



Research Article

Palivizumab for Respiratory Syncytial Virus Prophylaxis: Lessons Learned and Strategies for New Horizons

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Abstract

Background: The monoclonal antibody Palivizumab (PVZ) has been used for 25 years to prevent Respiratory Syncytial Virus (RSV) infections. Evidence regarding its performance in low and middle-income countries (LMIC) is scarce. In this uniquely conducted study in Brazil, we showed the real-life use of PVZ in a public health context.

Methods: This prospective cohort study was conducted during two consecutive RSV seasonality periods and included children < 2 years old with criteria for PVZ use. Effectiveness, breakthrough infections, adherence, and clinical-epidemiological characteristics of infants were analyzed. Infections were investigated using qRT-PCR.

Results: A total of 296 children were included. The main criterion for PVZ was prematurity (<1,500g), the average rate of PVZ adherence was above 90%. A total of 99 (33.4%) episodes of respiratory infection were identified and 47 (47.5%) were investigated, resulting in 11 (23.4%) RSV breakthrough infections, 20 (42.6%) other respiratory viruses, and 16 (34.0%) negative cases.

Conclusion: There was a satisfactory performance in preventing RSV severe disease. However, RSV breakthrough infections were still detected due to possible PVZ resistance, which warrants further investigations.

Keywords: Acute respiratory infections; breakthrough infections; palivizumab; prematurity; respiratory syncytial virus

Introduction

Respiratory Syncytial Virus (RSV) is a highly contagious human pathogen responsible for causing bronchiolitis in children, with approximately 34 million infections per year with 1% to 3% requiring hospitalization [1,2]. RSV infects about 80% of children under two years of age [3]. Reinfections occur throughout life

and may also occur during the same season [2]. Severe disease has been associated with host risk factors such as cardiovascular and pulmonary diseases, but early primo-infection in infants and newborns, and children from low- and middle-income countries (LMIC) present the worst outcomes, where it is estimated that 97% of fatal cases due to this infection are located [4].

Despite the global burden of RSV infection and the medical advances in its management, the currently available therapy has been mostly supportive. Recent advances in RSV immunopathogenesis

have contributed to the development of vaccines and monoclonal antibodies, leading to significant improvements in RSV preventive strategies [5].

Palivizumab (PVZ), a humanized monoclonal antibody, was licensed in 1998 in the USA and Europe. In Brazil, it was incorporated by the Brazilian Unified Health System in 1999. It has been recommended as a strategy for passive immunization of high-risk infants. The protection is short-lived, approximately 30 days, requiring monthly doses to maintain blood levels of IgG1 anti-RSV antibodies during the seasonality.

The effectiveness of this strategic preventive program has resulted in a 56% decrease in hospitalization rate. However, the requirement for monthly dose administration reduces adherence, and the high cost has limited its applicability mainly in high-income countries [6]. In Brazil, there is no systematic studies that examined the response to this intervention in different regions. It is essential to evaluate the impact of this intervention for future strategies, now that new extended half-lives monoclonal antibodies are available.

In this context, we evaluated the effectiveness of PVZ in preventing RSV infection in our region. The clinical-epidemiological characteristics and therapy adherence of infants eligible for PVZ were analyzed. Data on breakthrough infections was also reported.

Material and Methods

Study Design

A prospective cohort study was conducted in a reference public health facility for monoclonal antibody administration in partnership with the referral pediatric hospital (Pequeno Principe Hospital – HPP) in Curitiba, southern Brazil. Curitiba City has an estimated population of 1,963,726 inhabitants and an infant mortality rate of 8.3 deaths per 1000 live births (The Brazilian Institute of Geography and Statistics - IBGE).

Sample size

The sample size was calculated based on the total number of children who received PVZ in the public health unit in 2014 (N=112) and 2015 (N=247), totaling 359 children. Considering a confidence level of 95% and a 5% margin of error, it resulted in a sample of 186 participants in the two years of the study.

Inclusion and exclusion Criteria

Children between the ages of 0 and 2, with eligibility criteria to use the PVZ and were at the beginning of the PVZ dose series, during two consecutive RSV seasonality periods (2017 e 2018) were included in this study. Children whose parents did not respond to telephone contact or electronic message for monitoring

were excluded from the study.

The criteria to receive PVZ in the Brazilian public health system are preterm infants (gestational age up to 31 weeks), children up to two years of age with prematurity, chronic lung disease, or congenital heart disease with hemodynamic repercussions. It should be administered at a dose of 15mg/kg, intramuscularly every 30 days, normally in 5 doses, during the five months of the seasonal period.

Patient follow-up

After inclusion in the study, follow-up was conducted through a monthly telephone contact or electronic message by the study team or by direct notification of parents or legal guardians. During the recruitment process, parents or legal guardians were instructed to notify the study team of the onset of acute respiratory symptoms after each monthly dose of PVZ. A nasopharyngeal swab was collected for viral investigation, if the respiratory infection was confirmed, within seven days of the onset of symptoms. Follow-up occurred up to 30 days after administering the last dose of the PVZ regimen.

Breakthrough infections

Definition of a suspected case of breakthrough infections was a child who developed a respiratory infection, and in the viral investigation, RSV was detected within 30 days after receiving the PVZ.

Laboratory diagnosis of RSV

The qRT-PCR was used to detect respiratory viruses according to the Centers for Disease Control and Infection's protocol (CDC), modified for multiplex reaction [7]. Influenza A (IFA), influenza B (IFB), parainfluenza types 1, 2, and 3 (PIV1, PIV2, PIV3), respiratory syncytial virus (RSV), human adenovirus (hAdV), human coronavirus 229E (hCoV 229E), human coronavirus OC43 (hCoV OC43), human coronavirus HKU1 (hCoV HKU1), human coronavirus NL63 (hCov NL63), human rhinovirus (hRV), human metapneumovirus (hMPV), enterovirus (EV) and human bocavirus (hBoV) viruses were investigated.

Statistical analysis

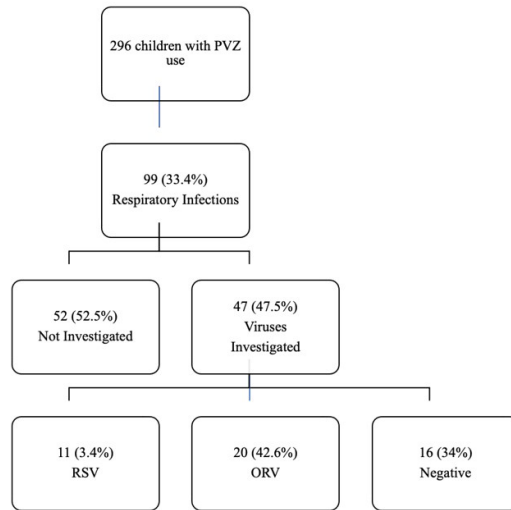
Descriptive analyzes were performed using the R statistical computing software environment (R Core Team, 2021) and quantitative and qualitative variables were summarized in terms of means, standard deviations, and frequencies.

Results

Study population and demographic data

During the two years of the study, 296 infants were included, and 99 (33.4%) episodes of respiratory infection were identified,

26 (26.2%) required hospitalization, and 47 (47.5%) infections were investigated (Figure 1). Sex distribution was homogeneous, and the median age was four months (interquartile range 0.4;24.2). The main criteria for using the monoclonal antibody was prematurity (Table 1), especially for those born during the seasonal period, with less than 1,500g (Figure 2A).



Note: PVZ: Palivizumab. RSV: Respiratory syncytial virus. ORV: Other respiratory virus.

Figure 1: Flowchart of the study.

Epidemiological and clinical features	N	% (IQR)
Total	296	100
Sex male	149	50.3
Sex female	147	49.7
Median age PVZ onset, months	4m	(0.4;24.2)
Ethnicity		
Caucasian	256	86.5
South Asian Americans	31	10.5
Afro-descendants	5	1.7
Asian- descendants	4	1,3
Criteria for PVZ use		
≤ 28 weeks	114	39.0
≥29 to 31 weeks	134	45.0
Congenital Heart Disease	45	15.0
Chronic Lung Disease	3	1.0
Birth weight		
<1000g	86	29.0
>1001g a 1500g	126	42.6
>1501g a 2000g	45	15.3
> 2001g	39	13.1
Type of milk		
Exclusive Breast milk	15	5.1
Breast milk + Milk formula	176	59.4
Exclusive milk formula	105	35.5

PVZ: palivizumab; IQR: Interquartile Range.

Table 1: Clinical and epidemiological characteristics of patients using palivizumab.

Palivizumab use and RSV seasonality

Adherence to PVZ use was high. Out of 1,191 doses released for the 296 children recruited, 1,164 doses (97.7%) were administered (Figure 2B). Participants who had acute respiratory infections and were subsequently investigated, the most identified respiratory viruses were RSV and rhinovirus (Figure 2C).

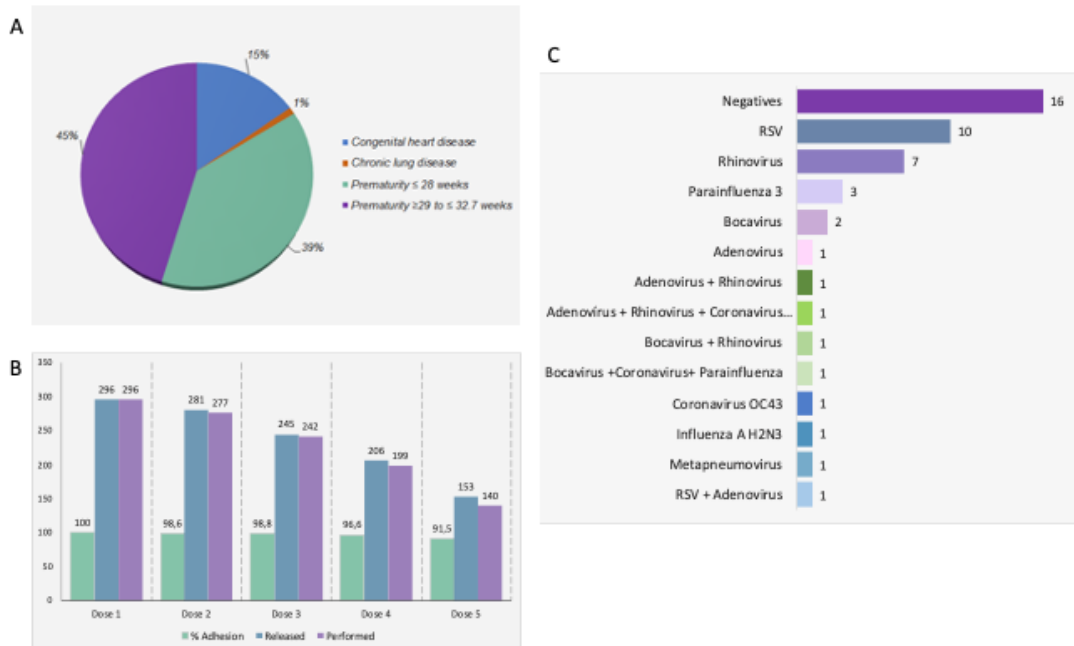


Figure 2: (A) Clinical criteria for palivizumab use in the 296 studied children (N=296). (B) Adherence to palivizumab doses (N=296). (C) Respiratory virus detected (N=47).

Regarding the month of birth and PVZ administration of the eligible children, 60% were born in the first semester of the year, and 53.4% within the seasonality period. RSV circulated more heavily throughout the research period in 2018, lasting until December 2018 (Figure 3).

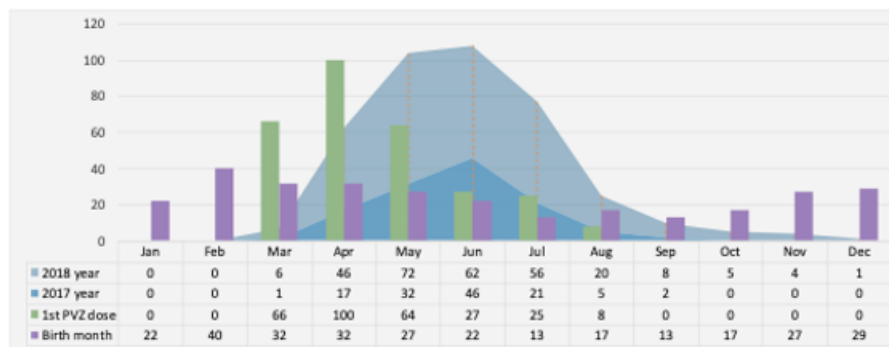


Figure 3: Concomitant analysis of the month of birth, 1st palivizumab dose, and hospitalized cases due to Respiratory Syncytial Virus seasonality (N=296)

Breakthrough infections

A total of 11 cases of RSV breakthrough infections were detected among the 47 acute respiratory infection (ARI) investigated, 72.7% (N=8) were male, and 81.8% (N=9) were hospitalized. The median time post-administration period for developing the infection was 14 days (IQR 12.2;20.7), and the median age was 7.2 months (IQR 4.5; 9.9). Regarding comorbidities, 27.2% (N=3) of the children had congenital heart disease, and 72.7% (N=8) were premature infants. Breakthrough infections occurred on average on the 14th day after the administration of the doses (Table 2).

Clinical data	N	%
Total RSV infections post- PVZ	11	100
Mean time to RSV infection	14 days	
Median age of cases	7.2 months	
Median age 1st. dose PVZ	5.5 months	
Risk Groups		
Congenital heart disease	3	27.2
Prematurity ≤ 28 weeks	4	36.4
≥ 29 to 31 weeks	4	36.4
Post-PVZ RSV Genotypes		
RSV A_ON1	3	27.2
RSV B_BA9	1	9.0
Not sequenced	7	63.6
RSV: Respiratory Syncytial Virus; PVZ: palivizumab.		

Table 2: Clinical data of patients with respiratory syncytial virus infection post-palivizumab use (N=11).

Other respiratory viruses

Twenty (42.6%) of the 47 cases of post-PVZ respiratory infections were caused by other respiratory viruses including, human rhinovirus (n=7; 35%), parainfluenza group (n=3; 15%), and human bocavirus (n=2; 10%). Other respiratory viruses, such as human adenovirus, influenza A H2N3, human metapneumovirus, human coronavirus OC43, adenovirus plus rhinovirus, adenovirus, coronavirus OC43, rhinovirus plus bocavirus, and bocavirus plus parainfluenza, had each one occurrence (n=1; 5%).

Discussion

Several clinical studies have been decisive in incorporating PVZ as a public health strategy in various countries. The effectiveness of monoclonal antibody therapy has been demonstrated in two large clinical trials, resulting in a 55% and 45% reduction in RSV hospitalizations [8, 9]. In this unique Brazilian PVZ cohort study, we had high adherence to monthly administration, but breakthrough infections occurred in 23% of the laboratory-investigated cases. No deaths were reported, suggesting a good performance of the immunoprophylaxis.

The analyzed sample was quantitatively representative of

the studied group and homogeneous regarding sex. The average age for the administration of the first PVZ dose was six months, which is considered late, given that the majority of RSV cases occur in infants under six months of age [10, 11]. Considering that this monoclonal antibody may be administered as early as day 7 of life with an average half-life of 28 days, its administration must be performed at the earliest possible time, reducing the exposure to RSV during the seasonal period.

When analyzing the distribution of RSV cases in children under two years of age hospitalized at HPP and the month of initiation of the PVZ regimen, it was observed that the administration of the first dose of PVZ was mostly concentrated in April (34.5 %). However, for timely protection, it would be ideal if PVZ doses were administered between February and March when local RSV circulation begins. However, the dynamics of this virus circulation, as beginning peak, and length of the RSV circulation may vary from year to year.

Comparing the age-temporality (month of infant’s birth) and the suitable starting period of PVZ series, infants born during the first semester had a greater indication for PVZ use. This fact is probably related to the regional seasonality period, which usually starts in April, the availability of this monoclonal antibody by the public health system, and the increased awareness of health teams during the RSV seasonal period. Therefore, it is essential to consider that if the children belong to the eligible group, regardless of their birth month, they should receive immunoprophylaxis 30 days before the onset of RSV season.

As shown in this 2-year monitoring, the RSV seasonality can vary, and in previous years, there have been periods of higher circulation. Furthermore, in other regions of Brazil, where the climatic seasons are less clearly defined, respiratory viruses such as RSV circulate more intensively during the rainy season, which does not correspond to the same time period when the public health system releases the monoclonal antibody.

Up to the fourth dosage, there was uniform adherence (mean = 99%), with a decline in adherence (mean = 91.5%) being observed at the fifth dose. Wong and collaborators reported that some authors consider adherence to four doses in each seasonal period adequate, even when the RSV season lasts five months. On the contrary, other authors, describe full adherence to the number of protected days and define “non-protected days” as those with an interval above 32 days [12].

Although there is a global impact of RSV infections in pediatric, elderly, and immunocompromised patients, therapeutic and preventive interventions are still limited. Only the monoclonal antibody anti-F protein, PVZ, and the antiviral ribavirin have been recommended for high-risk children and immunocompromised individuals. However, in recent years, there has been a substantial

investment in the development of drugs that may be used to prevent and treat this infection. Vaccines employing diverse platforms are currently under development and are at various stages of preclinical and clinical trials, with the most advanced trials being those intended for use in older adults and pregnant women [13].

Due to the association between disease severity and prematurity, vaccination for RSV prevention in children are restricted by the immaturity of young children's immune system. Thus, monoclonal antibodies remain the intervention currently presenting the best outcomes. PVZ was the first monoclonal antibody that was effective in preventing RSV infections. However, factors such as short half-life, therefore requiring repeated monthly applications, and high cost have limited the applicability of PVZ to high-risk children, such as premature infants, and patients with cardiovascular or pulmonary congenital diseases [6]. In addition, its effectiveness is directly related to adequate temporal administration, that is, during the seasonality of this virus, criteria for proper administration need to be better defined in regions with non-temperate climates, as these regions often lack epidemiological studies.

New monoclonal antibodies were developed to expand the therapeutic arsenal for the prevention of RSV infection, including Motavizumab, a humanized monoclonal antibody created from changes in the region that determines PVZ complementarity, which gave it a significant increase in potency. However, Motavizumab failed to receive U.S. Food and Drug Administration (FDA) approval due to adverse effects observed in clinical trials and comparative clinical studies between the two drugs showing no superiority to PVZ [13,14]. Suptavumab (REGN2222), another anti-RSV F antibody, has emerged as potentially more protective against this viral infection. However, it was not successful in clinical trials and it was discontinued [15]. Recently, findings from studies on the effectiveness of Nirsevimab, a human immunoglobulin of the IgG1 class that works as an inhibitor of the pre-fusion conformation of the RSV F protein, have been reported. A significant increase in viral neutralizing capacity was observed by binding in this conformational form of the F protein, compared to antibodies that bind in the post-fusion conformation. In addition, Nirsevimab has specific target substitutions of three amino acids in the Fc region of PVZ, known as YTE, which resulted in a significant increase in the half-life of this drug. Clinical trials have shown a greater effectiveness, approximately 70%, and longer half-life, limiting administration to fewer shots. Based on findings from clinical trials, this drug had its first approval for use in the USA and Europe in 2022 [13, 16, 17].

Failure of PVZ therapy to prevent RSV infections has been the most significant concern with this drug use. In the present study, 23% (11/47) cases of post-PVZ RSV infection were found among the investigated patients with respiratory illnesses. On

average, these breakthrough infections occurred on the 16th day following PVZ administration, within the period considered as active protection, since the average half-life has been 28 days. Also, breakthrough infections were more frequent between the first and second doses of PVZ. The PVZ's pharmacokinetics has shown that depending on the number of sequential doses applied, the level of blood concentration increases. Breakthrough RSV infections post-PVZ have been reported in countries such as Japan, Israel, Canada, and Turkey, with mutations in amino acids that neutralize the action of PVZ, demonstrating a resistance rate between 0.7% to 5.4% [18]. Currently, there is no program for monitoring failures in the use of PVZ or investigating the presence of viral mutations that may be related to this phenomenon in the Brazilian Public Health system.

The American Academy of Pediatrics (AAP) guidelines [19] on RSV prophylaxis recommend that if an infant receiving PVZ experiences an RSV hospitalization, monthly prophylaxis should be discontinued due to the low probability of the second episode of RSV hospitalization (<0.5%) in the same seasonal period. However, as these cases are not frequently investigated, patients continue to use the prophylaxis despite the presence of respiratory symptoms.

Despite the established preventive role of PVZ immunoprophylaxis, clinical evidence of its effectiveness is limited in certain population groups, especially in low- and middle-income countries. Furthermore, the most extensive reviews regarding the effectiveness of PVZ use were conducted in 2013 and 2014 [20], when access to viral diagnosis was restricted and not based on molecular methods. Therefore, PVZ protection data may be underestimated. In this regard, new scientific knowledge on effectiveness and resistance to PVZ must be examined in multiple population groups and updated on current practices, particularly when it represents a high cost to LMIC.

Ongoing development of new preventive and therapeutic strategies for RSV will gradually replace PVZ. However, in the context of LMIC, regions where RSV represents a significant burden, these new strategies need to be expanded. Availability of hospital beds, timely laboratory investigations to define seasonality patterns, the educational level of parents and guardians, the need for monitoring to identify the outcomes of these interventions, and, finally, the high cost of these new monoclonal antibodies continue to greatly limit their applicability in a large number of children worldwide, for whom PVZ may remain the only preventive alternative available. Therefore, there is a need for studies that examine the outcomes of this intervention.

As lessons learned with PVZ for future monoclonal antibodies, we can state that: (i) As the beginning of the PVZ administration in general is delayed (after the start of RSV

circulation), earlier administration at the beginning of the seasonal period would be preferred for seasonal effectiveness. (ii) There is a need to create a definition of cases of breakthrough infection, when it occurs. (iii) It is essential to implement an effective system for monitoring breakthrough infections. Alternatively, the administration of a new single-dose monoclonal antibody for the estimated period of protection, to conduct genomic surveillance of cases of protection failure and to investigate possible development of resistance. (iv) Considering the expensive prophylaxis, it is critical to monitor adherence with the objective of maximizing protection. (v) Finally, it is pivotal to revise clinical inclusion criteria in terms of extending them to new diseases or patient profiles and comparing local data from severe RSV cases that required hospitalization, including pediatric intensive care.

This study has some limitations. Not all patients with respiratory infections who were hospitalized or received treatment at other healthcare facilities had the opportunity to undergo testing for RSV. However, this study adds to the monitoring a representative number of children (N=296, estimated 186) in our city, providing data on the adherence rate to PVZ. In addition, it enabled us to understand the etiology of respiratory infections caused by other viruses, to analyze PVZ performance from a real-world perspective, to provide data regarding RSV breakthrough infections following PVZ and to warn of the possibility of PVZ resistance occurrence.

Conclusions

This study showed that premature infants were the most eligible children for immunoprophylaxis use. RSV infections were prevented with high adherence to PVZ dosage regimens. It also demonstrated new data on RSV breakthrough infections and possible resistance to PVZ in Brazil. The lessons learnt highlight the importance of periodically reviewing public health strategies, especially to align more cost-effective, accessible, and beneficial approaches to children.

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Ethical Considerations

This study was approved by the local Research Ethics Committee (#1,802,124), and Informed Consent Form (ICF) was signed by parents or guardians.

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