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REVIEW

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RSV disease in infants and young children: Can we see a brighter future?

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ABSTRACT

Respiratory syncytial virus (RSV) is a highly contagious seasonal virus and the leading cause of Lower Respiratory Tract Infections (LRTI), including pneumonia and bronchiolitis in children. RSV-related LRTI cause approximately 3 million hospitalizations and 120,000 deaths annually among children <5 years of age. The majority of the burden of RSV occurs in previously healthy infants. Only a monoclonal antibody (mAb) has been approved against RSV infections in a restricted group, leaving an urgent unmet need for a large number of children potentially benefiting from preventive measures. Approaches under development include maternal vaccines to protect newborns, extended half-life monoclonal antibodies to provide rapid long-lasting protection, and pediatric vaccines. RSV has been identified as a major global priority but a solution to tackle this unmet need for all children has yet to be implemented. New technologies represent the avenue for effectively addressing the leading-cause of hospitalization in children <1 years old.

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Introduction

The present study provides a narrative review of the recently published data on Human Respiratory Syncytial Virus (RSV) epidemiology and preventive interventions. RSV is a seasonal, highly contagious pathogen belonging to the *Pneumoviridae* (genus orthopneumovirus), a family of negative-strand RNA viruses.[1–7] RSV is a common cause of respiratory illness throughout life, but particularly in infants and older adults it is associated with significant morbidity and mortality.[8–10] For instance, around 90% of all children will be infected with RSV in their first two years of life, and up to 40% of these will develop a Lower Respiratory Tract Infection (LRTI) with the initial episode.[10–14]

RSV-associated LRTI are characterized predominantly as bronchiolitis or pneumonia, and can manifest with both acute and long-term consequences to the developing lungs.[15] On the one hand, RSV infections account for around 60% to 80% of infant bronchiolitis and up to 40% of pediatric pneumonias.[16,17] On the other hand, infants who have RSV bronchiolitis in early life may be at increased risk of developing asthma later in childhood, and at increased risk of recurrent wheezing.[18,19]

Management of RSV infection is mainly supportive and aims at both maintaining adequate oxygenation and hydration. No specific drugs are currently available. Hospitalization is required when either oxygen supplementation, or rehydration, or both are needed. Oxygen supplementation may be delivered via nasal continuous positive airway pressure (CPAP), or high flow nasal cannula (HFNC) therapy, or mechanical ventilation, depending on the severity of disease (eg, hypoxemia, respiratory failure).[20,21] Bronchodilators and corticosteroids have not shown a benefit for the management of RSV bronchiolitis and, therefore, are not recommended.[22–24]

Prevention of RSV illnesses in all infants is a major public health priority,[25] however, despite more than 60 years of attempted vaccine development,[26] there are no licensed vaccines or preventative options for all infants. The only currently approved prophylaxis for RSV is palivizumab (SYNAGIS®; USA approval 1998, EU approval 1999),[27] with license limited to infants who are either born at ≤35 weeks of Gestational Age (wGA) or children <2 years of age with chronic lung disease of prematurity [CLD] or hemodynamically significant congenital heart disease [CHD] (Synagis PI 2020, Synagis SmPC 2021). The group of infants eligible for this preventative may be further limited by local recommending bodies.

Close examination of the burden of RSV disease below demonstrates that in order to mitigate this impact significantly, protection from RSV would need to begin at the same time as the epidemic season, should last throughout the whole season and cover the entire cohort of infants entering their first epidemic season.[1–28–30]

Epidemiology and burden of disease

Before exploring the burden of RSV illness in a given birth cohort, analyses should take into account a number of factors, including: the age of the infant at the time of illness (which determines whether or not they are considered to be born in the season or out of season), gestational age at birth and preexisting conditions.[7–9–17–27–31–35]

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RSV is a major global health threat.[3,36] A recent systematic review estimated a global burden of disease equal to 33.1 million clinical cases in children less than 5 years of age in 2015.[36] Interestingly, around 90% of cases did occur in low- to middle-income countries, with 2.8 million cases (95% confidence intervals 1.1 to 6.1) in high-income countries.[36] Although RSV infections occur throughout the year, RSV causes disease in clearly defined and somewhat predictable seasonal epidemics. In much of the Northern Hemisphere (including the USA, the UK, France, and Germany), RSV outbreaks usually begin in November or December, reach their peak during the winter month of January or February, and end in March or April. There are usually no outbreaks during the warm, summer season. Instead, new infections occur at low rates. In contrast, in humid tropical locations, RSV outbreaks peak closer to the rainy season.[7,17,32] To summarize, the annual epidemics of RSV seemingly follow a "climate-driven" trend, with correlations between several annually averaged climate variables and timing and amplitude of the RSV cycle.[37,38]

The rate of hospitalization due to RSV has been conservatively estimated between 1.2%[39] and 1.6%[36] at global level, equal to 3.2 million episodes in 2015 alone,[36] 45% of them occurring in children aged 6 months or younger.[36] In other words, RSV represents a main cause of hospitalization, as stressed by US-based data reported in Figure 1 (Top five primary diagnoses in hospitalized infants <1 year of age in the USA).[3–36–40–42] The drivers for RSV hospitalizations are complex, and the outcome remains highly unpredictable, particularly in the first year of life,[43–45] and cannot be explained simply by preexisting conditions or infant age at the time of first RSV exposure. First of all, up to 75% of infants hospitalized in a given season are otherwise healthy and full-term children.[17,46,47] Pre-existing risk factors are recognized in only 22 to 32% of total admissions, with prematurity being diffusely recognized as the most significant predictor of RSV hospitalization,[47] and 23% of RSV deaths associated with infants lacking additional risk factors.[17,47,48] In a recent study from Arriola et al.[47] encompassing the RSV season 2014–2015, 65.8% of 336 ICU admission for RSV occurred in full-term children, and 59.8% of infants requiring mechanical ventilation were children without any risk factors.

The risk for RSV-associated hospitalization is usually acknowledged as higher for infants born "in season" compared to those born outside it. For example, in a recent retrospective study from France including a total of 407,025 RSV-associated hospitalizations in children aged <5 years (2010–2018), 13.9% of all patients were born between September and November.[8] However, the raw figures (96,466 RSV infections for the time period October to March, vs. 85,292 for April to September) and the monthly proportions were comparable (1.3% to 4.1% vs. 5.2% to 0.1%, p value = 0.937).[8]

The burden of RSV infections on primary care is also considerable. Although it is hard to measure due to a relative paucity of viral testing in the community, health-care utilization is estimated in around 97% of cases resulting in outpatient visits Figure 2. (Estimation of healthcare Utilization Related to RSV in Children <2 Year.[41,46,52]). For instance, between 2004 and 2009 RSV caused around 1.6 million outpatient visits every year in the US alone.[47,53] In England, it was estimated that 20% of children under 6 months of age will attend an outpatient health-care setting with an RSV-related LRTI.[33] The magnitude of the burden of RSV-related illness on outpatient settings remains significant throughout the first years of life.[53,54] Among Italian subjects with influenza-like illness or severe-acute respiratory illness during five recent, consecutive influenza seasons, RSV was prevalent (17.6–19.1%) in children <5 years of age. Although this epidemiological observation could be interpreted to suggest that RSV is more frequently spread among children of this age group, it is possible that school-age children are bringing RSV home and infecting the 12- to-23-month-old infants who have the highest rate of infection.[55] In other words, RSV infections nearly double the number of primary care consultation compared with influenza, resulting in a time- and resource-consuming issue, not only for medical professionals, but also for parents caring for their children.[33]

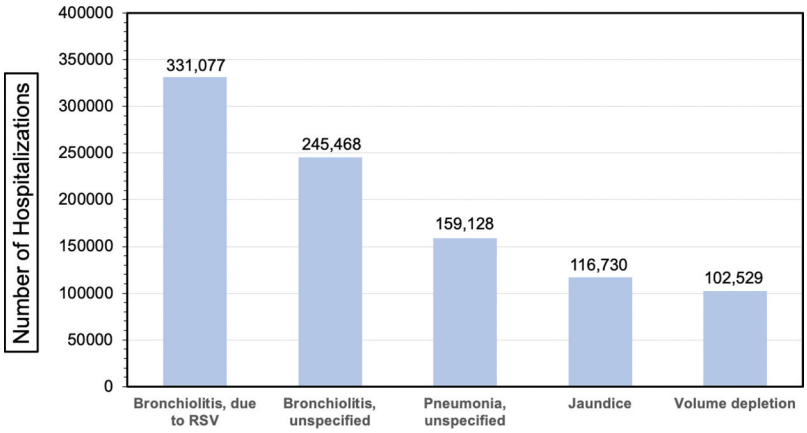

Figure 1. Top 5 primary diagnoses in hospitalized infants <1 year of age in the USA.[3,36,49–51]

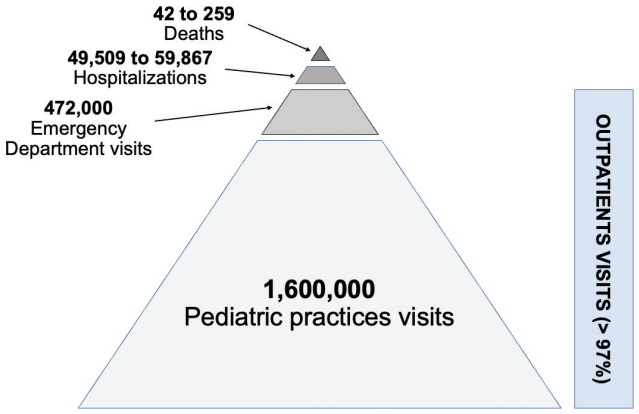

Figure 2. Estimation of healthcare utilization related to RSV in children <2 year.[41,46,52]

Virology

RSV is an enveloped, pleomorphic virus with a diameter of approximately 150 nm (range 120–300 nm).[56] Its genome is represented by a single-stranded, non-segmented negative-sense RNA molecule with a total length of approximately 15.2 kb,[1,56,57] that encodes a total of 11 proteins[56–58–60] (See Annex. Protein encoded by viral genome of RSV). Among them, two surface glycoproteins are crucial for infectivity and pathogenesis: G (attachment protein), and F (fusion protein) (Figure 3 Schematic representation of RSV and RSV genome (Adapted from Tognarelli et al., 2019).[56,57]

G mediates RSV attachment to the host cells. Studies on immortal cell lines have initially highlighted the role of surface glycosaminoglycans (GAG) as main viral receptors, and particularly of heparan sulfate proteoglycans (HSGP).[62,63] As HSGP is not expressed on the apical surface of ciliated epithelial cells,[63,64] other receptors mediate the interaction of G with airways cells in vivo. For instance, studies on human epithelial bronchial cell lines have shown that in vivo G mainly interacts with C × 3C chemokine receptor 1 (CX3CR1), also known as the fractalkine receptor or G-protein coupled receptor 13 (GPR13), whose tropism in human airways matches that of RSV.[62–64]

Moreover, G does not only represent an attachment factor, but also a substantial pathogenetic factor. On the one hand, when secreted from infected cells, it acts as a "decoy" for circulating antibodies.[56,57] On the other hand, it contributes to the suppression of interferon type I, leading to the imbalance in the Th-1/Th-2 response with a shift toward the type 2 response that is associated with RSV infection.[62,65,66]

Even though RSV is considered a single-serotype pathogen,[56] G is quite heterogeneous among circulating strains (RSV A vs. B),[56,57,67] with an even larger number of variants.[1,57,59,67] The genetic drift of the G gene is considered the main driver for the emergence of local variants, which in turn would be the main cause of seasonal reemergence of the pathogen, with new epidemics.[57,61,67,68]

F protein is a metastable class I fusion protein that is necessary for cell infection and represents the main target for vaccines and mAbs.[25,52,69] It mediates the entry process by binding to the cell and enabling the fusion of the virus envelope with the host cell plasma membrane,[52,56,57] a process that not only allows the virus passage into the host cells,[56,57,68] but significantly contributes to the immune escape strategy of RSV.[52,56,57,59,70] On the one hand, due to its critical role, F is highly conserved (i.e. around 90% homology between lineage A and B), and elicits both neutralizing antibodies (NA) and cytotoxic *T*-lymphocyte responses, being therefore considered as a suitable target for vaccine development and mAbs.[69,71,72] In fact, there is some evidence that serum and breast milk antibodies targeting F protein are associated with reduced disease.[73,74] On the other hand, RSV F protein is initially expressed as a single-chain precursor (F0) that becomes fusion competent after intracellular cleavage by a furin-like protease[75,76] into two resulting peptides, the C terminal F1, and the N terminal F2. F2 represents the actual fusion peptide. Triggered by unknown factors, F1 transition from a pre-fusion (pre-F) to post-fusion (post-F) conformation[58,72] by inserting its hydrophobic N terminus into a nearby membrane.[75] As a consequence, post-F conformation loses neutralization sensitive antigenic sites (Ø and V),[52,58,77] impairing the binding affinity for NA.[34,75,76,78] Therefore,

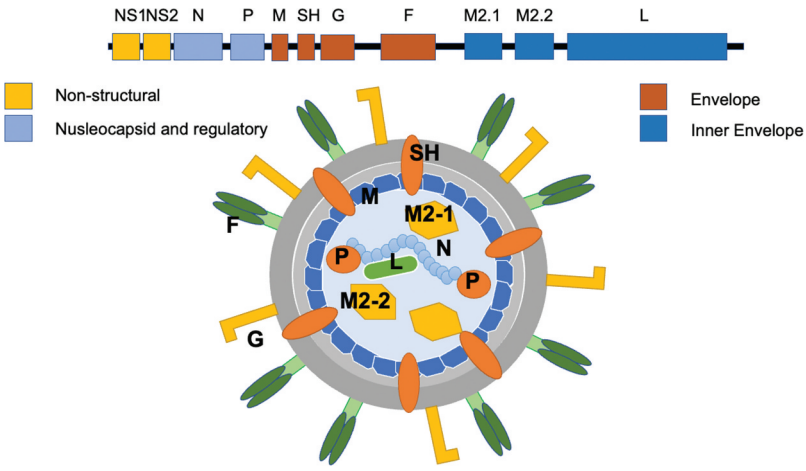

Figure 3. Schematic representation of RSV and RSV genome (Adapted from Tognarelli et al., 2019).[61]

alternative strategies for vaccines and mAbs based on the G protein have been recently assessed, with promising results.[49,79,80]

Clinical details

Pneumoviridae exhibit a large array of potential natural hosts, mostly cattle and rodents, but humans are the only known natural hosts for human RSV.[56,57,81] All new cases are therefore acquired through human contact, starting early in life, with infection beginning shortly after the waning of maternal antibodies.[3,4] As the half-life of maternal RSV-NA usually ranges from 36 to 42 days,[82,83] with even shorter estimates,[84] it is reasonable that all children become susceptible or even highly susceptible to RSV infection shortly after the first month of live.[1,55,85]

Although epidemiological data on the transmission patterns of RSV is not widely captured, some studies have demonstrated that community contact, including childcare settings, is the biggest contributor to infection risk. Contrary to other respiratory pathogens, such as *Bordetella pertussis*, where the main driver for the infection of newborns and infants is represented by the waning immunity in older age groups,[86–89] RSV usually is acquired by children from other individuals during the pediatric age,[1,56,67,85] and RSV in older siblings is an important source of infection in infants.[85] In a recent study from Kenya,[67] 54.8% of new cases were acquired at the community level, mostly from other children (siblings and cousins, 23.8% of all cases), while older subjects and even parents played a more marginal role.

With a basic reproduction number (R0) estimated at 3.0 ± 0.6,[90,91] RSV is a relatively contagious but highly circulating pathogen, and virtually all infants will be infected by RSV by 2 years of age.[41,45,53,84,85,92,93] Following the vanishing of maternal NA, seroprevalence rates for RSV-NA usually decrease from birth to the 10th month, with a subsequent and stark rebound in the following months that mirrors the natural infection rates.[3,5,82,83,94] For example, in a seroprevalence study, performed in Tuscany and North-Rhine Westfalia (Germany) during the winter season 2009/2010, seropositivity rates ranged between 72 and 68.8% in children aged 6 months to 5 years, compared to 95.5% to 100% in older children.[95] Similarly, in a study based on two Dutch cohorts (2006/2007 and 2016/2017), the probability of RSV infection was nearly 0 at 1 month of age, but evolved to a 100% at three years of age.[5] In other words, as a thumb-rule, around half of children are infected by RSV within 1 year after birth, and virtually all of them by the time they are 2 years old.[1–29–56–94–96–98]

As RSV does not elicit a long-lasting immunity, adults are constantly re-infected throughout life, with rates ranging from 2 to 12%, peaking in institutionalized elders.[99,100] On the one hand, the high re-infection rates sustain the circulation of the pathogen, increasing its capability to reach naïve, more vulnerable hosts. On the other hand, the repeated infections maintain the immune competence among healthy adults, that therefore rarely develop LRTI.[3–99–101]

The incubation period for RSV usually lasts around six days, with primary infection occurring through the upper respiratory tract, with further spread to the lower respiratory epithelium.[16,17,56] One to three days after the onset of common cold symptoms, such as nasal congestion, mild cough, fever and reduced appetite, LRTI may develop in up to 40% of affected infants, with symptoms including rapid breathing, wheezing, persistent cough, and difficulty feeding, which in turn can result in dehydration.[17,44,56,102,103] Bronchiolitis, the most common LRTI caused by RSV, is associated with necrosis and sloughing of the epithelium of the small airways, with edema and increased secretion of mucus. In young children, this leads to obstruction of air flow and the typical clinical picture of hyperinflation, atelectasis, and wheezing[16,104]

Disease prevention

Nonpharmaceutical interventions (NPIs)

RSV and SARS-CoV-2 are distinct pathogens, but share several characteristics, most notably their spread through respiratory inoculation of the upper airways with respiratory secretions from infected individuals.[56,68] Moreover, on surfaces, RSV can survive for several hours, particularly with low temperatures and high humidity, and remain viable for up to a half an hour on hands, emphasizing the role for NPIs, such as repeated hand washing, and social distancing.[16,17]

The first wave of the SARS-CoV-2 pandemic (March 2020) occurred during a typical Northern Hemisphere RSV season, and at the beginning of the Autumn in Southern Hemisphere, that is, when the number of RSV cases typically begin to rise. Available data from Italy, Finland, Belgium, UK and USA showed a sudden and earlier-than-expected end of the RSV epidemic season, with substantially no cases detected in the following months.[105–109] Similarly, in Western Australia detection of RSV in children <16 years of age was reduced by 94% compared with the previous years, and such reduction lasted well over the winter season.[109]

The lifting of these NPI measures further changed transitorily RSV epidemiology. In Australia, NPI were initially relaxed in April 2020, and even though RSV notification rates remained scarcely appreciable until August 2020, a substantial resurgence of RSV infections began between May and July, with unprecedented peaks between November and December 2020.[110,111]

This change has been interpreted as a direct consequence of the lifting of NPI measures that were taken to mitigate the spread of SARS-CoV-2, and blocked the normal transmission of RSV to susceptible infants at the community level.[50–107,108–110,111–113] Their extensive implementation during the RSV seasons avoided natural infection in naïve infants, that aged out of their maternal antibody protection prior to RSV exposure. In other words, the pandemic NPIs prevented RSV exposure, generating a larger RSV-vulnerable population, and preserving susceptibility to the pathogen during a subsequent season.[1,50,110,111,114] Even though is reasonable that the progressive shift of SARS-CoV-2 infection from a pandemic to an endemic infection will remove the causes for the recent outburst of RSV, further studies are needed to verify the behavior of RSV infections in the next seasons. More

precisely, we need to understand if the risk of LRTI following RSV infection is persistently becoming more or less severe, with the return to the common seasonal pattern previously observed.[51–105–114–117]

Although on an individual level it is clear that there is a place for the maintenance of basic NPI hygiene measures, such as handwashing, the level of NPI implemented during the SARS-CoV-2 pandemic is not a sustainable long-term option. The speed of resurgence of RSV infections following the relaxation of measures demonstrates that only the most stringent measures are capable of interrupting transmission, and resurgence is very high after them. This reinforces the need for other methods of prevention, such as pharmaceutical interventions.

Pharmacological interventions

There is currently no preventative option that is available for all infants.[118] Palivizumab, a F-protein targeting mAb, is indicated only for a small subset of infants born at ≤35 weeks of gestation 10,34, 335,or in those with specific comorbidities, this is usually no more than 5–7% of newborns. It must be injected once each month during the RSV season, for a total of 5 subsequent weight-dependent doses (i.e. 15 mg/kg). Real-world evidence has shown palivizumab to be effective in reducing hospitalizations and preventing lower respiratory tract infections on this specific population.[119]

In order to contribute to a significant reduction in the burden of infections and hospitalizations caused by RSV, future pharmacological interventions must be available to use on all infants and not to only restrictive groups.[49,69,120]

New preventative strategies are in development, including; maternal vaccines to protect neonates during the first months of life;[30,83] extended half-life mAbs to provide direct and rapid protection for at least 5 months after administration with a single dose;[83,121] and pediatric vaccines.[69,71,122]

The main approaches currently being investigated and developed are summarized below (Table 1. main immunization approaches for RSV in infants and children).

Table 1. Main immunization approaches for RSV in infants and children.

mAbs	Maternal Vaccines	Pediatric Vaccines
Immunisation of infants at start of RSV season: (a) Infants born in season immunized at birth (b) Infants born before the season immunised at the start of the season Rapid and direct protection Duration at least 5 months (RSV season) with one injection	Vaccination of pregnant women in third trimester to protect neonates born in the RSV season through transplacental transfer of maternal antibodies Protection of neonate from birth Duration equivalent to the half-life of maternal antibodies (variable in the various studies between 21–27 days and 36–42 days) with actual efficacy waning after the first trimester of age.	Older infants and children vaccinated as part of a schedule, allowing time to develop an immune response Requires a mature immune system and time to mount an effective response Protection for one season and potentially beyond

Maternal vaccines

In 2017, World Health Organization developed Preferred Product Characteristics (PPC) for RSV vaccines that, in terms of maternal immunization, could by summarized as guaranteeing an efficacy greater than 70% against confirmed severe RSV in the offspring, from birth to age 4 months.[123] To date, not only vaccines for RSV are not commercially available,[52,69,71,124] but, while we are waiting for the results of two large trials specifically focusing on maternal vaccination,[125,126] available studies have reported mixed and still unsatisfactory outcomes. On the one hand, pre-fusogenic F protein nanoparticle vaccine (NCT02624947) was initially reported as 53% effective in reducing LRTI-associated hospitalizations during the first 90 days of life,[127] but the subsequent peer-reviewed report substantially downgraded these results (i.e. 39.4%, 95%CI 5.3 to 61.2).[128] On the other hand, during the very same timeframe (i.e. first 90 days of life) infants received fewer antimicrobial prescription courses than infants of mothers assigned to placebo group, stressing the potential efficacy in avoiding bacterial complications of primary RSV infections.[129]

Nonetheless, the potential referral to maternal vaccination programs represents a promising preventive strategy.[128–130–132] Maternal vaccination is well established for other pediatric infections and often provides protection from pathogens to both mothers and infants, as demonstrated by maternal pertussis vaccination programs.[133–135] The rationale for maternal immunization programs targeting RSV is represented by the consolidated evidence that high titers of maternal antibodies reduce the risk of RSV infection and can delay the onset of severe illness in the first month of life,[84–138] even though disease severity is not regularly associated with differences in RSV-specific IgG titers, RSV-IgG avidity, or virus neutralization.[139–141]

The efficacy of maternal vaccination strategies clearly depends on the achievement of high vaccination rates, correct timing, efficacy of vaccines and duration in time, and vaccination strategies targeting pregnant women must therefore take in account some specificities of RSV and the specificities of antibody passage from the mother.[124,127]

First of all, in a sharp contrast to pertussis, for which maternal vaccination program have been successfully established, the burden of RSV remains significant throughout the first year, and is not mitigated by existing pediatric vaccine programs.[9,67,142] On the other hand, it is often impossible to predict the start of the RSV season far enough ahead to vaccinate the pregnant women and the conditions of future the newborn (like prematurity) that will affect the correct passage of antibodies.[1,28]

Second, while the RSV antibody transfer from mother to infant appears quite efficient,[140,141,143,144] Yildiz et al. have recently shown that it may be negatively affected in both small (weight <10th percentile) and large (weight >90th percentile) for gestational age infants.[143] In fact, there is a consolidated base of evidence that transplacental antibody transfer is generally impaired in pre-term and small for gestational age children, and that puts these children at increased risk for all infectious diseases, even for those that are vaccine preventable.[145–147]

Third, the estimated half-life for maternal RSV neutralizing antibodies is variable in the various settings, ranging from 21 to 27 days,[84] to 38 days (95%CI of 36–42 days),[82,83,144] and their effectiveness in guaranteeing infant protection during the entire length of a typical RSV season also remains somewhat uncertain.[30,82,83,144] In this regard, there is consolidated evidence that vaccines may be able to elicit higher titers of NA antibodies when compared to the natural infection, and transplacental transfer is in turn associated with higher concentration of antibodies in the recipient infant.[124,127,128,130,140,143,146] However, despite some promising results,[124,148] the actual duration of maternal NA elicited by vaccination remains and likely will remain largely undefined until later stages of RSV vaccine development. Nevertheless, most cases of RSV occur in the first months of life, when the levels of maternal NA may be considered substantially higher.[82,149,150]

In addition, compared to other infections like influenza or pertussis, the impact of maternal vaccination on RSV disease or carriage in pregnant women is unknown.[30,151] Although some reports have suggested that RSV infection in pregnancy may increase the risk of early delivery by cesarean section,[124,152,153] as well as higher rates of adverse pregnancy outcomes,[124,154,155] RSV usually does not cause significant disease in healthy adults, and the perception of direct benefit of vaccination to the mother may be therefore questionable. Nonetheless, a series of studies targeting knowledge, attitudes, and practices of pregnant women have stressed the substantial underestimation of both RSV disease burden and the potential health consequences of natural infections.[151,156] Unfortunately, diffuse uncertainties and misbeliefs are also shared by potential caregivers and achieving high vaccination rates will require the implementation of extensive educative interventions, particularly among professionals who are less familiar with potentially severe consequences of RSV infections.[151,156]

Extended half-life mAbs

Due to the mechanism of action, long-acting serum mAbs would allow for rapid and direct protection for infants.[1,14,29,56] Nirsevimab is the front-runner of these new mAbs, and was optimized from the human IgG1 antibody D25 that targets antigenic site Ø on the pre-F conformation.[121,157]

Providing direct and rapid protection lasting at least 5 months after administration, it has been shown to provide on healthy newborns of at least 35 weeks gestational age a stark reduction of medically attended RSV-associated lower respiratory tract infection (LRTIs) with an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; $P < 0.001$) and a reduction of hospitalizations for RSV-associated lower respiratory tract infection of an efficacy of 62.1%; (95% CI, −8.6 to 86.8; $P = 0.07$) from the start of the RSV season, including those born out of RSV season.[1,121] A single injection administered before the RSV season protected healthy late-preterm (>35w) and term infants from medically attended RSV-associated lower respiratory tract infections without the requirements of serial, monthly injections.[83,121] Similarly, designed extended half-life mAbs could therefore be administered through a more convenient approach.[83] Given that RSV seasons are characterized by sustained circulation of the pathogen for a usually predictable length of time, an extended half-life mAb could be administered to all infants at birth, as a pre-discharge intervention post-delivery, but also could be administered during routine visits, representing a seasonal immunoprophylaxis, and an interesting tool to protect before expected RSV epidemic waves.[1,83] As vaccination schedules in infancy have become increasingly crowded of vaccines,[28] extended half-life serum mAbs administered shortly before the return to the community of the newborn could guarantee extended flexibility to the vaccination services.[28,30]

Obviously, also mAbs are not deprived of possible drawbacks that must be considered when tailoring their role in the forthcoming preventive strategies.[158,159] First of all, despite their obvious convenience advantage in being delivered as a single dose, extended half-life mAbs could share some of the limits of conventional mAbs likewise Palivizumab, for example, in terms of efficacy being limited to only small high-risk groups, requiring several dosages or having high costs.[158–160] In fact, as recently stressed by Li et al.,[160] cost-effectiveness of programs with extended half-life mAbs strictly depends on the characteristics of RSV circulation, being appropriate for seasonal interventions, and in order to be cost effective an appropriate price needs to be set similar to vaccine strategies.[160,161] Similarly to the recommended PPC for RSV vaccines and maternal immunization, WHO has also issued PPC for mAbs,[162] stating that promising products like a single dose extended half-life mAbs need to have simplified delivery requirements and to be less costly than traditional mAbs, making them potentially suitable for use in all infants and not just those at high-risk.[160,161] Moreover, WHO recommends that extended half-life mAbs will target all infants at least for their first 6 months of life, through a one dose regime that could be given from birth. They ask for a targeted safety and reactogenicity to be comparable to PPC for vaccines and ideally with at least 70% efficacy against RSV confirmed severe disease for a duration of five months following administration. Second, extended half-life mAbs still require injections to the newborn, representing at the very same time a further logistic issue, and a potential ethical one. This could represent a high level of complexity in which countries, based on their current vaccination strategies and public health ecosystems, will need to analyze the best strategy possible to implement a preventative strategy. From an acceptance perspective, issues could also arise, similar with Palivizumab today, both in health-care professionals,[163] and among parents and caregivers,[164] and proper educational strategies should be implemented eventually. By expanding the potential targets of RSV preventive strategies, mAbs could be offered to otherwise healthy infants, and not only to those affected by potential risk factors.[128,158,161] As a consequence, we cannot rule out that parents may exhibit increasing resistance toward interventions felt as "unnecessary," particularly when tailored to cope with an often underscored pathogen as RSV.[156,164]

Despite the substantial progress seen today, as it will most probably be available before other strategies, even for extended half-life mAbs several further questions remain to be answered before their extensive recommendation.[121,157] First, as mAbs target-specific epitopes on the RSV F protein, there is the potential for emergence of resistant strains, and this will need to carefully monitored.[62,66,165,166] Second, mAbs specifically target F protein, with no effect on G, whose role in vivo has been increasingly stressed in more recent studies.[62,66,166] Moreover, also the protective potential of mAbs like Nirsevimab in the prevention of the development from RSV infection of asthma and chronic wheeze would need to be monitored over multi-year studies.[157,165]

Pediatric vaccines (older infants and children)

To date, no vaccine against RSV has been licensed. A prototype formalin-inactivated RSV vaccine was evaluated in the 1960s, but testing was discontinued due to lack of efficacy and resulting enhanced disease (i.e. enhanced RSV disease or ERD) in children following exposure to wild-type RSV leading to the death of several subjects.[52,69,72]

One of the challenges associated with vaccination in infants relates to the immaturity of the immune system of newborns limiting their response to antigens. Infants under 4–6 months have an impaired ability to generate effective, long-lived adaptive immune responses following immunization. Consequently, it has been shown that natural RSV infection produces a low immune response in young children <18 months old.[167] Risk of RSV disease for infants born during the season starts at birth, which makes active vaccination unfeasible in this cohort because of their relatively immature immune systems and the time required for an immune response to mount, potentially leaving them vulnerable at a crucial time.[17] Pediatric RSV vaccines would therefore be best suited to infants older than 6 months, or toddlers entering their second RSV season. At present, several vaccine strategies for protection against RSV in infants are being investigated and none to our knowledge is targeting new borns.[25,52,69,71]

Vaccines under development and receiving preliminary assessment by regulatory agencies include protein vaccines that use stabilized pre-F protein subunits or virus-like particles, and live vaccines that include attenuated RSV strains, or virus vectors expressing RSV proteins.[17,168] Briefly, particle-based vaccines are synthesized by self-assembling nanoparticles that express multiple copies of a selected antigen on their surface and mimic the native virions. Thanks to the high copy number of the selected antigen and the immune-boosting properties of the particulate matrix, these vaccines elicit strong humoral and cellular immune responses. The lack of the viral genome required for replication increases their safety, with a reportedly scarce risk for developing ERD.[69,71,122] On the contrary, subunit vaccines are created with RSV protein fragments. They are poorly immunogenic due to their non-replicating nature and their limited components. Booster doses and adjuvants are often necessary to make them effective. Moreover, they are at high risk for eliciting ERD because of their limited effect on CD4+ T cells.[69] Vector-based vaccines use a carrier vector to deliver RSV antigens and induce an immune response against RSV components exploiting the adjuvant effect of the vector.[69] Due to the chimeric nature of the vectors, there is no risk of reversion to wild-type RSV and of ERD. However, similar to other vaccines based on adenoviral vectors, the presence of preexisting anti-vector immunity or its potential development may challenge the clinical use of these vaccines.[69,120,122] Live-attenuated RSV vaccines (RSV-LAVs) are produced with versions of RSV that are able to replicate but have been modified to reduce disease induction. They can be created by traditional techniques (i.e., temperature or chemical sensitivity) or, thanks to an improved understanding of the RSV viral genome, by reverse genetics to create an attenuated replication-competent vaccine. ERD has not been observed with RSV-LAVs or replicating vaccine vectors.[69,169,181] Because these vaccines are typically administered intranasally, they generate superior mucosal immune responses and therefore are more likely to prevent upper respiratory infections as well as LRTI. More recently, promising results from a phase 1 study on a mRNA based, pre-F protein vaccine have been published, but further research is needed.[170]

Conclusions

RSV is a pathogen associated with a significant global burden.[7,8,17,32] As all infants are at risk of RSV infection and it is often impossible to ascertain which infants will develop serious disease, it is imperative to address as a public health problem RSV infections in all infants and to provide solutions that will protect them in an easy and effective manner. As up to 75% of hospitalization and around ¼ of RSV-associated deaths occur in otherwise healthy newborns, protection needs to extend beyond those currently protected by today's available mAb (palivizumab).[17–46,47,48]

A time- and resource-consuming health threat, RSV-related infections are difficult to prevent through common public health measures.[1,55,171,172] Universal NPI are not sufficient to manage recurrent RSV epidemics as these would have to be stringent and permanent, which is clearly not sustainable, particularly at the household level.[50,110,111,173] Less-than-universal NPI may fail to reduce circulation and spreading of RSV among susceptible individuals. In addition, the main target of preventive measures for RSV are children under 5 years of age, a group where the implementation and adherence to measures, such as the use of face masks, and improved hand hygiene may be particularly difficult.[174] Pharmacological prevention of RSV is therefore needed. To address the burden of RSV across health-care settings and to reduce impact of RSV on families, preventative measures would need to protect all infants.[8,16,17,33,42,104,142,175]

Effective vaccines for RSV are not yet commercially available.[26,52,69,72,122] Available data suggest its use in children will be limited by the age of use, timing its use on above 4/6 months of age. On the other hand, vaccines can be used on pregnant women to protect the new born but while maternal immunization approaches are of success in preventing other respiratory diseases short half-life transplacental antibodies might impair the reliability of maternal immunization,[30,64,65,78] Further studies on these vaccines are needed to understand efficacy, duration, and effectiveness of this intervention on the new born. Furthermore, it would be then important to evaluate

correct health system strategies to address all pregnant women giving birth during a season in order to protect all newborns. From this point of view, it is important to stress that even for vaccines with a consolidated preventive value for both mothers and infants, such as seasonal influenza vaccine, are still struggling to achieve substantial coverage rates.[176,177]

The only currently available pharmacological prophylaxis is a short-life mAb that requires monthly injections and is restricted to the most vulnerable infants like preterms, less than 7% of all newborns.[10–27–178–180]

The use of monoclonal antibodies with extended half-life is an appealing prospect, which could address many of the problems associated with other approaches in order to prevent the disease in all newborns, from birth, during a season.[1,28,30]

Immunization of neonates and infants through extended half-life mAbs seem to provides rapid and consistent protection against RSV from birth and for at least 5 months, which covers the entire duration of a typical RSV season,[121,157] and support an increased flexibility in the timing of administration that could address the need in infants born both within and outside of the season by immunizing them at the start of the season itself.[1,121]

The WHO recommendations for preferred product characteristics for mAbs seem to be covered in the recent clinical trials phase 3 publication of an almost ready to market extended half-life,[1,121,162] and we wait to see final product registration and characteristics. Meanwhile, early phase II studies on maternal immunization strategies are ongoing,[124,126,127,130] and although too early to understand if the results will cover WHO recommended PPC,[123] they might be a promising alternative solution to evaluate in the future.

The burden of RSV disease in infants throughout their first year of life, irrespective of gestational age at birth, preexisting conditions, or age at entry into the season, suggests that there is a need to evaluate new strategies to help protect all infants against RSV and mitigate this burden for infants, their caregivers, and the health-care systems.

Disclosure statement

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Annex: Protein encoded by viral genome of RSV

Protein	Function
M	Matrix protein. Non-glycosylated phosphorylated protein located external to the nucleocapsid layer, where it acts as a bridge between the lipid bilayer envelope and the nucleocapsid.
N	Nucleoprotein. Structural protein involved in the packaging of the viral RNA
P	Phosphoprotein. Interacts with L protein in the RNA replication.
L	RNA Polymerase. Replicates the viral RNA.
NS1/NS2	Non structural proteins. Involved in the evasion of the innate immune response
M2-1/ M2-2	Regulatory proteins, involved in the regulation of the transcription and replication of the genome
SH	Small hydrophobic protein. Involved in the immune evasion (?)
G	Glycoprotein G, involved in: docking of the virion to the C×3C Chemochine Receptor 1 (CX3CR1) and glycosaminoglycans of the cell surface; inhibiting production of Interferon type I; promotion of Th-2 polarized response
F	Glycoprotein F, fusion protein, eliciting the fusion between the virion and the targeted cell, with resulting infection of the cytoplasm. Target protein: **surface nucleolin**