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# Regional impact of prophylaxis with the monoclonal antibody palivizumab on hospitalisations for respiratory syncytial virus in infants

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## Summary

*Questions:* Palivizumab is approved in Switzerland for prevention of hospitalisation for RSV infection in children with one of the following risk factors: (1) history of prematurity ≤35 weeks and age ≤6 months or (2) chronic lung disease and age ≤1 year. Regional data on the expected effectiveness of this monoclonal antibody are not available.

*Methods:* (1) Retrospective, descriptive, single-site study on the characteristics of RSV hospitalisations during two consecutive seasons. (2) Extrapolation of data to generate population-based estimates on the impact of palivizumab if used according to the approved indications.

*Results:* Of 242 RSV hospitalisations, 216 (89.3%) and 26 (10.7%) occurred in children without and with risk factors, respectively. Patients without and with risk factors had similar clinical courses with respect to ICU admission rate (11.6 vs. 11.5%) and rate of mechanical ventilation (3.2 vs. 3.8%). Of a total of 28 ICU admissions, 13 (46%) occurred among infants aged ≤1 month without risk factors. Former premature infants were significantly older than patients with longer gestation (median age 7.5 vs. 3.7 months, p = 0.026). Applying the approved age criteria would have excluded 10 of 26 patients (38.5%) from eligibility for palivizumab. During the 1999/2000 RSV season, 36% of hospitalisations occurred after April 1, 2000. None of them may have been preventable had prophylaxis been started before November 1, 1999 and carried out for 5 months as recommended. In an annual birth cohort of 10 000, palivizumab as indicated would be expected to prevent between 5 and 7 RSV hospitalisations.

*Conclusions:* The impact of palivizumab on the prevention of RSV hospitalisations in the Canton of Bern, Switzerland, is expected to be small, and the approved indications may not target infants at greatest risk for severe disease.

*Keywords: respiratory syncytial virus; infant; chronic lung disease; prematurity; hospitalisation; palivizumab*

## Introduction

RSV is the leading cause of lower respiratory tract infections in infants. Up to 70% are infected during the first year of life [1]. Of these, 20% have evidence of lower respiratory tract disease, 2% are hospitalised, and 0.1% die from RSV infection [2]. Risk factors associated with increased RSV hospitalisation rates include prematurity (10–25%) [1, 3], CLD (15–45%) [1, 3], and congenital heart disease (15–25%) [4], but there is regional variability in both the severity of RSV disease and hospitalisation policies [5–9]. In healthy infants born at term, the severity of RSV infection is inversely correlated with age [1]. Hence, RSV infection is one of the major infectious diseases during the first year of life and effective means for its prevention are needed. Active immunisation and antiviral therapy face obstacles that will not be resolved in the near future [10]. Passive immunisation with anti-RSV antibodies, however, has been shown to prevent RSV infection both in laboratory animals [11] and in children [12, 13]. This observation led to the development of palivizumab, a neutralising, humanised, monoclonal, $IgG_1$ antibody directed against the F glycoprotein of RSV [14]. The efficacy of palivizumab in reducing the hospitalisation rate for RSV infection in high risk infants has been

**Abbreviations**

| | |
|---|---|
| RSV | Respiratory syncytial virus |
| CLD | Chronic lung disease |
| ICU | Intensive care unit |
| NNT | Number needed to treat |

demonstrated in a randomised, double-blind, placebo-controlled study (IMpact study) [15], and the American Academy of Pediatrics recommended its use in 1998 [16]. Although palivizumab has been registered in several European countries, its use remains controversial. Unresolved issues are (1) high cost in relation to moderate efficacy [17], (2) poor predictability of effectiveness due to regionally varying hospitalisation practices [5], and (3) marginal efficacy in children with CLD [15]. The purpose of this study was to generate regional data on the quantity and character of RSV hospitalisations and to estimate the overall impact of palivizumab if used for the indications mandatorily covered by Swiss health insurance companies. These include (1) infants born at ≤35 weeks' gestation who are aged ≤6 months at the beginning of the RSV season or (2) infants with chronic lung disease (CLD) who are ≤1 year of age and require medical therapy for CLD (e.g., supplemental $O_2$, bronchodilators, corticosteroids, or diuretics) [18].

## Patients and methods

### Study design

In a retrospective, descriptive, single-institution survey conducted at the Department of Paediatrics, University of Bern, Switzerland, between September 1, 1998 and June 30, 2000, hospitalisations for RSV infection during two consecutive RSV seasons (1998/1999 and 1999/2000) were reviewed. At this institution, standard emergency department guidelines require that all children aged ≤5 years who are admitted with clinical suspicion of RSV infection (i.e., rhinorrhoea, tachypnoea, wheezing, apnoea, or $O_2$ requirement) undergo testing for RSV. The cut-off value for the onset and end of an RSV season was arbitrarily defined as 5 RSV hospitalisations per month. Cases met the following criteria: (1) residence in the Canton of Bern, (2) age between 0 and 16 years, (3) hospitalisation for acute respiratory tract illness, and (4) detection of RSV in nasopharyngeal and/or tracheobronchial secretions within 72 hours of admission. Cases were excluded if RSV was first detected more than 72 hours after hospitalisation and/or if RSV was detected in the absence of acute respiratory tract illness. Case catchment and identification was carried out by retrieving all positive RSV results from the hospital clinical microbiology database. Clinical data sets for each patient identified were generated by review of the hospital chart. The results were used (1) to generate extrapolated, population-based RSV hospitalisation data, and (2) to estimate the potential impact of palivizumab (Synagis®) on the prevention of RSV hospitalisations based on published efficacy data [15].

### Laboratory methods

Nasopharyngeal secretions were sampled using a commercially available device (Vygon® infant mucus aspirator, Ecouen, France). RSV was detected by direct immunofluorescence (Light Diagnostics® Respiratory Panel DFA, Chemicon International, Inc., Temecula, CA).

### Statistical analysis

Population statistics for the Canton of Bern were obtained from the Federal Office of Statistics. Prematurity and CLD rates were used in accordance with the cost-effectiveness data for palivizumab in Switzerland [17]. The Federal Office of Public Health provided nationwide surveillance data on positive RSV test results notified weekly by diagnostic laboratories between 1991 and 1999. The estimated annual number of RSV hospitalisations occurring in the Canton of Bern was calculated by multiplying the average number of cases seen at our institution during the observation period by the factor 1.33, which takes into account the fact that 75% of the paediatric hospital beds in the Canton of Bern were located at this institution. Statview® version 4.5 (Abacus Concepts, Inc., Berkeley, CA) was used for statistical analysis. Continuous variables were analysed using the Mann-Whitney U test or the Kruskall-Wallis test. For dichotomous variables, contingency tables were used. The level of significance was 0.05.

## Results

### Characteristics of the patient population

Table 1 summarises demographic, clinical and outcome parameters of the 242 cases studied. Of these, 194 (80.6%) were aged ≤12 months. Forty-four (18.2%) patients and 26 patients (10.7%), respectively had a history of prematurity of ≤37 weeks and ≤35 weeks of gestation. During the 1998/1999 and 1999/2000 RSV seasons, the total numbers of RSV hospitalisations were 165 and 77 respectively. During the 1998/1999 season the median patient age on admission was significantly lower (3.2 months [range 0.2–49.2] vs. 6.4 months [0.3–70.9], p = 0.002), hospitalisation was significantly longer (7.0 days [1–30] vs. 5.0 days [1–30], p = 0.027), and more patients were admitted to the ICU (22 [13.3%] vs. 6 [7.8%], p = 0.209) than during the following winter. Other parameters noted in Table 1 did not differ between the two seasons (data not shown). Detailed data on the age of all children in the patient's household were available for 184 of 242 patients (76%). Of these, 43 (23.4%) were firstborns. In contrast, statistical data from the Canton of Bern indicate that in the general population 68.3% of children from families with children under 7 years of age are firstborns, predicting a total of 126 patients in our study population. Eldest siblings were thus significantly underrepresented (relative risk 0.34; 95% confidence interval, 0.26–0.45).

**Table 1**

Clinical and outcome parameters of RSV infection according to gestational age.

| Parameter[1] | gestational age (weeks) | | |
|---|---|---|---|
| | ≤35 | >35 | total |
| No. of patients (%) | 26 (10.7) | 216 (89.3) | 242 (100) |
| Male gender (%) | 13 (50) | 119 (55.1) | 132 (54.5) |
| Age on admission (months) | 7.5 [0.5–34.6][2] | 3.7 [0.2–70.9][2] | 4.0 [0.2–70.9] |
| Gestational age (weeks) | 31.5 [26–35] | 39.5 [36–43] | 39.0 [26–43] |
| Admission body weight (kg) | 5.9 [2.4–13.5] | 6.0 [2.4–22.4] | 6.0 [2.4–22.4] |
| *Risk factors for RSV hospitalisation* | | | |
| Chronic lung disease (%) | 9 (34.6) | 0 | 9 (3.7) |
| Other chronic pulmonary disease (%) | 0 | 6 (2.8) | 6 (2.5) |
| Congenital heart defect (%) | 2 (7.7) | 5 (2.3) | 7 (2.9) |
| Immunodeficiency | 0 | 1 (0.5) | 1 (0.4) |
| Duration of hospitalisation (days) | 7.5 [2–23][3] | 6.4 [1–30][3] | 7.0 [1–30] |
| No. of patients with $O_2$ requirement (%) | 19 (73.1)[4] | 118 (54.6)[4] | 137 (56.6) |
| Duration of $O_2$ requirement (days) | 4.0 [0–17][5] | 2.0 [0–26][5] | 2.0 [0–30] |
| No. of patients in ICU (%) | 3 (11.5) | 25 (11.6) | 28 (11.6) |
| No. of patients requiring mechanical ventilation (%) | 1 (3.8) | 7 (3.2) | 8 (3.3) |
| No. of deaths (%) | 0 | 1 (0.5) | 1 (0.4) |

[1] Continuous data are given as median [range] where appropriate
[2] p = 0.026 [3] p = 0.031 [4] p = 0.073 [5] p = 0.025

**Table 2**

Clinical outcome of RSV infection in children of over 35 weeks' gestational age hospitalised for RSV infection.

| Age group (months) | No. of patients | duration of hospitalisation (days) | | $O_2$ requirement | | duration of $O_2$ requirement | | admission to ICU | | mechanical ventilation | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | median | range | No. | % | median | range | No. | % | No. | % |
| ≤1 | 31 | 9.0[1] | 1–27 | 28[2] | 90 | 6.0[3] | 0–20 | 13[4] | 42 | 3 | 10 |
| 1–2 | 40 | 6.0[1] | 1–28 | 25[2] | 62 | 2.0[3] | 0–19 | 7[4] | 17 | 2 | 5 |
| 2–3 | 28 | 6.5[1] | 1–28 | 13[2] | 46 | 0[3] | 0–14 | 2[4] | 7 | 1 | 4 |
| 3–6 | 33 | 6.0[1] | 1–10 | 10[2] | 30 | 0[3] | 0–5 | 0[4] | 0 | 0 | 0 |
| 6–12 | 44 | 5.0[1] | 1–19 | 22[2] | 50 | 0.5[3] | 0–9 | 1[4] | 2 | 0 | 0 |
| >12 | 40 | 4.0[1] | 1–30 | 19[2] | 47 | 0[3] | 0–26 | 3[4] | 7 | 2 | 5 |

[1] p <0.0001 [2] p <0.0001 [3] p <0.0001 [4] p <0.0001

## Course of RSV infection in relation to established risk factors

Table 1 summarises key parameters of RSV hospitalisations according to gestational age. It is evident that, in absolute numbers, the major burden of RSV disease rests on infants without established risk factors. In comparison with children of >35 weeks' gestation, former premature infants of ≤35 weeks were significantly older at the time of admission for RSV infection. Although their hospitalisation was longer, adverse outcome as judged by frequencies of ICU admission, mechanical ventilation and death did not differ in the two groups. Of 17 patients with prematurity of ≤35 weeks, 7 (41%) would not have been eligible for prophylaxis because they were aged over 6 months on November 1. Of 9 patients with CLD, 3 (33%) would not have been eligible for the same reason. The course of RSV infection in infants with CLD was mild (median age 9.3 months [range 6.3–34.6], duration of hospitalisation 8.0 days [range 2–17], duration of $O_2$ therapy 4 days [range 0–17], ICU admission rate and mortality 0 respectively).

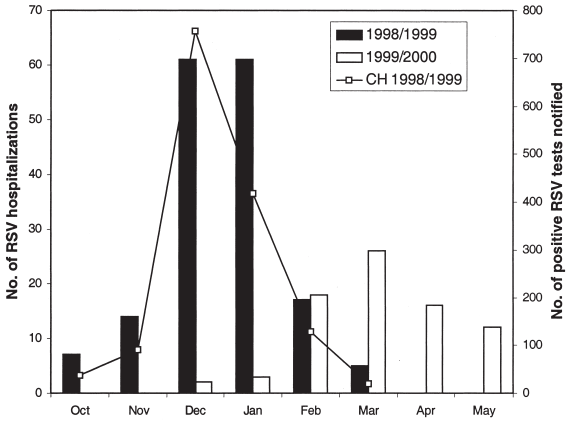


**Figure 1**

Frequency distribution of RSV hospitalisations according to month of admission during the RSV seasons 1998/1999 (shaded bars) and 1999/2000 (open bars) at the University Children's Hospital in Bern. The line graph labelled CH 1998/1999 indicates the nationwide frequency distribution of positive RSV test results communicated to the Federal Office of Public Health during the 1998/1999 season.

## Course of RSV infection in relation to chronological age

Clinical outcome as a function of chronological age is summarised in Table 2. Former premature infants of ≤35 weeks with and without CLD were excluded from this analysis. The data document that severity of disease, judged by duration

**Table 3**

Estimated RSV hospitalisation rates and effectiveness of palivizumab in infants under 12 months of age in the Canton of Bern.

| Subgroup (gestational age) | annual birth cohort in the Canton of Bern[1] | RSV hospitalisations | | | | risk reduction by palivizumab (%)[4] | No. of hospitalisations prevented | No. needed to treat (NNT)[8] |
|---|---|---|---|---|---|---|---|---|
| | | Bern 1998/1999 | Bern 1999/2000 | Canton of Bern[2] | rate (%)[3] | | | |
| ≤35 | 200 | 14 | 4 | 12[5] | 6.0 | 55[5] | 7[5] | 29 |
| ≤35 + CLD | 25 | 4 | 2 | 4 | 16.0 | 39 | 2 | 13 |
| All neonates[6] | 5000 | 24 | 7 | 21 | 0.4 | 80 | 17 | 294 |
| All infants[7] | 10000 | 141 | 53 | 129 | 1.3 | 80 | 103 | 97 |

[1] data provided by Federal Office for Statistics and [18].
[2] calculated by multiplying the average of both seasons by 1.33 to account for the fact that the study site provided only 75% of all paediatric hospital beds in the Canton of Bern.
[3] estimated number of RSV hospitalisations in the Canton of Bern divided by birth cohort of corresponding subgroup.
[4] as published [15]
[5] If patients exceeding the approved age limits for palivizumab are excluded (i.e., 4 and 2 cases in the first and second seasons respectively), the estimated annual number of RSV hospitalisations in the Canton of Bern is 9 rather than 12, and the number of hospitalisations potentially prevented by palivizumab is 5 rather than 7. Not included in this calculation is the observation that RSV hospitalisations may occur outside the period during which palivizumab is administered.
[6] Describes the hypothetical administration of a single dose of palivizumab at birth to all neonates born between October 1 and March 31. This population comprises half of the annual birth cohort.
[7] describes the hypothetical administration of palivizumab to all infants during the first RSV season of their life
[8] number of patients needed to receive prophylaxis in order to prevent one hospitalisation for RSV infection

of hospitalisation, necessity and duration of supplemental $O_2$ therapy, and ICU management were inversely associated with chronological age. Of the 31 infants admitted for RSV infection during the first month of life, none had an identifiable risk factor such as congenital heart disease, pulmonary disease, or another underlying disorder.

### Distribution of cases over time

Figure 1 depicts monthly RSV hospitalisation frequencies for both RSV seasons. Peak frequencies differed by 2–3 months, and 28 of 77 cases (36.4%) of the 1999/2000 season occurred after March 31. National laboratory notification data (available for the 1998/1999 season only) and local RSV hospitalisation rates showed a concurrent frequency distribution.

### Impact of palivizumab on RSV hospitalisation frequency

The mean annual RSV admission rate for infants aged ≤12 months residing in the Canton of Bern was 10.5 per 1000 infants born at term (i.e.100 hospitalisations for an estimated 9500 live births at term), 50.8 per 1000 infants of ≤37 weeks' gestation (44 for an estimated 500 infants of ≤37 weeks), and 60 per 1000 infants of ≤35 weeks' gestation. Table 3 summarises the projected impact of palivizumab on RSV hospitalisation of infants aged ≤12 months in the Canton of Bern if used for the indications approved in Switzerland. The bottom two rows describe the hypothetical use of palivizumab in all children, (1) as a single dose given to all neonates born between October 1 and March 31, and (2) as standard prophylaxis during the whole RSV season.

## Discussion

Palivizumab has recently been approved by the Swiss Intercantonal Office for the Control of Medicines (IKS) and the Swiss Federal Office for Social Security (BSV) for RSV prophylaxis in high-risk infants. A national panel of experts had previously advised against its use [17]. Clinicians are left with the dilemma of having a new drug available which is publicised in the lay media and whose cost is covered by health care insurances, but which is not recommended for use. Hence, the product's price (CHF 5000 to 7500 per patient), inconvenient mode of administration (5 intramuscular injections at monthly intervals) and limited efficacy with no known beneficial effect on long-term sequelae and mortality [15] warrant evaluations of the projected effect of palivizumab under regional field conditions [5–7, 9].

Indeed, the data presented here disclose some characteristics of RSV epidemiology which have a direct bearing on the usefulness of palivizumab locally but may be irrelevant elsewhere. For instance, the estimated overall admission rate for RSV infection among children aged below 12 months was greater than reported from nearby Geneva during the 1994/1995 RSV season (10.5 vs. 5.3 per 1000 term infants) [5]. This difference may reflect regional and temporal variability in disease severity or differences in admission policy, as is suggested by the lower rate of $O_2$ requirement in hospitalised children in Bern (56.6 % vs. 78.8%). The comparison of two RSV seasons in this study showed considerable season-to-season variability with respect to both the frequency and severity of RSV hospitalisations. Concurrent with this observa-

tion, national laboratory notification data collected between 1991 and 1999 suggest a biannual periodicity with early-onset, high-frequency seasons alternating with late-onset, low-frequency seasons (data on file, Swiss Federal Office of Public Health). The epidemiological basis for such periodicities is not known [19, 20], but fluctuations in protective maternal antibody concentrations and variable circulation of RSV subtypes may be involved [21]. During the 1999/2000 season, more than one third of all hospitalisations occurred after March 31 (Figure 1). Such late cases may not have been amenable to standard 5-dose prophylaxis initiated before November 1, as generally recommended. A national surveillance system providing weekly updates on RSV detection rates in respiratory secretions would provide data on which to base rational timing of RSV prophylaxis, and, in addition, it could warn paediatric hospitals to increase admission capacities in anticipation of the annual RSV season.

Analysis of hospitalised children with a history of prematurity of ≤35 weeks (Table 1) shows that these patients were significantly older than children of >35 weeks' gestation, and that 38% would not have been eligible for RSV prophylaxis because of age exceeding 6 months or 1 year (in the presence of CLD) respectively, at the beginning of the RSV season which is customarily set for November 1. Hence these age limits would have considerably reduced the number of hospitalisations prevented by palivizumab in these recognised risk groups. A possible explanation for the comparably higher age at RSV hospitalisation among former premature infants is that many of them lived in the protected environment of newborn nurseries during the early weeks of their lives.

Equally important was the finding that, although former premature infants of ≤35 weeks' gestation were hospitalised and required supplemental $O_2$ for a somewhat longer period, there were no differences with respect to the rates of ICU admission, mechanical ventilation or death when compared with infants of longer gestation (Table 1). In the light of this local epidemiological context the 35-week cut-off given in the official recommendation appears arbitrary, since it restricts palivizumab not to those with the greatest risk of severe disease but to those with a somewhat greater RSV hospitalisation rate (Table 3).

The calculated number of infants needed to treat (NNT) with palivizumab in order to prevent one RSV hospitalisation in the Canton of Bern (Table 3) was consistent with previously published figures [17]. Even among infants with CLD for whom the NNT was lowest (13), the prevention of one hospitalisation (i.e. CHF 65 000 based on minimum costs for palivizumab prophylaxis of CHF 5000 per case and season) would cost far more than one hospital stay. Thus, it is clear that the use of palivizumab is not cost-effective.

As shown in Table 2, the major risk factor for a severe course of RSV hospitalisation was young chronological age in infants without recognisable risk factors. Children of >35 weeks' gestation and ≤1 month of age would constitute ideal candidates for palivizumab prophylaxis, because (1) the efficacy of palivizumab is likely to exceed 80% [15] and (2) according to our data nearly 50% of ICU admissions occur in these children (Table 2). Hence, if palivizumab were reasonably priced, the administration of a single dose to all neonates would be likely to have a substantial impact on the overall burden of RSV disease, while the currently approved indications are not (Table 3).

The study design has several shortcomings that may affect the accuracy of estimates of the number of hospitalisations prevented by palivizumab (Table 3). These include (1) the limited duration of the survey and the relatively small number of cases reviewed, (2) the lack of raw data on premature deliveries at ≤35 weeks in the Canton of Bern, (3) extrapolation of the total number of RSV hospitalisations in the Canton of Bern based on the availability of paediatric hospital beds, and (4) case catchment by RSV immunofluorescence assay which, although it is the gold standard for RSV rapid diagnosis in terms of sensitivity and specificity, may under- or overestimate the true number of infections by 10 to 20% [22, 23]. None of these factors appears to underestimate systematically the true number of RSV hospitalisations, and consequently none of them is likely to underestimate substantially the potential usefulness of palivizumab.

In conclusion, the projected impact of palivizumab in the Canton of Bern is modest. It may be negligible (1) if the approved age limits are strictly applied *and* (2) if epidemiological surveillance to guide the timing of prophylaxis is unavailable. Federal regulators adopted indications for palivizumab which were established in a single overseas trial. These indications restrict palivizumab arbitrarily to two apparent high-risk groups, while, as suggested in this article, the true burden of RSV disease may be carried by others. Under the current circumstances, the routine use of palivizumab does not seem justified.

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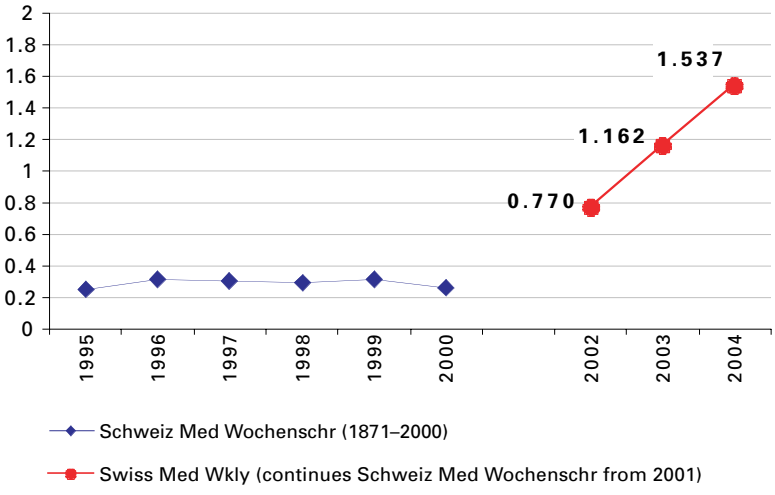


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