

Prevention of Respiratory Syncytial Virus Bronchiolitis

Prévention des bronchiolites à virus respiratoire syncytial

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ABSTRACT

Acute bronchiolitis is the leading cause of hospital admissions among infants worldwide and is associated with increased morbidity. The Respiratory Syncytial Virus (RSV) is the most common causative agent and is often linked to a more severe and prolonged form than that caused by other viral agents. The annual outbreaks of bronchiolitis place substantial strain on pediatric emergency departments, hospital bed availability, and saturation of resuscitation beds. Most RSV bronchiolitis hospitalizations occur during the first three months of life in healthy term neonates. Management for RSV-related lower respiratory tract disease is mainly supportive.

Recent advancements in RSV prevention strategies have emerged, including the approval of two new effective options: a maternal vaccine (RSVpreF) and a long-acting monoclonal antibody (Nirsevimab).

The aim of this review is to screen recent literature and Tunisian data regarding RSV Bronchiolitis and summarize current evidence concerning knowledge and attitudes regarding RSV prevention strategies.

Key-Words: Respiratory Syncytial Virus, Acute bronchiolitis, Children, Nirsevimab, Maternal RSV vaccine

RÉSUMÉ

La bronchiolite aiguë (BA), constitue un enjeu majeur de santé publique, tant au niveau national qu'international. Elle représente la première cause d'hospitalisation en pédiatrie chez les nourrissons. Le Virus Respiratoire Syncytial (VRS) est le principal virus responsable et souvent associé aux formes sévères et prolongées.

Les épidémies automno-hivernales de BA entraînent chaque saison un afflux important dans les urgences pédiatriques et une surcharge dans les unités hospitalières à l'origine de la saturation des lits notamment en réanimation pédiatrique. Plus de la moitié des nourrissons hospitalisés pour bronchiolite aiguë à VRS sont des nourrissons nés à terme, sans comorbidités, et sont âgés de moins de 3 mois.

Aucun traitement curatif n'existe, et le traitement est uniquement symptomatique. Récemment, deux interventions visant à prévenir l'infection au VRS chez les nourrissons ont été approuvées, soit un vaccin pour les femmes enceintes, soit un anticorps monoclonal à longue durée d'action (Nirsevimab).

Dans ce contexte, nous nous proposons de revoir la littérature internationale et les données tunisiennes concernant la bronchiolite à VRS, et résumer les preuves actuelles concernant ces nouvelles stratégies de prévention.

Mots clés : Virus Respiratoire Syncytial, Bronchiolite aiguë, Nourrisson, Nirsevimab, Vaccin maternel anti-VRS

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INTRODUCTION

Lower Respiratory Tract Infections (LRTIs) have been the leading cause of hospitalizations and deaths among children under the age of five for the past decade. Respiratory Syncytial Virus (RSV) is identified as the most common cause of these infections (1). In 2019, between 66,000 and 190,000 RSV-related deaths occurred in children under 60 months of age, accompanied by approximately 33 million RSV-associated acute LRTIs and 3.6 million hospital admissions for RSV-related acute LRTIs. More than 95% of these deaths occur in low- and middle-income countries, with 50% involving infants under six months of age (2).

RSV infections are responsible for up to 40% of pediatric pneumonia cases and between 50% and 80% of Acute Bronchiolitis (AB) cases. Nearly 90% of children are infected with RSV within their first two years of life, and approximately 70% of infants contract the virus during their first year (3, 4).

RSV is highly contagious and tends to recur in seasonal epidemics. In temperate regions like Tunisia, RSV is primarily transmitted during colder months, usually from November to March (3-5). Infants commonly acquire the virus through close contact with older siblings or other children in the same household, making household exposure a significant risk factor for transmission (6).

Most RSV bronchiolitis hospitalizations occur within the first three months of life, particularly in healthy term neonates born 1-2 months before peak RSV activity. Certain subgroups, such as preterm infants and those with immunodeficiencies, Down syndrome, chronic lung disease, or significant congenital heart disease, are at higher risk of severe illness (3, 5). While most cases of AB are benign and can be managed on outpatient, 3% of affected infants require hospitalization, and 2-6% need intensive care (3).

Annual outbreaks of AB significantly impact hospital capacity, including bed availability in pediatric emergency departments, Intensive Care Units (ICU), and medical staff resources, which disrupts the provision of other healthcare services (4). Inadequate access to timely healthcare and a shortage of intensive care units contribute to higher rates of severe disease and death.

Beyond the immediate risk, RSV-associated LRTI in infancy can lead to long-term respiratory consequences, including asthma, recurrent wheezing, and impaired lung function. These sequelae can persist in adulthood, resulting in a continued need for healthcare services (7).

The economic impact of RSV-related LRTIs is substantial, with hospitalizations being the largest contributor to medical costs. A systematic review assessing the costs of managing RSV-LRTI episodes found the average cost per inpatient episode to be 3000€ and 300€ for outpatient care (8).

Current management of AB is primarily supportive, focusing on symptom relief and avoiding unnecessary antibiotics, steroids, and nebulization (3).

In Tunisia, a 2007 study by Menif et al. assessed bronchiolitis management practices. At that time, most pediatricians prescribed bronchodilators (93.3%) and

corticosteroids (88.7%) during the initial phase of acute bronchiolitis (9).

In 2013, the Pediatric Tunisian Society published clinical guidelines to standardize the diagnosis and treatment of AB in children (10).

Despite this, the use of non-recommended therapies remains widespread. A 2015 cross-sectional study by Belhadj I et al. (11) found that only 1.4% of clinicians adhered completely to the guidelines. Compared to Menif et al. (9) earlier study, there was a reduction in the prescription of bronchodilators (36%) and corticosteroids (6.6%), but a notable increase in the use of antibiotics (22.9%).

VIROLOGY

RSV is an RNA virus from the Paramyxoviridae family, with two primary antigenic groups, RSV-A and RSV-B, circulating worldwide. Its surface proteins, G (attachment) and F (membrane fusion), are key targets for the immune response. The F gene is relatively conserved and often targeted by anti-RSV monoclonal antibodies for prevention. There are two types of the F protein: pre-fusion and post-fusion. Antibodies targeting the pre-fusion form are more effective at preventing RSV infection (12).

To investigate the epidemiologic and evolutionary dynamics of RSV in Tunisia, Romano Get al, analyzed 92 RSV-positive samples, collected between October and December 2021. Most patients included in this study were children hospitalized in intensive care units for severe acute respiratory infections (SARI) at the Children's Hospital of Tunis (n = 86). Dominance of RSV-A (96.9% of the samples tested positive) and substantial genetic heterogeneity, particularly affecting the G protein were noted. Continued surveillance is crucial to inform and guide preventive interventions.

BURDEN OF RSV IN TUNISIA

Studies conducted in three Tunisian regions (the north, center, and south) have documented the burden of RSV. The highest rate of infection occurred in healthy term infants during the first months of life. Seasonal variation showed that most RSV cases occurred during winter.

A prospective study conducted in pediatric intensive care department at Children's Hospital, of Tunis (north), which serves as a sentinel site for national surveillance of SARI, including 631 cases of bronchiolitis out of 1229 hospitalized patients across three consecutive RSV seasons (2021-2022; 2022-2023; 2023-2024). RSV was identified in 72.3% of viral infections, with a peak in December and January (14). Majority of patients (79%) were less than 3 months old and 22% were newborns. Around 75% of cases were healthy term infants with no documented pre-existing risk factor.

Another retrospective study was carried out at Farhat Hached Hospital in Sousse (center) over a 13-year period (2003-2015). A total of 5,131 hospitalized cases of bronchiolitis were included, 34% were admitted to the

neonatology ward (aged 0–1 month) and 10 % required admission to an ICU. RSV detection was performed using a direct immunofluorescence assay. The overall rate of RSV-associated bronchiolitis was 34.5%. Among patients admitted to ICU, RSV infection was detected in 47.3% of cases. The RSV outbreak typically began in October, peaking in January (41.6%) (15).

In Sfax (south), a study was conducted from 2009 to 2010 in the pediatric A department at Hedi Chaker University Hospital and included infants 368 patients with LRTI. Nasopharyngeal aspirates were analyzed using indirect immunofluorescence assay and PCR. At least one respiratory pathogen was identified in 319 cases (86.7%). The most frequently detected viruses were RSV (42.7%), rhinovirus (32.9%), and adenovirus (28.5%) (16). A recent retrospective cross-sectional study included 403 infants under one year hospitalized for AB between February 2023 and February 2024 in the same pediatric department. The median age of patients was 2.5 months, and 54.3% were younger than 3 months. Nasopharyngeal samples were collected for virological testing using RT-PCR. RSV was the most frequently identified pathogen (44.2%) and the only virus significantly associated with disease severity. The peak of RSV infection occurred during the months of January and February (17).

RSV Bronchiolitis is more severe and prolonged than that caused by other viral agents. In a cross-sectional retrospective study including 380 infants transferred to PICU for severe bronchiolitis, Hamouda et al. (18) identified factors like young age (≤ 2 months), failure to thrive, apnea, dehydration, isolation of RSV and bacterial coinfections as predictors of a longer hospital stay or death.

PREVENTION

The immediate goal in managing RSV is to reduce severe LRTI and RSV-associated hospitalizations.

Non pharmacological prevention

The Tunisian Pediatric Society conducts annual training for healthcare professionals and implements public awareness campaigns via media and social networks to emphasize the importance of preventing respiratory viral infections, particularly AB. The current national prevention strategy is based on several non-pharmacological measures, including:

- Hand hygiene using hydroalcoholic disinfectants, or, if unavailable, handwashing with soap and water.
- Disinfection of objects and surfaces in community settings, outpatient clinics, and hospitals. Medical equipment (e.g., stethoscopes, examination tables, baby scales) must be disinfected between each patient.
- Mandatory masks are used by symptomatic parents and healthcare workers during epidemic periods to limit transmission to infants.
- Exclusion of sick infants from community environments such as daycare centers and kindergartens.
- Avoidance of exposure to secondhand smoke.

- Avoiding kissing infants during RSV epidemics.
- Promoting and supporting breastfeeding.
- Ensuring proper ventilation of indoor spaces (10).

Pharmacological prevention

Advancements in RSV infection prevention have been heralded with the approval in 2023 of new extended half-life RSV monoclonal antibody and a maternal RSV vaccine as strategies to reduce the burden of RSV-LRTI in infants (19-25).

Monoclonal antibodies

- **Palivizumab**, approved since 1998, targets RSV's F protein site II. Because the half-life of palivizumab is only 9–27 days, monthly injections for up to a total of five subsequent weight-dependent doses are required throughout the RSV season. Palivizumab has been demonstrated in numerous well-controlled, randomized, double-blind studies to provide protection against recurrent obstructive episodes and, in the long run, against the onset of pediatric asthma (26). However, its high-cost limits access, especially in low- and middle-income countries like Tunisia.

- **Nirsevimab** (Beyfortus®) is a human recombinant monoclonal antibody against RSV. It binds to the F protein on the surface of the RSV and inhibits virus-host cell fusion. It has a modified Fc-region, extending the elimination half-life. Nirsevimab provides immediate passive immunity through a single intramuscular injection administered before the onset of RSV season. This protection lasts for at least 150 days (25,27).

Three pivotal clinical trials involving large cohorts of preterm and term infants, including those at high risk of severe disease and otherwise healthy children—demonstrated that Nirsevimab is safe and effective in reducing both medically attended RSV-associated lower respiratory tract infections (RSV-LRTIs) and RSV-related hospitalizations (28,29,30).

Implementation plans in several high-income countries have focused on seasonal administration to all infants, in alignment with regional RSV circulation patterns. These strategies often include catch-up doses for infants born just before the start of the RSV season (20, 23, 24).

Real-world evidence consistently supports Nirsevimab's effectiveness (31,32). In Galicia, Spain, the antibody was administered seasonally from September 2023 to March 2024 to three target groups: (1) infants born during the campaign (at birth), (2) infants under 6 months of age at the beginning of the campaign, and (3) children aged 6–24 months with high-risk underlying conditions. More than 90% of eligible infants received the antibody. Interim effectiveness analysis showed that 82% (95% CI: 65.6–90.2) of hospitalizations due to RSV-LRTIs and 86.9% (95% CI: 69.1–94.2) of hospitalizations for severe RSV-LRTIs were prevented during the first three months of the campaign (32).

A meta-analysis conducted during the 2023–2024 RSV season, including data from the USA and three European countries, reported a vaccine effectiveness of 90.5% (95%

CI: 87.1–92.9) against RSV-associated LRTIs (33).

Another recent meta-analysis of studies from five countries (France, Italy, Luxembourg, Spain, and the USA) linked Nirsevimab use to a significant reduction in RSV-related outcomes: 83% effectiveness against RSV-related hospitalization, 81% against ICU admission, and 75% against RSV-LRTIs. However, Nirsevimab did not reduce the length of hospital stay for infants who were hospitalized with RSV. Subgroup analyses indicated that its effectiveness in preventing RSV-related hospitalization varied depending on infant age and country of use (34). Nirsevimab has a favorable safety profile. The most commonly reported adverse events are rash and injection-site reactions (19, 34). While the risk of RSV mutations and resistance to monoclonal antibodies must be considered, breakthrough variants remain extremely rare despite widespread use (35).

-Clesrovimab: is an extended half-life human IgG1 mAb against the highly conserved antigenic site IV of the RSV-F glycoprotein, in phase 3 evaluation for the prevention of RSV disease in infants. It has activity against both the pre-F and post-F conformations (25).

Maternal Vaccination

Maternal immunization is an established method to protect young infants from severe infection. The first vaccination authorized for use during pregnancy that can provide protection to infants for the first few months of life by transplacental antibody transfer is RSVpreF, a bivalent stabilized RSV prefusion F protein vaccine without adjuvant (36).

To maximize the transfer of neutralizing antibodies from the mother to the fetus, maternal immunization is usually administered during the second or third trimester. However, the specific IgG subclass, antigen specificity, and maternal features including chronic illnesses, advanced age, high parity, a high body mass index, uncontrolled HIV infection, and hypergammaglobulinemia can all affect the efficiency of this transfer.

In the pivotal phase 3 trial, enrolling 7420 pregnant women <49 years between 24- and 36-weeks' gestation, the RSV pre-F vaccine was shown to be efficacious in preventing 70% (95% CI: 51–83%) of severe RSV-LRTI and 49.2% (95% CI: 31.4–62.8) of RSV-associated medically-attended-LRTI in the first 180 days of life. An excess in preterm births was observed in the vaccine group. Two upper-middle-income countries (UMICs) were the only locations where this general non-statistically significant imbalance was noted (37).

In Argentina, the effectiveness of the maternal vaccine during the first year of its implementation (2024) among pregnant mothers with a gestation of 32–36 weeks was 71.3% against RSV-LRTI hospitalizations and 76.9% against severe RSV-LRTI from birth through 6 months of age (38). The effectiveness of the vaccine in preventing RSV-associated hospitalization among infants was 57.7% (95% CI: 28.2–75.1) during the 2024–2025 RSV season in the United Kingdom, where the vaccine is recommended from 28 weeks of gestation. The effectiveness was 72.4% (95% CI: 47.8–85.4) among infants whose mothers were vaccinated at least 2 weeks before delivery (39).

The uncertainly effectiveness of maternal immunization in very-premature infants and safety signals after RSV vaccination including potential associations with preterm birth, and hypertensive disorders emphasizes the need for rigorous post-marketing surveillance and the careful monitoring of reported adverse events following immunization (40).

RSV PREVENTION STRATEGY

WHO's position

Given the global burden of severe RSV disease among young infants, the WHO Strategic Advisory Group of Experts (SAGE) on immunization recommends:

- All countries should introduce passive immunization for the prevention of severe RSV disease in young infants.
- The decisions to include the maternal RSV vaccine and/or the long-acting monoclonal antibody would need to consider the cost, financing, supply, anticipated coverage and feasibility of implementation within the existing health system (19).

In the Tunisia setting

Educating and informing healthcare workers and parents about protective measures remains a key aspect of prevention.

The expert working group of the Pediatric Tunisian Society recommends passive immunization with Nirsevimab if feasible and affordable. A seasonal approach, with administration of a single dose of a long-acting monoclonal antibody is recommended, given in the following manner:

1- Babies without risk factors:

- Babies aged less than or equal to 3 months at the start of the RSV season (born July to September): give Nirsevimab in October and

- Babies born during the season (01 October – 31 March): injection at the discharge visit, ideally at the maternity ward, or if hospitalized after birth, preferentially before discharge or earlier at the discretion of the treating physician.

2- Babies with risk factors (prematurity <32 weeks, hemodynamically significant congenital heart disease, immunodeficiency, neuromuscular disorders, Down syndrome, and chronic lung disease) aged less than 12 months at the start of the RSV season.

It is administered as an intramuscular injection using a single-dose, prefilled syringe. It is dosed by weight and age (50 mg for children weighing <5 kg and 100 mg for those weighing ≥ 5 kg).

Nirsevimab can be co-administered with other vaccines, including all inactivated and live attenuated vaccines, in a separate area of the body (at least 2.5 cm apart).

Contraindications

Anaphylaxis or severe allergy to Nirsevimab or its components.

Administration of Nirsevimab may not be required if

the mother received an RSV vaccine (RSVpreF) in the third trimester of pregnancy and the interval between vaccination and delivery is ≥ 14 days.

Approved RSV prevention

Table 1. Approved RSV prevention

Product	Description	Recommended use	Dose
Nirsevimab	Monoclonal antibody: RSVpreF protein-directed fusion inhibitor, extended half-life	- Infants aged <3months entering their first RSV season - Babies born during the season (01 October – 31 March) - Infants with risk factors aged less than 12 months at the start of the RSV season.	- 50 mg for infants weighing <5 kg - 100 mg for infants weighing ≥ 5 kg (Intramuscular injection)
ABRYSVO	Bivalent RSVpreF vaccine	Pregnant people during weeks 32 through 36 of pregnancy (a 0.5 mL single dose)	

CONCLUSION

RSV is the most prevalent cause of LRTI in young infants, and it significantly contributes to LRTI mortality. The long-acting monoclonal antibody and/or maternal RSV vaccine have shown high efficacy in reducing RSV hospitalization during the first 6 months of life.

Ensuring access to preventive strategies targeting RSV remains a major public health priority. A national-level reflection is warranted to address the logistical and economic challenges associated with the implementation of these new preventive interventions.

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