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ORIGINAL ARTICLE

# Benefits of home-based administration of palivizumab in high-risk groups

## Beneficios de la administración domiciliaria de palivizumab en grupos de alto riesgo

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**What do we know about the subject matter of this study?**

Prophylaxis with palivizumab (PVZ) reduces the risk of hospitalization due to respiratory syncytial virus (RSV). In Chile, its administration is warranted for preterm infants under 32 weeks and for patients with hemodynamically significant congenital heart disease (HSCHD) by the Ricarte Soto Law. Its administration presents several barriers, including the need for transfer and contact with other users.

**What does this study contribute to what is already known?**

The study demonstrates the feasibility of implementing monthly home administration of PVZ as an appropriate and timely strategy that is associated with high adherence rates and a dosing interval according to the current recommendations, with the benefit of reducing the risk of RSV infections in waiting rooms.

## Abstract

Palivizumab, a humanized monoclonal antibody against the respiratory syncytial virus (RSV), currently is indicated in groups at higher risk of developing severe RSV disease, such as extreme premature infants and patients with hemodynamically significant heart disease. In Chile, this strategy is guaranteed by Law 20850 (Ricarte Soto Law). Nevertheless, barriers to its administration included the need to transfer these labile patients and exposure to other users, with the risk of contagion in waiting rooms. **Objective:** to describe the impact of the palivizumab administration strategy in a home care program for high-risk patients. **Patients and Method:** retrospective, descriptive, observational cohort study of patients born before 32 weeks of gestation or weighing less than 1500 grams, who received palivizumab between January 2019 and December 2021 at the *Hospital Dr. Sótero del Río*. **Results:** 272 patients were included (median gestational age: 30 weeks). The percentage of doses administered at home was 35.9% (2019) and 37.2% (2021). Each dose of 2020 following the administration in Neonatology, was administered at home during the COVID-19 pandemic. The median

**Keywords:**
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interval between doses was as recommended. Adherence was over 90%. The unadjusted incidence of RSV infection was 5.7% (2019), 0% (2020), and 0.9% (2021). **Conclusions:** palivizumab administration was adequate and timely; home indication was associated with high adherence rates and an administration interval between doses in line with current recommendations.

## Introduction

Respiratory syncytial virus (RSV) is a major cause of respiratory infections in infants. It is the main agent of lower respiratory tract infection in infants and preschoolers worldwide, causing 1/3 of cases of pneumonia globally, hospitalization of more than 3.2 million patients per year, and the death of 59,600 children under 5 years of age from RSV-associated disease annually, especially in low-income countries[1-3].

While age younger than 6 months at the beginning of the RSV season is associated with a more complicated disease course (bronchiolitis, pneumonia), there are other risk factors that contribute to more severe outcomes, such as prematurity, bronchopulmonary dysplasia (BPD), and hemodynamically significant congenital heart disease (HSCHD), the latter presenting the highest hospitalization rates, a longer hospital stay, and a greater admission in Intensive Care Units with ventilatory support requirement[4,5].

Palivizumab (PVZ) is a humanized monoclonal antibody directed against the RSV fusion glycoprotein, which prevents the fusion of the viral particle with the host cell membrane, resulting in the inhibition of replication[6,7]. The available evidence indicates that prophylaxis with PVZ reduces the risk of hospitalization due to RSV in these groups of patients[6].

In Chile, the administration of PVZ is warranted by Law 20,850 (Ricarte Soto Law [RSL]), a system of financial protection for beneficiaries of all social security health systems[8]. Through the RSL, access to monthly PVZ administration is warranted during the period of high viral circulation with a maximum of 5 doses per year, from 2016 in preterm infants with BPD, and from 2019 in all preterm infants younger than 32 weeks of gestational age at birth and patients with HSCHD under 1 year of age at the beginning of the RSV season.

Timely administration of the drug is essential to achieve optimal efficacy, with good adherence to treatment and an adequate dosing interval, which is sometimes challenging due to non-attendance at check-up visits. In addition, the administration of the drug in health centers has certain disadvantages, including the need to transfer these labile patients, as well as the contact with other users with respiratory involvement and different morbidities in the waiting rooms.

In 2018, a Home Care Program (HCP) was implemented in the *Hospital Sótero del Río* for preterm infants under 32 weeks or 1500 g during the first 6 months after discharge from the Neonatology Unit. This program was achieved by the alliance between the Neonatology Unit, the Adult Home Hospitalization Unit (AHHU), and the Pediatric Bronchopulmonary Unit, as a strategy to reduce respiratory readmissions during the first months after discharge. The HCP consists of comprehensive care of the patient together with her/his family, changing and bringing secondary care to the patient's home. The program is implemented by a multidisciplinary team that includes physicians, nurses, kinesiologists, family education, blood and urine tests, physical exercises, and education to prevent neurodevelopmental disorders. In addition, a helpline with neonatologists is available to guide the patient's family and address their concerns.

The administration of PVZ is part of the HCP, and the corresponding immunizations are administered at home up to 6 months of age. Subsequently, PVZ is administered at the Therapeutic Diagnostic Center (TDC).

The objective of this study is to describe the impact of timely administration of PVZ through a Home Care Program in high-risk patients.

## Patients and Method

A retrospective study of patients treated with PVZ who received RSV prophylaxis between January 2019 and December 2021 (extension of the usual administration period in Chile due to the late peak in 2021), either in the context of the HCP or in the TDC of the *Complejo Asistencial Dr. Sótero del Río*, according to their age group, in a program for a total duration of 6 months. During the COVID-19 pandemic, all doses following administration in neonatology were administered through the HCP. Given the seasonal behavior of RSV, the first dose is administered from May to September of each calendar year.

Patients born before 32 weeks of gestation or with less than 1500 grams and their twin sibling, and those who were less than 1 year of chronological age at the beginning of the high viral circulation period were

included. Other patients covered by the RSL, such as infants with HSCHD, were not included. The population assisted at the hospital that did not meet the RSL criteria was excluded.

Demographic, clinical, and intervention-related data (gestational age, sex, birth weight, presence of BPD, unit of dose administration [neonatology, TDC, HCP], number of doses administered, adherence, dosing interval, incidence of RSV infection, and RSV-associated hospitalization) were obtained from medical records. Data were stratified by calendar year (2019, 2020, 2021) to consider the potential impact of the COVID-19 pandemic on healthcare delivery. RSV diagnosis was confirmed by immunofluorescence testing.

The study was approved by the Scientific Ethical Committee of the *Complejo Asistencial Dr. Sótero del Río*.

### Statistical analysis

The data collected were anonymized and tabulated in spreadsheets. For continuous numerical variables, the normality of the distribution was assessed through the Shapiro-Wilk test ($n < 50$) and the Kolmogorov test ($n \geq 50$). Outliers were calculated using the Grubbs' test and were excluded from the analysis. Variables were characterized by central measurement and dispersion parameters (mean and standard deviation [SD] for those with normal distribution; median and range for those with another distribution pattern). Categorical variables were characterized according to their frequency. Statistical tests to compare quantitative (Student's t-test, Mann-Whitney U test, Wilcoxon test, according to distribution) and qualitative (chi-square or Fisher's exact test) variables were performed with the SPPS software (IBM, version 19.0.0.329).

## Results

Two hundred and seventy-two patients were included. Table 1 summarizes their main baseline characteristics. No significant differences were observed regarding birth weight, gestational age, sex distribution, and prevalence of BPD when the population was stratified according to calendar year.

The percentage of patients receiving at least 4 total doses of PVZ was 37.5% in 2019, 86.2% in 2020, and 92.3% in 2021, with a mean (± SD) indicated doses per patient of 3.5 ± 1.1, 4.7 ± 0.8, and 4.7 ± 0.7, respectively. The proportion of doses administered at home was 35.9% in 2019 and 37.2% in 2021, while it reached 81.8% of cases in 2020 in the context of movement restrictions associated with the COVID-19 pandemic, where home administration was extended up to 1 year of age (table 2).

**Table 1. Baseline characteristics of the study population**

| Period | 2019 | 2020 | 2021 |
|---|---|---|---|
| n | 88 | 80 | 104 |
| Birth weight* (median, range) | 1370 g (540-2510) | 1410 g (575-2510) | 1310 g (510-2158) |
| Gestational age* (median, range) | 30 semanas (24-35) | 30 semanas (25-34) | 30 semanas (24-37) |
| Female sex (%)** | 45.4% | 51.2% | 44.2% |
| Bronchopulmonary dysplasia** | 45.4% | 42.5% | 41.3% |

*p > 0.05 (2020 vs. 2019; 2021 vs. 2020; 2021 vs. 2019; Wilcoxon test). **)p > 0.05 (2020 vs. 2019; 2021 vs. 2020; 2021 vs. 2019; chi-squared test).

**Table 2. Palivizumab doses administered**

| Period | 2019 | 2020 | 2021 | Totales |
|---|---|---|---|---|
| n | 88 | 80 | 104 | 272 |
| Patients receiving ≥ 4 PVZ doses (n) | 33 | 69 | 96 | 198 |
| Proportion of patients receiving ≥ 4 PVZ doses | 37.5% | 86.2% | 92.3% | 73% |
| Total PVZ doses administered | 132 | 276 | 384 | 792 |
| PVZ doses administered at home | 47 | 226 | 143 | 416 |
| Proportion of PVZ doses administered at home | 35.6% | 81.8% | 37.2% | 52.5% |
| PVZ doses administered in the Neonatology Unit | 10 | 8 | 27 | 45 |
| Proportion of PVZ doses administered in the Neonatology Unit | 7.5% | 2.9% | 7% | 5.7% |
| PVZ doses administered at the TDC | 75 | 42 | 214 | 331 |
| Proportion of PVZ doses administered at the TDC | 56.9% | 15.3% | 55.8% | 41.8% |

PVZ: palivizumab; TDC: Therapeutic Diagnostic Center.

The interval between successive doses administered remained within the desired range throughout the period evaluated, with a tendency to optimize to 29 days for home administration (table 3).

Adherence to PVZ treatment, defined as the number of patients who received the total recommended doses, was over 90% (figure 1), with no significant differences in stratification by calendar year. During 2020, a year in which 81.8% of PVZ administration took place at home, adherence was 98.7% (95% confidence interval: 93.2% - 100%).

In the study population, 5 cases of RSV infection were reported in 2019 and 1 outpatient case in 2021, equivalent to an unadjusted incidence of 5.7% and 0.9%, respectively. Of the 5 patients diagnosed in 2019, 4 required hospitalization for a median of 5 days (range: 2 to 8). Two of these patients had received a single dose of PVZ. No cases of RSV infection were reported during 2020. In 2021, 1 patient who had reached 3 doses of PVZ died of a non-RSV-related cause.

No adverse events leading to treatment discontinuation were reported in this population.

**Table 3. Interval in days between palivizumab doses**

| Period | 2019 median (range) | 2020 median (range) | 2021 median (range) |
|---|---|---|---|
| *Time from dose 1 to dose 2* | | | |
| All doses | 31 (27-35) | 29 (24-38) | 30 (25-40) |
| Doses at TDC | 32 (27-35) | 31 (28-38) | 30 (26-35) |
| Doses through HCP | 29,5 (27-33) | 28 (24-36) | 30 (25-40) |
| *Time from dose 2 to dose 3* | | | |
| All doses | 30 (23-39) | 28 (26-34) | 29 (25-42) |
| Doses at TDC | 29 (23-38) | 30 (27-32) | 30 (24-42) |
| Doses through HCP | 30,5 (23-39) | 28 (26-34) | 28 (25-33) |
| *Time from dose 3 to dose 4* | | | |
| All doses | 31 (27-36) | 30 (27-36) | 32 (22-48) |
| Doses at TDC | 31 (28-36) | 31 (28-36) | 32 (24-48) |
| Doses through HCP | 30 (27-34) | 30 (27-35) | 32 (22-43) |
| *Time from dose 4 to dose 5* | | | |
| All doses | 32 (27-36) | 29 (26-40) | 29 (15-45) |
| Doses at TDC | 32 (27-36) | 31,5 (26-40) | 29,5 (15-45) |
| Doses through HCP | 32 (32-34) | 29 (27-33) | 29 (25-35) |

HCP: Home Care Program; TDC: Therapeutic Diagnostic Center.

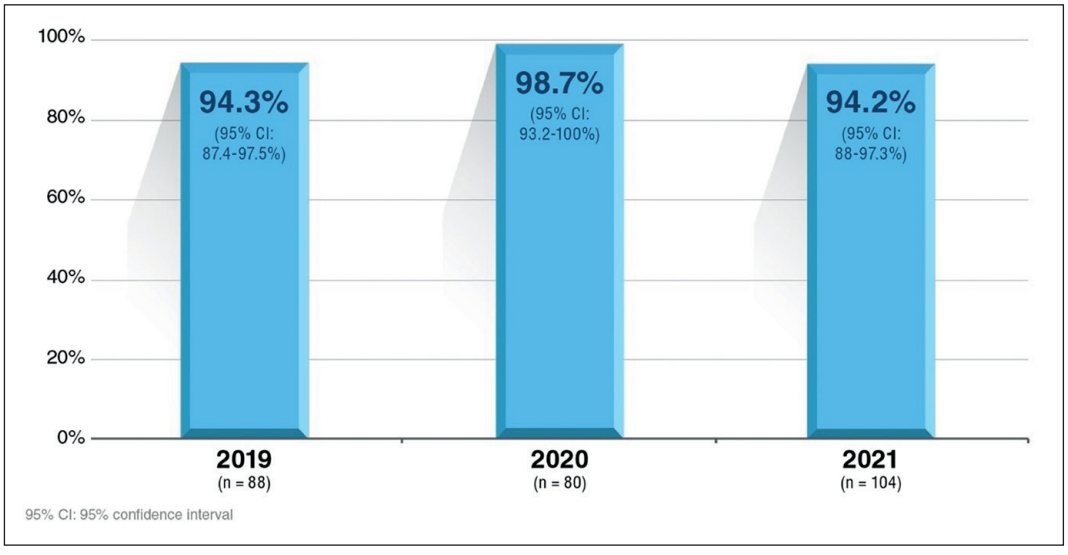


**Figure 1.** Adherence to palivizumab treatment stratified by calendar year.

## Discussion

In this cohort of preterm patients, the administration of PVZ was adequate and timely both at the TDC and through the HCP. The longer home indication period was associated with higher adherence rates and with an administration interval between doses in line with current recommendations (25 to 35 days) (9), with a tendency to optimize to 29 days. These results are especially noteworthy when considering that, according to the review carried out, there are no data available on similar home administration programs at the regional level.

Programs limited to home administration of the drug have been described in the United States[10], Europe[11], and the United Kingdom[12]. In our case, home administration of PVZ is part of an HCP financed by the *Fondo Nacional de Salud* (FONASA)[a], without the sponsorship of external contributors or pharmaceutical companies as described in other regions of the world. The beneficiaries of the HCP consist of a population particularly susceptible to recurrent hospitalization. According to the international experience of other home care transition programs, the frequency of readmission is associated with the degree of prematurity and the presence of BPD, among other factors[13]. In our population, both characteristics were predominant, with a median gestational age of 30 weeks and a prevalence of BPD higher than 40%, highlighting the importance of implementing this preventive strategy. Similarly, according to national data before the availability of PVZ (1995-2001), patients discharged from hospital and requiring supplemental oxygen therapy had higher rates of readmission due to lower respiratory infection (45% vs. 34% for other patients). Also, mortality of infants with BPD at 2 years was as high as 13%[14].

Based on data from the IMpact study, the intramuscular administration of a monthly dose of PVZ proved to be an effective and safe strategy for the prevention of severe forms of RSV infection among preterm and BPD patients[15]. These results were confirmed by real-world registries showing lower RSV hospitalization rates than those described in randomized controlled clinical studies[16]. However, the need to transfer treated patients to a hospital setting, with the additional risk of exposure to other infants with respiratory infections, represents a barrier to its timely indication. The availability of home application is a strategy to facilitate access for the target population which, in our experience, was associated with a reduced incidence of RSV infection and hospitalization.

The proportion of patients receiving at least 4 total doses of PVZ increased from 37.5% in 2019 to values above 85% in the following years. This was due to the inclusion of all preterm patients younger than 32 weeks as beneficiaries of the RSL in July 2019 (middle of the RSV season), regardless of the history of BPD, who were able to receive only the remaining doses to end the season of high virus circulation. It is important to consider that the suggested period for the first dose in the country is from May to September, for a better interpretation of the results obtained.

Of note, in a study of readmission prevalence at the *Hospital Sótero del Río* conducted between 2009 and 2015 with 807 preterm patients under 32 weeks or 1500 g at birth, 43.3% (n = 307) of them were hospitalized at least once during the first 2 years after discharge. These hospitalizations occurred mainly during the first 6 months (63.8%, n = 196) and during winter (61%). The main cause was respiratory (75.4%) and the main causative agent was RSV (44%) (17). In our analysis, performed in the same hospital and in a population with similar characteristics but which received PVZ within the framework of the RSL, only 4.6% of the cases were attributed to RSV, with a marked decrease compared with previous evidence.

In a study conducted in the same hospital to evaluate this HCP, a decrease in the prevalence and severity of hospitalizations due to respiratory causes in the first 6 months after discharge was found. The main causative agent of respiratory infections was RSV, but the proportion decreased significantly in the HCP group compared to the non-interventional group (12.5% vs. 44%, respectively). When PVZ was used in combination with the HCP, no patients required hospitalization due to RSV (unpublished data)[18].

In the context of the benefits observed in this high-risk group, the availability of promising information about other preventive strategies, such as bivalent vaccines for pregnant women, infant vaccines (in development), and other monoclonal antibodies should be highlighted[19].

The lack of complete treatment adherence data before the implementation of the HCP, the single-center nature of the study, the retrospective collection of data, and the lack of assessment of unavailable variables (maternal education, breastfeeding, smoking, etc.) are recognized as limitations, although the latter were not part of the objectives of the study. Likewise, the modification of the PVZ administration plan until the end of 2021 because of the late disease peak could have influenced the results obtained. However, the number of patients evaluated and the defined characteristics of the intervention's target population are highlighted as strengths.

It is concluded that the home administration of

[a]National Health Fund: Chilean national public healthcare system.

PVZ was effective and adequate, with adherence rates above 90%, and a dosing interval consistent with current recommendations.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

## Conflicts of Interest

Carolina Ortiz, Ignacia Vásquez, Alejandra Zamorano, and Ivonne D'Apremont declare having received payment of fees for lectures from AstraZeneca .

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