

# Palivizumab prophylaxis of RSV infections in Bosnia and Herzegovina

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## Abstract

**Background:** Palivizumab is indicated for respiratory syncytial virus (RSV) prophylaxis in high-risk children.

**Methods:** Observational study, based on 4 sites in Bosnia and Herzegovina (B&H), with institutional reports of infants at high risk for RSV who received at least 1 dose of palivizumab during the 2008-2013 RSV seasons.

**Results:** Across 6 RSV seasons, from 2008/9 to 2013/14, 589 infants were enrolled (0.29% of livebirths population). Of all infants, 290 (49.2%) were enrolled for prematurity only, 82 (13.9%) for bronchopulmonary dysplasia/chronic lung disease (BPD/CLD), 201 (34.1%) for congenital heart disease (CHD), and 13 (2.2%) for other reasons; 365 (61.9%) infants in total were born before 33 weeks. Average gestational age of preterm infants enrolled for prematurity only was  $30.2 \pm 3.2$  weeks; for preterm infants with BPD/CLD it was  $28.3 \pm 3.7$  weeks. Overall average of palivizumab injections was  $4.1 \pm 1.0$ . Hospitalization rate related to severe lower respiratory infections (LRI) during the period of protection by palivizumab was 1.2%. Respiratory infections which deserved medical attention were observed in 3.7% infants included in palivizumab prophylaxis.

**Conclusion:** RSV prophylaxis in B&H is provided systematically and successfully, following the national guidance established in 2009, with the aim of achieving a good cost-benefit ratio, with very low hospitalization rate for severe LRI in prophylaxed infants. New randomized controlled trials (RCTs) and American Academy of Pediatrics (AAP) guidance revised in 2014 will be taken into account in establishing a new national recommendation.

## Keywords

Palivizumab, RSV prophylaxis, preterm infants, BPD/CLD, CHD.

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## Introduction

Respiratory syncytial virus (RSV) has been recognized as one of the most common causes of serious infections of the lower respiratory tract in young children in the wide world. The main risk factors for severe RSV disease in children include prematurity, bronchopulmonary dysplasia/chronic lung disease (BPD/CLD) and congenital heart disease (CHD). Additional risk factors may include male gender, birth during RSV season, younger age of RSV acquisition, malnutrition, breastfeeding for < 2 months, birth weight, family history of wheezing and atopy, environmental factors – as crowding, passive exposure to tobacco smoke, day-care attendance, the number of older school-age siblings [1-4].

The lack of effective therapy against RSV infection makes prophylactic interventions the best strategy to avoid acute and chronic complications of the disease [5].

Palivizumab is a neutralizing humanized mouse IgG1 mono-clonal antibody directed against one of the two most antigenically stable sites of the F glycoprotein of the virus, site A [6]. The IMPact-RSV trial was the first to examine the correlation between use of palivizumab in high-risk infants and RSV hospitalization rates. Palivizumab resulted in a 55% reduction in RSV hospitalization compared to placebo [7].

Palivizumab was licensed in June 1998 by the US Food and Drug Administration. Safety and efficacy have been established for infants born at or before 35 weeks' gestation with or without CLD and for infants and children with hemodynamically significant CHD (HSCHD).

Palivizumab is administered intramuscularly at a dose of 15 mg/kg monthly (every 30 days) during the RSV season, which typically in European countries starts in November and

ends in March or April. A maximum of 5 doses is generally sufficient prophylaxis during one season.

The American Academy of Pediatrics (AAP) published a policy statement on the use of palivizumab in November 1998 [8]. Since that time, AAP has updated its guidance for the use of palivizumab several times, last time in 2014 [9-11]. The most notable changes in guidance published in 2009 were related to the indications for prophylaxis of premature infants with 32 to 35 weeks' gestational age (GA). These changes included 3 doses of palivizumab within chronological age of 90 days at the start of RSV season and in addition at least 1 more risk factor (day care attendance and/or have siblings < 5 years of age in the same household) [10]. Indications did not change for infants GA < 29<sup>+0 days</sup> weeks up to 1 year (5 doses), 29-32<sup>+6 days</sup> weeks in the first 6 months (5 doses), infants with BPD up to 2 years if they were receiving treatment for this during the 6 months before the outbreak of RSV (5 doses), and infants with HSCHD with or without cyanosis, if they required treatment for this up to 2 years (5 doses). AAP updated recommendation with further significant restrictions in 2014, limiting prophylaxis for preterm infants with GA < 29<sup>+0 days</sup> weeks up to 1 year, infants with GA < 32 weeks if they require FiO<sub>2</sub> more than 21% for 28 days or longer, infants with HSCHD up to 1 year, infants with BPD/CLD up to 2 years if they have been receiving treatment for this during the 6 months before the outbreak of RSV, and infants with certain chronic illnesses [11].

Palivizumab is widely approved across Europe, the USA, Canada, Asia, and Latin America; however, in an effort to ensure optimal balance of benefit and cost from this intervention, clinical guidelines are country specific and vary with regard to their recommendations for prophylaxis. Prospective observational studies and registries provide valuable information regarding the use of palivizumab in routine clinical practice and have accumulated a wealth of real-world information on the clinical effectiveness of RSV immunoprophylaxis with palivizumab. Overall respiratory-related hospitalizations following prophylaxis for preterm infants < 35 weeks GA and CLD patients ranged from 2.6% to 14.9% across studies while the corresponding RSV rates inclusive of HSCHD were 0.2-9.0% [12]. The Bosnian Neonatal Society established National guidance for RSV prophylaxis in 2009.

## Patients and methods

This observational study included data on the demographics, clinical characteristics and outcomes of infants and young children who received palivizumab for prophylaxis of serious lower respiratory infections (LRI) caused by RSV from 2008 to 2013 in Bosnia and Herzegovina (B&H). A total of 4 tertiary level centers distributed throughout B&H participated during seasons (University Clinical Center Sarajevo, University Clinical Center Tuzla, University Clinical Hospital Mostar, University Clinical Center Banja Luka; the last one joined in 2010/11). Decisions regarding prophylaxis were made by the health-care providers at each site. The same guideline for administration is used and institutional review is provided.

The recommendations of the Bosnian Neonatal Society established in 2009 for groups at high risk for severe RSV infection were as follows: children with HSCHD, with or without cyanosis, if they are < 2 years of age at the time of the RSV outbreak; children < 2 years of age, if they have CLD and have been receiving treatment for this during the 6 months before the outbreak of RSV; premature infants without CLD, when: their GA was < 29 weeks and at the time of RSV onset they are aged < 1 year, their GA was  $\leq$  32 weeks if they have 2 or more additional risk factors and at the onset of the RSV season they are aged < 6 months.

Risk factors (for infants GA 29-32 weeks) are defined as follows: BW < 1,500 g; the presence of a neurological disorder; the presence of other siblings in the home or crowding at home; attending a nursery school; passive smoking; low family socio-educational level. We also included previously mechanically ventilated infants with GA 29-32 weeks who were discharged during winter season [13]. Infants and young children were eligible for enrollment at a participating site if they received their first dose of palivizumab for RSV prophylaxis during the periods from 2008 to 2013. Subjects were enrolled by the local

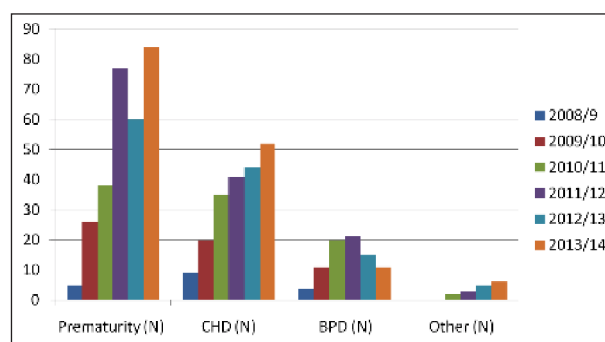
physician. Data were collected from uniform “palivizumab registration charts” completed for each child and presented as institutional reports at annual meetings at the end of each winter season. The following data were registered: diagnosis with risk factors, GA and clinical condition of the child, dose and date of palivizumab injection, adverse side effects, respiratory infections which deserved medical attention and hospitalizations due to severe LRI.

Data were examined using standard descriptive statistical methods.

## Results

All cumulative data through 6 seasons from 2008 to 2014 are summarized in **Tab. 1** in relation to total number of liveborns per year. Across all the 6 seasons, 589 infants were enrolled (0.29% of livebirths in total). RSV prophylaxis with palivizumab in B&H started in 2008/9 and it has slowly increased over the seasons. Since 2010/11 RSV prophylaxis has been carried out in the whole territory of B&H.

Of 589 patients in total, 290 (49.2%) were prophylaxed for prematurity only, 82 (13.9%) for BPD/CLD, 201 (34.1%) for CHD, and 13 (2.2%) for other reasons (**Fig. 1**). For 3 patients (0.5%) some of the medical data are missing.



**Figure 1.** Palivizumab (Synagis®) use according to indication across seasons 2008/09 to 2013/14.

CHD: congenital heart disease; BPD: bronchopulmonary dysplasia.

**Table 1.** Palivizumab use across seasons.

Year	2008	2009	2010	2011	2012	2013	Total
Livebirths <sup>a</sup>	34,176	34,550	33,528	31,811	32,547	30,684	197,296
RSV prophylaxis	18	57	93	139	124	158	589

RSV: respiratory syncytial virus.

<sup>a</sup>Agency for Statistics of Bosnia and Herzegovina (BHAS), Demography 2013 [21].

**Table 2.** Demographic features of prophylaxed infants.

		GA (weeks)		n	%	GA (weeks) ± SD
Prematurity only		< 29		137	23.2	30.2 ± 3.2
		29-32 <sup>+6 d</sup>		146	24.7	
		33-35 <sup>+6 d</sup>		7	1.2	
BPD/CLD		≤ 32 <sup>+6 d</sup>		82	13.9	28.3 ± 3.7
CHD		≤ 35 <sup>+6 d</sup> (n = 16)	> 35 <sup>+6 d</sup> (n = 185)	201	34.1	37 ± 5.5
Other	airway anomaly	-		3	2.2	38 ± 3.2
	neuromuscular disorder			1		
	pulmonary anomaly			2		
	multisystem anomaly			2		
	immunocompromised			1		
	cardiac anomaly > 2 years			2		
	various medical disorders			2		

GA: gestational age; BPD/CLD: bronchopulmonary dysplasia/chronic lung disease; CHD: congenital heart disease.

Demographic features of prophylaxed infants are summarized in **Tab. 2**. Over the 6 seasons there were 22 (3.7%) infants with respiratory infections that deserved medical attention and 7 (1.2%) hospitalizations due to severe LRI.

## Discussion

Over several years, international registries have closely monitored patients who have received RSV prophylaxis, in order to determine utilization and compliance relative to country-specific or national pediatric guidelines and position statements [14-20].

RSV prophylaxis in B&H started in 2008/9 following the initiative of the Bosnian Neonatal Society. In establishing the national guidelines for RSV prophylaxis, other professionals (pediatric cardiologists, pediatric pulmonologists) from tertiary level institutions in B&H were also included. The national guideline was based on previously published randomized controlled trials (RCTs) and AAP recommendations [7-11]. Since B&H belongs to the middle developed countries with limited resources, a balance between benefit and cost effectiveness is required. Our recommendation was more restrictive than AAP 2009 recommendation [10] regarding two groups of premature infants: infants with GA 33-35 weeks and infants with GA 29-32 <sup>+6 days</sup> weeks.

Prophylaxis with palivizumab to late preterm infants is still a matter of concern since this drug is too expensive to be used for the entire population of late preterm infants. The cost-effectiveness of the use of palivizumab in the late

preterm has been analyzed by several studies to identify environmental or individual risk factors for severe RSV infection. An attempt was made to use risk scores derived from the risk factors to detect the subjects for whom the administration of palivizumab could be effective in reducing RSV-related mortality and morbidity [17]. We did not recommend a routine administration of palivizumab for infants with GA 33-35 weeks. In AAP 2014 modified guidance, this group of preterm infants was also not included for RSV prophylaxis.

Infants born at 32 weeks' gestation or earlier may benefit from RSV prophylaxis even if they do not have BPD/CLD. Most experts recommend prophylaxis to be reserved for infants in this group who are at greatest risk of severe infection. For these infants, major risk factors to consider include their GA and chronologic age at the start of the RSV season [9].

Prophylaxis for preterm infants with GA 29-32 <sup>+6 days</sup> weeks was recommended with restrictions: if they are younger than 6 months and if they have 2 or more additional risk factors. Risk factors are defined as follows: BW < 1,500 g; the presence of a neurological disorder; mechanical ventilation > 48 h before discharge in RSV season; the presence in the home of other siblings younger than 5 years; attending a nursery school; low family socio-educational level. Epidemiologic factors, like exposure to tobacco smoke, should be controlled by the family of an infant at increased risk of RSV disease. High-risk infants should be kept away from crowds and from situations where exposure

to infected individuals cannot be controlled. In AAP recommendation, updated and modified in 2014 [11], prophylaxis is recommended only for infants < 32 weeks if they required  $\text{FiO}_2 > 0.21$  for 28 days or longer. The new recommendation of AAP will be taken into account in establishing a new national guidance.

During the period 2008-2013, according to the Agency for Statistics of B&H, 197,296 children were live born [21]. Estimated number of children at risk for severe RSV disease is about 0.4%. During the 6 examined seasons, 589 infants were enrolled (0.29% of total number of livebirths). Number of infants included in RSV prophylaxis has gradually increased since 2008/9. Clinical Center Banja Luka (Republic of Srpska) joined in 2010/11, and RSV prophylaxis has been carried out in the whole territory of B&H, with an average number of approximately 140 children per year.

For the cumulative data across all the 6 seasons with 589 enrolled patients in total, 290 (49.2%) were enrolled for prematurity only, 82 (13.9%) for BPD/CLD, 201 (34.1%) for CHD, and 13 (2.2%) for other reasons. Total number of preterm infants including preterm infants with BPD and HSCHD was 379 (64.3%). In comparison, the Canadian registry of palivizumab with data roughly from the same period, included a total of 5,286 children; of them, 70.8% were prophylaxed for prematurity only, 8.5% for BPD/CLD, 9.6% for CHD, and 11.1% for other reasons [12, 22].

Following the national guidance published in 2009, health care providers decided to provide RSV prophylaxis for premature infants as follows. In the category of infants enrolled for prematurity only ( $n = 290$ ), 137 infants were born before 29 weeks' gestation (47.2%); almost the same proportion of infants between 29 and  $32 + 6 \text{ days}$  weeks' gestation, 146 (50.3%); and 7 (2.4%) infants between 33 and 35 weeks' gestation. In total, accounting for preterm infants with BPD/CLD, 365/589 (61.9%) of infants were born before 33 weeks' gestation. Since infants with  $\text{GA} < 29$  weeks account approximately for 5% of all preterm infants, and infants with  $\text{GA} 28-32 + 6 \text{ days}$  weeks approximately for 15% of all preterm infants [23], it is obvious that less than half of infants with  $\text{GA} 28-32 + 6 \text{ days}$  weeks were covered with RSV prophylaxis. Late preterm infants with  $\text{GA} 33-35$  weeks, who generally account for approximately three quarters of the preterm birth population, were rarely included, comparing to 40-60% in other studies/registries [12, 18, 19, 23]. Average  $\text{GA}$  of

infants enrolled for prematurity only was  $30.2 \pm 3.2$  weeks; for infants with BPD/CLD it was  $28.3 \pm 3.7$  weeks, which is similar or lower if compared to the other observational studies/registries during the same period [16, 20, 24].

The number of infants with BPD/CLD has decreased since 2011/12, which is a result of less invasive treatment of premature infants including noninvasive ventilation and INSURE (INTubation SURfactant Extubation) strategy. Prevalence of enrolled infants with BPD largely varies from 8.5% in CARESS (the Canadian registry of palivizumab) study [12] to 81% in a French cohort study [18, 25].

The number of infants with CHD has increased from the first to the sixth season, with physicians listing this diagnosis as the most common reason for prophylaxis in the group with  $\text{GA} > 35$  weeks. Decisions regarding prophylaxis with palivizumab in children with CHD are made by pediatric cardiologists on the basis of the degree of physiologic cardiovascular compromise. Prophylaxis for those infants was provided during 2 years of life; 83 (41.7%) of patients with CHD were older than 1 year and 2 patients (0.9%) older than 2 years. Over the 6 seasons, a history of CHD was documented in 201 (34.1%) infants, calculated per season. Since 85 of them were prophylaxed for more than 1 season, the total number of enrolled infants with CHD was 116/589 (19.6%), which is comparable with other studies/registries [12, 24, 26]). A history of CHD was more common in subjects born after 35 weeks' gestation (92.0%) compared to those born before 33 weeks' gestation or between 33 and 35 weeks' gestation. In AAP 2014 updated and revised guidance, RSV prophylaxis for infants with HSCHD is indicated during the first year of life. This recommendation is still not accepted by pediatric cardiologists in B&H.

Category "other" is generally small, but it has gradually increased from 2008 to 2014; similar trend is present in other studies/registries [12, 18].

Majority of the patients received at least 4 injections per season, with an overall average of  $4.2 \pm 1.0$  injections per infant. LRI-related hospitalizations following prophylaxis by palivizumab was low and constant over seasons (1.2%), lower or comparable with other observational studies/registries [12, 18, 20]. In 3.7% of the prophylaxed infants, respiratory infections which deserved medical attention were noted (outpatients). Overall LRI hospitalization rate in the infants at low risk

who were not included in palivizumab prophylaxis in our country varies from 2.8% to 3.7%, which suggests that palivizumab is highly effective in the prevention of severe LRI. No serious adverse events related to palivizumab were reported (there were 2 infants with skin rash and 1 with cry and irritability), similar to other reports [7, 17, 18]. No deaths associated with palivizumab prophylaxis or LRI was observed.

## Conclusion

RSV prophylaxis in B&H is provided systematically and successfully, following the national guidance established in 2009, with the aim of achieving a good cost-benefit ratio. Over the past 6 years, palivizumab has been proven to be highly effective in preventing LRI in children aged < 2 years. Overall LRI related rehospitalization rate was very low, 1.2%. New RCTs and revised AAP 2014 guidance, will be taken into account in establishing a new national recommendation for RSV prophylaxis.

## Declaration of interest

The Authors declare that there is no conflict of interest.

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