DRUGS IN CONTEXT

FULL TEXT ARTICLE

ISSN 1740-4398 A continuous publication, open access, peer-reviewed journal

www.drugsincontext.com

BRIEF REPORT

Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children

Saleh al-Alaiyan[1], Paul Pollack[2], Gerard F Notario[3]

[1]Neonatology Section, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [2]GI Immunology Medical Affairs, Global Pharmaceutical and Research Division, AbbVie Inc., North Chicago, IL, USA; [3]Virology Global Project Team, Global Pharmaceutical Research and Development, AbbVie Inc., North Chicago, IL, USA

Citation

al-Alaiyan S, Pollack P, Notario GF. Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children. Drugs in Context 2015; 4: 212270. doi: 10.7573/dic.212270

Article URL

http://www.drugsincontext.com/safety-pharmacokinetics-extended-use-palivizumab-saudi-arabian-infants-children

Correspondence

Gerard F Notario, MD, AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064, USA.
gerard.notario@abbvie.com

Provenance

Submitted, peer-reviewed externally

Dates

Submitted: 26 November 2014
Revised manuscript submitted: 4 February 2015
Accepted for publication: 6 February 2015
Publication date: 27 February 2015

Publisher and contact information

Drugs in Context is published by Just Medical Media Ltd
Undermount, Rydal, Ambleside, Cumbria, LA22 9LT, UK
ISSN 1740-4398
Just Medical Media Limited is registered in England
Number 6891187
VAT GB 945 1713 22

Julia Savory
Head of Digital Publishing and Submissions Management
julia@justmedicalmedia.com
Tel: +44 (0)1242 910 999

Abbreviations

AE, adverse event; CLDP, chronic lung disease of prematurity; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus

RESPIRATORY EDITORIAL BOARD

DRUGS IN CONTEXT

FULL TEXT ARTICLE

A continuous publication, open access, peer-reviewed journal

BRIEF REPORT

Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children

Saleh al-Alaiyan[1], Paul Pollack[2], Gerard F Notario[3]

[1]Neonatology Section, Department of Pediatrics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [2]GI Immunology Medical Affairs, Global Pharmaceutical and Research Division, AbbVie Inc., North Chicago, IL, USA; [3]Virology Global Project Team, Global Pharmaceutical Research and Development, AbbVie Inc., North Chicago, IL, USA

Citation

al-Alaiyan S, Pollack P, Notario GF. Safety and pharmacokinetics of extended use of palivizumab in Saudi Arabian infants and children. Drugs in Context 2015; 4: 212270. doi: 10.7573/dic.212270

Abstract

Background: The peak season of respiratory syncytial virus (RSV) infections in warmer climates may extend beyond the typical five-month RSV season of temperate regions. Additional monthly doses of palivizumab may be necessary in warmer regions to protect children at high risk for serious infection by the RSV.

Methods: In a Phase II, single-arm, single-center, non-comparative, open-label, prospective study conducted in Saudi Arabia, children at high risk for RSV infection received up to seven monthly injections of palivizumab (15 mg/kg) during the 2000–2001 RSV season. Key enrollment criteria were no previous exposure to palivizumab and gestational age ≤35 weeks, ≤6 months of age at enrollment, or chronic lung disease and ≤24 months of age at enrollment. We wished to assess the safety, immunogenicity, and pharmacokinetics of palivizumab as an extended seven-dose regimen.

Results: Of 18 enrolled patients, 17 patients received seven palivizumab injections. Seven adverse events (AEs) occurred in five patients. Bronchiolitis was the most commonly reported AE. Six serious AEs occurred in four patients. No AEs were considered related to palivizumab. Trough levels of palivizumab in serum were >40 µg/mL in most patients after the first injection and in 16/18 and 14/17 patients after the fourth and sixth injections, respectively. Except for one patient at one visit, the anti-palivizumab titer was <1:10 at all visits.

Conclusion: These data suggest that an extended palivizumab regimen of up to seven monthly doses during the RSV season exhibited an acceptable safety profile in children at high risk for RSV infection in Saudi Arabia.

Keywords: infants, open-label, palivizumab, pediatrics, pharmacokinetics, respiratory syncytial virus, safety, Saudi Arabia.

Introduction

Most children have experienced at least one infection with the respiratory syncytial virus (RSV) by 2 years of age [1,2]. Because of the high prevalence of RSV infections, more serious cases leading to hospitalization and intensive medical treatment incur a substantial economic burden on families and healthcare systems [3,4].

Risk factors for serious infection with RSV include: preterm birth; chronic lung disease of prematurity (CLDP; also known as bronchopulmonary dysplasia); cyanotic or complicated congenital heart disease; and immunodeficiency disease or immunosuppression caused by therapy [5–7]. Children born preterm who attend daycare or who live in a household with one or more siblings younger than 5 years of age are at a higher risk of contracting serious RSV infections [8].

Additional factors that may predispose preterm children to more serious infections include low weight upon hospital admission and exposure to tobacco smoke [9]. Infants born preterm with CLDP are at a higher risk of developing RSV-associated pneumonia if they are part of a multiparous birth [10].

Despite identification of these distinct risk factors, a study conducted in the USA (N=919) showed that most RSV-infected children who had been hospitalized for respiratory infection had been healthy and without any risk factors before study entry. This finding suggested that even children without an obvious risk factor may be vulnerable to serious infection by the RSV [11].

No vaccine has been approved for the prevention of RSV infection. Prophylactic treatment with the virus-neutralizing

and fusion-inhibiting monoclonal antibody palivizumab* has been shown to decrease the number of hospitalizations due to RSV infection in children who are at high risk [12]. Palivizumab has been approved by the US Food and Drug Administration and the European Medicines Agency, and is available for use in ≈80 countries [13,14].

The American Academy of Pediatrics recommends prophylactic administration of palivizumab to children in high-risk groups as up to five monthly intramuscular injections of 15 mg/kg during the RSV season [15]. In temperate climates in the northern hemisphere, administration usually begins in November/December and extends through March/April [5]. However, substantial variation may occur in the timing of the season within and especially between regions [16,17]. Cases of RSV infection occurring throughout the year have been reported in some parts of the world, particularly in regions with warmer climates [17–19]. Timing and length of the RSV season have obvious implications for the most effective use of palivizumab in the prevention of RSV infections.

Worldwide in 2005, ≈33.8 million episodes of RSV-related acute lower respiratory tract infection (LRTI) occurred in children younger than 5 years, which accounted for ≈22% of all acute LRTIs in this population [20]. In Saudi Arabia, RSV has been reported to account for 40% (children aged <1 year) to 83% (children aged <5 years) of all LRTIs [21]. Most cases occur from November through March, but infections in Saudi Arabia have been reported at other times of the year [22–26]. The peak season of RSV infections in Saudi Arabia may be expanded beyond that which occurs in temperate areas. Hence, additional monthly doses of palivizumab may be necessary to ensure the protection of children at high risk of serious infection.

Therefore, the present study was designed and conducted to assess the safety and pharmacokinetics of palivizumab if given as an extended seven-dose regimen to children in Saudi Arabia at high risk for serious disease caused by RSV infection.

Methods

Study design

This was a Phase II, single-arm, open-label, non-comparative, prospective study in which palivizumab (15 mg/kg) was administered to children approximately every 30 days at a single site in Riyadh, Saudi Arabia. Patients meeting the inclusion criteria received ≤7 doses during the 2000–2001 RSV season.

The study was approved by the King Faisal Specialist Hospital and Research Centre Office of Research Affairs as the independent ethics committee. The study was conducted in accordance with the Declaration of Helsinki, guidelines set by the International Conference on Harmonisation, and all applicable local and federal regulations (including regulations of the government of Saudi Arabia, the King Faisal Specialist Hospital and Research Centre and its Research Advisory Council, and Good Clinical Practice guidelines). Before enrollment, written informed consent was obtained from the patient's parent/legal guardian. As part of ethics approval, the sponsor was required to submit a final report within one year of approval and to inform the Office of Research Affairs of: proposal amendments; study termination; serious or unexpected adverse events (AEs); or any event or new information that could possibly affect the benefit–risk ratio of the study.

Patients

The study was limited to children who had never received palivizumab and who were judged by the investigator to be at risk for RSV infection and eligible to receive palivizumab. Pertinent inclusion and exclusion criteria are presented as online supplementary material. which is published here: http://www.drugsincontext.com/wp-content/uploads/2015/02/Palivizumab-in-Saudi-Arabian-children-supplementary-material.docx

Study product

Abbott Laboratories (North Chicago, IL, USA) provided vials containing palivizumab (100 mg) as sterile lyophilized monoclonal antibody, 50 mM histidine, 3.2 mM glycine, and 6% (w/v) mannitol. Palivizumab was stored at 2–8°C and was reconstituted with 1.0 mL of sterile water for injection at a final concentration of 100 mg/mL of palivizumab at pH 6.0. The solution was allowed to sit for 20 min to clarify and was used <3 h after reconstitution.

Palivizumab (100 mg/mL) was administered to patients at 15 mg/kg based on the patient's weight at each study visit, which occurred every 25–30 days after the date of the first dose. Palivizumab was administered *via* intramuscular injection in the anterolateral aspect of the thigh.

Study assessments

The primary objectives of the study were to determine the safety, tolerance, and pharmacokinetics of an extended number of palivizumab injections over seven months, as well as to evaluate the generation of antibodies to palivizumab in that time frame. Safety parameters included AEs and vital signs.

A complete medical history and relevant patient demographics (including possible risk factors for serious RSV infection) were obtained at the first study visit. At each study visit, safety and tolerance were monitored. A complete physical examination (vital signs, weight, height, chest examination) was undertaken, and information was collected regarding AEs (including intercurrent illness, concomitant medications, and hospitalizations). On days when the study drug was

*Synagis; MedImmune LLC, Gaithersburg, MD, USA; AbbVie Inc., North Chicago, IL, USA.

ISSN: 1740-4398

administered, vital signs were recorded immediately before and 30 min after administration. Study investigators maintained telephone contact with the parents/legal guardians between study visits every 1–2 weeks. Parents/legal guardians were to call study personnel to report abnormalities during study visit intervals and to bring the child to the study site if medical evaluation was necessary (if time permitted). Serious AEs were those that resulted in: death; risk of death at the time of the event; inpatient hospitalization; or development of a persistent or significant disability/incapacity. Any patient hospitalized with a respiratory illness had a nasopharyngeal aspirate, wash, or swab tested for the presence of RSV antigens using the TESTPACK RSV* kit. Blood samples for testing of pharmacokinetics and immunogenicity were obtained at the first, second, fifth, and seventh visits before palivizumab administration for analyses of trough levels of palivizumab in serum and anti-palivizumab antibodies as described previously [27].

Statistical analyses

A sample size of 25 patients was considered to be sufficient to evaluate the study objectives. Power analyses were not undertaken at the time of planning the study. For one event (e.g., RSV infection) in 25 subjects (event rate of 4%), the corresponding 95% confidence interval (CI) would have been from 0.1% to 20.4%. For one event in 18 subjects, the corresponding 95% CI would be from 0.1% to 27.3%.

All enrolled patients who received ≥1 dose of palivizumab were included in the analyses (intention-to-treat). Because of the small sample size and occurrence of only one RSV-positive hospitalization, planned statistical analyses were not carried out. Baseline characteristics, safety, pharmacokinetics, and immunogenicity were summarized using mean, standard error, median, and range for continuous variables, and using frequency and percentage for categorical variables.

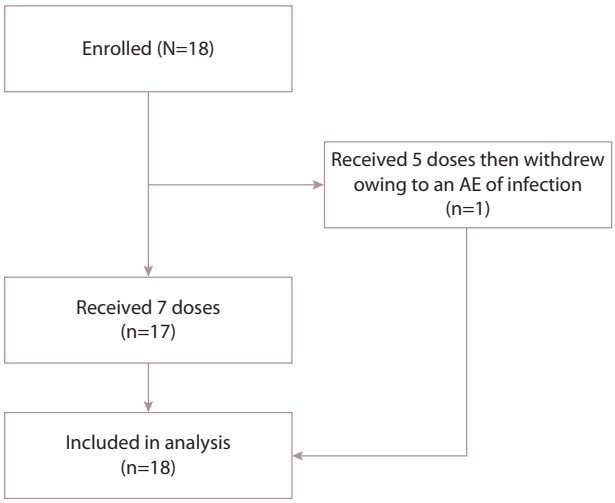
Results

Study patients and disposition

Due to a lack of patient availability, only 18 patients were enrolled in the study. The complete set of seven monthly doses of palivizumab was received by 17 patients (94.4%). The remaining patient received five doses and discontinued the study owing to infection (Figure 1). Median age of patients at enrollment was 14 (range, newborn–29) weeks. Median weight of patients at enrollment was 2.2 (range, 1.6–5.6) kg. Most patients were female (n=12 [66.7%]) and Caucasian (n=17 [94.4%]).

Table 1 lists the possible risk factors for RSV infection among patients. Most patients were part of multiparous births. Median gestational age at birth was 28 weeks and the median weight at birth was 0.98 kg. Four patients had CLDP. For patients who did not have CLDP, the initial risk factor was gestational age at birth ≤35 weeks and being ≤6 months of age at the time of enrollment per inclusion criteria. Six patients lived in a household with one person who smoked but all patients lived in households in which the primary caregiver did not smoke. Only one patient attended daycare and no patient had siblings in daycare.

Figure 1. Patient disposition.



AE, adverse event.

Table 1. Risk factors for infection by the respiratory syncytial virus (N=18).

Risk factor	n (%)
Multiple birth status	
Single	6 (33.3)
Twin	3 (16.7)
Triplet or greater	9 (50.0)
Birth order	
1	12 (66.7)
2	4 (22.2)
3	2 (11.1)
Number of smokers in household	
None	12 (66.7)
1	6 (33.3)
≥2	0
Does the primary caregiver smoke?	
Yes	0
No	18 (100.0)
Is the patient in daycare?	
Yes	1 (5.6)
No	17 (94.4)

*Abbott Laboratories.

(*Continued*)

ISSN: 1740-4398

Table 1. Risk factors for infection by the respiratory syncytial virus (N=18) (continued).

Risk factor	n (%)
Number of siblings in daycare	0
Number of people living in the household[a]	
3	4 (22.2)
6	4 (22.2)
7	1 (5.6)
9	1 (5.6)
10	6 (33.3)
11	2 (11.1)
Number of siblings living in the household	
0	4 (22.2)
2	5 (27.8)
3	3 (16.7)
6	1 (5.6)
7	1 (5.6)
8	4 (22.2)
Supplemental oxygen required?	
Yes	1 (5.6)
No	17 (94.4)
Chronic lung disease	
Yes	4 (22.2)
No	14 (77.8)
Gestational age at birth, wk[b]	27.9 (23–34)
Birth weight, kg[b]	0.98 (0.44–2.22)

[a]Study patient not included in the number of people living in the household.
[b]Median (range).

AEs

Five patients (27.8%) experienced ≥1 AE during the study (total number of AEs was seven; Table 2). The most frequently reported AE was bronchiolitis. No deaths occurred during the study. One of the seven AEs (melena) was not considered serious and occurred between the third and fourth months of treatment. The other six AEs, reported in four patients, were considered serious. Two of these patients were hospitalized once each for bronchiolitis, both of whom tested negative for RSV infection at that time; both AEs occurred between the fourth and fifth months of treatment. The third patient was hospitalized twice, once for a chest infection and CLDP, and once for CLDP and bronchopneumonia; both AEs occurred between the third and fourth months of treatment. RSV testing for this patient was negative during the hospitalization for chest infection and CLDP and was not performed during the hospitalization for CLDP and bronchopneumonia. The fourth patient was also hospitalized twice: once for bronchiolitis and once for a chest infection that was classified as a "medically important event." The patient tested positive for RSV infection during hospitalization for bronchiolitis, tested negative during hospitalization for chest infection and, ultimately, was withdrawn from the study during the fifth month of treatment. All AEs were considered by the investigator to be not related or probably not related to the study drug. Data on respiratory-related hospitalization are presented in Table 3.

Pharmacokinetics and immunogenicity

The mean (± standard deviation) trough concentration of palivizumab in serum was 44.72 µg/mL (18.67 µg/mL) after the first dose, a level considered to be protective in the cotton-rat model [27]. Trough concentrations of palivizumab

Table 2. Adverse events (N=18).

		Severity			Relationship to study drug			
Body system COSTART term	**Total (%)**	**Mild**	**Moderate**	**Severe**	**Not**	**Probably Not**	**Possibly**	**Probably**
Total patients[a]								
≥1 AE	5 (28)	2	1	2	4	1	0	0
Body as a whole[b]								
Infection	2 (11)	0	1	1	2	0	0	0
Digestive system								
Melena	1 (6)	1	0	0	1	0	0	0
Respiratory system[b]								
Bronchiolitis	3 (17)	1	1	1	3	0	0	0
Lung disorder	1 (6)	0	0	1	1	0	0	0
Pneumonia	1 (6)	0	1	0	0	1	0	0

[a]Two patients experienced two events each; one event was categorized under two body systems (lung disorder and infection) per medical decision. Thus, the total number of events shown (n=8) exceeds the total number of actual events (n=7) and the total number of patients (n=5) who experienced AEs.
[b]Serious AE.
AE, adverse event.

ISSN: 1740-4398

Table 3. Respiratory-related hospitalizations (N=18).

	n (%)	Mean (SD)
Number of patients hospitalized[a,b]	4 (22.2)	
Number of hospitalizations[a,b]	5 (27.8)	
Hospitalizations[a,c]		
Outpatient admissions	3 (60.0)	
Emergency admissions	2 (40.0)	
Admission to the intensive care unit	0	
Length of hospital stay, days	–	6.19 (6.35)
RSV status[a,d]		
Number of RSV-negative patients	3 (16.7)	
Number of RSV-positive patients	1 (5.6)	
Primary diagnosis[a,c]		
Number of upper respiratory tract infections	0	
Number of lower respiratory tract infections	5 (100.0)	
Supplemental oxygen[a,c]		
Not required	1 (20.0)	
Oxygen required	4 (80.0)	
Days of oxygen required	–	12.50 (11.68)
Maximum daily requirement, L/min	–	1.00 (0)
Mechanical ventilation[a,c]		
Not required	2 (60.0)	
Required	3 (40.0)	

[a]One patient was hospitalized twice, so the number of hospitalizations exceeds the number of hospitalized patients.
[b]Percentage of total patients enrolled (N=18).
[c]Percentage and/or mean of total number of hospitalizations (n=5).
[d]One patient was hospitalized twice but was tested for RSV infection only during the first hospitalization (negative), so RSV status during the second hospitalization was not known.
RSV, respiratory syncytial virus.

in serum rose between visits five and seven, but the difference between these two values was not significant. Anti-palivizumab titers were <1:10 in all patients at all visits except for one patient who had a titer of 1:20 at the second visit. This patient's titer was <1:10 at visits five and seven.

Discussion

The present study provides evidence that seven monthly doses of palivizumab were well tolerated by pediatric patients at high risk of serious respiratory disease caused by the RSV. All serum levels of palivizumab were within the range of those observed in previous palivizumab studies, and were correlated with protection [12,27,28]. This is the first prospective study examining this number of palivizumab injections in this population (though a retrospective global study also showed that >5 doses were well tolerated by infants) [29]. Patients in pivotal studies of palivizumab had only received ≤5 injections [2,28]. In addition to a recent study in Taiwan showing the effectiveness of six doses of palivizumab in preventing RSV hospitalization in 127 infants born prematurely or with CLDP [30], the results reported here have particular relevance for those regions in which cases of RSV occur outside of the five-month season that is typical in areas with temperate climates. In countries such as Saudi Arabia, additional doses of palivizumab beyond the five-dose regimen recommended by the American Academy of Pediatrics may be necessary to provide added protection for vulnerable members of the pediatric population during extended periods of widespread RSV activity. Palivizumab exhibited an acceptable safety profile in patients receiving seven injections, with no evidence of a substantial antibody response to the study drug. The AEs that occurred were nearly all related to the respiratory system and were typical of those seen commonly in the high-risk population of patients treated in this study.

The RSV is a major cause of respiratory infections among infants and young children in Middle East countries [26,31–33]. In Saudi Arabia, the RSV can be the cause of ≤83% of all LRTIs in children <5 years of age [21]. Studies in Jordan, Qatar, and Saudi Arabia have shown that the peak season of RSV infection occurs in the winter months, with the highest number of infections reported between December and February [24,31,32]. However, in Saudi Arabia and Qatar, cases have been detected beyond the time of the "typical" RSV season [24–26,32].

Cases of RSV infection have also been reported throughout the year in other countries with warmer climates, though ambient humidity and rainfall have been proposed to have an effect on infection rates [17,34,35]. A survey of five North American cities demonstrated a bimodal relationship between temperature and RSV infections, as well as a direct relationship to relative humidity [35]. Peak RSV activity in Riyadh occurs in late autumn and early winter at a time when temperatures are relatively mild (14–21°C) but humidity levels are relatively high (36–47%) [23,35,36]. Similarly, in Jordan, the prevalence of RSV infection is higher at times of lower temperatures and higher humidity [31]. Lower levels of humidity during other times of the year may mitigate (but not totally eliminate) the number of RSV infections because cases have been reported outside of the peak season [24,25]. Therefore, meteorologic variables may be

only among the multiple factors that influence the rate and timing of RSV infection [34].

This study was limited by the small number of patients enrolled. Furthermore, specimen collection for RSV testing was not standardized to a single method but instead allowed for collection via nasopharyngeal aspirates, washes, or swabs. Finally, no comparative placebo group was included in this study: using a placebo in these patients after palivizumab received approval would not have been ethical.

Conclusions

The timing of prophylactic administration of palivizumab to coincide with (or shortly precede) the annual RSV infection season is expected to yield the greatest clinical benefit to those patients most at risk for infection. In many parts of the world, the RSV season has been relatively well established and the recommended five-dose injection regimen is appropriate. Nevertheless, the exact timing of the RSV season is not always predictable, even within a particular country or region [16]. Moreover, in some parts of the world, the RSV season may stretch over a greater period of time, even in regions with temperate climates [37]. In such regions, additional doses of palivizumab may be necessary to adequately protect children in high-risk groups. The data on safety and immunogenicity noted in this report provide evidence that a regimen of up to seven doses of palivizumab exhibits an acceptable safety profile in these individuals. However, further studies with a larger sample size and randomized with an ethically suitable comparative arm are required to confirm these findings.

Contributions

SA participated in the conception and design of the study as well as the acquisition, analyses, and interpretation of data. PP participated in the conception and design of the study as well as the analyses and interpretation of data. GFN participated in the analyses and interpretation of data. All authors helped to draft the manuscript and approved the final version of the manuscript.

Potential conflicts of interest

The International Committee of Medical Journal Editors' (ICMJE) Potential Conflicts of Interests forms for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2015/02/dic.212270-COI.pdf

SA declares no conflict of interest. PP is a former employee and GFN is a current employee of AbbVie Inc., and may hold stock or options of this organization.

Funding declaration

This work was supported by AbbVie Inc., North Chicago, IL, USA.

Acknowledgments

The authors thank Jessie R Groothuis, MD, for her contributions to this manuscript, as well as the investigators, study-site staff, and patients who participated in the study. This study was conducted, analyzed, and supported by AbbVie Inc. Medical-writing support was provided by Daniel McCallus, PhD, at Complete Publication Solutions, LLC; this support was funded by AbbVie Inc. Portions of these data were presented in a poster entitled "The safety and tolerance of palivizumab in Saudi Arabian infants and children with or without chronic lung disease (CLD)" at the XIII International Symposium on Respiratory Viral Infections, Rome, Italy, 13–16 March 2011.

References

1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986;140(6):543–6. http://dx.doi.org/10.1001/archpedi.1986.02140200053026
2. American Academy of Pediatrics. Summaries of infectious diseases: respiratory syncytial virus. In: Pickering LK, ed. Red Book: 2012 Report of the Committee on Infectious Diseases. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:609–18.
3. Stewart DL, Romero JR, Buysman EK, Fernandes AW, Mahadevia PJ. Total healthcare costs in the US for preterm infants with respiratory syncytial virus lower respiratory infection in the first year of life requiring medical attention. Curr Med Res Opin 2009;25(11):2795–804. http://dx.doi.org/10.1185/03007990903290894
4. Stang P, Brandenburg N, Carter B. The economic burden of respiratory syncytial virus-associated bronchiolitis hospitalizations. Arch Pediatr Adolesc Med 2001; 155(1):95–6. http://dx.doi.org/10.1001/archpedi.155.1.95
5. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Technical report: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134(2):e620–38.
6. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. J Pediatr 1995;126(2):212–19. http://dx.doi.org/10.1016/S0022-3476(95)70547-3

7. Groothuis JR, Gutierrez KM, Lauer BA. Respiratory syncytial virus infection in children with bronchopulmonary dysplasia. Pediatrics 1988;82(2):199–203.
8. Resch B. Respiratory syncytial virus infection in high-risk infants - an update on palivizumab prophylaxis. Open Microbiol J 2014;8:71–7. http://dx.doi.org/10.2174/1874285801408010071
9. Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. PLoS ONE 2011;6(7):e22425. http://dx.doi.org/10.1371/journal.pone.0022425
10. Simoes EA, King SJ, Lehr MV, Groothuis JR. Preterm twins and triplets. A high-risk group for severe respiratory syncytial virus infection. Am J Dis Child 1993;147(3):303–6. http://dx.doi.org/10.1001/archpedi.1993.02160270065020
11. Hall CB, Weinberg GA, Iwane MK et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009;360(6):588–98. http://dx.doi.org/10.1056/NEJMoa0804877
12. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998;102(3):531–7. http://dx.doi.org/10.1542/peds.102.3.531
13. Synagis® (palivizumab). Full Prescribing Information, MedImmune, LLC, Gaithersburg, MD, 2014.
14. European Medicines Agency. Synagis (palivizumab) EPAR summary. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000257/human_med_001070.jsp [Last accessed: April 25, 2014].
15. American Academy of Pediatrics Committee on Infectious Diseases, American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics 2014;134(2):415–20. http://dx.doi.org/10.1542/peds.2014-1666
16. Mullins JA, Lamonte AC, Bresee JS, Anderson LJ. Substantial variability in community respiratory syncytial virus season timing. Pediatr Infect Dis J 2003;22(10):857–62. http://dx.doi.org/10.1097/01.inf.0000090921.21313.d3
17. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003;22(2 Suppl):S21–S32. http://dx.doi.org/10.1097/01.inf.0000053882.70365.c9
18. Halstead DC, Jenkins SG. Continuous non-seasonal epidemic of respiratory syncytial virus infection in the southeast United States. South Med J 1998;91(5):433–6. http://dx.doi.org/10.1097/00007611-199805000-00004
19. Light M. Respiratory syncytial virus seasonality in southeast Florida: results from three area hospitals caring for children. Pediatr Infect Dis J 2007;26(11 Suppl):S55–S59. http://dx.doi.org/10.1097/INF.0b013e318157dac1
20. Nair H, Nokes DJ, Gessner BD et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375(9725):1545–55. http://dx.doi.org/10.1016/S0140-6736(10)60206-1
21. Akhter J, Johani A. Epidemiology and diagnosis of human respiratory syncytial virus infections. In: Resch B, ed. Human Respiratory Syncytial Virus Infection: InTech; 2011:161–76. http://dx.doi.org/10.5772/29105
22. Bakir TM, Halawani M, Ramia S. Viral aetiology and epidemiology of acute respiratory infections in hospitalized Saudi children. J Trop Pediatr 1998;44(2):100–3. http://dx.doi.org/10.1093/tropej/44.2.100
23. Jamjoom GA, al-Semrani AM, Board A et al. Respiratory syncytial virus infection in young children hospitalized with respiratory illness in Riyadh. J Trop Pediatr 1993;39(6):346–9. http://dx.doi.org/10.1093/tropej/39.6.346
24. Al-Muhsen S. Clinical profile of respiratory syncytial virus (RSV) bronchiolitis in the intensive care unit at a tertiary care hospital. Curr Pediatr Res 2010; 14(2):75–80.
25. Shier MK, Badr MA. Respiratory syncytial virus infection in patients visiting King Khalid University Hospital. Minoufiya Medical Journal 2005;18(2):11–18.
26. al-Hajjar S, Akhter J, al Jumaah S, Hussain Qadri SM. Respiratory viruses in children attending a major referral centre in Saudi Arabia. Ann Trop Paediatr 1998;18(2):87–92.
27. Subramanian KN, Weisman LE, Rhodes T et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. Pediatr Infect Dis J 1998;17(2):110–15.
28. Feltes TF, Cabalka AK, Meissner HC et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003;143(4):532–40. http://dx.doi.org/10.1067/S0022-3476(03)00454-2
29. Simoes EA. Immunoprophylaxis of respiratory syncytial virus: global experience. Respir Res. 2002;3(Suppl 1): S26–S33.
30. Chi H, Hsu CH, Chang JH et al. A novel six consecutive monthly doses of palivizumab prophylaxis protocol for the prevention of respiratory syncytial virus infection in high-risk preterm infants in Taiwan. PLoS ONE 2014;9(6):e100981. http://dx.doi.org/10.1371/journal.pone.0100981
31. Al-Toum R, Bdour S, Ayyash H. Epidemiology and clinical characteristics of respiratory syncytial virus infections in Jordan. J Trop Pediatr 2006;52(4):282–7.

32. Wahab AA, Dawod ST, Raman HM. Clinical characteristics of respiratory syncytial virus infection in hospitalized healthy infants and young children in Qatar. J Trop Pediatr 2001;47(6):363–6. http://dx.doi.org/10.1093/tropej/47.6.363
33. Hijazi Z, Pacsa A, Eisa S et al. Respiratory syncytial virus infections in children in a desert country. Pediatr Infect Dis J 1995;14(4):322–4. http://dx.doi.org/10.1097/00006454-199504000-00016
34. Noyola DE, Mandeville PB. Effect of climatological factors on respiratory syncytial virus epidemics. Epidemiol Infect 2008;136(10):1328–32. http://dx.doi.org/10.1017/S0950268807000143
35. Yusuf S, Piedimonte G, Auais A et al. The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. Epidemiol Infect 2007;135(7):1077–90. http://dx.doi.org/10.1017/S095026880600776X
36. Kingdom of Saudi Arabia Ministry of Defence & Aviation. Surface annual climatological report. Available at: http://www.pme.gov.sa/Riyadh%20Old.htm [Last accessed: February 24, 2015].
37. Boivin G, Caouette G, Frenette L et al. Human respiratory syncytial virus and other viral infections in infants receiving palivizumab. J Clin Virol 2008;42(1):52–7. http://dx.doi.org/10.1016/j.jcv.2007.11.012