European Journal of Pediatrics (2018) 177:903–911
https://doi.org/10.1007/s00431-018-3142-x

ORIGINAL ARTICLE

Palivizumab use in infants with Down syndrome—report from the German Synagis™ Registry 2009–2016

Arne Simon[1] · Susanne Gehrmann[2] · Gudrun Wagenpfeil[3] · Stefan Wagenpfeil[3]

Received: 6 November 2017 / Revised: 14 February 2018 / Accepted: 29 March 2018 / Published online: 12 April 2018

Abstract

Infants with Down syndrome (DS) face an increased risk of respiratory tract infections. Recent studies describe DS as independent risk factor for a complicated clinical course in infants with respiratory syncytial virus (RSV) infection. The prospective observational German Synagis™ Registry comprises data from 249 children below 25 months of age with DS and palivizumab prophylaxis 2009–2016 (1191 administrations; mean 4.8 per patient and season). The median gestational age and the birth weight in patients without and with DS were 31 versus 37 weeks ($P < 0.001$) and 1590 versus 2750 g, respectively ($P < 0.001$). Patients with DS significantly more often had congenital heart disease (CHD), siblings in kindergarten or school, treatment with oxygen at home, immunodeficiency, and neuromuscular impairment. The RSV-related hospitalization rate in patients with DS was 1.20%; the hospitalization rate in patients without DS was 0.71%.

Conclusion: Data from 249 children with DS receiving palivizumab prophylaxis in seven consecutive RSV seasons (2009–2016) in Germany reveal important differences between patients with and without DS concerning the main indication for palivizumab use and additional risk factors. Bearing in mind the limitations of an uncontrolled postmarketing observational study, the results confirm the field effectiveness of palivizumab prophylaxis in this special population.

What is Known:
- *Recent studies describe the Down syndrome as independent risk factor for a complicated clinical course in infants with RSV infection.*

What is New:
- *Compared with other infants receiving palivizumab prophylaxis, patients with Down syndrome significantly more often had congenital heart disease, siblings in kindergarten or school, treatment with oxygen at home, immunodeficiency, and neuromuscular impairment.*
- *In infants with palivizumab prophylaxis breakthrough, RSV-related hospitalization rates were not significantly higher in those with Down syndrome.*

Keywords Down syndrome · Respiratory syncytial virus · Palivizumab prophylaxis · RSV-related hospitalization · Bronchiolitis

Abbreviations

BPD	bronchopulmonary dysplasia
CHD	congenital heart disease
CLD	chronic lung disease of prematurity
eCRF	electronic case report form
DS	Down syndrome
LRTI	lower respiratory tract infection
PMOS	postmarketing observational study

Communicated by Nicole Ritz

✉ Arne Simon
Arne.Simon@uks.eu

Susanne Gehrmann
susanne.gehrmann@abbvie.com

Gudrun Wagenpfeil
gw@med-imbei.uni-saarland.de

Stefan Wagenpfeil
Stefan.Wagenpfeil@uniklinikum-saarland.de

[1] Department of Pediatric Oncology and Hematology, Children's Hospital Medical Center, University Hospital of Saarland, Homburg, Germany

[2] Medical Unit Leader, Medical Affairs Department, AbbVie Deutschland GmbH & Co.KG, Wiesbaden, Germany

[3] Institutes for Medical Biometry, Epidemiology and Medical Informatics (IMBEI), Campus Homburg, Saarland University, Homburg, Germany

RSV	respiratory syncytial virus
RSVHR	respiratory syncytial virus hospitalization rate
RTI	respiratory tract infection
SAE	serious adverse event

Introduction

Children with Down syndrome (DS; trisomy 21), the most common chromosomal abnormality in live-born neonates, have an increased incidence of respiratory tract infection (RTI) during the first 24 months of life [20]. This is due to anatomical, physiological, or functional abnormalities of the respiratory system and impairments of the humoral and cellular immune response. Children with DS are more prone to infections with viral pathogens [1, 12, 16, 19, 22]. Preterm infants with DS have an increased risk of bronchopulmonary dysplasia (BPD; also known as chronic lung disease of prematurity [CLD]) [2]. During the first 2 years of life, RTI represent the most common reason for hospitalization in children with DS, and lower respiratory tract infection (LRTI) in infants and young children with DS can cause persistent pulmonary hypertension. Approximately one half of all children with DS have congenital heart disease (CHD); in 10% of these children, cardio-surgical interventions are needed to correct or alleviate CHD [8].

Respiratory syncytial virus (RSV) is one of the most relevant viral pathogens responsible for RTIs in neonates, infants, and toddlers ≤ 24 months [7]. A number of recent publications argued that DS is an independent risk factor for complicated RSV infection, even in children without prematurity or hemodynamically significant CHD [1, 9–12, 18, 27–29]. Bloemers et al. [1] have shown a significantly higher hospitalization rate during RSV infection in children with DS (9.9 vs. 0.7%). Even in children with DS and no other risk factors, such as prematurity or CHD [5, 6, 25], the RSV-related hospitalization rate (RSVHR) was 7.6% (relative risk [RR], 12.6 vs. healthy controls). Kristensen et al. [10] identified additional risk factors for RSV-related hospitalizations in Danish children with CHD in multivariate analysis. Megged et al. [12] confirmed the results of Bloemers et al. [1] in a cohort study in Israel. The RSVHR of 18% ($n = 41/222$) in children with DS was high compared with studies performed in other high-risk populations, and 49% of the RSV-related hospitalizations in children with DS took place in children > 12 months.

The current recommendations for palivizumab[1] use in the USA (AAP 2014) and in Germany [4, 5] cite DS as an additional risk factor for a complicated course of RSV infection[5], such as day care attendance, older siblings, exposure to tobacco smoke at home, or crowded homes. The German Synagis™ Registry was created in 2002 as a postmarketing observational study (PMOS) [21]; the analysis presented here focuses on the results from this registry in children with DS compared with children without DS 2009–2016.

Materials and methods

This PMOS was conducted using a prospective, single-arm, multicenter design in Germany according to protocol dated April 2006. Infants and toddlers, who received ≥ 1 dose of palivizumab according to the local product label and the current recommendations for palivizumab use in Germany [4, 5], were eligible for participation. Each patient included in this study was to be observed during his/her first palivizumab treatment (2009–2016, between September 1 and June 30 during the corresponding RSV season). The corresponding data were documented in a protected Internet-based data entry system (electronic case report form (eCRF); MedSurv GmbH, Friedrich-Ebert-Str. 1, D-61130 Nidderau, Germany) by participating physicians. Baseline documentations included socio-demographic factors, perinatal history, and previously known risk factors for a complicated RSV infection.

In this analysis, we excluded patients who received palivizumab in > 1 consecutive RSV seasons ($n = 982$). Furthermore, we included only children below 25 months of age at the start of immunization.

Settings

Primary care pediatricians from hospital outpatient facilities and neonatologists from inpatient facilities were invited to participate in this PMOS and enroll patients at their discretion. No additional diagnostic or monitoring procedures were applied, other than those which would ordinarily be applied in the course of the individual therapeutic strategy. Only data that were part of routine medical care were collected. The prescription of palivizumab was clearly separated from the decision to include the patient in this PMOS. The attending neonatologist (inpatients) or primary care pediatrician (outpatients) was responsible for administering prophylaxis with palivizumab according to approved standards of administration and monitoring. All therapeutic decisions, including decisions for hospitalization, RSV testing, or monitoring subjects at a pediatric intensive care unit, were at the discretion of the attending physicians. Participation in the registry did not influence any decision regarding medical treatment.

Palivizumab dose

The recommended dose of palivizumab is 15 mg/kg of body weight, given once a month during anticipated periods of RSV risk in the community. Where possible, the first dose should

[1] Synagis®; formerly licensed by Abbot Laboratories Limited, UK, now licensed by Medimmune/AbbVie®).

be administered before the beginning of the RSV season. The majority of experience with palivizumab is with five injections during one season. Data, although limited, are available for ≥ 5 injections; therefore, the benefit in terms of protection ≥ 5 doses has not been established.

Hospitalization due to RSV infection

On any occurrence of a hospitalization, the attending physician completed a separate RSV hospitalization form. Information in the eCRF about the hospitalization based on this report. Diagnostic testing for RSV infection in infants and children hospitalized despite palivizumab prophylaxis is of particular importance to allocate the hospitalization to the categories "RSV-related" or "Not RSV-related" and to identify palivizumab failures (RSV-related hospitalization during palivizumab prophylaxis) [24]. Nasal swabs to detect or exclude an RSV infection were not consistently performed on admission in all subjects included in this registry who were hospitalized with a RTI during the observation period. To minimize the risk of allocation bias concerning the most important outcome parameter (RSV-related hospitalization), we requested the documenting physician to confirm that the hospitalization was related to a microbiologically confirmed RSV infection and to add ≥ 1 clinical RSV-related diagnosis (e.g., RSV-bronchiolitis).

Reporting of severe adverse events

According to good clinical practice, the participating physicians consented to follow legal regulations and report serious adverse events (SAEs) in case of any adverse event or reaction that requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or requires medical intervention to prevent one of the other outcomes listed above. If the physician documented a hospitalization in the eCRF, the Internet-based data entry system automatically executed an alert to complete and send a SAE report form to the pharmacovigilance department of AbbVie.

Statistics

Statistical analyses were conducted using means of IBM-SPSS™ version 23 (IBM, Armonk, New York, USA). Quantitative data (e.g., birth weight) were analyzed using the statistical parameters mean, standard deviation (SD), minimum, low (25), median (50), upper (75), and maximum quartile (100). Qualitative data (e.g., sex) were presented using means of absolute and relative frequencies. The calculation of percentages was based on the valid data per parameter, excluding patients with missing values for each of the parameters to be analyzed ("valid data analysis"). Accordingly, this resulted in different sample sizes. In general, description of results within the report was based on the valid data analysis. Comparisons of quantitative and categorical data between patients with and without DS were conducted using the Mann-Whitney U test and Fisher exact test, respectively. P values were two sided and subject to a significance level of < 0.05. We did not correct for the issue of multiple testing due to the exploratory nature of the study.

Results

Number of evaluable patients with DS and palivizumab administration schedule

Between September 1, 2009, and May 31, 2016 (7 consecutive RSV seasons), a total of 63,572 immunizations were documented for 12,729 evaluable patients, with an average of 5.0 immunizations per patient per season. Table 1 shows the number and proportion of patients with DS ($n = 249$).

Descriptive data of the evaluable patient population with DS

Most patients were male (without DS, 55%; with DS, 53%). The median gestational age at birth and the median birth weight in patients without and with DS was 31 versus 37 weeks ($P < 0.001$) and 1590 versus 2750 g, respectively ($P < 0.001$). The median age at first palivizumab administration was 3.2 and 3.4 months in patients without and with DS, respectively ($P = 0.071$). Table 2 shows the distribution of risk factors for a complicated clinical course of RSV infection in patients without and with DS. Patients with versus without DS had significantly more often CHD and cyanotic CHD, siblings in kindergarten or school, treatment with oxygen at home, immunodeficiency, and neuromuscular impairment.

Main indication for palivizumab

Figure 1a, b shows the main indications for palivizumab in patients without and with DS as indicated by the documenting physician in the eCRF. In this registry, CHD was the main indication for palivizumab in 64% of all children with DS (vs. 12% in those without DS). In contrast to patients without DS, in which premature birth comprised 75% of all main indications for palivizumab, this was the case in only 19% of the patients with DS.

Number of palivizumab administrations and administrations per patient

A total of 62,381 immunizations were documented for the 12,480 evaluable patients without DS, with an average of

Table 1 Number and proportion of patients with DS in seven consecutive RSV seasons (2009–2016)

Seven consecutive RSV seasons	Only patients included in the registry for the first RSV season*			
	All	Patients without Down syndrome (trisomy 21)	Patients with Down syndrome (trisomy 21)	Proportion of included patients with DS (%)
2009–2010	2133	2108	25	1.2
2010–2011	1812	1787	25	1.4
2011–2012	1911	1870	41	2.1
2012–2013	1926	1888	38	2.0
2013–2014	1759	1720	39	2.2
2014–2015	1602	1555	47	2.9
2015–2016	1586	1552	34	2.1
2009–2016	*12,729*	*12,480*	*249*	*2.0*

Italic is only used to point out that these values are cumulative results

DS Down syndrome, *RSV* respiratory syncytial virus

*$n = 48$ patients with DS were included again during a second RSV season (excluded in this analysis)

5.0 immunizations per patient per season; 45.4% of the subjects without DS received > 5 monthly injections ($n = 5669$). In patients with DS, 1191 immunizations were documented, with an average of 4.78 immunizations per patient per season ($P = 0.102$). One hundred four infants with DS (41.8%) received > 5 monthly injections ($P = 0.275$). Figure 2 shows the cumulative monthly distribution of palivizumab administrations.

Table 2 Risk factors for complicated RSV infection in patients without and with Down syndrome

Risk factors	Patients without DS			Patients with DS			Fisher exact test (two sided)
	N	*n*	%	*N*	*n*	in %	*P* value
Premature birth (<36 weeks)	12,480	10,716	85.9	249	68	27.3	< 0.001
Multiple births	11,651	3774	32.4	218	19	8.7	< 0.001
Siblings in kindergarten or school	10,535	4760	45.2	232	139	59.9	< 0.001
Congenital heart disease	12,296	3219	26.2	248	211	85.1	< 0.001
Smoking in the family	6209	2007	32.3	123	30	24.4	0.064
Family history of asthma	10,389	1121	10.8	200	7	3.5	< 0.001
Family history of atopy	10,407	2018	19.4	199	21	10.6	0.001
Chronic lung disease*	12,180	2313	19.0	242	33	13.6	0.038
Chronic lung disease therapy†	12,060	1773	14.7	231	30	13.0	0.512
Treatment with oxygen at home	12,251	739	6.0	239	24	10.0	0.019
Immunodeficiency	12,040	145	1.2	231	26	11.3	< 0.001
Cyanotic congenital heart disease	12,130	728	6.0	233	56	24.0	< 0.001
Neuromuscular impairment	8255	717	8.7	180	69	38.3	< 0.001
Serious neuromuscular disease	8212	401	4.9	181	27	14.9	< 0.001
Neuromuscular impairment positive‡	11,956	1091	9.1	229	90	39.3	< 0.001
Attending day care	12,148	350	2.9	241	11	4.6	0.121
Crowded living condition	10,373	2546	24.5	202	46	22.8	0.620
Breastfeeding ≤ 2 months	11,198	5695	50.9	219	99	45.2	0.102

N is the total number of patients with informative data about the corresponding risk factor in the CRF; *n* is the number of patients in which the corresponding risk factor is marked as positive by the documenting physician

DS Down syndrome, *RSV* respiratory syncytial virus

* Chronic lung disease of prematurity is synonymous to "bronchopulmonary dysplasia"

† Therapy with steroids or bronchodilators directed against chronic lung disease during the previous 6 months

‡ Neuromuscular impairment positive or serious neuromuscular disease positive

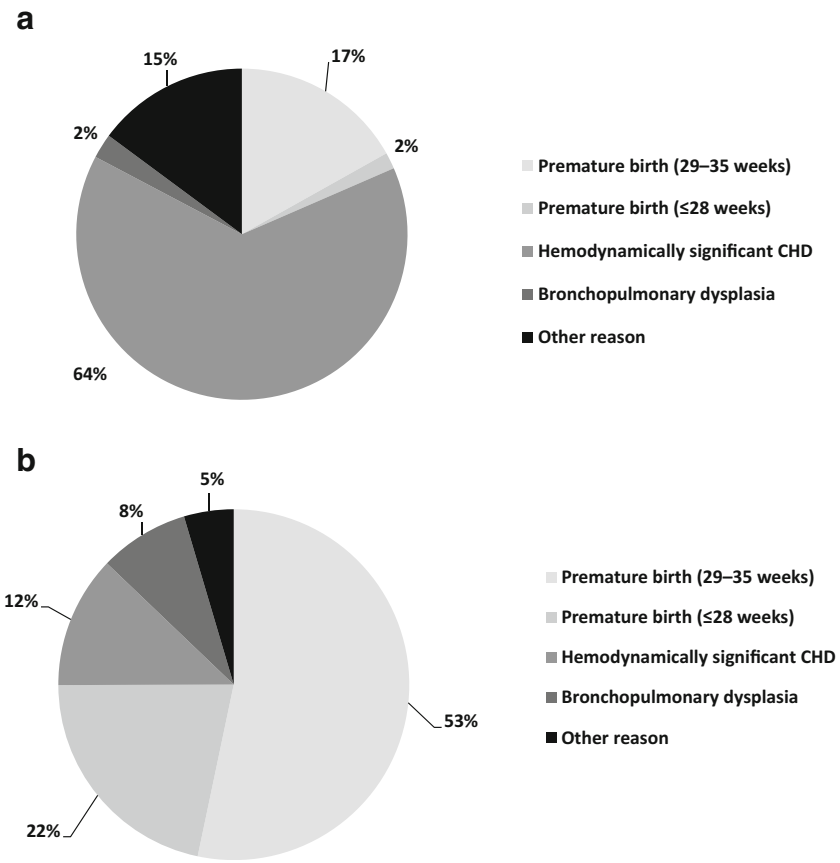

Fig. 1 **a** Main indication for palivizumab in 249 children with Down syndrome (2009–2016). **b** Main indications for palivizumab in 12,480 children without Down syndrome (2009–2016)

Parenteral adherence and location of the first palivizumab administration

Parental adherence to the passive immunization schedule in patients without DS was rated as good, satisfying, and bad for 93.5, 5.5, and 1.0%, respectively. In patients with DS, the corresponding values were 95.1, 3.7, and 1.2%. In patients without DS, prophylaxis began in the hospital in 24.6% of the evaluable population (12,480 infants). The corresponding rate in patients with DS ($n = 249$) was 22.1% ($P = 0.030$).

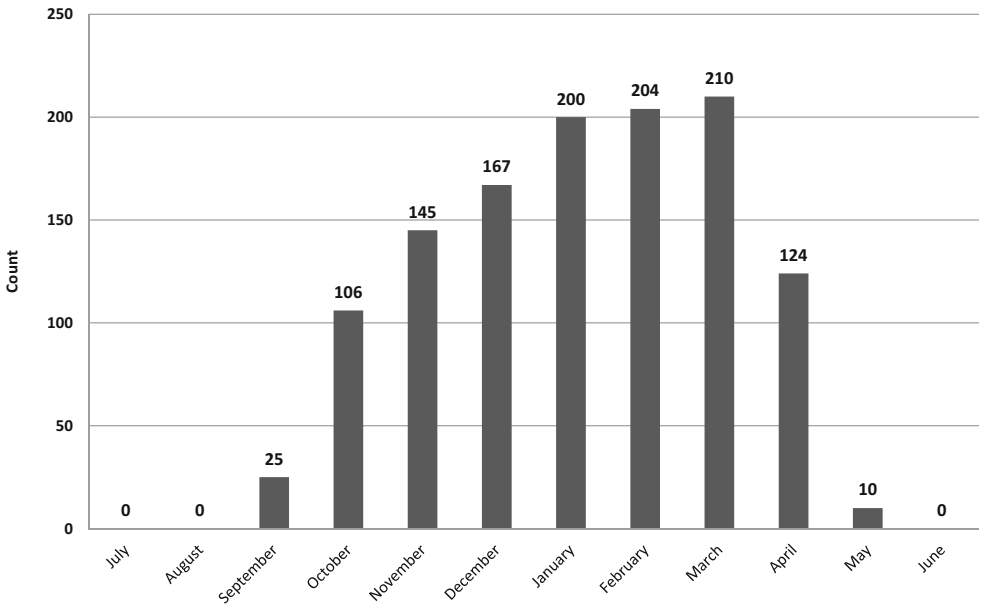

Fig. 2 Monthly distribution of palivizumab administrations in 249 children with Down syndrome (2009–2016)

Outcome hospitalization and RSV-related hospitalization

During the observation period, we observed 92 RSV-related hospitalizations in 87 patients. The RSV-related hospitalization rate in patients with DS was 3/249 (1.20%). The hospitalization rate in patients without DS was 89/12480 (0.71%). Table 3 shows different risk factors in patients with ≥ 1 RSV-related hospitalization (univariate analysis; 2009–2016). In this palivizumab registry, DS was no longer a significant risk factor for RSV-related hospitalization. Conversely, premature birth and neuromuscular impairment still had a significant impact on RSVRH despite palivizumab administration.

Clinical course of hospitalizations in patients with DS

The clinical diagnoses in the three children with DS and RSV-related hospitalization were bronchiolitis ($n = 1$) and pneumonia ($n = 2$). Two of three patients with DS RSV-related hospitalization received oxygen because of the infection and intensive care monitoring (for 48 h); one of these children was mechanically ventilated for 24 h. No deaths related to RSV infection were reported.

Serious adverse events

In total (referring to 63,572 palivizumab immunizations), participating physicians reported 668 SAEs from 2009 to 2016 (105 SAEs/10,000 palivizumab administrations). Of these, 28 SAEs were reported in 15 patients with DS (235 SAEs/10,000 palivizumab administrations). Excluding RSV-related hospitalizations, most SAEs ($n = 20$) were due to RTIs leading to hospitalization without detection of RSV in respiratory samples. No SAE was causally related to the use of palivizumab. Two patients with DS died during the observation period (unrelated to RSV infection or to palivizumab prophylaxis).

Discussion

This report from a prospective observational registry in Germany adds further information to our current knowledge about patients with DS receiving palivizumab prophylaxis. Patients with DS receiving palivizumab significantly differ from patients without DS concerning the main indication for palivizumab use, the presence of additional risk factors (in particular CHD and premature birth, birth weight, and gestational age at birth). In line with data from other studies, our data confirm the effectiveness of palivizumab in patients with DS, with a low RSV-related hospitalization rate (1.2%) [1, 10, 12, 20, 23, 28, 29]. DS was no longer a significant risk factor for RSV-related hospitalization in patients receiving palivizumab. The higher (crude, not related to palivizumab) incidence rate of SAEs in patients with DS (235 vs. 105 SAEs/10,000 palivizumab administrations) underscores the vulnerability of the DS population, in particular in terms of hospitalization due to RTI (20/28 SAEs, excluding RSV-related hospitalizations; 71%). Our data did not elucidate any safety concerns related to palivizumab in patients with DS.

The main limitation of PMOS, such as the German Synagis™ Registry and other registries for palivizumab use (recently reviewed by Paes et al. [14]), is the missing control group. In this regard, we cannot comment on the RSVHR in children with or without DS who did not receive palivizumab during the observation period. Changes in the health system, such as preventative education initiatives targeted at parents/caregivers (e.g., concerning day care attendance of high-risk children, smoking at home), variability in RSV epidemiology, and hospital admission, may have decreased the RSVHRs in recent years.

In Germany, palivizumab administration is guided by recommendations of pediatric scientific societies [4, 5], but not supported by a comprehensive active national program to identify eligible patients and to ensure adherence to the

Table 3 Univariate analysis of different risk factors in patients with ≥ 1 RSV-related hospitalization (2009–2016)

		Patients with RSV-related hospitalization									
		Yes				No		Univariate logistic regression			
		Number	%	95% CI (Blyth-Still-Casella)		Number	%	*P* value	Odds ratio	95% CI	
Down syndrome	No	84	0.67%	0.54%	0.83%	12,364	99.3%	0.316	1.810	0.568	5.765
	Yes	3	1.21%	0.33%	3.44%	244	98.8%				
Premature birth	29–35 weeks	35	0.48%	0.34%	0.67%	7221	99.5%	<0.001	2.382	1.511	3.757
	< 29 weeks	40	1.14%	0.83%	1.54%	3464	98.9%				
NMI	No	67	0.61%	0.47%	0.77%	10,918	99.4%	0.003	2.265	1.309	3.921
	Yes	16	1.37%	0.83%	2.17%	1151	98.6%				
CHD	No	63	0.69%	0.53%	0.88%	9033	99.3%	0.950	1.015	0.633	1.627
	Yes	24	0.70%	0.45%	1.04%	3390	99.3%				

CHD congenital heart disease, *CI* confidence interval, *NMI* neuromuscular impairment, *RSV* respiratory syncytial virus

recommended administration schedule [15, 26]. In addition, not all infants and children who received palivizumab during the observational period are included into the German Synagis™ Registry.

Further studies on RSV-related hospitalizations in children with DS

The working group of Paes et al. coordinates the Canadian registry of palivizumab (CARESS), a prospective, observational database that documents the utilization, compliance, and health outcomes of children who receive RSV prophylaxis with palivizumab in hospital and community settings in Canada [3, 13, 15, 17, 18, 27]. Referring to data from 2006 to 2012, Paes et al. compared the results of children with standard indications for palivizumab (group 1, $n = 4880$) with patients who had received palivizumab due to special indications (group 2; $n = 952$) [17]. Twenty percent of the children in the special indications group had DS. Children from group 2 had higher rates of breakthrough RSV infections (hospitalization due to confirmed RSV infection during palivizumab use, 2.35 vs. 1.40%; $P = 0.062$). Zachariah et al. [29] studied the RSVHR of children with DS ($n = 630$) and found a RSVHR of 13.5% ($N = 85$). Interestingly, 50 of 85 children had no other risk factors than DS. This study confirms the higher risk of RSV-related hospitalization in children with DS (odds ratio, 3.5; 95% CI, 3.10–4.12; DS with additional risk factors, 5.99; 95% CI, 5.38–6.68). Stagliano et al. [23] performed a retrospective cohort study of children enrolled in the US Uniformed Services Health Database, including 633,200 children. Children with DS had a RSVHR of 9.6 versus 2.8% in children without DS. In the multivariate adjusted analysis, DS (adjusted hazard ratio (aHR), 3.46; 95% CI, 2.75–4.37) was more strongly associated with RSVHR than any other risk factor, except immunodeficiency (aHR, 5.06; 95% CI, 4.05–6.32). Sánchez-Luna et al. [20] included 93 infants up to 1 year of age with DS and 68 matched controls without DS in a multicenter epidemiologic study in Spain. The hospitalization rate for all acute RTI and the RSVHRs were significantly higher in the DS cohort (44.1 vs. 7.7%; $P < 0.0001$ and 9.7 vs. 1.5%; $P = 0.03$).

RSV-related hospitalizations in children with DS during palivizumab prophylaxis

Our literature search identified two studies explicitly discussing RSVHRs in children with DS while receiving palivizumab prophylaxis. Paes et al. [18] from the CARESS Registry performed a subgroup analysis (data from 2006 to 2012; $n = 13{,}310$ enrolled children; DS, $n = 600$ [4.5%]). RSVHR was 1.53% (DS), 1.45% (standard indications), and 2.27% (other special indications).

According to the results of Yi et al. [27], palivizumab administration during the first 2 years of life in children with DS led to a significant reduction of the RSV-related hospitalization risk (RSVHR in children with DS 1.5% with and 9.9% without palivizumab prophylaxis; incidence rate ratio, IRR, 3.6; 95% CI, 1.52–8.67).

The studies discussed herein consistently show an increased risk of RSV-related hospitalization in children with DS (9.9–19.5% [1, 9]) and confirm DS as an independent risk factor for a complicated course in RSV infection. Under the assumption that palivizumab may cause a 50% relative risk reduction of RSVHR, Yi et al. [27] calculated the necessary number of children with DS in a prospectively randomized study to be at least 896. This equates to all children with DS born in Germany annually. One has to keep in mind that many children with DS qualify for palivizumab prophylaxis following standard indications. Due to ethical reasons, these children would not be eligible for randomization in the placebo group of a randomized study.

Conclusion

The German Synagis™ Registry, comprising data from 249 children with DS receiving palivizumab prophylaxis (2009–2016), describes important differences between patients with and without DS concerning the main indication for palivizumab and additional risk factors for a complicated RSV infection. Bearing in mind the limitations of an uncontrolled PMOS, the results confirm the field effectiveness of palivizumab prophylaxis in this population.

Authors' Contributions AS is the scientific advisor of the German Synagis Registry, developed the online eCRF together with SG and wrote the draft of the manuscript. SG coordinated the internal review of the manuscript. GW and SW performed the statistical data analysis. All authors contributed to the final version of the manuscript.

Funding The German Synagis Registry is supported by an unrestricted scientific grant of AbbVie GmbH, Wiesbaden, Germany.

Compliance with ethical standards

Conflict of interest AbbVie Deutschland GmbH & Co KG, Wiesbaden, Germany provided financial support for this Registry. AbbVie participated in the review and approval of the manuscript. Susanne Gehrmann is Medical Unit Leader in the Medical Affairs Department of AbbVie Deutschland GmbH & Co.KG, Wiesbaden and may own AbbVie stock or stock options. Arne Simon has received scientific grants from Abbott GmbH, Wiesbaden for the DSM RSV Paed Study and honoraria for the development and scientific administration of Internet-based Version of the German Synagis™ Registry from AbbVie Deutschland GmbH & Co.KG, Wiesbaden, Germany. Stefan Wagenpfeil has received scientific grants from AbbVie Deutschland GmbH & Co. KG for epidemiologic evaluation of the German Synagis™ Registry. Gudrun Wagenpfeil has no conflicts of interest to declare.

Informed consent Parents/legal guardians provided written informed consent for data recording on the eCRF and anonymized data analysis and publication for scientific purposes. Before the practical implementation of the protected Internet data entry platform, the medical advisor of the study (AS) obtained approval for the POMS by the Ethics Committee of the Medical Faculty, University of Bonn, Germany (reference no. 132/08). This approval was prolonged to July 2012 on September 9, 2010. After a change of affiliation to the University Hospital Homburg/Saar, approval for the study was obtained by the Ethics Committee of the Medical Association of the Saarland on April 13, 2013 (reference no. Ha89/13).

References

1. Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den Ende K, Kimpen JL, Strengers JL, Bont LJ (2007) Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis—a prospective birth-cohort study. Pediatrics 120(4): e1076–e1081. https://doi.org/10.1542/peds.2007-0788
2. Boghossian NS, Hansen NI, Bell EF, Stoll BJ, Murray JC, Laptook AR, Shankaran S, Walsh MC, Das A, Higgins RD (2010) Survival and morbidity outcomes for very low birth weight infants with Down syndrome. Pediatrics 126(6):1132–1140. https://doi.org/10.1542/peds.2010-1824
3. Chan P, Li A, Paes B, Abraha H, Mitchell I, Lanctot KL (2015) Adherence to palivizumab for respiratory syncytial virus prevention in the Canadian Registry of Palivizumab. Pediatr Infect Dis J 34(12):e290–e297. https://doi.org/10.1097/inf.0000000000000922
4. Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), Deutsche Gesellschaft für Pädiatrische Kardiologie (DGPK), Deutsche Gesellschaft für Pädiatrische Pneumonologie (DPP), Deutsche Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI) (2008) Stellungnahme zur Prophylaxe von schweren RSV-Erkrankungen bei Risikokindern mit Palivizumab. http://wwwdgpide/pdf/Palivizumab_LL_final_30Sep2008pdf (30. September 2008)
5. Deutsche Gesellschaft für Pädiatrische Infektiologie (DGPI), Deutsche Gesellschaft für Pädiatrische Kardiologie (DGPK), Gesellschaft für Pädiatrische Pneumologie (GPP), Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin (GNPI), Berufsverband der Kinder- und Jugendärzte (BVKJ), Bundesverband „Das frühgeborene Kind“ e.V. (2012) AWMF-LL 048-012 - Leitlinie zur Prophylaxe von schweren Erkrankungen durch Respiratory Syncytial Virus (RSV) bei Risikokindern 28. Oktober2012
6. Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, Connor EM, Sondheimer HM (2003) Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 143(4):532–540
7. Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, Auinger P, Griffin MR, Poehling KA, Erdman D, Grijalva CG, Zhu Y, Szilagyi P (2009) The burden of respiratory syncytial virus infection in young children. N Engl J Med 360(6): 588–598. https://doi.org/10.1056/NEJMoa0804877
8. Kabbani MS, Giridhar S, Elbarbary M, Elgamal MA, Najm H, Godman M (2005) Postoperative cardiac intensive care outcome for Down syndrome children. Saudi Med J 26(6):943–946
9. Kristensen K, Hjuler T, Ravn H, Simoes EA, Stensballe LG (2012) Chronic diseases, chromosomal abnormalities, and congenital malformations as risk factors for respiratory syncytial virus hospitalization: a population-based cohort study. Clin Infect Dis 54(6): 810–817. https://doi.org/10.1093/cid/cir928
10. Kristensen K, Stensballe LG, Bjerre J, Roth D, Fisker N, Kongstad T, Svendsen AL, Nielsen BW (2009) Risk factors for respiratory syncytial virus hospitalisation in children with heart disease. Arch Dis Child 94(10):785–789. https://doi.org/10.1136/adc.2008.143057
11. Medrano Lopez C, Garcia-Guereta Silva L, Lirio Casero J, Garcia Perez J (2009) Respiratory infections, Down's syndrome and congenital heart disease: the CIVIC 21 study. An Pediatr (Barc) 71(1): 38–46. https://doi.org/10.1016/j.anpedi.2008.11.007
12. Megged O, Schlesinger Y (2010) Down syndrome and respiratory syncytial virus infection. Pediatr Infect Dis J 29(7):672–673. https://doi.org/10.1097/INF.0b013e3181d7ffa5
13. Paes B, Manzoni P (2011) Special populations: do we need evidence from randomized controlled trials to support the need for respiratory syncytial virus prophylaxis? Early Hum Dev 87(Suppl 1):S55–S58. https://doi.org/10.1016/j.earlhumdev.2011.01.012
14. PaesB, MitchellI, LiA, HarimotoT, LanctotKL (2013) Respiratory-related hospitalizations following prophylaxis in the Canadian registry for palivizumab (2005-2012) compared to other international registries. Clin Dev Immunol2013:917068. doi:https://doi.org/10.1155/2013/917068, 1, 15
15. Paes B, Mitchell I, Li A, Lanctot KL (2012) A comparative study of respiratory syncytial virus (RSV) prophylaxis in premature infants within the Canadian Registry of Palivizumab (CARESS). Eur J Clin Microbiol Infect Dis 31(10):2703–2711. https://doi.org/10.1007/s10096-012-1617-7 [doi]
16. Paes B, Mitchell I, Li A, Lanctot KL (2012) Respiratory hospitalizations and respiratory syncytial virus prophylaxis in special populations. Eur J Pediatrin press. https://doi.org/10.1007/s00431-011-1654-8 [doi]
17. Paes B, Mitchell I, Li A, Lanctot KL (2012) Respiratory hospitalizations and respiratory syncytial virus prophylaxis in special populations. Eur J Pediatr 171(5):833–841. https://doi.org/10.1007/s00431-011-1654-8 [doi]
18. Paes B, Mitchell I, Yi H, Li A, Lanctot KL (2014) Hospitalization for respiratory syncytial virus illness in Down syndrome following prophylaxis with palivizumab. Pediatr Infect Dis J 33(2):e29–e33. https://doi.org/10.1097/inf.0000000000000019
19. Perez-Padilla R, Fernandez R, Garcia-Sancho C, Franco-Marina F, Aburto O, Lopez-Gatell H, Bojorquez I (2010) Pandemic (H1N1) 2009 virus and Down syndrome patients. Emerg Infect Dis 16(8): 1312–1314. https://doi.org/10.3201/eid1608.091931 [doi]
20. Sanchez-Luna M, Medrano C, Lirio J (2016) Down syndrome as risk factor for respiratory syncytial virus hospitalization: a prospective multicenter epidemiological study. Influenza Other Respir Viruses 11:157–164. https://doi.org/10.1111/irv.12431
21. Simon A, Nowak H, Sterz R (2011) Use of Palivizumab in Germany: data from 2002–2007. Klin Padiatr 223(5):292–298. https://doi.org/10.1055/s-0030-1270515 [doi]
22. Simon A, Volz S, Fleischhack G, Tillman R, Muller A, Bode U, Schildgen O (2007) Human coronavirus OC43 pneumonia in a pediatric cancer patient with down syndrome and acute lymphoblastic leukemia. J Pediatr Hematol Oncol 29(6):432–434
23. Stagliano DR, Nylund CM, Eide MB, Eberly MD (2015) Children with Down syndrome are high-risk for severe respiratory syncytial virus disease. J Pediatr 166(3):703–709e702. https://doi.org/10.1016/j.jpeds.2014.11.058
24. Sullivan C, Morgan C (2014) PC.74 The importance of testing for Respiratory Syncytial Virus (RSV) in infants presenting with bronchiolitis who are receiving palivizumab. Arch Dis Child Fetal Neonatal Ed 99(Suppl 1):A61.3–A6A61. https://doi.org/10.1136/archdischild-2014-306576.175
25. The IMpact-RSV Study Group (1998) Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 102(3 Pt 1):531–537

26. Whelan B, Musters E, Murray A, Moore E, Lievaart L, Visser S, Toxopeus E, van Veen A, Notario G, Campbell FJ (2016) Review of the home care programmes for respiratory syncytial virus (RSV) prophylaxis in Ireland and The Netherlands. Drugs Therapy Perspectives: Rational Drug Selection Use 32:119–130. https://doi.org/10.1007/s40267-015-0275-0
27. Yi H, Lanctot KL, Bont L, Bloemers BL, Weijerman M, Broers C, Li A, Kiss A, Mitchell I, Paes B (2014) Respiratory syncytial virus prophylaxis in Down syndrome: a prospective cohort study. Pediatrics 133(6):1031–1037. https://doi.org/10.1542/peds.2013-3916
28. Zachariah P, Ruttenber M, Simoes EA (2011) Hospitalization due to respiratory syncytial virus in children with congenital malformations. Pediatr Infect Dis J 30(5):442–445. https://doi.org/10.1097/INF.0b013e318201813b [doi]
29. Zachariah P, Ruttenber M, Simoes EA (2012) Down syndrome and hospitalizations due to respiratory syncytial virus: a population-based study. J Pediatr 160(5):827–831. https://doi.org/10.1016/j.jpeds.2011.11.004