

Respiratory syncytial virus: an overview of clinical manifestations and management in the Indian pediatric population

Abhishek B J, Agadi Hiremath Viswanatha Swamy, Sanatkumar Bharamu Nyamagoud, Anupama George, Namratha D

Department of Pharmacy Practice, KLE College of Pharmacy, Hubli, Karnataka, India

Abstract

Respiratory syncytial virus (RSV) plays a major part in causing lower respiratory tract infections in younger populations, especially in infants and pediatric patients, causing a higher rate of morbidity

Correspondence: Dr. Abhishek B J, Department of Pharmacy Practice, KLE College of Pharmacy Hubli, Karnataka - 580031, India.
Tel.: 7411223912.
E-mail: abhishekbj021@gmail.com

Key words: respiratory syncytial virus, rhinorrhoea, RSV-associated acute lower respiratory infection, RSV glycoprotein, bronchiolitis, probiotic and prebiotic, vitamin D-cathelicidin.

Contributions: all authors have contributed significantly, agreed with the content of the manuscript, and given fair contributions to the work.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: the data that support the findings of this study are available from various search engines online.

Funding: none.

Acknowledgments: the authors would like to take this opportunity to express their gratitude and respectful thanks to the Vice-Chancellor, Registrar and Dean of KAHER, deemed to be university, Belagavi and to all the faculties of the Institution

Received: 26 December 2024.

Accepted: 7 August 2024.

Early view: 4 October 2024.

Publisher's note: all claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

©Copyright: the Author(s), 2024

Licensee PAGEPress, Italy

Monaldi Archives for Chest Disease 2025; 95:2888

doi: 10.4081/monaldi.2024.2888

This article is distributed under the terms of the Creative Commons Attribution-NonCommercial International License (CC BY-NC 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

and mortality in the respective population, affecting 60% of the population globally. Typically, identifying the virus in the patient's respiratory secretions is important for laboratory validation of a clinically suspected RSV infection. Unfortunately, the only available preventive measure to lower the incidence for infants who are at high risk of RSV-induced hospitalization is palivizumab prophylaxis. Treatment strategies to manage RSV involve using an antiviral drug, ribavirin, along with bronchodilators, nebulized adrenaline (epinephrine), and nebulized hypertonic saline. Providing patients with alternative treatment options like vitamin D-cathelicidin as well as probiotics and prebiotics can help reduce the intensity of the infection. This review article focuses on the epidemiology, clinical manifestation, prophylaxis, and available treatment options for RSV infections in infants, children, and young adults.

Introduction

Respiratory syncytial virus (RSV) is a non-segmented single-stranded, negative-sense, enveloped RNA virus that is a part of the pneumovirus genus and subfamily of the paramyxoviridae family of viruses [1]. The two primary viral antigens on the surface, the G (attachment glycoprotein) and the F (fusion) protein, are essential to the pathogenicity of RSV [2,3].

Premature newborns, infants with chronic lung diseases such as interstitial lung disorders, bronchopulmonary dysplasia, and cystic fibrosis, and infants with hemodynamically severe congenital heart disease all have greater rates of RSV disease morbidity and mortality [3]. RSV is known to be one of the main causes of lower respiratory disease among young children. RSV causes respiratory illness in young children under 5 years and presents a significant global health burden, due to which most of the patients before the age of 2 are infected before, and bronchitis is the primary medical cause of neonatal hospitalization [1]. It is the most significant cause of lower respiratory tract infection (LRTI) in pediatrics all over the world, globally, with over 33 million cases and roughly 160,000-190,000 casualties yearly, or 6.7% of all deaths among babies aged <1 year. Begley *et al.* found that the prevalence of RSV among adults was significant among patients in the age group between 18 to 45, as well as patients above 65.

In developing countries, the majority of the deaths of approximately 118,200 children annually are associated with RSV, with almost 50% of the deaths occurring in younger children who are below 6 months of age and infants [4]. RSV-ALRI (RSV-associated acute lower respiratory infection) will result in approximately 100,000 RSV-ALRI deaths in LMIC in 2019. RSV infection affects 60-70% of newborns in their initial year of life, and most of all pediatrics aged 2; of these, 2-3% require hospitalization for RSV-induced bronchiolitis [4]. It is said that RSV has become one of the most common reasons for infant hospitalization [5]. An increasing

number of experts acknowledge that RSV has a significant role in adult severe respiratory diseases. In the US, there are an estimated 60,000 to 160,000 hospitalizations linked to RSV and 6,000 to 10,000 deaths per year among persons 65 and older.

According to estimates from the World Health Organization, RSV causes <60% of acute respiratory infections among kids globally and <80% of them in babies under 1 year old during the height of the viral season. RSV is thus by far the most common reason for pediatric bronchiolitis and pneumonia [6]. There is a widespread notion in industrialized nations that RSV is predominantly a significant agent in newborns and that the illness is typically less prevalent and severe in older children [7]. Similar to other respiratory viruses, RSV infections typically rise in colder climates, during rainy seasons, and during low temperatures [8].

Clinical manifestations

Clinical criteria are very different, enough to accurately distinguish RSV-associated from other, non-RSV-related respiratory tract infections (RTI) because of the high number of possible bacteria that can cause comparable symptoms, referring to respiratory illness. The signs and symptoms of RSV infection among premature newborns are typically atypical and may include adjustments to feeding and breathing [4].

Symptoms

The initial symptoms are typically upper respiratory tract manifestations such as mucosal inflammation and sneezing, congestion, and rhinorrhea; gradually, the symptoms evolve to lower respiratory tract manifestations like cough and increased airway obstruction. All of these mentioned clinical manifestations are induced by the immune response of the body rather than cytotoxicity and viral replication, and therefore, symptoms of bronchiolitis, like wheezing, are generally absent or not observed [9]. Table 1 shows the clinical manifestations and description of RSV.

Diagnosis

RSV infection affects 60-70% of newborn babies in their initial year and almost every child by the age of 2; of these, 2-3% require hospitalization for RSV-induced bronchiolitis [4]. Rapid diagnostic testing is necessary to influence clinical decision-making since clinical illnesses usually have a brief duration. The detection of virus-specific nucleic acid sequences or viral antigens, or virus in respira-

tory secretions, is the accurate diagnosis of RSV infection [10]. The detection of virus-specific nucleic acid sequences, viral antigens, or viruses in respiratory secretions is an accurate diagnosis of RSV infection [10].

If we look into the pathophysiology of RSV in humans, the initiation of viral attachment to the host cell is done by the RSV glycoprotein and the RSV fusion protein, which is crucial to the RSV viral life cycle and mediates viral cell membrane fusion [11].

RSV is a common respiratory pathogen that can cause severe respiratory illness, especially in infants, young children, and older adults. Diagnostic tests play a crucial role in identifying RSV infections, guiding treatment decisions, and implementing infection control measures. Several diagnostic methods are available for detecting RSV, each with its advantages and limitations.

Viral testing

This conventional technique entails gathering respiratory specimens, such as throat swabs or nasal secretions, and cultivating them in a lab to separate and identify the virus. Although viral culture has a high degree of specificity, its turnaround time (several days) may restrict its therapeutic value, particularly in acute care settings [12].

Immunofluorescence assay

Immunofluorescence assay (IFA) uses antibodies that have been fluorescently tagged to identify RSV antigens in respiratory specimens. Rapid results are usually obtained in a matter of hours, which makes it appropriate for prompt clinical decision-making. The sensitivity of IFA, however, can differ based on how well specimens are collected and processed, which could result in false-negative results [12].

Polymerase chain reaction

RSV RNA is amplified in respiratory samples by polymerase chain reaction (PCR), which has a high specificity and sensitivity. It is able to distinguish between RSV subtypes (A and B) and identify low virus levels. Quick results from rapid PCR assays, including point-of-care tests, help with timely clinical treatment and infection control [13].

Antigen detection test

RSV antigens are directly detected in respiratory specimens by quick antigen assays like lateral flow immunoassays. These tests are quick (typically within 15-30minutes) and convenient. They might, however, not be as sensitive as PCR, which could occasionally result in false-negative results [13].

Table 1. Clinical manifestation and description of respiratory syncytial virus.

Clinical manifestation	Description
Upper respiratory tract manifestations	Mucosal inflammation Sneezing Congestion Rhinorrhea
Lower respiratory tract manifestations	Cough Increased airway obstruction
Absence of bronchiolitis-like symptoms	Symptoms of bronchiolitis, such as wheezing, are generally absent or not observed
Induced by immune response	These clinical manifestations are induced by the immune response of the body rather than cytotoxicity and viral replication

Serological testing

RSV-specific antibodies are found in blood samples by serological assays, which can reveal viral infection in the past or present. These assays have use in population immunity assessments and epidemiological research. However, because antibody formation takes time, serological testing is not frequently employed for acute RSV diagnosis [14].

Who is at risk?

It is crucial to identify children who should be taken into consideration for severe and deadly RSV infection, as the potential for treatment or prophylaxis against RSV infection increases. Groups who are at high risk for severe RSV infection are infants with a history of premature delivery, with or without chronic lung illness [15], pediatric patients with cystic fibrosis [16], with congenital heart disease [17], immune-compromised patients, or patients with immunodeficiency [18]. According to a study done by Simoes, there are certain independent risk factors that can influence in development of RSV infection [15]. Table 2 shows the high-risk groups and their independent risk factors for RSV infection.

Prophylaxis

It is imperative to prevent infections with the RSV, particularly in high-risk groups such as newborns, young children, elderly people, and people with underlying medical disorders. Reducing hospitalizations and problems associated with RSV can be achieved through effective preventative initiatives. The most potent, affordable, and successful way to prevent infectious diseases is vaccination. By granting passive protection through placental antibody transfer, RSV vaccination during pregnancy is likely to improve serum neutralizing antibody responses established by prior natural infections and may lower the prevalence of RSV-associated LRTI in young newborns [16]. Prevention of RSV diseases in all newborn babies is a top public health priority. In clinical studies, passive RSV antibody methods have been successful [17]. Previous research on an RSV fusion protein vaccination given to expectant mothers showed that the mother's RSV-specific antibodies were effectively passed on to the child [18].

Vaccination programs

Vaccination is still one of the best ways to avoid contracting RSV. Even though there is no licensed RSV vaccine available for general public usage just yet, research is still being done to create safe and efficient vaccinations. Specifically, vaccination of the mother during pregnancy has demonstrated potential in preventing severe RSV disease in the first few months of life in the infant [19].

In India, several vaccines for RSV are available, including Synflorix (Pfizer), Prevenar 13 (Pfizer), and Rotarix (GSK). These vaccines offer indirect protection against RSV by targeting related pathogens or boosting immune responses. However, specific RSV vaccines designed solely for RSV prevention are still in development or limited in availability in India [20].

Palivizumab prophylaxis

In order to prevent severe RSV infections, prophylaxis with the monoclonal antibody palivizumab is advised for a few high-risk newborns. Updated guidelines on palivizumab use are provided by the American Academy of Pediatrics, which emphasizes the drug's efficiency in lowering hospitalizations linked to RSV in eligible newborns [20].

Hand hygiene and respiratory etiquette

Using alcohol-based hand sanitizers or encouraging frequent hand washing with soap and water are two effective ways to help prevent the spread of respiratory swine fever. Furthermore, promoting respiratory etiquette helps stop the spread of virus-containing respiratory droplets. Examples of this include concealing sneezes and coughs with tissues or elbows [21].

Environmental hygiene and disinfection

Preventing RSV outbreaks requires maintaining clean and sanitary conditions, particularly in healthcare and childcare settings. Toys and high-touch surfaces should be regularly disinfected to help limit the virus's survival and spread [22].

Refraining from close contact with sick people

People should stay away from people who are sick with respiratory ailments, especially if they are more likely to get a severe

Table 2. High-risk groups and their independent risk factors for respiratory syncytial virus infection.

High-risk groups	Independent risk factors for RSV infection
Infants with a history of premature delivery	Male gender Multiple gestations Young maternal age Exposure to environmental tobacco smoke Breastfeeding for less than 3 months Exposure to older siblings Crowded living conditions Low socioeconomic status
Infants with or without chronic lung illness	Exposure to environmental tobacco smoke
Pediatrics with cystic fibrosis	Exposure to environmental tobacco smoke
Pediatrics with congenital heart disease	Exposure to environmental tobacco smoke
Immune-compromised patients	Immunodeficiency or compromised immune system

RSV, respiratory syncytial virus.

RSV infection. To stop the transmission of RSV and other respiratory infections, this also entails remaining at home while exhibiting respiratory symptoms [22].

Education and awareness about public health

Educating the public about RSV, its symptoms, transmission channels, and preventive measures is essential to encouraging adherence to prevention protocols. Healthcare professionals are essential in teaching communities, caregivers, and patients about RSV preventive techniques [11].

Treatment

Guidelines on RSV and bronchiolitis have been created by the American Academy of Pediatrics, and they emphasize both prevention and therapeutic approaches (Table 3) [23].

Therapeutic approaches

Antiviral drugs

Antiviral medications work by preventing the spread of viruses and lessening the severity of RSV infections. One such drug that has been used to treat severe RSV infections, particularly in patients with impaired immune systems, is ribavirin. Its effectiveness is still debatable, though, and its serious adverse effects prevent it from being used widely [24].

Monoclonal antibodies

Specifically designed to target RSV proteins, such as the fusion protein, monoclonal antibodies (mAbs) have demonstrated potential in preventing severe RSV infections in high-risk populations, such as preterm infants and individuals with chronic lung disease. One Food and Drug Administration-approved mAb that is used prophylactically to lower RSV-related hospitalizations in high-risk infants is palivizumab [25].

Immunomodulatory therapies

The ability of immunomodulatory drugs to alter immune responses and lessen inflammation linked to severe RSV infections has been investigated. Examples of these drugs include corticosteroids and mAbs that target immunological pathways. However,

more research is needed to determine their effectiveness and safety in managing RSVs [26].

Vaccines

A number of vaccines, including live attenuated, subunit, and viral vector-based vaccinations, are being developed to combat RSV. By boosting immune responses to RSV, these vaccinations seek to lessen transmission and avert serious disease. However, the complicated biology of the virus and the possibility of vaccine-enhanced illness have made the development of a safe and effective RSV vaccine difficult [27].

Non-therapeutic approaches

Infection prevention and control

In communities and hospital settings, non-pharmacological treatments are essential for reducing the spread of RSV. Hand hygiene, respiratory etiquette (such as cough etiquette), ambient disinfection, and isolation precautions for afflicted persons are some of these methods. Strong infection control procedures can help stop the spread of RSV and safeguard susceptible groups [28].

Supportive care

The cornerstone of managing RSV, particularly in mild to moderate cases, is supportive care. This covers proper diet and hydration, oxygen therapy for respiratory distress, and symptomatic treatment (such as bronchodilators for wheezing, antipyretics for fever). The goals of supportive care are to reduce symptoms and enhance patient outcomes [29].

Public health interventions

In order to manage RSV infections at the community level, public health methods are crucial. These include surveillance systems, outbreak investigations, and immunization programs (such as palivizumab prophylaxis in high-risk newborns). To lessen the burden of sickness, these treatments assist in tracking RSV trends, identifying risk factors, and putting targeted interventions into action [30].

Prebiotics and probiotics

In a randomized experiment, probiotic and prebiotic treatment in preterm infants (32 to 36 weeks) decreased the prevalence of viral RTIs in comparison to placebo [30].

Table 3. Guidelines from the American Academy of Pediatrics about bronchiolitis.

Therapy	American Academy of Pediatrics recommendation	Evidence level
Inhaled bronchodilators (<i>i.e.</i> , albuterol, nebulized epinephrine)	Should not be routinely used Can consider trial and continue only if clinical response	B
Corticosteroids	Should not be routinely used	B
Ribavirin	Should not be routinely used	B
Palivizumab prophylaxis	Should not be given to select infants (premature infants <35 weeks gestation, children with congenital lung or heart disease)	A
Antibacterial medication	Should not be used in children with comorbid bacterial infection	B
Oral or intravenous fluids	Should assess hydration status and provide fluids accordingly	X
Chest therapy	Should not be routinely used	B
Oxygen	Indicate if oxygen saturations are persistently <90 percent in room air	D

Guidelines on respiratory syncytial virus and bronchiolitis were created by the American Academy of Pediatrics, and they emphasize both prevention and therapeutic approaches [23].

Vitamin D-cathelicidin

Innate immunity is heavily dependent on cationic host defense peptides called cathelicidins, which have bactericidal properties and recently discovered antiviral qualities, particularly those against influenza [30,31]. As per a previous trial done by Currie *et al.* [32], in addition to reducing the bronchial epithelial cells' sensitivity towards infection, the simultaneous exposure of the virus and human cathelicidin LL-37 resulted in a considerable dose-related reduction in infectivity. This reduction was partially caused by a direct effect on the viral particles. Furthermore, C-reactive protein expression was significantly reduced after RSV-infected human epithelial cells were continuously treated with LL-37, suggesting that LL-37 possesses immunomodulatory actions against RSV.

Discussion and Conclusions

Given the substantial morbidity and death that RSV infections are linked to, particularly in high-risk populations like newborns, young children, and people with underlying medical disorders, prevention and control of RSV infections are imperative. Aiming to lower complications associated with RSV and enhance patient outcomes, the aforementioned treatments cover both therapeutic and non-therapeutic approaches.

Therapeutic approaches

Antiviral Pharmaceuticals

In patients with immunocompromised conditions, ribavirin, an antiviral drug, has been used to treat severe RSV infections. But there is still disagreement over its effectiveness, and using it widely is hampered by its negative effects. New antiviral drugs with better safety and efficacy profiles are still being researched.

Monoclonal antibodies

In high-risk newborns, palivizumab, an mAb that targets RSV, has shown promise in avoiding severe RSV infections. Future therapeutic treatments could benefit from the investigation of other mAbs that target RSV proteins, such as the fusion protein.

Immunostimulatory medication

Immunomodulatory drugs are being investigated to control immune responses and lessen inflammation linked to severe RSV infections. These drugs include corticosteroids and mAbs that target immunological pathways. To ascertain their efficacy and safety in RSV management, more research is required.

Vaccines

Research is concentrated on developing vaccines against RSV; many types of vaccines are being developed to stimulate immune responses against RSV, limiting severe sickness, and minimizing transmission. Vaccine design must take challenges like vaccine-enhanced disease into account.

Non-therapeutic approaches

Infection prevention and control

In order to stop the spread of RSV in clinical and community settings, non-pharmacological measures like hand washing, respira-

tory etiquette, environmental cleaning, and isolation precautions are essential. Sturdy infection control procedures can stop the spread of RSV and safeguard susceptible groups.

Supportive care

When treating RSV infections, especially in mild to moderate cases, supportive care is essential. Symptomatic relief, oxygen therapy, proper diet, and hydration all contribute to symptom alleviation and better patient outcomes.

Public health interventions

To prevent RSV infections at the community level, public health initiatives such as surveillance systems, outbreak investigations, and immunization programs (such as palivizumab prophylaxis) are crucial. In order to lessen the burden of sickness, these programs track RSV trends, pinpoint risk factors, and put specific actions into action.

New approaches

What are probiotics and prebiotics? Probiotics and probiotics may lessen the frequency of viral respiratory tract illnesses, such as RSV, according to research. By altering the gut microbiome, these therapies strengthen the body's defenses against respiratory infections.

Research has looked into the function of cathelicidin and vitamin D in innate immunity against RSV. Supplementing with vitamin D may increase the production of cathelicidin, which has antiviral qualities and regulates immunological responses. Research is still being done to create new antiviral medications that specifically target RSV proteins or viral replication pathways. These medications may be more widely applicable, more effective, and have fewer adverse effects while treating RSV infections.

In conclusion, an all-encompassing strategy that incorporates therapeutic interventions, non-therapeutic measures, and cutting-edge tactics is necessary to successfully prevent and treat RSV infections. To create novel therapies and preventative measures to lessen the effects of RSV on public health, interdisciplinary research and cooperation are required. A rising infectious condition called RSV infection will have serious repercussions, such as a higher hospitalization rate for infants. In order to determine the best preventive measures and concentrate on efficient infection control, it is crucial to carry out additional research.

References

1. Furness JC, Habeb A, Spencer DA, O'Brien CJ. To the editor: bronchoalveolar lavage (BAL) in pediatric cystic fibrosis (CF): its clinical use modified by audit in a regional CF center. *Pediatr Pulmonol* 2002;33:234.
2. Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus - a comprehensive review. *Clin Rev Allergy Immunol* 2013;45:331-9.
3. Piedimonte G, Perez MK. Respiratory syncytial virus infection and bronchiolitis. *Pediatr Rev* 2014;35:519-30.
4. Taleb SA, al Thani AA, al Ansari K, Yassine HM. Human respiratory syncytial virus: pathogenesis, immune responses, and current vaccine approaches. *Eur J Clin Microbiol Infect Dis* 2018;37:1817-27.
5. Simões EAF, Center KJ, Tita ATN, et al. Prefusion F protein-

- based respiratory syncytial virus immunization in pregnancy. *N Engl J Med* 2022;386:1615-26.
6. Campbell PT, Geard N, Hogan AB. Modelling the household-level impact of a maternal respiratory syncytial virus (RSV) vaccine in a high-income setting. *BMC Med* 2020;18:319.
 7. Riddell CA, Bhat N, Bont LJ, et al. Informing randomized clinical trials of respiratory syncytial virus vaccination during pregnancy to prevent recurrent childhood wheezing: A sample size analysis. *Vaccine* 2018;36:8100-9.
 8. Silvestri M, Marando F, Costanzo AM, et al. Respiratory syncytial virus-associated hospitalization in premature infants who did not receive palivizumab prophylaxis in Italy: a retrospective analysis from the Osservatorio Study. *Ital J Pediatr* 2016;42:40.
 9. Popow-Kraupp T, Aberle JH. Diagnosis of respiratory syncytial virus infection. *Open Microbiol J* 2011;5:128-34.
 10. Piedimonte G, Perez MK. Respiratory syncytial virus infection and bronchiolitis practice gaps.
 11. Broor S, Parveen S, Maheshwari M. Respiratory syncytial virus infections in India: epidemiology and need for vaccine. *Indian J Med Microbiol* 2018;36:458-64.
 12. Petrocelli PA, Cunsolo V, Melito M, et al. Diagnosis of respiratory syncytial virus (RSV) infection in children by respiratory panel utilized during the COVID-19 pandemic. *Annali Istituto Superiore Sanità* 2023;59:31-6.
 13. Caliendo AM. Multiplex PCR and emerging technologies for the detection of respiratory pathogens. *Clin Infect Dis* 2011;52:S326-30.
 14. Barr R, Green CA, Sande CJ, Drysdale SB. Respiratory syncytial virus: diagnosis, prevention and management. *Ther Adv Infect Dis* 2019;6:2049936119865798.
 15. Simoes EAF. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr* 2003;143:S118-26.
 16. Abman SH, Ogle JW, Butler-Simon N, et al. Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. *J Pediatr* 1988;113:826-30.
 17. MacDonald NE, Hall CB, Suffin SC, et al. Respiratory syncytial viral infection in infants with congenital heart disease. *N Engl J Med* 1982;307:397-400.
 18. Lin GL, Drysdale SB, Snape MD, et al. Distinct patterns of within-host virus populations between two subgroups of human respiratory syncytial virus. *Nat Commun* 2021;12:5971.
 19. Brady MT, Byington CL, Davies HD, et al. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics* 2014;134:e620-38.
 20. Hill-Ricciuti A, Walsh EE, Greendyke WG, et al. Clinical impact of healthcare-associated respiratory syncytial virus in hospitalized adults. *Infect Control Hosp Epidemiol* 2023;44:433-9.
 21. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet* 2017;390:946-58.
 22. Weinstein RA, Hall CB. Nosocomial respiratory syncytial virus infections: the "cold war" has not ended. *Clin Infect Dis* 2000;31:590-6.
 23. Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med* 2020;383:415-25.
 24. Bordi P, Del Re M, Tiseo M. Crizotinib resensitization by compound mutation. (2016). *N Engl J Med* 2016;374:1790.
 25. Donia A, Hassan SU, Zhang X, et al. Covid-19 crisis creates opportunity towards global monitoring & surveillance. *Pathogens* 2021;10:256.
 26. McNally JD, McEvoy CT. Immunomodulatory therapy for the prevention and treatment of respiratory syncytial virus infection. *Pediatr Allergy Immunol Pulmonol* 2019;32:99-106.
 27. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet* 2022;399:2047-64.
 28. Paes B, Mitchell I, Li A, Lanctôt KL. A comparative study of respiratory syncytial virus (RSV) prophylaxis in premature infants within the Canadian Registry of Palivizumab (CARESS). *Eur J Clin Microbiol Infect Dis* 2012;31:2703-11.
 29. Silver AH, Nazif JM. Bronchiolitis. *Pediatr Rev* 2019;40:568-76.
 30. Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. Nebulized hypertonic saline for acute bronchiolitis: a systematic review. *Pediatrics* 2015;136:687-701.
 31. McDade P. Assessing Clinical Outcomes of the 2014 American Academy of Pediatrics Bronchiolitis Guideline. 2018. Available from: https://repository.library.georgetown.edu/bitstream/handle/10822/1053077/McDade_georgetown_0076D_13809.pdf?sequence=1&isAllowed=y.
 32. Zhang L, Mendoza-Sassi RA, Wainwright CE, et al. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev* 2023;4:CD006458.