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Respiratory Syncytial Virus infection: New prevention strategies

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ABSTRACT

Respiratory Syncytial Virus is the most common respiratory pathogen in infants and young children. Despite its global impact on human health, no effective treatment is available except for supportive therapy. In the last two decades, our understanding of the pathogenesis and immunopathology of RSV have continued to evolve, leading to significant advancements in RSV prevention strategies. These include both the development of new potential vaccines and the successful implementation of passive immunization, which, together, will provide coverage from infancy to old age. In this review, we provide an update of RSV prevention.

The Respiratory Syncytial Virus (RSV) is the main agent causing hospitalizations for lower respiratory tract infections (LRTIs) in children, especially those related to bronchiolitis and pneumonia.[1] Nearly 70 % of infants are infected with RSV in their first year of life, and nearly all children (90 %) are infected within the first two years of life, with up to 40 % of these developing a LRTI with the initial episode.[2] Globally, RSV causes nearly 34 million LRTI and 3.4 million hospitalizations per year in infants and children < 5 years of age, with an estimated annual increase of 10 %.[1] In many countries, including Italy, RSV currently represents a public health issue.[3]

Although preterm infants, children with congenital heart or chronic lung disease, neuromuscular disorders or Down's syndrome are the subjects with the highest risk of severe disease, most the hospitalized paediatric cases occur amongst otherwise healthy younger children.[4]

In addition to acute disease, there is evidence suggesting that RSV infection in childhood may trigger persistent or recurrent wheezing and asthma in later life, linking RSV morbidity to chronic illness.[4]

The virus is characterized by a large envelope and negative-sense RNA, coding for 11 glycoproteins. Two main proteins of the lipidic envelope, the fusion protein (F) and the G protein, are antigenically significant, thus inducing neutralizing antibody response. Considering the different *in vitro* reaction to monoclonal antibodies due to the virion external G protein, RSV has been classified into two subtypes, A and B. These two major serotypes can simultaneously circulate during epidemic season, but, usually, one prevails over the other. RSV genome sequencing has enabled the identification of multiple genotypes. RSV is continuously evolving leading to the emergence of new genotypes and the disappearance of older ones. Genetic modifications have been detected mostly in the RSV G gene, whereas the F glycoprotein sequence is highly conserved; RSV F protein is initially expressed as a meta-stable state (pre-fusion, RSV pre-F) on the surface of the virus and its function is to drive membrane fusion between the viral envelope and the host cell. To initiate fusion, pre-F undergoes a dramatic conformational shift, resulting in a very stable post fusion form (F).[5,6]

In the last decades many trials have been carried out in order to define which are the best therapies, both pharmacological and non-pharmacological but there is a paucity of specific and non-specific approaches used to treat RSV infection. None of the medical therapies investigated have shown clear efficacy.

Emphasis remains on the prevention of severe disease and hospitalization. Moreover, as sterilizing immunity to RSV is not achieved through infection and, thus, reinfection occurs throughout life in children and adults, the need for efficient, long-standing immunization is imperative. The first vaccination for RSV was assessed shortly after the first isolation of RSV in severely ill babies. Unfortunately, the initial formalin-inactivated RSV vaccine showed that upon natural exposure to RSV, infants who were vaccinated experienced vaccine-enhanced RSV disease (ERD), with an 80 % admission rate and the death of two infants.[7] Consequently, ERD stalled the development of RSV vaccines for many years due to safety concerns.

However, as our understanding of RSV structural biology and the mechanism of action has continued to evolve, there have been many

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advancements in RSV prevention strategies. Stabilisation of the pre-F conformation of the RSV F protein has led to the determination of viral epitopes that elicit highly neutralising antibodies and therefore they are used as a target for many anti-RSV monoclonal antibodies (mAbs) and vaccines in development.[6]

MAbs are intended for use in neonates or young infants to reduce the risk of the first RSV infection. On the contrary, vaccines can be administered to pregnant women in order to prevent first RSV infection in neonates and younger infants and to infants, older children, and old adults to prevent infection in naïve or already naturally immunized subjects.

Monoclonal antibodies (mAbs)

For years, chances of prevention of RSV infection were confined to palivizumab, a humanized mAb against the RSV F protein, inhibiting RSV entry and infection. Palivizumab is administered intramuscularly on a monthly basis during the RSV season. The main disadvantage of palivizumab is the cost and limited duration of effect based on the half-life of the antibody. The need for repeated monthly administration is associated with missed doses, reducing the treatment's overall efficacy and the cost has limited its widespread use, especially in low-income country.[8] The selection of the population who receive this immune prophylaxis varies between jurisdictions, but the aim is to target high-risk infants (e.g., prematurity, severe bronchopulmonary dysplasia, congenital heart disease, or severe immunodeficiency) in order to reduce severe disease in a cost-effective manner.

This results in millions of infants remaining at risk of severe or even life-threatening disease every year.

In recent years, hundreds of new mAbs with greater efficacy and fewer logistical barrier to administration than Palivizumab were developed. To increase efficacy, mAbs targeting highly neutralization sensitive epitopes were produced.[9]

In November 2022, the EMA approved a new long-acting, human, recombinant mAb for the prevention of RSV infection in newborns and infants during their first RSV season (nirsevimab, Beyfortus, AstraZeneca/Sanofi Pasteur).[10] Nirsevimab targets the highly conserved site Ø of the prefusion conformation of the RSV F protein and contains a triple aminoacid substitution in the Fc domain that extends its half-life, allowing for a single dose to cover a typical RSV season in regions with temperate climates. In 2020, a phase 2b, randomized, placebo-controlled clinical trial evaluated nirsevimab in a single 50 mg intramuscular dose in 1453 healthy preterm infants born at a gestational age between 29 and 34 weeks and 6 days and reported a reduction in the risk of RSV hospitalization of 78.4 % (95 % CI, 51.9 to 90.3), maintained for 150 days after dose administration.[11] In 2022, a phase 3, randomized, placebo-controlled clinical trial evaluating the efficacy of nirsevimab in 1490 late preterm (at least 35 weeks of gestational age) or full-term neonates reported a 74.1 % reduction (CI 95 %, 49.6 to 87.1) in medical care related to lower respiratory tract infections caused by RSV.[12] Nirsevimab was safe and well tolerated. Total number of adverse events was similar in treated children and controls (13.4 % vs 12.8 %) as it was the incidence of severe adverse events (6.8 % vs 7.3 %), none of which was considered related to Nirsevimab or placebo.[12] These findings, together with an expected low price, made several experts think that this drug could totally modify the total RSV burden in neonates and infants.

Maternal immunization

Maternal immunization is a promising potential strategy for protecting infants during their period of greatest vulnerability to RSV infection and severe disease. Maternal immunization avoids the challenges of direct neonatal immune system including impaired antibody affinity maturation and less efficient antigen presentation. The aim of vaccination in pregnancy is to boost the maternal RSV antibody levels that will be available in neonates through the trans placental transfer and to maintain this protective level for 3–6 months of life. One of the challenges to maternal vaccination is the timing: depending on the time of year in which a third trimester vaccination occurs there is a risk that any conferred immunity may not last throughout the infant's first RSV season. It is expected that passive immunization continues during breastfeeding period, protecting the infant from early and recurrent infections. Therefore, the protected population might be more limited in cases of extreme prematurity where the infant may not receive the full benefit of antibody transfer.[9]

Recently (August 2023), the US FDA has approved the first RSV vaccine for use in older adults and during the third trimester of pregnancy, especially between the 32nd and 36th week of gestational age (Pfizer's Abrysvo). Abrysvo is a bivalent subunit vaccine candidate based on developing the prefusion F protein as a stable molecule in this preF formulation administered as a single-dose regimen. The antigens that compose the vaccine are equal to 60 μg of the preF protein from both RSV-A and RSV-B strains of the virus.[13] Subsequently, the EMA licensed Abrysvo in the European Market as an immunizing agent against LRTI in the age group of adults 60 years of age or older and during the 24th and 36th weeks of gestational age for maternal use to provide infant protection.[14] As stated in the prescribing information of Abrysvo, a not statistically significant disproportionate incidence of preterm births occurred between vaccinees and placebo recipients. For this reason, it is recommended to use the vaccine according to the indication (32th–36th weeks), because a causality between vaccination and preterm birth cannot be excluded based on the existing data.[15]

Infant immunization

Paediatric RSV vaccine development has been complicated by the immaturity and Th2-bias of the infant immune system, by the presence of maternal neutralizing antibodies, and by the risk of development of enhanced respiratory disease (ERD) after infection following immunization. To overcome these problems and to produce safe and effective vaccines, several methods of production have been used. Vaccines under development include protein vaccines that use stabilized pre-F protein subunits or virus-like particles, live vaccines that include attenuated RSV strains, or virus vectors expressing RSV proteins or mRNA vaccines. During the period of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, mRNA vaccines were manufactured and licensed for market use in a short period of time, constituting a source of information regarding adverse events through large-scale pharmacovigilance. High levels of immunity induction can be reached without invading the genome of the recipient, providing a good safety profile.

At the time of writing, the US FDA has approved two RSV vaccines for use in older adults (GSK's Arexvy and Pfizer's ABRYSVO),[16] but no vaccine is still approved in paediatric population.

In conclusion, the future management of RSV prevention will likely combine the different strategies of active and passive immunization. In the neonatal and early infancy periods, the immunization goals may be achieved by passive mAbs administration or maternal vaccinations, or a combination of both. As passively acquired immune responses wane over time, active immunization through vaccines will provide complementary protection for the older paediatric and adult age groups. Within the next years, a variety of immunizing agents is expected to be approved for market use, collecting data from current clinical studies.

CRediT authorship contribution statement

Anna Chiara Vittucci: Writing – review & editing. **Livia Antilici:** Writing – original draft. **Andrea Dotta:** Supervision. **Renato Cutrera:** Supervision. **Alberto Villani:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

ACV participated at advisory boards and has received consulting fees from Sanofi and Pfizer. AV participated at advisory boards sponsored by MSD. All other authors declare no competing interests.

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