Palivizumab for the Prophylaxis of Respiratory Syncytial Virus Disease: Expert Opinion and Recommendations for the Gulf Cooperation Council Region

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Abstract

Respiratory syncytial virus (RSV) infection poses a significant health threat to infants and young children. Considering the substantial burden in the Gulf Cooperation Council (GCC) countries, prevention of RSV remains a major public health priority. Globally, palivizumab prophylaxis has proven effective in reducing hospitalization and preventing complications in high-risk infants. While several national-level recommendations have been developed for palivizumab prophylaxis, few countries follow external guidelines due to lack of regional directives. For effective RSV management, recommendations should be based on regional evidence and local clinical practices. Hence, it is imperative to establish uniform recommendations for palivizumab prophylaxis for the GCC region. A synthesis of targeted nonsystematic literature searches on the prevalence of RSV, the efficacy of palivizumab immunoprophylaxis, and optimal timing for initiating RSV immunoprophylaxis programs were reviewed. Experts were invited to share their insights on disease burden, current immunoprophylaxis practices, barriers to compliance, and strategies to improve adherence to palivizumab prophylaxis. These recommendations are intended to bridge the existing gaps and serve as a unified reference guide for local physicians and those involved in recruiting eligible patients in RSV immunoprophylaxis programs, thus allowing for effective RSV management. By promoting alignment in recommendations and addressing obstacles to compliance, this collaborative initiative aims to reduce the overall burden of RSV-related illness in the region.

Keywords: Respiratory syncytial virus disease, Palivizumab, Lower respiratory tract infection

Introduction

Respiratory syncytial virus (RSV) accounts for significant morbidity and mortality burden on a global scale among children younger than 5 years of age, with the greatest burden in infants aged under 6 months. A systematic literature review (2017-2020) documented nearly 33 million episodes of RSV-associated acute lower respiratory tract infections (LRTIs) globally in children aged ≤5 years, resulting in 3.6 million hospitalization events and 26,300 in-hospital deaths.[1] Approximately half of these RSV-related hospital admissions (1.4 million) and in-hospital deaths (13,300) were reported among infants aged ≤6 months. More than 97% of the RSV-attributable mortality occurred in low- and middle-income countries.[1] The RSV-related LRTIs during early childhood can lead to long-term respiratory sequelae such as recurrent wheezing, asthma, and impaired lung function.[2] Premature infants and children with pre-existing cardiac, pulmonary, neuromuscular, and immunosuppressive disorders have greater susceptibility to develop severe RSV.[3] Several environmental and host-related risk factors like male gender, low birth weight, poor socioeconomic status, younger siblings, day care attendance, lack of breast feeding, and family history of atopy can predispose healthy children to severe RSV infection.[4,5] The RSV infection displays a seasonal transmission pattern with distinct regional and geographical variability, with marked winter-spring predominance (between October and May) in temperate countries and greater interseasonal variability with lesser pronounced spikes in tropics.[6] In the Gulf Cooperation Council (GCC) region, RSV is highly prevalent between August and February, peaking in winter months (December and January) and then decreasing during March and July.[7]

Epidemiological evidence suggests a high prevalence of RSV infection in GCC region with a wide variability in the rates of RSV incidence.[7-13] In the light of considerable burden, preventing RSV LRTIs in infants is a major public health priority. Currently, palivizumab, a monoclonal antibody (mAb), is a widely used passive immunization preventive strategy against RSV for high-risk infants and young children. It targets F protein, crucial for virus attachment and fusion, thereby neutralizing the virus and preventing its entry into the cells.[14] However, its widespread use is limited due to substantial expense and monthly dosing requirements despite a well-proven efficacy in reducing RSV-related hospitalizations. Recently, newer alternatives like nirsevimab (longer-acting, single-dose mAb) are recommended for passive immunization against RSV.[15] A significant shift in RSV management is expected in the coming years, but prioritizing reinforcement of palivizumab prophylaxis is crucial based on the accessibility of novel treatments within the region.

In GCC region, several national-level recommendations for RSV immunoprophylaxis have been developed in alignment with local epidemiological data.[8,16] Yet due to the lack of regional directives, some countries still adhere to the American Academy of Pediatrics (AAP) guidelines.[17] However, effective RSV management requires a combination of evidence-based recommendations, regional surveillance, and medical practices, suggesting an urgent need to align guidelines for RSV immunoprophylaxis across the GCC region. This paper intends to provide an overview of the regional and country-specific burden of RSV, identify challenges in the utilization of palivizumab, and provide expert recommendations in facilitating optimization of RSV immunoprophylaxis programs across the region.

Methods

The concept of formulating a GCC steering committee meeting was convened in June 2023 to discuss the epidemiology and burden of RSV, current unmet needs, and challenges in effective RSV management in the GCC region. It was decided to work with experts from across the GCC to share their collective opinions on current RSV immunoprophylaxis practices, obstacles to compliance, and measures to enhance compliance with palivizumab prophylaxis. Evidence on the prevalence of RSV, the efficacy of palivizumab immunoprophylaxis, and optimal timing for initiating RSV immunoprophylaxis programs were complied. Based on their clinical experience and the latest published evidence on the efficacy of palivizumab prophylaxis in high-risk infants, the experts shared practical recommendations to address existing gaps and to facilitate local physicians in effective RSV management in the region. These recommendations may serve as a unified reference guide for healthcare practitioners (HCPs), RSV program directors, and those involved in recruiting eligible patients in RSV immunoprophylaxis programs, thus allowing optimal utilization of resources and cost-effective practices across the region.

Prevalence and disease burden in the GCC region

Despite the considerable burden of RSV, there is a paucity of epidemiological studies evaluating prevalence in the GCC countries. In Saudi Arabia, the prevalence of RSV among young children <5 years of age experiencing acute LRTIs ranged from 0.2% to 70.2% from 1991 to 2018.[10] Another recent study from Saudi Arabia (2015–2022) revealed a high RSV infection rate of 56.8% in children ≤5 years.[7] A systematic review of RSV-related evidence from 2001 to 2019 found Qatar had a higher annual RSV incidence rate of 48.5% (2010–2011), whereas Oman had the lowest incidence at 1.8% (2011–2012).[9] In Bahrain (2018-2021), RSV was the third most prevalent viral infection (14.3%), after Flu-A (37.5%) and SARS-CoV-2 (33%).[13]

Regional data indicated a higher prevalence of RSV infections among children under 12 months of age, particularly among males.[9,18] Preterm infants with comorbid conditions like chronic lung disease (CLD), bronchopulmonary dysplasia (BPD), and hemodynamically significant-congenital heart disease (CHD) exhibited increased susceptibility to RSV infection. Other risk factors included multiple births, siblings attending school or daycare, exposure to tobacco smoking, daycare environments, and a family history of asthma.[19,20] The RSV infections tend to be more common during the winter season, indicating a strong seasonal activity of the virus.[7] According to the phylogenetic analysis studies, the prevalent Saudi strains of group-A RSV can be classified into the NA1 and ON1 genotypes, while the group B-RSV tends to cluster within the BA genotype.(2,26,27)[10,21,22] The RSV-A subgroup was more dominant than the RSV-B subgroup.[10,22] A study conducted in Kuwait investigating genetic variations in the RSV strains prevailing during the 2016 season found a predominance of RSV-A (67.5%) over the RSV-B subgroup (32.5%). While the circulating strains of RSV-A group were new and untyped that did not align with any of the known group-A genotypes, most of the RSV-B group strains belonged to BA10 genotype.[23]

Evidence on efficacy of palivizumab immunoprophylaxis in a high-risk population

Early preterm infants

Preterm infants exhibit higher incidence of RSV infection and subsequent hospitalization.[24] Among preterm infants, those born at <29 weeks gestational age (wGA) are more susceptible to experiencing severe RSV infection, which can result in extended duration of hospitalization and increased healthcare costs.[25] The current AAP recommendations advocate palivizumab prophylaxis for infants born at <29 wGA who are <12 months of age at the onset of RSV season (Box 1). Additionally, infants born at ≥29 wGA may qualify for RSV prophylaxis based on the presence of certain high-risk conditions, such as CLD or BPD.[17]

Box 1

Consistent with the current international guidelines, the experts recommend palivizumab prophylaxis to infants born before 29 wGA and who are under 12 months of age at the start of the RSV season.

Preterm children with CLD and BPD

Palivizumab prophylaxis has been proven effective in children with CLD or BPD. According to a meta-analysis, palivizumab prophylaxis resulted in 65% reduction in RSV hospitalization, compared to untreated infants.[32] A Cochrane database review concluded that palivizumab prophylaxis effectively reduced RSV-related hospitalizations among patients with CLD.[33] Additionally, the Canadian CARESS study revealed that children receiving palivizumab had similar rate of RSV hospitalization in the first and second years of life (hazard ratio [HR], 1.1; 95% confidence interval (CI): 0.4–2.9; p = 0.920).[34] Paes and Estrany suggested considering palivizumab prophylaxis in the first 2 years for all children with CLD, regardless of severity of disease.[35] Box 2 provides the expert recommendation for managing RSV in infants with CLD or BPD.

Box 2

Palivizumab is recommended for all patients with CLD or BPD who are below 12 months of age and can be extended during the second season for those who continue to receive CLD medications within 6 months at the onset of the RSV season.

Children with congenital heart abnormalities

Palivizumab prophylaxis for children with hemodynamically significant-CHD resulted in a reduction of 45% in hospital admissions due to RSV ($p = 0.003$), 56% in total days of RSV-related hospitalizations ($p = 0.003$), and 73% in the total number of RSV-related hospital days requiring supplemental oxygen ($p = 0.014$).[39] Another study demonstrated a 19% reduction in the frequency of RSV hospitalizations following palivizumab prophylaxis among children with CHD compared to the pre-prophylaxis period (2000 to 2002).[40] Chiu et al documented a significant decline in RSV hospitalization rate in patients with hemodynamically significant-CHD following palivizumab prophylaxis by 53% and 49%, before and after match comparison with control group ($p = 0.009$ and $p = 0.029$, respectively). Additionally, palivizumab recipients had shorter duration of hospitalization and lower rate of intensive care unit (ICU) admission. Efficacy outcomes were more pronounced in patients with cyanotic hemodynamically significant-CHD. Moreover, there was reduction in annual rate of RSV-related hospitalization from pre-palivizumab (4.8%) to post-palivizumab period (2.0%; $p = 0.038$).[41]

In line with global findings, a study conducted in Saudi Arabia assessed the efficacy of palivizumab prophylaxis among 530 children with hemodynamically significant-CHD, cyanotic CHD, and moderate-to-severe pulmonary hypertension. Over the course of 6 RSV seasons (2010–2016), only 13 patients (2.5%) required RSV-related hospitalization, with only 1 patient necessitating ICU admission. Importantly, no adverse events and deaths were attributed to RSV during the study period.[42]

In the CARESS registry data (2005-2015), the risk of RSV-related hospitalization (HR, 2.0; 95% CI: 0.2–16.5; $p = 0.52$) and respiratory illness-related hospitalization (HR, 1.9; 95% CI: 0.7–4.6; $p = 0.18$) were found to be similar for the first and second year of life. Also, the second-year infants revealed a more complicated disease course with significantly longer duration of hospitalization (51.2 versus 24.9 days in the first season).[43] Box 3 provides the expert recommendation for infants with hemodynamically significant-CHD and children with hemodynamically unstable cardiac conditions.

Box 3

Palivizumab prophylaxis is recommended for all infants under 12 months with hemodynamically significant-CHD (cyanotic or acyanotic). Palivizumab prophylaxis is recommended for children aged 12 to 24 months who remain hemodynamically unstable and are still on medication for cardiac conditions 6 months prior to the start of the epidemic season.

Infants who undergo cardiopulmonary bypass in the current RSV season are recommended to receive an additional dose of palivizumab. The dose should be administered promptly once the infant is stable after the procedure, even if it is within a month of the previous dose; subsequent doses should be given on a monthly basis as scheduled. This recommendation is based on a 58% reduction in the serum concentration of palivizumab after such procedures. Children younger than 2 years undergoing cardiac transplantation during the RSV season may be considered for palivizumab prophylaxis.

Children with neuromuscular disorders, anatomic abnormalities, and immunodeficiency

Currently, there is limited evidence supporting the efficacy of palivizumab prophylaxis among subpopulations such as children with pulmonary malformations, anatomical lung abnormalities with impaired lower airway clearance, severe upper airway obstruction, immunodeficiency, metabolic disorders, congenital diaphragmatic hernia, and lung transplantation. Table 1 summarizes the evidence regarding effectiveness of palivizumab in children with down syndrome, cystic fibrosis, and those with severe immunodeficiency.[26-30] Despite the lack of conclusive evidence in these patients, in the experts' view, these patient categories are likely to benefit from RSV immunoprophylaxis (Box 4).

Table 1: Effectiveness of palivizumab on RSV-related hospitalization in children with down syndrome, cystic fibrosis, severe immunodeficiency.

Author/Year	Study design	Study population	Sample size	RSV-related hospitalization outcomes
Studies on effectiveness of palivizumab in children with Down syndrome				
Paes et al 2014[26]	CARESS prospective registry (2006-2012)	High-risk infants receiving at least 1 dose of palivizumab	13,310 (of which 600 children had DS)	RSV hospitalization rate for children with DS who received prophylaxis (1.53%) was similar to children with other standard indications (1.45%).
Kimura et al 2020[27]	2007-2015	≤2 years	632 Palivizumab = 384 Control = 248	RSV-related hospitalization occurred in 4.2% patients with prophylaxis and 6.0% patients without prophylaxis. Palivizumab led to significant reduction in RSV-related hospitalization (odds ratio: 0.41, 95% CI: 0.18–0.92, p = 0.03).
Studies on effectiveness of palivizumab in children with cystic fibrosis				
Kua and Lee 2017[28]	Systematic review	<2 years	3891	Palivizumab prophylaxis reduced the risk of RSV hospitalization.
Sanchez-Solis et al 2015[29]	Random-effects meta-analysis		Palivizumab = 354 Untreated = 463	Palivizumab prophylaxis significantly reduced the hospitalization rate, compared to untreated group (0.018 vs 0.126, respectively; p < 0.001).
Fink et al 2019[30]	Cystic Fibrosis Foundation Patient Registry data (2008–2015)	≤2 years	4267 (of which 1588 received palivizumab)	Patients receiving prophylaxis showed similar long-term outcomes (pulmonary function, annual risk of hospitalization, or time to first positive sputum culture), compared to those who did not receive palivizumab.
Effectiveness of palivizumab in immunocompromised children				
Teusink-Cross et al 2016[31]	Retrospective chart review (2013–2015)		31 with hematopoietic stem cell transplantation received palivizumab prophylaxis	No change was noted in RSV incidence and disease course after restrictive palivizumab utilization, compared to the previous season.

CI, confidence interval; DS, Down syndrome; RSV, respiratory syncytial virus; vs, versus.

Box 4

Although conclusive evidence is lacking for these high-risk populations, the expert panel recommends palivizumab immunoprophylaxis for the following conditions:

Down syndrome: recommended for children with concomitant qualifying heart disease, CLD, airway obstruction, with inability to clear airway due to weak cough, or those born prematurely (<35 wGA)

Cystic fibrosis: <12 months for infants with CLD and/or nutritional deficiency; <24 months for those with preclinical or clinical evidence of severe CLD (based on computed tomography or radiological findings on admission) OR weight for length below 10th percentile

Children with anatomic pulmonary abnormalities or neuromuscular disorders: <24 months with difficulties in managing respiratory secretions

Children with severe immunodeficiency: <24 months during the RSV season

RSV prophylaxis in moderate- and late-preterm infants

From 2009 to 2012, the AAP advocated palivizumab prophylaxis to all preterm infants born at <32 wGA and those born at 32 to <35 wGA, and <3 months of chronological age (CA) at the onset of RSV season with at least 1 additional risk factor such as childcare attendance or living with a sibling under 5 years of age in the same household.[44] However, in 2014, the AAP discontinued recommending palivizumab for infants born ≥29 wGA unless they had specific comorbidities.[17] Subsequent studies evaluating the impact of revised AAP recommendations demonstrated notable reduction in palivizumab use and concurrent increase in the risk of RSV hospitalization along with higher disease severity and utilization of healthcare resources among born between 29 to 35wGA.[45,46]

Predictive model for risk factors in infants born 29–35 wGA

Researchers have highlighted the vulnerability of young preterm infants, and a need to reevaluate palivizumab prophylaxis in the >29 wGA subpopulation based on specific risk factors.[47] Several guidelines such as those from Spain,[48] Italy,[49] the Netherlands,[50] and Canada[51] have adopted risk-scoring tools (RST) to assess the risk of RSV hospitalization based on predetermined risk factors, thus allowing for targeted and cost-effective prophylaxis. Blanken et al developed an international risk-scoring tool (IRST) to predict the risk of RSV hospitalization in moderate and late preterm infants (32–35 wGA) based on the risk factors such as proximity of birth to RSV season (birth between 3 months before and 2 months after the start of RSV season), second-hand smoke exposure in the household or smoking during pregnancy, and siblings and/or day care.[52] The IRST showed high accuracy at predicting RSV-related hospitalization (area under the receiver operating characteristic curve [AUROC]: 0.773; sensitivity: 68.9%; specificity: 73.0%).[52]

Implementation of IRST with fewer risk factors has displayed a comparable predictive accuracy to the Canadian 7-variable RST (AUROC, IRST: 0.773 [sensitivity: 68.9%; specificity: 73.0%] versus Canadian RST: 0.762 [68.2%; 71.9%]) among moderate to late preterm infants (32–35 wGA). While the percentage of high-risk infants were similar for IRST (0.7%) and Canadian RST (CRST) (0.6%); the latter demonstrated a lower number needed to treat (7.5 versus 14.3), and fewer infants classified as moderate risk (9.8% versus 19.9% for CRST and IRST, respectively).[53] Additionally, the cumulative risk scores obtained from the CRST and the IRST have been shown to be moderately correlated ($r_s = 0.64$, $p < 0.001$).[54] Moreover, a cost-utility analysis demonstrated palivizumab to be highly cost-effective when administered to Canadian moderate to late preterm infants identified with moderate and high risk of RSV hospitalization using IRST, compared to without prophylaxis.[55]

Long-term respiratory outcomes after RSV infection in infants born 29 to 35 wGA

There is compelling literature evidence indicating that severe RSV infection during infancy in premature infants may cause long-term respiratory sequalae in later childhood. A Scottish study revealed that previous RSV-related hospitalization during 6 to 23 months of age was strongly associated with subsequent development of wheezing and asthma at 2 years of follow-up, which gradually decreased over time and persisted until 6 years of life.[56] A systematic review and meta-analysis established a significant association between early life RSV infection and recurrent wheeze and asthma in children aged 6 to 12 years at follow-up.[57] Additionally, caregivers for the infants born at 29 to 35 wGA and who were hospitalized due to confirmed RSV infection, have been reported to experience significant stress during hospitalization which continued until 1 month post-discharge. Allied to this, RSV hospitalization is also associated with several socioeconomic implications, such as missed work or productivity loss, financial burden, disruption of family health and routine, separation from siblings, and strained family relationships.[58]

Studies have suggested that palivizumab prophylaxis for RSV infection reduced subsequent wheezing in premature infants (≤35 wGA).[32,59-61] The MAKI trial showed a nearly 50% reduction in recurrent wheezing among palivizumab recipients than placebo (11% versus 21%; p = 0.01) during the first year of life.[59] Subsequent follow-up of this study at the age of 6 years revealed reduction in parent-reported current asthma among infants treated with palivizumab than control group (absolute risk reduction, 9.9%; 95% CI, 2.2–17.6).[60] These findings were supported by the Japanese CREW study which revealed lower rate of physician-diagnosed recurrent wheezing in palivizumab recipients relative to untreated patients, at the age of 3 years (6.4% versus 18.9%; p < 0.001).[61] Box 5 provides the expert recommendation for managing RSV in moderate and late preterm infants.

Box 5

For moderate preterm infants (born 29^0–32^6 wGA) with CA of ≤6 months at the start of RSV epidemic.

For late preterm infants (33^0 to 35^0) wGA: ≤6 months when the RSV season begins or if they are born during the season and have any of the specified risk factors such as attending childcare, residing permanently with siblings or children under 5 years old in the same household, and contact with environmental air pollutants.

Impact of COVID on RSV seasonality, disease course, and outcomes

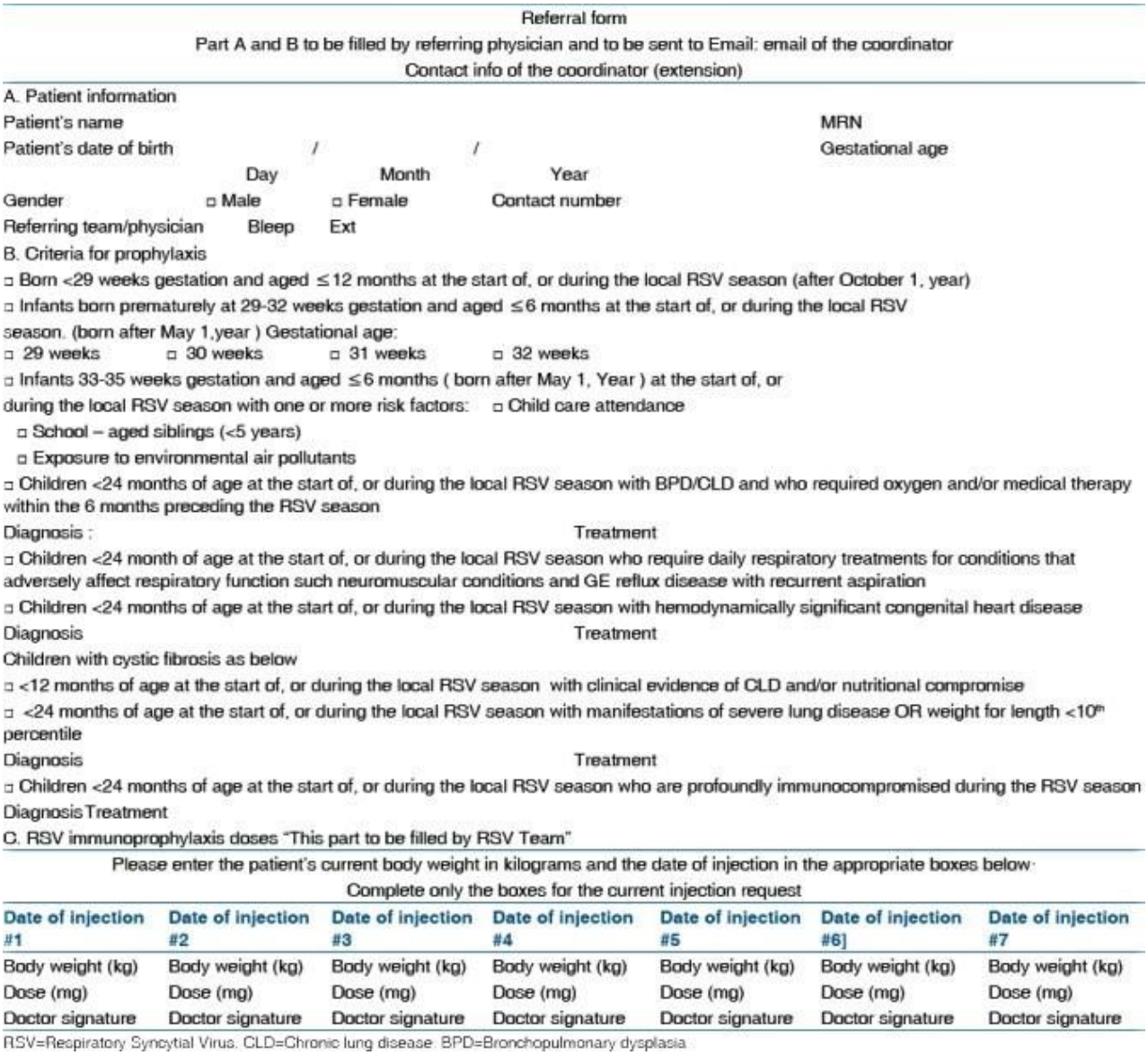
Regional differences in the duration and timing of the RSV season are influenced by demographics, climatic conditions, and population density.[9] Stringent public health measures implemented during COVID-19 pandemic led to dramatic reduction in RSV incidence during the usual epidemic season. However, with relaxation of restrictions, definitive shifts in the RSV seasonality pattern were observed, delaying the onset of RSV season.[62] Subsequently, the reemergent RSV outbreaks were more severe and affected a broader patient population than in typical RSV seasons.

In Qatar, RSV incidence decreased from 21.2% in 2019 to 0.7% in 2020 but returned to typical pre-pandemic levels (22.3%) in 2021 following relaxation of pandemic restrictions.[63] In Saudi Arabia, RSV infections were more common from August to February, peaking during December to January. No RSV cases were reported during the COVID-19 pandemic. However, in August 2021, the number of RSV-positive cases experienced a 2-fold rise, compared to previous years.[7]

In response to shifting RSV epidemiology during the COVID-19 pandemic, specialized taskforces reconsidered the criteria for palivizumab prophylaxis. Since 2021, the AAP recommended palivizumab prophylaxis in eligible patients during interseasonal RSV spread and considered providing more than 5 consecutive doses of palivizumab depending on the RSV seasonality duration in a region.[64] In the United Kingdom, the RSV immunoprophylaxis programs have also been modified, allowing eligible children to start early in July (instead of October) and implementing 7-monthly dosing regimen.[65]

The Saudi Pediatric Pulmonology Association faced several challenges in conducting RSV immunoprophylaxis programs amid the COVID-19 period. Due to increased strain on healthcare facilities, infants particularly those with

compromised immune system became more susceptible to RSV. Additionally, concerns about contracting COVID-19 in hospitals contributed to non-adherence to medical recommendations. Re-engagement of high-risk infants born before the pandemic further complicated the immunoprophylaxis initiatives.[66] To its response, several changes in clinical practices were implemented including increasing RSV clinics, extending operational days, setting up drive-through facilities, scheduling appointment, implementing home vaccinations to limit COVID-19 exposure, and expediting referrals to specialists.[66] A specialized referral form was disseminated among HCPs including pediatricians and staff in neonatal ICU and pediatric emergency rooms to enhance awareness (Figure 1).[8]



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 ◻ Male ◻ Female Contact number

Referring team/physician Bleep Ext

B. Criteria for prophylaxis

◻ Born <29 weeks gestation and aged ≤ 12 months at the start of, or during the local RSV season (after October 1, year)

◻ 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:

◻ 29 weeks ◻ 30 weeks ◻ 31 weeks ◻ 32 weeks

◻ Infants 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: ◻ Child care attendance

◻ School – aged siblings (<5 years)

◻ Exposure to environmental air pollutants

◻ 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

◻ Children <24 month 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 neuromuscular conditions and GE reflux disease with recurrent aspiration

◻ 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

◻ <12 months of age at the start of, or during the local RSV season with clinical evidence of CLD and/or nutritional compromise

◻ <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

◻ 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]	Date of injection #7
Body weight (kg)	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)	Dose (mg)
Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature	Doctor signature

RSV=Respiratory Syncytial Virus. CLD=Chronic lung disease. BPD=Bronchopulmonary dysplasia

Figure 1: Referral form to facilitate patient enrollment in RSV immunoprophylaxis program during COVID-19 pandemic. BPD, bronchopulmonary dysplasia; CLD, chronic lung disease; GE, gastroesophageal; MRN, medical record number; RSV, respiratory syncytial virus. Source reference: Alharbi A, Alqwaiee M, Al-Hindi MY, et al. Bronchiolitis in children: The Saudi initiative of bronchiolitis diagnosis, management, and prevention (SIBRO). Published online March 31, 2022. doi:10.4103/atm.ATM_60_1.[8] Permission conveyed through Copyrights Clearance Center.

Overall, in the view of disrupted RSV activity in post-pandemic seasons, the experts recommend a flexible approach along with regular surveillance and frequent reassessment of immunoprophylaxis guidelines to mitigate future RSV surges.

Optimal timing for initiating rsv immunoprophylaxis programs

Anticipating the onset of RSV epidemic season is currently a challenge due to atypical seasonal pattern observed in the post-pandemic years. The experts recommended relying on local RSV surveillance data to better understand the trend of annual RSV incidence over the recent years to optimize the start month, duration of administration, and the number of doses.

Optimizing the dosage and timing of palivizumab administration based on the local RSV season may lead to improved outcomes. A retrospective study conducted among the high-risk Saudi population (2009 to 2017) evaluated the effectiveness of 3 palivizumab regimens: 4-week interval dosing regimen starting in November (season 1), 4-week interval dosing regimen commencing in mid-September (season 2), and 3-week interval dosing regimen starting in mid-September for the remaining study duration. Although a decline in the RSV incidence rate was noted with the 3-week interval regimen (3.9% versus 5.9% and 9.1% in seasons 1 and 2, respectively), the differences among the 3 groups were statistically insignificant.[18] A study from Qatar found that RSV-related hospitalizations peaked during November and December which coincided with the first and second dose interval, potentially attributed to the lower serum levels of palivizumab early in the prophylaxis regimen,[20] suggesting to consider early initiation of the dosing schedule to align with the peak of RSV season. Consequently, the Saudi guidelines recommend starting RSV immunoprophylaxis program early (preferably in mid-September). Regional experts also suggested maintaining a shorter interval between the 2 consecutive initial doses than the recommended interval. A Phase II study from Saudi Arabia during the 2001-2002 season exhibited favorable safety profile of 7 monthly dosing regimen of palivizumab prophylaxis among high-risk children.[67]

Summary of recommendations for RSV immunoprophylaxis with palivizumab across different patient categories

Table 2 presents a comprehensive summary of recommendations for RSV immunoprophylaxis with palivizumab, across various patient populations.[36-38] These recommendations serve as a practical guide for healthcare practitioners in determining the optimal use of palivizumab for RSV prevention in vulnerable populations in the GCC region.

Table 2: Expert recommendations for RSV immunoprophylaxis with palivizumab among different patient populations.

Dosing schedule and administration	
• Dosing: 15 mg/kg once in a month during RSV season (minimum 5 doses), packaged in 100 mg vials, and the opened vials are recommended to be used within 6 hours. • Administration: Intramuscular injection, ideally in the anterolateral region of the thigh. The gluteal muscle is not recommended as a routine injection site due to the potential risk of sciatic nerve damage. Administration should adhere to standard aseptic procedures.[36] • RSV immunoprophylaxis program is recommended to be initiated early. Regional experts suggested maintaining a shorter duration between the initial 2 doses followed by regular interval of 4 weeks in subsequent doses. • Depending upon the severity or interseasonal circulation of RSV due to COVID-19, the dosing schedule can be extended beyond the 5-dose regimen. • **In experts' opinion, local surveillance data should guide the optimal timing of start month, duration of administration and the number of doses.**	
Patient Population	**Eligibility Criteria**
Preterm infants without comorbidities	Early preterm infants (<29 wGA): ≤12 months when the RSV season starts
	Moderate preterm infants (29-33 [29^0 to 32^6] wGA): ≤6 months at the beginning of the RSV season
	Late preterm infants (33-35 [33^0 to 35^0] wGA): ≤6 months when the RSV season begins or if they are born during the season and have any of the specified risk factors:

	• attending childcare, • permanently residing with children under 5 years old in the same household (including siblings), • being exposed to environmental air pollutants (smoking during pregnancy or in household).
Children with CLD/BPD	Palivizumab prophylaxis is recommended for all infants who are <12 months of age. ≤24 months for those who continue to receive medications for CLD for at least 6 months from the start of the RSV season
Children with CHD	Infants aged ≤12 months with hemodynamically significant-acyanotic CHD, who are: • receiving medications for congestive heart failure, • requiring cardiac surgery • with severe pulmonary hypertension. Infants aged 12 months or younger with hemodynamically significant cyanotic CHD: • Decisions regarding the administration of palivizumab prophylaxis should involve discussion with a pediatric cardiologist. These recommendations are applicable to eligible infants who are <12 months of age the beginning of the RSV season. Children aged 12–24 months who remain hemodynamically unstable and continue to take medication for cardiac conditions 6 months before the onset of epidemic season. Following cardiopulmonary bypass surgery or extracorporeal membrane oxygenation (in children <24 months of age), a single postoperative palivizumab dose (15 mg/kg) is recommended during the season, even when post-surgical defects are absent. The dose should be administered promptly once the infant is stable following the procedure, even if it is within a month of the previous dose, subsequent doses should be given on a monthly basis as scheduled. Infants who are not considered at increased risk from RSV typically do not require immunoprophylaxis, including: • Young children and Infants with hemodynamically insignificant cardiac conditions (such as secundum ASD, small VSD, PS, uncomplicated AS, mild COA, and PDA) • Infants who have undergone corrective surgery, unless they still require medication for congestive heart failure • Infants not receiving medical treatment for mild cardiomyopathy • Children in their second year of age, unless otherwise specified.
Down syndrome	Children with concomitant qualifying heart conditions, CLD, complications with airway clearance or born prematurely (prior to 35 weeks, 0 days GA)
Cystic Fibrosis	<12 months for infants with CLD and/or nutritional deficiency <24 months for children with severe lung conditions OR weight for length below 10th percentile
Anatomic pulmonary defects or neuromuscular disorder	<12 months at the start of the RSV season
Profoundly immunocompromised	<24 months during the RSV season
Multiple birth sets	If an infant at high risk of RSV is eligible for the season, the siblings from the same birth set also qualify for prophylaxis.
Special situations	For breakthrough RSV cases, monthly prophylaxis dose should continue until the completion of 5 doses. Coadministration with routine vaccines in the immunization schedule: Palivizumab does not affect the reaction of immune system to other vaccines, hence can be safely administered with them.[37,38]

	For eligible ICU patients nearing discharge, particularly during or close to RSV reason, administering the recommended dose of palivizumab prophylaxis 48-72 hours before discharge is advisable to mitigate poor compliance post-discharge.

BPD, bronchopulmonary dysplasia; CHD, congenital heart disease; CLD, chronic lung disease; GA, gestational age; ICU, intensive care unit; OR, odds ratio; RSV, respiratory syncytial virus; wGA: weeks gestational age.

Barriers in utilization of palivizumab in RSV prophylaxis in the region

In the experts' opinion, high cost of prophylactic regimen was not a limiting factor for the GCC countries; several other factors such as the lack of centralized database or registry, poor compliance to the dosing regimen, lack of parental understanding on RSV burden and benefits of immunoprophylaxis, and cultural misbeliefs were the key obstacles to successful RSV immunoprophylaxis. Inaccurate use of terminology such as '*immunization'* or '*vaccination'* instead of '*immunoprophylaxis'* is also known to contribute to non-adherence to the full dosing regimen.

The experts emphasized that compliance with dosing schedule, both in timing and frequency, is critical to achieving appropriate immunoprophylaxis efficacy. However, equating palivizumab to a vaccine may lead to false perceptions that a single injection may provide immunity against RSV infection. Non-adherence or deviation from the recommended dosing schedule may lower the efficacy of palivizumab and increase the risk of breakthrough RSV infection and hospitalization.[68] Studies showed significantly higher rate of RSV-related hospitalization in children who were noncompliant with monthly dosing of palivizumab prophylaxis.[69,70]

Expert recommendations to overcome barriers to RSV immunoprophylaxis

In the light of these challenges, the expert panel members collectively shared several strategies aimed at enhancing compliance with RSV immunoprophylaxis in the region, including extensive parental counselling, dedicated monitoring teams focusing on high-risk patient population, frequent telephonic reminders to parents/caregivers prior to appointment, and at-home or local administration. Using these interventions, a study from Qatar reported significant improvement in the compliance rate over the 3 successive RSV seasons (2009–2012) from 57.7% to 94.2% ($p < 0.05$). Improved compliance with palivizumab administration resulted in a decline in hospitalization rate from 3.7% to 1.7%.[20] Another hospital-based study from Dubai (925 children enrolled over 5 RSV seasons) reported a considerable reduction in RSV-related hospitalization rate from 9.23% in 2012 to 2013 to 0.67% in 2016 to 2017, attributed to a high compliance rate of 90.9% over the study period.[19] Such findings underscore the critical importance of compliance in achieving effective outcomes with palivizumab in RSV prophylaxis.

Parental beliefs or perception regarding immunoprophylaxis is an important consideration while designing interventional strategies to aid compliance. Therefore, it is critically important that the parents/caregivers are empowered with clear understanding of RSV burden, potential risk of long-term respiratory morbidity in severe cases and the importance of palivizumab prophylaxis. Experts also emphasized on the importance of appropriate terminology to aid compliance; HCPs should be encouraged to use the term '*immunoprophylaxis'* rather than '*vaccine'* to accurately convey its purpose and potential benefits.

Digital referral forms incorporating user-intuitive instructions may aid HCPs and nurses in streamlining the referral process and facilitate expeditious patient enrollment. Active follow-up of the cases, particularly those presented at the emergency department is imperative to ascertain reasons for any missed referrals. It is recommended to establish and maintain a database to facilitate dosing schedule, dispatch timely reminders, and contact eligible candidates for subsequent seasons. To prepare for upcoming season, drug supplies can be procured in advance and an announcement be disseminated regarding the eligibility criteria.

More importantly, comprehensive analysis of regional data and establishing local registries may help yield valuable insights into region-specific sociodemographic risk factors which may be beneficial for evaluating the need for potential revisions in the recommendations for RSV prophylaxis. For RSV surveillance, multiplex polymerase chain reaction and antigen assays can be performed on patients hospitalized with respiratory infections during the outpatient department visits. Seasonality onset may be delineated by analyzing laboratory reports and employing clinical criteria, particularly focusing on the pattern of admissions among high-risk demographic groups. In the United

Arab Emirates, the main microbiology laboratory disseminates an official announcement at the onset of RSV season, which is defined by either a mean RSV positivity rate of >3% as determined by polymerase chain reaction analysis or occurrence of 2 or more RSV-related hospitalizations for 2 consecutive weeks. Additionally, the RSV Hospitalization Surveillance Network (RSV-NET) interactive dashboards can be used to monitor real-time trends of laboratory-confirmed RSV-related hospitalizations and allow comparison among different demographic population groups and across seasons.

Figure 2 provides an overview of the region-specific barriers to RSV immunoprophylaxis and their expert-recommended solutions.

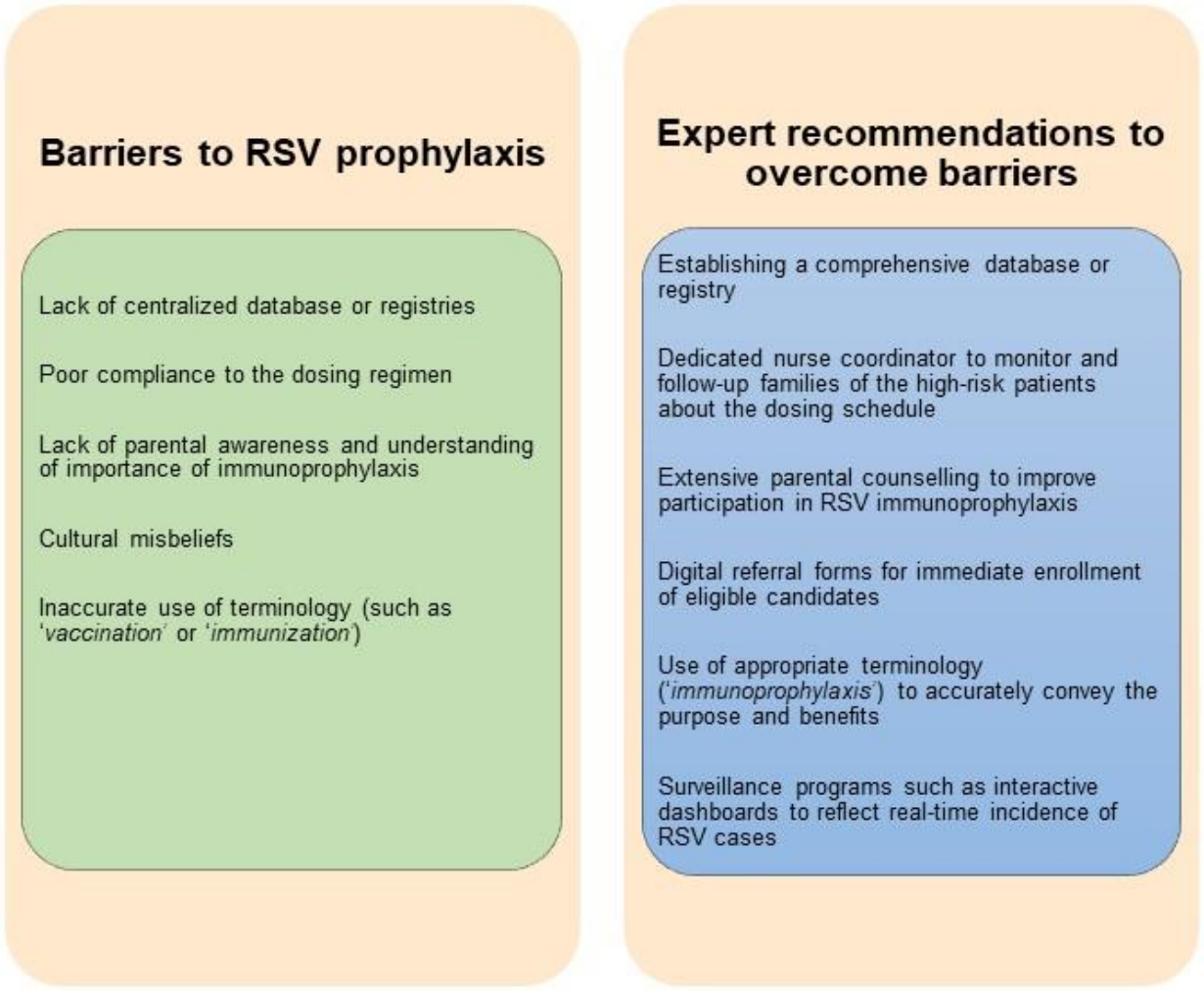


Figure 2: Expert recommendations to overcome the barriers to RSV immunoprophylaxis. RSV, respiratory syncytial virus.

Conclusion

The RSV remains the leading cause of LRTIs among young children in the GCC region. Hospitalization and morbidity caused by RSV have substantial impact on high-risk children and their families. More than the financial burden, the lack of centralized database, poor compliance to dosing regimen, parental ignorance, and cultural misbeliefs, act as significant regional barriers to overcoming the challenges posed by the disease and its consequences. Expert recommendations to reinforce palivizumab prophylaxis include establishing comprehensive databases or local

registries, extensive parental counselling, and dedicated monitoring of high-risk population groups. These expert recommendations may serve as a reference guide for HCPs, RSV program leaders, and those involved in enrolling eligible patients in preventive RSV programs. Moreover, recent advances in RSV prevention strategies such as longer-acting mAbs and vaccines targeting infants, pregnant women, and adults offer significant promise for the near future.

Disclosures

ASA is the chairman of Saudi Pediatric Pulmonology Association and SIBRO. AA is the Medical Director of Pulmonary Function Laboratory, Sidra Medicine. HSMA is the member of infection control and infectious disease council in SEHA. ARA, EA, LO, MKA, and MSE declared that they have no financial disclosures. Medical writing assistance for this manuscript is funded by AstraZeneca FZ LLC.

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