSV season and the long-term immunogenicity and efficacy of RSVpreF across two RSV seasons compared with placebo. Eligible participants were enrolled and randomised 1:1 ratio to receive one intramuscular injection of unadjuvanted RSVpreF vaccine at a dose of 120 μ g (containing 60 μ g each of RSV A and RSV B antigens) or placebo. RSVpreF was highly efficacious against RSV-LRTI (lower respiratory tract infection) during the first season with a vaccine efficacy of 66.7% (96.66% CI: 28.8%, 85.8%) in reducing RSV-LRTI cases with ≥ 2 symptoms,

and vaccine efficacy of 85.7% (96.66% CI: 32.0%, 98.7%) in reducing RSV-LRTI with ≥ 3 symptoms, versus placebo. RSVpreF was efficacious against RSV-ARI (acute respiratory infection) during the first season, with a vaccine efficacy of 62.1% (96.66% CI: 32.0%, 98.7%), versus placebo. In the same time it was a safe and well tolerated vaccine with local and systemic events mostly mild to moderate and short lived. Adverse events profile did not suggest any safety concerns for RSVpreF vaccination in adults 60 years of age and older (39).

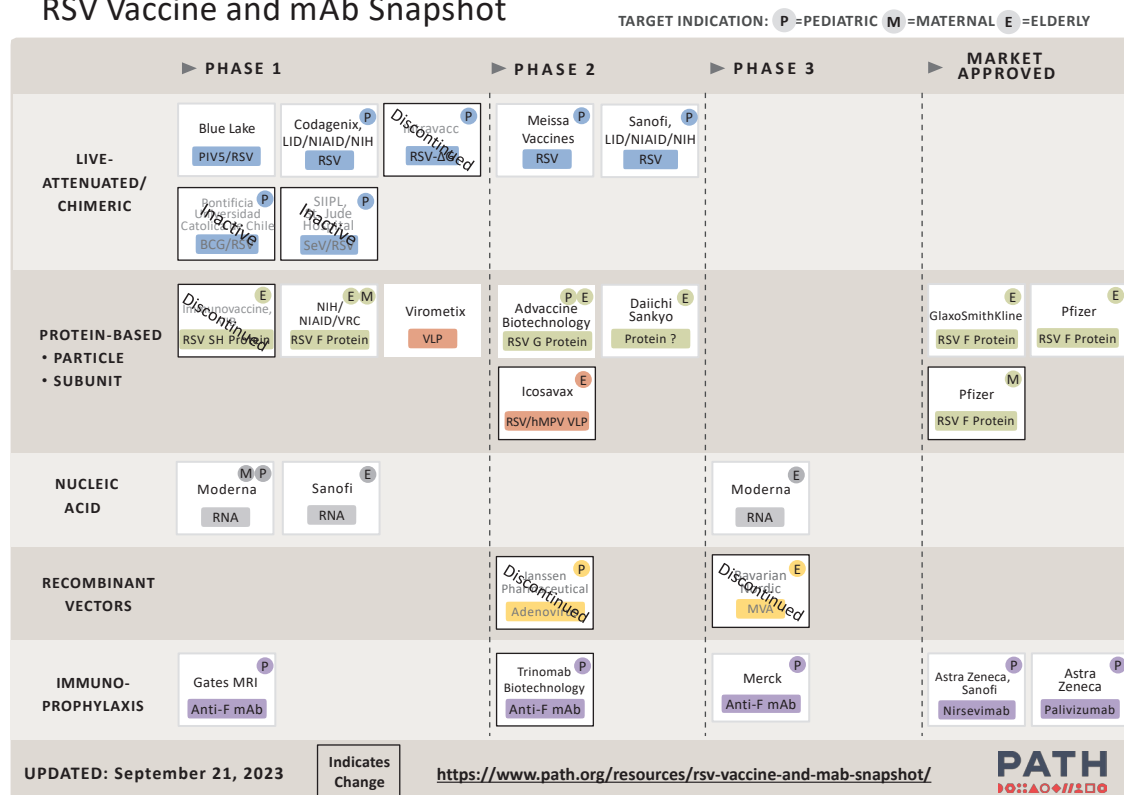
2. RSVPreF3 vaccine - Respiratory Syncytial Virus recombinant glycoprotein F stabilised in the pre-fusion conformation (40) is another offer

It is indicated for active immunization for the prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus in adults 60 years of age and older. Administered as a single dose, for intramuscular injection only, preferably in the deltoid muscle RSVpreF3 can be administered also concomitantly with seasonal influenza vaccine (quadrivalent, standard dose, unadjuvanted, inactivated). By combining the RSV-specific antigen, F-protein in prefusion conformation, with an adjuvant system (AS01E), RSVpreF3 is designed to enhance antigen-specific cellular immune response and neutralizing antibodies response in individuals with pre-existing immunity against RSV. The adjuvant AS01E

facilitates the recruitment and activation of antigen presenting cells carrying vaccine-derived antigens in the draining lymph node, which in turn leads to the generation of RSVPreF3-specific CD4+ T cells. Efficacy against RSV-associated LRTD in adults 60 years and older was evaluated in an ongoing, Phase III, randomised, placebo-controlled, observer-blind clinical study. The primary population for efficacy analysis included 24 960 participants randomised equally to receive 1 dose of RSVpreF3 vaccine and placebo. At the time of the primary efficacy analysis, participants had been followed for the development of RSV associated LRTD for a median of 6.7 months. The primary objective was to demonstrate the efficacy in the prevention of a first episode of confirmed RSV-A and/or B associated LRTD during the first season. Efficacy in preventing first RSV-associated LRTD with an onset from 15 days after vaccination compared to placebo was 82.6% (96.95% confidence interval of 57.9% to 94.1%) in participants 60 years of age and older. Vaccine efficacy against RSV-LRTD was observed through the median follow-up period of 6.7 months. The vaccine efficacy against RSV A-associated LRTD cases and RSV B-associated LRTD cases was 84.6% (95% CI [32.1, 98.3]) and 80.9% (95% CI [49.4, 94.3]), respectively.

3. Several vaccine candidates are currently in development for RSV infection (41)

RSV Vaccine and mAb Snapshot



RSV Vaccine Recommendations

Health organizations around the globe acknowledge the limitations in providing preventive care for RSV infection and have recommended including primary or secondary preventive measures for RSV in their guideline publications (42-45).

Recently, in June 2023, the Joint Committee on Vaccination and Immunisation (JCVI) released an independent report (46) with advice on RSV immunization programme in United Kingdom. Regarding the programme for older adults, the committee noted that an *“RSV vaccine programme for adults aged 75 years and above could be cost effective at a potential price that combines the cost of the product and its administration, noting that this would be influenced by multi-year protection from a single dose.”*

As one of the leading causes of respiratory illness in older adults and adults at higher risk, RSV infection can cause serious respiratory illnesses and complications that substantially affect patient morbidity, mortality, and health-related quality of life. Additionally, RSV exerts a significant economic burden on healthcare systems and is often underestimated due to limitations in diagnosis. RSV vaccines represent an opportunity to protect older adults from severe RSV illness.

Funding

None.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

No informed consent was necessary.

Data Availability Statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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