Saudi experts' recommendation for RSV prophylaxis in the era of COVID-19

Consensus from the Saudi Pediatric Pulmonology Association

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ABSTRACT

يعد الفيروس المخلوي التنفسي السبب الأكثر شيوعًا لالتهاب القصيبات والالتهاب الرئوي الفيروسي في طب الأطفال في جميع أنحاء العالم. يصل معدل انتشار الفيرس إلى 23.5% فى الاطفال الذين يعانون من أمراض الجهاز التنفسي السفلي الحادة في المملكة العربية السعودية . يفرض مرض فيروس كورونا– 19 تحديات صحية عامة واجتماعية واقتصادية في المملكة. قامت الجمعية السعودية لأمراض الرئة للأطفال ، وهي مجموعة تابعة لجمعية الصدر السعودية، باعطاء النصائح والتوجيهات فى هذه الورقه البحثيه لإزالة التحديات المحتملة المحيطة ببرنامج الوقاية المناعية من الفيروس المخلوي التنفسي في المملكة العربية السعودية خلال فترة كورونا والتى تتضمن بعض التوصيات لإدارة هذه التحديات زيادة عدد عيادات الوقاية المناعية لهذا الفيروس، خدمات الرعاية المنزلية، بالإضافة إلى تشجيع الإحالات السريعة إلى أخصائي برنامج الوقاية المناعية من الفيروس المخلوي التنفسي في المملكة العربية السعودية. سيكون التدريب الإضافي مطلوبًا لموظفي الرعاية الصحية لإضافة الوقاية المناعية من الفيروس المخلوي التنفسي إلى جدول التحصين المنتظم.

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and viral pneumonia in pediatrics worldwide. In the Kingdom of Saudi Arabia (KSA), the prevalence of RSV is 23.5% in pediatric patients with acute lower respiratory tract illness. Coronavirus disease (COVID-19) poses critical public health and socioeconomic challenges in KSA. The Saudi Pediatric Pulmonology Association (SPPA), a subsidiary of the Saudi Thoracic Society (STS), developed a task force to determine the potential challenges and barriers to the RSV immunoprophylaxis program during the era of COVID-19 and to compose a practical, nationwide, and multidisciplinary approach to address these challenges. Some of the recommendations to manage these challenges include increasing the number of RSV immunoprophylaxis clinics, drive-thru visits, home-care services, and swift referrals to the RSV immunoprophylaxis program specialists. Additional training is required for healthcare personnel to add RSV immunoprophylaxis to the regular immunization schedule.

Keywords: respiratory syncytial virus, immunoprophylaxis, RSV, COVID-19

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1. Introduction. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and viral pneumonia in pediatric patients and is the leading cause of lower respiratory tract illness in infants' first year of life.[1,2] Approximately, 70% of bronchiolitis cases stem from an RSV infection.[3] According to the World Health Organization (WHO), the estimated annual burden of RSV-related acute lower respiratory illness (ALRI) is approximately 33 million worldwide, with approximately 3 million hospitalizations and 59,600 deaths.[4] Respiratory syncytial virus infection represents a grave condition in developing countries, with approximately 99% of RSV-related deaths and 93% of RSV-related ALRI deaths occurring in developing countries.[5] The prevalence of RSV infection is high in the Middle East and North Africa (MENA). In a systematic review of all RSV-related articles in the MENA region from 2001 to 2019, high annual incidence rates of RSV were reported in Jordan (64%), followed by Pakistan (52.6%), Tunisia (50%), Qatar

(48.5%), Algeria (47.8%), Egypt (46.6%), and Iran (46.1%), whereas the lowest incidence was reported in Oman (1.8%).[2] In the Kingdom of Saudi Arabia (KSA), the prevalence of RSV infection is 23.5% in pediatric patients with ALRI.[6]

The RSV is highly contagious, with a 98% risk (attack rate) in cases of first-time infection during outbreaks and 75% in cases of reinfection.[7] Transmission usually occurs through close contact or exposure of the nasal mucosa or conjunctiva to the patient's droplets or secretions. This knowledge can be useful for limiting the spread of the virus, where isolation and quarantine measures can be used to reduce the virus transmission.[8]

The pathophysiology of bronchiolitis is characterized by heightened mucus production, widespread inflammation, edema of the airways, and necrosis of the respiratory epithelial cells.[9] The destruction of airway epithelial cells is caused by the RSV binding to the epithelial cells and subsequently replicating, causing necrosis and ciliary destruction.[10] This cell destruction triggers an immune response characterized by the proliferation of lymphocytes and polymorphonuclear cells (PMNCs), while increased mucus secretion results in the generation of edematous submucosa and adventitial tissues. The cascade of these events leads to bronchiolar obstruction, air trapping, and various degrees of lobar collapse.[10]

Management strategies for viral bronchiolitis vary widely between different studies; however, there has been a recent shift in favor of minimal supportive therapy.[3,11] This type of minimally invasive intervention involves nasopharyngeal suction, oxygen therapy, and sustained hydration with fluid management. Other forms of respiratory support include high-flow nasal cannula (HFNC) oxygen, continuous positive airway pressure (CPAP), mechanical ventilation, heliox, and chest physiotherapy. Evidence of the efficacy of pharmacological agents in treating bronchiolitis is generally scarce;[3] however, immunoprophylaxis using the monoclonal antibody palivizumab is the recommended route for RSV infection prevention. Additionally, limited handling is preferred to avoid infant exhaustion, especially because infants are generally intolerant of interventions.[3]

Premature infants born prior to 37 weeks of gestational age (wGA) are particularly prone to severe morbidities due to anatomical, metabolic, and immunological predisposing characteristics.[12] As mentioned previously, RSV infection is the leading cause of hospitalizations for lower respiratory tract infections (LRTI) in infants. It is imperative that premature infants receive adequate prophylactic care to avoid severe bronchiolitis.[12] The Food and Drug Administration (FDA) approved palivizumab in 1998, a monoclonal antibody that remains, to date, the main prophylactic intervention against RSV infection.[13] Since its inaugural licensure, the American Academy of Pediatrics (AAP) has updated its RSV immunoprophylaxis guidelines 5 times, most recently in 2014. Current AAP guidelines limit RSV immunoprophylaxis to premature infants born at <29 wGA, infants <32 wGA with chronic lung disease (CLD), and infants <12 months with chronic heart disease (CHD).[13] Up to 5 monthly doses should be administered over the course of the RSV season,[14] which could be a challenge in areas with active COVID-19 lockdown and strained healthcare services. The AAP 2014 guideline was based on the cost-effectiveness ratios for RSV immunoprophylaxis.[15]

The AAP 2014 guideline recommends that premature infants who previously qualified to receive immunoprophylaxis under the 2012 guidelines do not receive immunoprophylaxis (without other qualifying conditions). Besides, infants with CHD aged less than one year are no longer recommended to get RSV immunoprophylaxis according to the AAP 2014 guideline, while the 2012 guidelines recommended the RSV immunoprophylaxis for infants with CHD aged <2 years at the beginning of RSV season.[16]

2. Respiratory syncytial virus epidemiology, immunoprophylaxis, and management in KSA. The number of children <5 years of age who succumb to RSV-associated ALRI ranges from 66,000 to 1,99,000, with 99% of the deaths occurring in developing countries. Respiratory syncytial virus is endemic to some areas, particularly South American countries. Data from the southern hemisphere show that RSV immunity is effective against other viruses as well (such as, Argentina). High-risk patients for RSV include premature infants and infants with chronic lung diseases or cardiac abnormalities. Respiratory syncytial virus-related LRTI in early life is a significant risk factor for developing persistent wheezing and asthma through

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early childhood. The monoclonal antibody palivizumab confers passive immunity against RSV.

There are more than 5 million (15.4%) LRTI cases in the KSA.[17] In 1991-1992, respiratory viruses were identified in approximately 62% of the 127 children with ALRI in Riyadh, and of these, 54% were positive for RSV.[18] In a comprehensive study by Al-Hajjar et al[19] carried out in Riyadh, KSA a total of 1429 samples were tested for respiratory viruses, and the RSV was the most common viral pathogen detected (29%). In a study by Al-Qassim, RSV was detected in 45% of 282 children with ALRI during 2003-2004.[20]

3. Status of RSV immunoprophylaxis program. Patients requiring the injection have easy access to the immunization program in the KSA. The new pre-mixed formulation of the RSV immunoprophylaxis injection is liquid and ready to use. Additionally, pharmacists need to relinquish the exclusive privilege of preparing the injection and allow clinics to do it as well to ensure maximum availability. In terms of availability, insurance companies did not entirely cover high-risk groups in the past. This was rectified when the guidelines came out, as insurance companies started accepting the vast majority of palivizumab requests. This was further facilitated by the drastic reduction in time, resulting from the new ready-to-administer liquid formulation.

There was a significant improvement in the national RSV immunoprophylaxis program after the Saudi initiative of bronchiolitis diagnosis, management, and prevention (SIBRO) program was rolled out in July 2018. The Saudi Council of Cooperative Health Insurance revised its policy to include the RSV immunoprophylaxis program as a mandatory requirement in the Saudi healthcare system.

4. Saudi Initiative of Bronchiolitis Diagnosis, Management, and Prevention (SIBRO). In July 2018, the SIBRO guidelines were declared by the Saudi Pediatric Pulmonology Association (SPPA) - a subdivision of the Saudi Thoracic Society (STS) - when they found that RSV infection was widespread in the country and the national guidelines according to the most recent and the best evidence-based practice was needed urgently.[11]

The SIBRO developed evidence-based guidelines for using palivizumab immunoprophylaxis in different patient categories (Tables 1 & 2). The SIBRO team focused mainly on high-risk groups such as premature infants and children with CLD and cardiac abnormalities. It was a great achievement for the SPPA to release such an important national guideline because the adoption of external guidelines might carry some concern as the management of RSV infection is always a mix of actions based on the published evidence and the local practice.

5. Respiratory syncytial virus immunoprophylaxis programs in the era of COVID-19 in the KSA. ***5.1. Burden of COVID-19 in the KSA.*** The coronavirus pandemic is the most recent outbreak caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China.[21] The infection caused by the SARS-CoV-2 is called "coronavirus disease-19" (COVID-19). Other versions of coronaviruses have emerged at various points, such as those responsible for the SARS outbreak in 2002 and Middle East respiratory syndrome (MERS) outbreak in 2012. As of November 21, 2020, the SARS-CoV-2 reached 219 countries, infecting over 55,961,380 persons, resulting in over 1,343,700 deaths worldwide.[22] The devastating impact of the virus has been far-reaching, causing a significant strain on healthcare systems worldwide and major economic losses.[23,24] The draining of healthcare resources by COVID-19 impacts the quality and availability of healthcare for other conditions, including RSV diagnosis, management, and immunoprophylaxis.

The KSA is one of the most severely affected countries with COVID-19 in the MENA region. As of September 21, 2020, the total disease burden reached over 330,246 cases, with over 4,512 deaths.[22] The first confirmed case in the KSA was reported on March 2, 2020, but decisive social distancing measures were applied even before the first case was reported. These measures ranged from suspension or cancellation of sporting, religious, and entertainment gatherings to temporary closure of mass gathering at the Umrah, mosques, and educational establishments and even total curfew.[25] The lockdown measures implemented by the Saudi government have been largely successful in keeping infection levels under control. A study published in April 2020 predicted that the number of infections in the KSA could be limited to 0.4 million cases by September 2020.[26] The current number of cases is still below 0.4 million, which is a sign of effective management of the local virus transmission

5.2. COVID-19 infection in the pediatric population in KSA. Children of all ages can contract COVID-19. However, children younger than 12-14 years appear to be affected less frequently than adults. In surveillance data from various countries, children typically account for 1-9% of laboratory-confirmed cases. In the KSA, children account for almost 8% of all confirmed COVID-19 cases; the increased rate was reported from the beginning of the pandemic; according to statistics

Table 1 - Saudi Initiative of Bronchiolitis Diagnosis, Management, and Prevention recommendations on using Palivizumab across different patients' categories.[11]

Patient segment	Recommendations	Level of evidence
Early preterm (=28 weeks, 6 days GA)	≤12 months of age	1B
Mid preterm (29 weeks GA, 0 days to 32 weeks, 6 days GA)	≤6 months of age	1B
Late preterm (33 weeks, 0 days weeks GA to 35 weeks, 0 days GA)	≤6 months of age at the start of the RSV season OR born during RSV season with at least one of the following risk factors: Attendance at child care Children <5 years of age who live permanently in the same household (including siblings) Exposure to environmental air pollutants	1B
Infants and children with CLD	<12 months for all; <24 months if still receiving medications for CLD within 6 months from the beginning of the epidemic season	1B
Infants and children with hemodynamically significant CHD	<12 months for all; <24 months if still receiving medications for the cardiac condition <6 months from the beginning of the epidemic season. Postoperative dose after cardio bypass	1B
Children with anatomic pulmonary abnormalities or neuromuscular disorders	<24 months may be considered for infants with impaired ability to handle respiratory secretions.	3B
Immunocompromised children	<24 months may be considered for children who are profoundly immunocompromised during the RSV season	2B
Children with down syndrome	Recommended for children with accompanying qualifying heart disease, CLD, airway clearance issues, or premature birth (<35 weeks, 0 days GA)	2B
Children with cystic fibrosis	<12 months with clinical evidence of CLD and/or nutritional compromise for <24 months with manifestations of severe lung disease or weight for length <10th percentile	2A
Special situations: If an infant who is receiving prophylaxis experiences a breakthrough of RSV	If an infant who is receiving prophylaxis experiences a breakthrough of RSV, the monthly prophylaxis should continue as planned until a maximum of 5 doses have been administered	3B

RSV: Respiratory Syncytial Virus, CLD: chronic lung disease, CHD: congenital heart disease, GA: gestational age

published by the Ministry of Health (MOH), the rate of children with COVID-19 increased from 4.8% in March 2020 to 12% at the end of May.[27,28] In Jeddah, in a retrospective study conducted from March 1 to May 13, 2020, involving 191 patients aged below 18 years screened for COVID-19 by RT-PCR, 24 results were positive. The patients' ages ranged from 13 days to 17 years (average, 8.4 years; standard deviation, 5.87 years).[29] Most cases of infection in children were attributable to household exposure, usually with an adult as the index patient. Infected children shed SARS-CoV-2 virus with nasopharyngeal viral loads comparable to or higher than those shed by adults.[30]

In the pediatric population, neonates are vulnerable to COVID-19 infection; frequently, they are infected by respiratory droplets or secretions during the postnatal period when they exposed to their mothers or other caregivers infected with the SARS-CoV-2. Approximately, 2-5% of the infants born to mothers with positive COVID-19 status show positive results on SARS-CoV-2 testing in the first 24-96 hours of life. To reduce the risk of transmission from mother to newborn, the MOH neonatology services improvement program published guidelines for neonates born to mothers with suspected or confirmed COVID-19 infection.[31] Furthermore, a recent study from a single tertiary care center in Riyadh, KSA showed the immense impact of the COVID-19 pandemic on childhood vaccinations, mainly the significant drop in vaccination visits during April and May 2020. From March to May 2020, there were drops in the vaccination visits of 49.93%, 71.90%, and 68.48%, respectively, compared to the same period from 2017 to 2019.[32]

5.3. Consensus development for RSV immunoprophylaxis program in KSA in the era of COVID-19. The Saudi Pediatric Pulmonology Association (SPPA) developed a taskforce to determine the potential challenges and barriers to the RSV immunoprophylaxis program in the KSA during the era of COVID-19 and to compose a practical, nationwide, multidisciplinary approach to address these problems. This initiative involved multi-multidisciplinary teams of pediatric pulmonologists, pediatric infectious disease specialists, and neonatologists from both the

Table 2 - Respiratory syncytial virus prophylaxis program.[11]

Referral form
Part A and B to be filled by referring physician and to be sent to Email: email of the coordinator
Contact info of the coordinator (extension)

A. Patient information

Patient's name: MRN:

Patient's date of birth: / / Gestational age:
Day Month Year

Gender: º Male º Female Contact number:

Referring team/physician: Bleep: Ext:

B. Criteria for prophylaxis

º Born at <29 weeks gestation and aged ≤12 months at the start of or during the local RSV season (after October 1, year)
º Infants born prematurely at 29-32 weeks gestation and aged ≤6 months at the start of or during the local RSV season (born after May 1, year)
Gestational age:
º 29 weeks º 30 weeks º 31 weeks º 32 weeks
º Infants born at 33-35 weeks gestation and aged ≤6 months (born after May 1, Year) at the start of or during the local RSV season with one or more risk factors:
º Child care attendance
º School-aged siblings (<5 years)
º Exposure to environmental air pollutants
º Children <24 months of age at the start of or during the local RSV season with BPD/CLD and who required oxygen and/or medical therapy within the 6 months preceding the RSV season

Diagnosis Treatment
º Children <24 months of age at the start of or during the local RSV season who require daily respiratory treatments for conditions that adversely affect respiratory function such as neuromuscular conditions and GE reflux disease with recurrent aspiration
º Children <24 months of age at the start of or during the local RSV season with hemodynamically significant congenital heart disease

Diagnosis Treatment
Children with cystic fibrosis as below
º <12 months of age at the start of or during the local RSV season with clinical evidence of CLD and/or nutritional compromise
º <24 months of age at the start of, or during the local RSV season with manifestations of severe lung disease OR weight for length <10th percentile

Diagnosis Treatment
º Children <24 months of age at the start of or during the local RSV season who are profoundly immunocompromised during the RSV season

Diagnosis Treatment

C. RSV immunoprophylaxis doses "this part to be filled by RSV team"

Please enter the patient's current body weight in kilograms and the date of injection in the appropriate boxes below·
Complete only the boxes for the current injection request

Date of injection #1	**Date of injection #2**	**Date of injection #3**	**Date of injection #4**	**Date of injection #5**	**Date of injection #6**
Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)	Body weight (kg)
Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)	Dose (mg)
Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature

RSV: respiratory syncytial virus, CLD: chronic lung disease, BPD: bronchopulmonary dysplasia

government and private sectors all over the KSA. Previously, the SIBRO also published a guideline on the diagnosis, management, and prevention of childhood bronchiolitis in the KSA.[11]

5.4. Respiratory syncytial virus immunoprophylaxis challenges in the era of COVID-19. Due to the current COVID-19 pandemic and the lockdown, infants and their parents are facing many difficulties in terms of visiting clinics. Additionally, there is a fear of going to the hospital due to the belief that hospitals are the main source of COVID-19, which creates compliance issues. Overloaded hospitals during a pandemic can expose infants to RSV, and this situation is complicated by the immune-deficient status of these high-risk infants. Another problem cause by the pandemic is that high-risk infants born a few months prior to the pandemic will be difficult to recall and might not receive the needed immunoprophylaxis. This situation is worsened by the sheer size of the KSA.

5.5. Proposed solutions for RSV immunoprophylaxis program challenges:

I. Encourage referral sources (mainly neonatologists) to expedite the referral of high-risk patients to pediatric pulmonologists.
II. Dispense full course of palivizumab vials. However, this could cause some medication waste.
III. Discuss ways to improve home care quality with caregivers.
IV. Home vaccinations were successful during the pandemic at most of the major health care tertiary hospitals, reaching the number of vaccinations comparable to that reported last year (without COVID-19). Home vaccinations could be adopted for high-risk RSV infants to limit their exposure to the risk of RSV. However, this would require additional training of the vaccinating staff, especially in terms of limiting waste during injection preparation and administration.
V. Seek approval to open specialized RSV clinics in hospitals.
VI. Set up drive-thru clinics to facilitate injection administration.
VII. Minimize the number of patients per day and increase the number of clinics. This would require punctuality from the patients.
VIII. Set a specific appointment time for each patient and allow walk-in patients.
IX. Increase number of available days for clinic visits.
X. Include RSV immunoprophylaxis doses in the regular immunization schedule. This would require a separate clinic for RSV immunoprophylaxis programs to avoid exposing high-risk infants to RSV.
XI. Experts have seen success with this approach in their own hospitals, where extending the immunoprophylaxis clinic working hours help spread the appointments throughout the day and reduce crowding.
XII. Separate the RSV immunoprophylaxis program clinic from the regular vaccination areas.
XIII. Gather high-risk infants born during the pandemic as a group to administer their prophylactic injections.

6. Future of RSV amid COVID-19. Neonates are particularly susceptible to COVID-19, as 10% of coronavirus patients are pediatric patients, with 40% of them aged below 2 years. As such, experts predict challenging times ahead with the potential emergence of another COVID-19 wave, in addition to delays in the release of the seasonal flu vaccine. Conversely, the SIBRO's initiative to release clear RSV diagnosis and management guidelines has significantly reduced the number of infants who develop severe bronchiolitis, as per anecdotal accounts from experts. These guidelines will help address potential issues from another COVID-19 wave.

New promising treatment options for RSV infection have emerged in the recent years. Nirsevimab is an extended half-life monoclonal antibody that has been approved by FDA in February 2019 to be used for prevention of LRTI caused by RSV.[33] It acts by the same mechanism of palivizumab through binding to the cells that express RSV protein. Nirsevimab is administered as a passive immunoprophylaxis agent to protect infants against RSV. Currently, the phase-3 trials are being conducted and anticipated to be published in 2023 (NCT03979313, NCT02878330). However, the phase-2 trials have shown a high efficacy in immunoprophylaxis against RSV. Infants who received Nirsevimab have shown a lower RSV LRTI and incidence of hospitalization compared to the infants who received placebo.[34] Nirsevimab is preferable to be used over the current options as it only requires a single dose for the whole RSV season, unlike palivizumab who require a monthly injection.[34] Also, Nirsevimab revealed a higher neutralizing activity and longer half-life than palivizumab.

The COVID-19 pandemic has highlighted the importance of epidemiological studies in the KSA. The KSA spared no expense to contain the pandemic and invested heavily into spreading awareness and enforcing precautionary protocols. This proactive approach can be applied to extremely low birth weight infants, where investment from the state can be a cost-effective measure to limit the spread of RSV. This investment can take the form of free RSV prophylaxis, which would help relieve the financial burden on the infant's family.

7. Conclusion. Respiratory syncytial virus mortality is an issue in developing countries, which can be exacerbated by the pandemic and overloaded healthcare institution. The closure or partial closure of clinics alongside a warranted fear of going to the hospital are the main challenges facing vulnerable patients. Some of the recommendations to manage these challenges include increasing the number of RSV immunoprophylaxis program clinics, drive-thru visits, and home vaccinations and encouraging swift referrals to specialists in the RSV immunoprophylaxis program. These solutions are not without faults, as additional training would be required for healthcare personnel to administer home

vaccinations, and adding an RSV immunoprophylaxis program to the regular immunization schedule would exert an additional load on the healthcare system.

The new liquid form used in the RSV immunoprophy, which subsequently allowed for increased insurance coverage of high-risk infants. Including the RSV immunoprophylaxis doses into the regular immunization schedule can help mitigate RSV-related mortality; however, further examination of the benefits and feasibility of this recommendation is required. The short-term success of RSV immunoprophylaxis is threatened by the emergence of another COVID-19 wave, in addition to delays in the release of the seasonal flu vaccine. This presents an immense challenge to healthcare experts. State investments in RSV epidemiological studies and free vaccinations can help alleviate the brunt of the pandemic.

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