

Prospective Population-based Study of RSV-related Intermediate Care and Intensive Care Unit Admissions in Switzerland over a 4-Year Period (2001–2005)

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Abstract

Objectives: Respiratory syncytial virus (RSV) infections are a leading cause of hospital admissions in small children. A substantial proportion of these patients require medical and nursing care, which can only be provided in intermediate (IMC) or intensive care units (ICU). This article reports on all children aged < 3 years who required admission to IMC and/or ICU between October 1, 2001 and September 30, 2005 in Switzerland.

Patients and Methods: We prospectively collected data on all children aged < 3 years who were admitted to an IMC or ICU for an RSV-related illness. Using a detailed questionnaire, we collected information on risk factors, therapy requirements, length of stay in the IMC/ICU and hospital, and outcome.

Results: Of the 577 cases reported during the study period, 90 were excluded because the patients did not fulfill the inclusion criteria; data were incomplete in another 25 cases (5%). Therefore, a total of 462 verified cases were eligible for analysis. At the time of hospital admission, only 31 patients (11%) were older than 12 months. Since RSV infection was not the main reason for IMC/ICU admission in 52% of these patients, we chose to exclude this subgroup from further analyses. Among the 431 infants aged < 12 months, the majority (77%) were former near term or full term (NT/FT) infants with a gestational age \geq 35 weeks without additional risk factors who were hospitalized at a median age of 1.5 months. Gestational age (GA) < 32 weeks, moderate to severe bronchopulmonary dysplasia (BPD), and congenital heart disease (CHD) were all associated with a significant risk increase for IMC/ICU admission (relative risk 14, 56, and 10, for GA \leq 32 weeks, BPD, and CHD, respectively). Compared with NT/FT infants, high-risk infants were hospitalized at an older age (except for infants with CHD), required more invasive and longer respiratory support, and had longer stays in the IMC/ICU and hospital.

Conclusions: In Switzerland, RSV infections lead to the IMC/ICU admission of approximately 1%–2% of each annual birth cohort. Although prematurity, BPD, and CHD are significant risk factors, non-pharmacological preventive strategies should not be restricted to these high-risk

patients but also target young NT/FT infants since they constitute 77% of infants requiring IMC/ICU admission.

Abbreviations: BPD: Bronchopulmonary dysplasia; CHD: Congenital heart disease; CMV: Conventional mechanical ventilation; CPAP: Continuous positive airway pressure; GA: Gestational age; HFOV: High-frequency oscillatory ventilation; IMC: Intermediate care unit; ICU: Intensive care unit; MNDS: Minimal neonatal data set; RSV: Respiratory syncytial virus

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Introduction

Respiratory syncytial virus (RSV) infection remains the most important etiology of lower respiratory tract infection in young children. It has been estimated that in the USA, RSV accounts for 125,000 hospitalizations and 450 deaths every year [1]. Virtually all infants are infected by 2 years of age. Immunity, unfortunately, is not durable, and re-infections are common throughout life. Although subsequent infections are nearly always mild, such patients can infect others who are at high risk for severe RSV disease, such as premature infants, infants with bronchopulmonary dysplasia (BPD), infants with hemodynamically significant congenital heart disease (CHD), or immunocompromised individuals.

There is no curative treatment for RSV lower respiratory tract infection at the present time, and commonly

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employed symptomatic treatment modalities (i.e., inhaled β_2 -agonists, inhaled racemic epinephrine, inhaled and systemic corticosteroids) are of very limited, if any, value [2–9]. The provision of supplemental oxygen, frequent suctioning, adequate nutrition, and hydration remain the mainstay of RSV treatment [10]. Although only a minority of hospitalized infants with RSV disease will require admission to an intermediate care (IMC) or intensive care unit (ICU) for more advanced respiratory support, these patients consume a large portion of IMC/ICU resources during RSV epidemics.

Active immunization against RSV is currently not available. The intravenous administration of polyclonal anti-RSV antibodies (RSV-IGIV, RespiGam[®], MedImmune, Gaithersburg, MD) [11, 12] and the intramuscular administration of monoclonal anti-RSV antibodies (palivizumab; Synagis[®], MedImmune) [13, 14] have both been shown to be effective in reducing RSV-related hospitalization rates in high-risk groups. Unfortunately, the costs of these drugs are very high. Recently, various national expert committees have published recommendations for the use of palivizumab (Synagis[®]) in high-risk patients [15–25]. While these experts agree that palivizumab is effective, their assessment of the cost-effectiveness of this intervention varies substantially. In Switzerland, an expert committee has recommended that palivizumab prophylaxis should be restricted to infants < 12 months of age with severe BPD and infants with CHD and additional risk factors (cyanotic CHD, pulmonary hypertension, congestive heart failure) [24].

We have collected data on all children under 3 years of age with severe RSV infection who required IMC/ICU admission over a 4-year period in Switzerland. We were particularly interested in IMC/ICU admission rates and outcomes in children from high-risk groups who could potentially benefit from palivizumab prophylaxis. Two participating pediatric centers serving approximately 20% of the Swiss pediatric population (the Children's Hospitals of Lucerne and Bern) concurrently collected data on all RSV-related hospital admissions involving patients under 3 years of age in order to obtain nation-wide estimates of hospital resource utilization during RSV epidemics.

Patients and Methods

Case Definition

All infants and children aged < 3 years who required IMC/ICU admission because of an RSV infection were included. No uniform IMC/ICU admission criteria could be used because, apart from illness severity, availability of resources (manpower, monitoring equipment) on the regular wards plays an important role in deciding on patient transfers to the IMC/ICU. RSV infection was defined as an acute respiratory illness characterized by one or several of the following clinical symptoms: rhinorrhea, tachypnea, wheezing, oxygen requirement and/or apnea associated with the detection of RSV antigen (direct immunofluorescent assay or EIA), or a positive PCR result in a nasopharyngeal swab or aspirate. Although there were no predefined criteria for RSV

testing, most participating hospitals have a policy that requires RSV testing for all young patients admitted with respiratory symptoms for infection control purposes.

Data Collection

Data collection extended over a period of 4 years, from October 1, 2001 until September 30, 2005. RSV-related ICU/IMC admissions were prospectively reported to the Swiss Pediatric Surveillance Unit (SPSU) by all 39 Swiss pediatric hospitals on a monthly basis. This instrument is comparable to surveillance units in several other countries (<http://www.inopsu.com>).

Reported cases were validated with a detailed questionnaire and included information on date of birth, gestational age (GA), birth weight, co-morbidities (i.e., BPD defined as a requirement for supplemental oxygen at 36 weeks postmenstrual age [26], CHD), date of hospital admission/discharge, date of IMC/ICU admission/discharge, date of first positive RSV test, whether or not the patient received palivizumab (Synagis[®]) prior to hospitalization, main reason for IMC/ICU admission (bronchiolitis: rhinorrhea, tachypnea, wheezing, oxygen requirement; RSV-associated apnea; not related to RSV infection), respiratory support required (supplemental oxygen, continuous positive airway pressure [CPAP], conventional mechanical ventilation [CMV], high-frequency oscillatory ventilation [HFOV], including the duration for each mode of respiratory support), and death (including cause of death and whether an autopsy was performed).

At the Children's Hospitals of Lucerne and Bern, data on all RSV-related hospitalizations (i.e., including those patients hospitalized on regular wards) were also prospectively recorded during the same time period in order to estimate the proportion of each annual birth cohort requiring hospitalization for RSV infection and to calculate the proportion of hospitalized RSV patients who require IMC/ICU care. On average, 20% (14,480 live births/year) of each annual Swiss birth cohort (approximately 72,400 live births/year) are served by these two hospitals.

Ethics approval was granted by the ethics committee of the institution of the principal investigator (TMB) and extended to all participating pediatric centers in accordance with SPSU guidelines.

Statistics

Statistical analyses were performed using SPSS ver. 16.0 (SPSS, Chicago, IL). Proportions were compared using contingency tables. Non-normally distributed continuous variables were compared using non-parametric tests (Mann-Whitney U-test). Confidence intervals (95% CI) were calculated for relative risks (RR). A p-value of < 0.05 was considered to be statistically significant.

Results

The response rate to the monthly SPSU inquiries was 100%. Of the 577 cases of RSV reported during the study period, 90 were excluded because the patients did not fulfill the inclusion criteria (never admitted to IMC/ICU: 63 cases; patient > 3 years of age: eight cases; duplicate reporting: 19 cases). Questionnaires were not returned or incomplete in 25 (5%) of the remaining 487 cases. Ultimately, a total of 462 verified cases could be analyzed in detail. Of these, 431 (89%) of the patients were < 12 months old, and 31 (11%) were between 12 and 36 months old at the time of hospital admission (Figure 1).

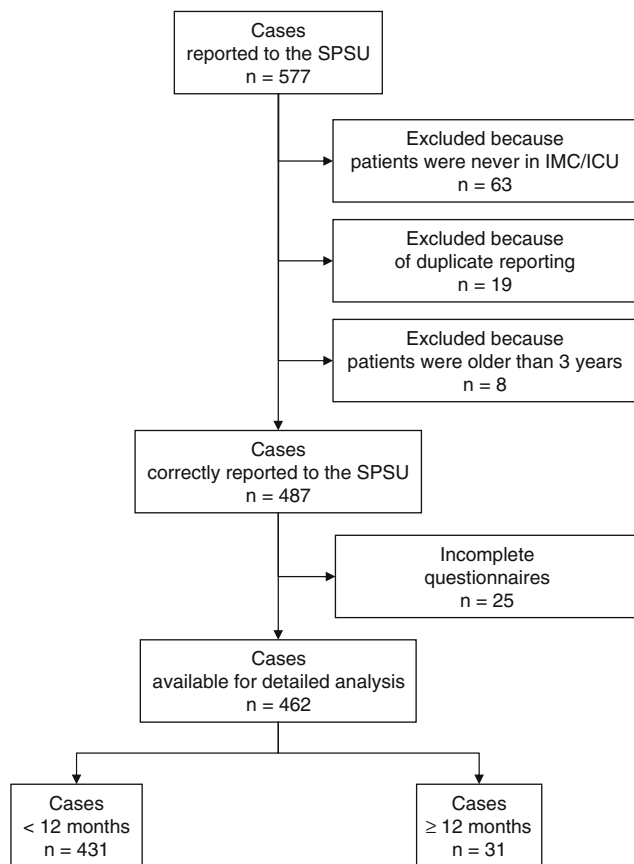


Figure 1. Patients recruited with the help of the Swiss Pediatric Surveillance Unit (SPSU) over the 4-year-study period (October 1, 2001 to September 30, 2005).

Children aged between 12 and 36 Months at the Time of IMC/ICU Admission (n = 31)

Patients ages between 12 and 36 months at the time of IMC/ICU admission constituted a heterogeneous group, and in more than half of them (16 cases) RSV infection was not the main reason for IMC/ICU admission. We therefore chose to exclude this group from further detailed analysis.

Three patients in this group died (case fatality rate 9.7%): a 22-month-old child with CHD (hypertrophic obstructive cardiomyopathy, atrial septal defect) and probable mitochondriopathy with CNS involvement died following a redirection of care; a 14-month-old child died from multiorgan failure secondary to bacterial sepsis; a 13-month-old child died from respiratory failure while on immunosuppressive therapy for a rare immune enteropathy. This patient had not received palivizumab.

Infants aged < 12 months at the Time of IMC/ICU Admission (n = 431)

The study covered four RSV seasons: two seasons with a low peak incidence (2001/2002: 64 cases; 2003/2004: 72

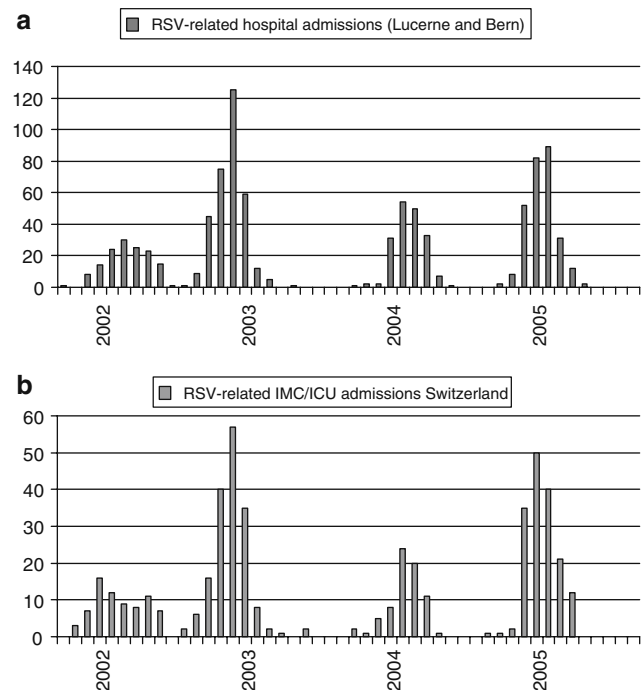


Figure 2. Respiratory syncytial virus (RSV)-related admissions of infants aged < 12 months (at the time of admission) to hospital and intermediate care/intensive care units (IMC/ICU). A 2-year periodicity of RSV epidemiology in Switzerland is evident for both hospital admissions (A; Children's Hospital of Lucerne and Children's Hospital of Bern) and IMC/ICU admissions (B; Switzerland).

cases) and two seasons with a high peak incidence (2002/2003: 152 cases; 2004/2005: 143 cases), confirming previous observations of a 2-year periodicity of RSV epidemiology in Switzerland [27]. This was evident for both RSV-related hospital admissions in Lucerne and Bern (Figure 2a) and RSV-related IMC/ICU admissions in the entire country (Figure 2b).

The majority of these patients (77%, n = 333) were near term (NT) or full term (FT) infants (defined as infants with a GA \geq 35 0/7 weeks) without additional risk factors. Among the 98 patients with a GA < 35 weeks (23%), there were 39, 40, and 19 preterm infants with a GA of < 28 weeks, 28–31 weeks, and 32–34 weeks, respectively.

Main Reason for IMC/ICU Admission

In the majority of patients, the main reason for IMC/ICU admission was bronchiolitis regardless of GA. Apnea was more commonly indicated as the main reason for IMC/ICU admission in former premature infants with a GA < 35 weeks than in NT/FT infants (18/98 [20%] vs 36/333 [11%]; odds ratio [OR] 1.86, 95% CI 1.00–3.44). This was also true for those with CHD compared to all others (OR 2.35, 95% CI 1.00–5.49), but not for patients with BPD (OR 1.43, 95% CI 0.47–4.34).

Table 1 summarizes patient demographics, risk factors, age on admission, and the main reason for IMC/ICU admission.

Analyses of Risk Factors (Prematurity, BPD, CHD)

Based on data from the Swiss Minimal Neonatal Dataset (MNDS) [28] and data on the incidence of CHD in Switzerland [29], we were able to calculate both IMC/ICU admission rates and RR for patients with a GA < 32 weeks, 28–31 weeks, < 28 weeks, and those with BPD or CHD, respectively, and compare these with the general population for RSV-related IMC/ICU admission (Table 2). The RR associated with these comorbidities were calculated based on an IMC/ICU admission rate of 0.14% for the general population. As expected, BPD represented the condition associated with the greatest risk for IMC/ICU admission in the first year of life (RR 55.6, 95% CI 37.5–82.5), followed by prematurity < 32 weeks (RR 13.7, 95% CI 10.4–17.9) and CHD (RR 9.9, 95% CI 7.6–13.9). Interestingly, however, prematurity < 28 weeks was not associated

with greater risks than prematurity of 28–31 weeks of gestation (Table 2).

Therapy Requirements and Length of Stay

Overall, nearly 90% of all infants required supplemental oxygen while in IMC/ICU care. As expected, a substantial proportion of infants was supported with CPAP (25%) and CMV (17%), whereas HFOV was only used in 3% of patients. A GA < 32 weeks and BPD were associated with a more frequent use of non-invasive respiratory support (CPAP) (39% and 38%, respectively) and HFOV (12% and 13%, respectively).

For all 431 infants included in this study, the median length of stay (LOS) in an IMC/ICU was 5 days, and the median overall LOS was 9 days. Prematurity with a GA < 35 weeks, BPD, and CHD were each significantly associated with a longer LOS in the ICU/IMC and overall LOS, respectively (Table 3). On average, during the study period, severe RSV infections in infants < 12 months old were responsible for 826 IMC/ICU days and 1,233 overall hospital days annually in Switzerland.

	All infants (n = 431)	Gestational age (weeks)					BPD (n = 24)	CHD (n = 34)
		≥ 35 (n = 333)	32–34 (n = 39)	28–31 (n = 40)	< 28 (n = 19)			
Median birth weight in grams (range)	3,180 (515–4,960)	3,370 (1,480–4,960)	2,070 (1,050–2,690)	1,480 (655–2,290)	820 (515–1,120)	900 (515–2,820)	2,530 (655–4,960)	
Median age in months (range)	2 (0.5–12)	1.5 (0.5–12)	2 (0.5–12)	2 (0.5–12)	5 ^a (2–12)	5 (0.5–12)	2 (1–9)	
Bronchopulmonary dysplasia (BPD), n (%)	24 (6)	2 (< 1)	1 (3)	5 (13)	16 (84)	24 (100)	4 (12)	
Congenital heart disease (CHD), n (%)	34 (8)	21 (< 1)	2 (5)	9 (23)	2 (11)	4 (17)	34 (100)	
Main reason for IMC/ICU admission								
Bronchiolitis, n (%)	367 (85)	389 (87)	32 (82)	31 (78)	15 (79)	19 (79)	24 (71)	
Apnea, n (%)	54 (13)	36 (11) ^b	6 (15)	8 (20)	4 (21)	4 (17)	8 (21) ^c	
Other, n (%)	10 (2)	8 (2)	1 (2)	1 (2)	0	1(4)	2 (6)	

IMC/ICU: Intermediate care/intensive care unit; ^a p < 0.0001 gestational age (GA) < 28 weeks vs GA ≥ 28 weeks; ^b Odds ratio (OR) 1.86 (95% CI 1.00–3.44) for GA < 35 weeks vs GA ≥ 35 weeks; ^c OR 2.35 (95% CI 1.00–5.49) for CHD vs non-CHD

Gestational age categories and pre-existing co-morbidities	Population at risk	RSV IMC/ICU admission			
		n	Rate (%)	Relative risk	95% CI
All infants	289,597 ^a	431	0.1	1.0	
Gestational age ≤ 32 weeks	2,896 ^b	59	2.0	13.7	10.4–17.9
Gestational age 28–31 weeks	2,172 ^b	40	1.8	12.4 ^c	9.0–17.1
Gestational age < 28 weeks	724 ^b	19	2.6	17.6 ^c	11.2–27.6
BPD	290 ^b	24	8.3	55.6	37.5–82.5
CHD	2,317 ^b	34	1.5	9.9	7.0–13.9

RSV: Respiratory syncytial virus; ^a Data provided by the Swiss Federal Office for Statistics; ^b Estimates based on incidences for GA 28–31 weeks of 0.75%, GA < 28 weeks of 0.25%, BPD of 0.1%, and CHD of 0.8%, respectively (data sources Swiss Minimal Neonatal Dataset and [24]); ^c Relative risk for gestational age < 28 vs 28–31 weeks 1.43 (95% CI 0.83–2.44), p = 0.254

Gestational age categories and pre-existing co-morbidities	n	Median LOS in days (interquartile range)	
		Overall	ICU/IMC
All infants with severe RSV infection	431	9 (6–13)	5 (3–10)
Gestational age \geq 35 weeks	333	8 (6–13) ^a	5 (3–8) ^a
Gestational age < 35 weeks	98	11 (6–19)	8 (4–13)
Gestational age < 32 weeks	59	11 (7–23)	8 (4–15)
Gestational age < 28 weeks	19	11 (7–15)	10 (3–15)
BPD	24	11 (7–32)	10 (4–26)
CHD	34	15 (9–27) ^b	8 (4–14)

^a $p < 0.001$ for gestational age ≥ 35 weeks vs < 35 weeks; ^b $p < 0.0001$ for CHD vs all non-CHD

Infants with Passive Immunization

In the entire cohort of infants admitted to IMC/ICU for RSV-related illness, nine had received passive immunization with palivizumab. The incubation period of RSV is 2–8 days. In two patients, the first dose of palivizumab was given too late (1 day prior to hospital admission). In another two patients, palivizumab was given more than 30 days after the previous dose, thus exceeding the recommended dosing interval. Therefore, five of the nine patients who had received passive immunization with palivizumab can be considered to be true prophylaxis failures.

Fatal Cases

Two patients who were < 12 months of age at the time of IMC/ICU admission died during their hospital stay (case fatality rate 0.5%). Both had significant co-morbidities. The first patient was a 10-month-old former extremely premature infant (GA 25 1/7 weeks, birth weight 515 g) with severe BPD who had received prophylaxis with two doses of palivizumab, with the last dose having been administered 30 days prior to IMC/ICU admission. The second patient was an 8-month-old former term infant with epidermolysis bullosa, tracheobronchomalacia, and profound hypoxic-ischemic encephalopathy following cardiac arrest and resuscitation, eventually leading to a redirection of care. This patient had not been immunized with palivizumab.

Extrapolated Nation-wide Estimates of RSV-related Hospital Admissions

Based on the local data collected at the Children's Hospitals of Lucerne and Bern for infants < 12 months of age, we extrapolated that during the study period 1.36% of the annual birth cohort in Switzerland required hospital admission for RSV infection, i.e., an estimated 1,000 admissions per year. Assuming an IMC/ICU admission

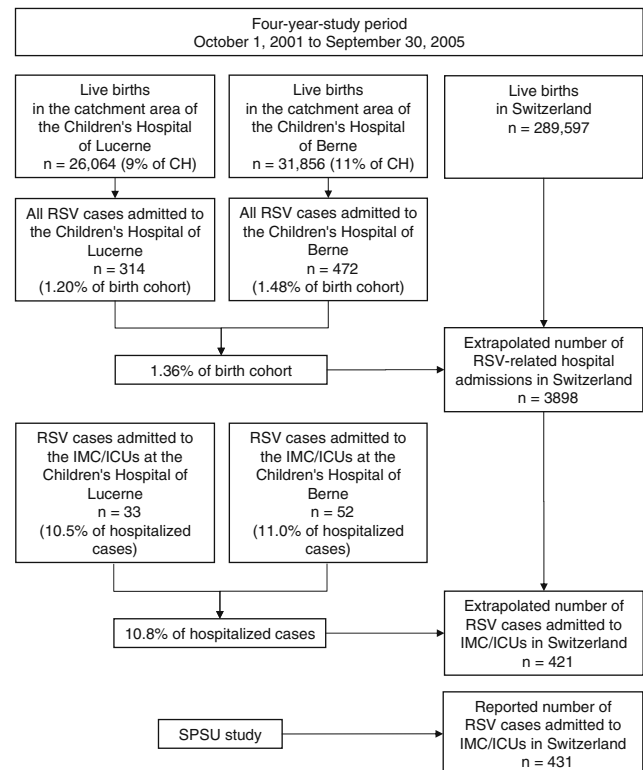


Figure 3. Extrapolation of RSV-related hospital admissions and RSV-related IMC/ICU admissions of infants < 12 months of age in Switzerland (CH) based on local data from the Children's Hospitals of Lucerne and Berne and a comparison with observed IMC/ICU admissions reported to the Swiss Pediatric Surveillance Unit (SPSU) during the 4-year-study period.

rate of 10.8% for infants hospitalized for RSV infection (the average annual IMC/ICU admission rate observed in Lucerne and Bern), 421 admissions would be expected over the 4-year period, which is close to the 431 cases recorded in our study (Figure 3). This finding suggests that case catchment was excellent. Finally, using these nation-wide estimates, we calculated that infants with RSV infections (including those who required IMC/ICU admission) consumed more than 4,800 hospital days in Switzerland annually during the study period, with more than approximately 17% of these days spent on ICU/IMC wards. The vast majority of hospital resources were used for the management of RSV infections in infants without identifiable risk factors.

Discussion

Using the SPSU, we were able to prospectively study severe RSV infections leading to IMC/ICU admission in a cohort of 462 infants and children aged < 3 years over a 4-year period in Switzerland.

We chose to focus our analyses on the 431 infants with severe RSV infections who were < 12 months old at the

time of IMC/ICU admission. We calculated that, on average, 1.36% of every annual birth cohort are admitted because of RSV infections in Switzerland. Similar RSV-related hospitalization rates in infants have recently been reported from the UK (1.1%–1.9%) [30–31], The Netherlands (0.9%–1.1%) [32], and the USA (1.7%) [33]. Our calculated IMC/ICU admission rate of 10.8% is comparable to the single-center experience from the Driscoll Children's Hospital in Texas reported by Purcell et al. [34]. From 1991 to 2002, between 6.1% and 11.2% of patients admitted to this institution with severe RSV disease required ICU admission.

Although prematurity, BPD, and CHD were associated with significantly increased RSV hospitalization and IMC/ICU admission risks (Table 2), 77% of the patients admitted to IMC/ICU were former NT or FT infants without any identifiable risk factor other than young age at the time of RSV infection (median age on admission 1.5 months). In 2003, the Israeli RSV Monitoring Group reported their observation that 84% of patients with RSV bronchiolitis admitted to 11 ICU in Israel during the 2000/2001 RSV season were born at term and did not have BPD [35]. *López Guinea et al.* [36] from Spain have described an age of < 6 weeks as the most common risk factor (45%) for ICU admission due to bronchiolitis, with the vast majority of cases (74%) being caused by RSV infection. Using logistic regression analysis, the Osservatorio RSV Study Group identified three predictors of severe RSV-induced lower respiratory tract infection over four consecutive epidemics (2000–2004) in Italy [37]: chronological age < 3 months at the beginning of the RSV season (adjusted OR 8.46, 95% CI 3.09–23.19), birth weight < 1,500 g (adjusted OR 7.70, 95% CI 1.29–45.91), and birth order \geq second child (adjusted OR 1.92, 95% CI 1.21–3.06). Finally, there is a growing body of evidence that genetic polymorphisms, particularly in genes involved in innate immunity, play an important role in RSV susceptibility and illness severity [38].

In 23% of the patients in our study, one or more risk factors (prematurity, BPD, CHD) were described. Moderate to severe BPD was associated with the highest RR for hospital (Lucerne, Bern) and IMC/ICU (Switzerland) admission (Table 2). The estimated RSV-related hospital admission rate for these patients was 13.8%, which is comparable to the hospitalization risk of infants with BPD in the Impact trial (12.8%) [13], and more than 50% of these latter infants were also admitted to IMC/ICU. Interestingly, however, the level of respiratory support of BPD patients (CPAP 38%, CMV 25%, HFOV 13%) was similar to that provided to very preterm infants (GA \leq 32 weeks) without BPD, and there was no difference in the length of hospital stay. The observed case fatality rate in our study (0.5%) was very close to that determined in the German database for the inpatient management of RSV-infected children (0.4%) [39]. One of the two patients who died was a high-risk preterm infant with

BPD who had received appropriate palivizumab prophylaxis.

In accordance with other published reports [35, 40], our study suggests that palivizumab prophylaxis in high-risk patients as defined by the American Academy of Pediatrics (AAP) will only have a very modest impact on overall RSV-related hospital and IMC/ICU admissions and resource utilization. According to our estimates combined with the 39% reduction in hospitalization rate shown in the Impact Study [13] (NNT 19), palivizumab prophylaxis would not be cost effective in patients with moderate to severe BPD (drug costs CHF 95,000–152,000 compared with direct costs of hospitalization of CHF 20,000). Others have come to similar conclusions [41–43]. In contrast, *Nuijten et al.* [44], using a more complex model of cost-effectiveness analysis that includes long-term downstream consequences (e.g., asthma, productivity losses) and incorporates the effect of RSV on mortality, concluded that palivizumab prophylaxis is cost effective in high-risk patients.

Of 462 verified cases, only 31 patients (6.7%) were older than 12 months at the time of IMC/ICU admission, thereby confirming previous observations that RSV illness severity is closely related to age [37, 45]. More than half of these patients were admitted for reasons other than RSV infection. Although three patients died in this group (mortality rate 9.7%), only one death was directly related to RSV lower respiratory tract infection in a patient on immunosuppressive therapy. RSV is an important and well-recognized cause of morbidity and mortality in immunocompromised children and adults [46].

The main weakness of our study is the fact that no uniform scoring system was used to determine illness severity. Therefore, it is possible that there may have been significant differences in IMC/ICU admission criteria between the participating centers. On the other hand, the fact that most patients required supplemental oxygen, 25% required CPAP, and 20% were on mechanical ventilation suggests that these patients were indeed a severely ill subgroup of RSV-infected patients. In addition, even if some patients were admitted to IMC/ICU for logistical reasons, such as a shortage of regular ward beds or an understaffing of regular wards, we believe that our study adequately reflects IMC/ICU resource utilization due to the RSV epidemics in Switzerland. Finally, it must be taken into account that our nation-wide estimates of RSV-related hospital admissions were extrapolated from the experiences at the Children's Hospitals of Lucerne and Bern, which serve only 20% of the population. Therefore, they can only be regarded as rough estimates, and actual numbers may differ.

Conclusion

In Switzerland, RSV infections lead to the hospitalization of approximately 1.36% of every annual birth cohort; 10.8% of these patients require IMC/ICU care during

their hospital stay. Prematurity, BPD, and CHD are significant risk factors that deserve special consideration. However, non-pharmacological preventive strategies (e.g., parental education about risks of RSV infection in young infants, the promotion of frequent hand-washing, avoidance of passive smoking, decreasing the exposure to sick children) should not be restricted to high-risk groups but also target young NT/FT infants since this group constitutes 77% of infants requiring IMC/ICU admission for RSV infection.

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References

- Black CP: Systematic review of the biology and medical management of respiratory syncytial virus infection. *Respir Care* 2003; 48: 209–31; discussion 231–3.
- Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F, Mayowe V: Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane Datab Syst Rev* 2005; CD001279.
- Spurling GK, Fonseka K, Doust J, Del Mar C: Antibiotics for bronchiolitis in children. *Cochrane Database Syst Rev* 2007; CD005189.
- Perrotta C, Ortiz Z, Roque M: Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev* 2007; CD004873.
- Ventre K, Haroon M, Davison C: Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev* 2006; 3: CD005150.
- Gadomski AM, Bhasale AL: Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 2006; 3: CD001266.
- Blom D, Ermers M, Bont L, van Aalderen WM, van Woensel JB: Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. *Cochrane Database Syst Rev* 2007; CD004881.
- Patel H, Platt R, Lozano JM, Wang EE: Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 2004; CD004878.
- Hartling L, Wiebe N, Russell K, Patel H, Klassen TP: Epinephrine for bronchiolitis. *Cochrane Database Syst Rev* 2004; CD003123.
- Hodge D, Chetcuti PA: RSV: management of the acute episode. *Paediatr Respir Rev* 2000; 1: 215–220.
- Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. *Pediatrics* 1997; 99:93–99.
- Groothuis JR, Simoes EA, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. *N Engl J Med* 1993; 329: 1524–1530.
- Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMPact-RSV Study Group. *Pediatrics* 1998; 102: 531–537.
- 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: 532–540.
- American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003; 112: 1442–1446.
- National Advisory Committee on Immunization. Statement on the recommended use of monoclonal anti-RSV antibody (palivizumab). *Can Commun Dis Rep* 2003; 29: 1–15.
- Carbonell Estrany X, Quero Jimenez J: Recommendations for the prevention of respiratory syncytial virus infections. Standards Committee of the Spanish Society of Neonatology. Board of Directors of the Spanish Society of Neonatology. *An Esp Pediatr* 2000; 52: 372–374.
- Carbonell-Estrany X, Quero Jimenez J: Guidelines for respiratory syncytial virus prophylaxis. An update. *An Esp Pediatr* 2002; 56: 334–336.
- Chantepie A: Use of palivizumab for the prevention of respiratory syncytial virus infections in children with congenital heart disease. Recommendations from the French Paediatric Cardiac Society. *Arch Pediatr* 2004; 11: 1402–1405.
- Figueras Aloy J, Quero J, Domenech E, et al. Recommendations for the prevention of respiratory syncytial virus infection. *An Pediatr (Barc)* 2005; 63: 357–362.
- Forster J: Practice guideline by the German Society for Pediatric Infectious Diseases with respect to prevention of RSV infections through immunoglobulin administration. *Klin Padiatr* 1999; 211: 476.
- Naver L, Eriksson M, Ewald U, Linde A, Lindroth M, Schollin J: Appropriate prophylaxis with restrictive palivizumab regimen in preterm children in Sweden. *Acta Paediatr* 2004; 93: 1470–1473.
- Tulloch R, Marsh M, Blackburn M, et al. Recommendations for the use of palivizumab as prophylaxis against respiratory syncytial virus in infants with congenital cardiac disease. *Cardiol Young* 2003; 13: 420–423.
- Aebi C, Barrazone C, Günthardt J, et al. Konsensus-Statement zur Prävention von Respiratory Syncytial Virus (RSV)-Infektionen mit dem humanisierten monoklonalen Antikörper Palivizumab (Synagis). Update 2004. *Paediatrica* 2004; 15: 12–16.
- Aebi C, Barrazone C, Hammer J, Kind C, Nadal D, Pfister RE: Update zum Konsensus-Statement zur Prävention von Respiratory Syncytial Virus (RSV)-Infektionen bei Säuglingen mit dem humanisierten monoklonalen Antikörper Palivizumab (Synagis). *Paediatrica* 2002; 13: 58–60.
- Jobe AH, Bancalari E: Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001; 163: 1723–1729.

27. Duppenhaler A, Gorgievski-Hrisoho M, Frey U, Aebi C: Two-year periodicity of respiratory syncytial virus epidemics in Switzerland. *Infection* 2003; 31: 75–80.
28. Bucher HU, Fawer CL, von Kaenel J, Kind C, Moessinger A: Intrauterine and postnatal transfer of high risk newborn infants. *Swiss Society of Neonatology. Schweiz Med Wochenschr* 1998; 128: 1646–1653.
29. Duppenhaler A, Ammann RA, Gorgievski-Hrisoho M, Pfammatter JP, Aebi C: Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease. *Arch Dis Child* 2004; 89: 961–965.
30. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al Shammari N, Thomas HM: Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005; 16: 386–392.
31. Nicholson KG, McNally T, Silverman M, Simons P, Stockton JD, Zambon MC: Rates of hospitalisation for influenza, respiratory syncytial virus and human metapneumovirus among infants and young children. *Vaccine* 2006; 24: 102–108.
32. Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E: Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J* 2007; 30: 1158–1166.
33. Sangare L, Curtis MP, Ahmad S: Hospitalization for respiratory syncytial virus among California infants: disparities related to race, insurance, and geography. *J Pediatr* 2006; 149: 373–377.
34. Purcell K, Fergie J: Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatr Infect Dis J* 2004; 23: 418–423.
35. Prais D, Danino D, Schonfeld T, Amir J: Impact of palivizumab on admission to the ICU for respiratory syncytial virus bronchiolitis: a national survey. *Chest* 2005; 128: 2765–2771.
36. Lopez Guinea A, Casado Flores J, Martin Sobrino MA, et al. Severe bronchiolitis. *Epidemiology and clinical course of 284 patients. An Pediatr (Barc)* 2007; 67: 116–122.
37. Rossi GA, Medici MC, Arcangeletti MC, et al. Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics. *Eur J Pediatr* 2007; 166: 1267–1272.
38. Janssen R, Bont L, Siezen CL, et al. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. *J Infect Dis* 2007; 196: 826–834.
39. Simon A, Ammann RA, Wilkesmann A, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. *Eur J Pediatr* 2007; 166: 1273–1283.
40. Duppenhaler A, Gorgievski-Hrisoho M, Aebi C: Regional impact of prophylaxis with the monoclonal antibody palivizumab on hospitalisations for respiratory syncytial virus in infants. *Swiss Med Wkly* 2001; 131: 146–151.
41. Embleton ND, Harkensee C, McKean MC: Palivizumab for pre-term infants. Is it worth it? *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F286–F289.
42. Meberg A, Bruu AL: Respiratory syncytial virus infections in congenital heart defects – hospitalizations and costs. *Acta Paediatr* 2006; 95: 404–406.
43. Reeve CA, Whitehall JS, Buettner PG, Norton R, Reeve DM, Francis F: Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. *J Paediatr Child Health* 2006; 42: 253–258.
44. Nuijten MJ, Wittenberg W, Lebmeier M: Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. *Pharmacoeconomics* 2007; 25: 55–71.
45. Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics* 2004; 113: 1758–1764.
46. Kim YJ, Boeckh M, Englund JA: Community respiratory virus infections in immunocompromised patients: hematopoietic stem cell and solid organ transplant recipients, and individuals with human immunodeficiency virus infection. *Semin Respir Crit Care Med* 2007; 28: 222–242.