An epidemiological investigation of high-risk children for Respiratory Syncytial Virus infections

RWE palivizumab utilization as a RSV preventive treatment in Lazio (Italy)

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1. BACKGROUND

Respiratory Syncytial Virus (RSV) is a common RNA virus belonging to *Paramyxoviridae* family [1,2]. RSV is considered the leading cause of lower respiratory tract (LRT) infections in children and infants within the early childhood, especially over the first 24 months of life [3,4,5]. Unfortunately, RSV infections may lead to severe consequences that require hospitalizations and provoke morbidity and mortality in pediatric population [6,3]. Previous studies reported that specific factors increase hospitalization risk after RSV infection in children, including prematurity and comorbidities both in preterm and full-term children, such as chronic lung disease (i.e., bronchopulmonary dysplasia (BPD)), congenital heart disease (CHD), neurological and neuromuscular diseases [7,5]. In particular, BPD has been associated with the highest risk of hospitalization following RSV infections in children younger than 24 months [8] and relevant risks of hospitalization and mortality have been attributed also to children with CHD over the first 2 years of life [8,9].

Globally, it has been recently reported that in 2019 there were 3.6 million RSV-associated LRT infection hospital admissions in children under 5 years of age, of which 1.4 million were children aged 0-6 months, and 26,300 resulted in in-hospital death in children under 5 years, of which around 50% were children aged 0-6 months [6]. Similarly in Italy, over an observational period of 5 years (2014-2019), 62.5% of hospitalization due to RSV infections were reported in children under 3 months of age and 41% in children younger than 30 days [10].

Remarkably, one of the main causes of hospitalization in early childhood is bronchiolitis [4], that is also the most common LRT infection due to RSV [11], accounting for ~ 80% of cases in children younger than 6 months [12]. Moreover, RSV infection was found to be associated with healthcare resource utilization (HCRU) and long-term respiratory sequelae, such as highly sensitivity to lower respiratory infections, recurrent wheezing and asthma [13,14,15]. A causal relationship between RSV infection and respiratory sequalae has not been demonstrated yet and the debate is still open whether some children have a genetic predisposition to develop respiratory dysfunctions or whether there is direct damage from RSV that induces changes in the airways.

At present, while no specific therapy is approved for treatment of RSV infection and a series of vaccines and a monoclonal antibody (e.g., nirsevimab) are under investigation [16], palivizumab, a humanized monoclonal antibody directed against the RSV F fusion protein [17], is the only approved preventive treatment. Specifically, the seasonal prophylaxis therapy with palivizumab has been found to reduce RSV hospitalization in high-risk infants and children [18,19]. However, palivizumab prescription is restricted to specific high-risk populations of children and definition of these populations is the core of a long lasting medical and economical discussion worldwide, starting with

its approval for prevention of serious RSV LRT disease in 1998 by the US Food and Drug Administration [20].

In 2015 the Italian Medicine Agency (AIFA) established reimbursement of palivizumab prescription for prevention of serious RSV-lung diseases that would require hospitalization in high-risk groups of infants: preterm infants (born at ≤ 35 weeks of gestational age (WGA)) who are < 6 months old; children who are < 2 years old and have received treatment for BPD within the previous 6 months; children who are < 2 years old and were born with hemodynamically significant CHD [21].

In 2016, according to the updated American Academy of Pediatrics (AAP) recommendations [22], AIFA restricted the National Health System (NHS) reimbursement criteria for palivizumab prescriptions as follow [23]: children born at ≤29 WGA and who are < 1 year old; children with BPD who are <1 year old and born at <32 WGA; children who are <2 years old and required treatment for BPD within the previous 6 months; children who are <1 year old with hemodynamically significant CHD.

In addition, in 2016 AIFA allowed the reimbursement by the NHS also for prophylaxis with palivizumab for: children ≤1 year of age and with severe congenital malformations (e.g., neuromuscular, tracheo-bronchial); children ≤2 years of age in children with primitive or secondary immunodeficiencies.

Despite the fact that restriction of recommendations was based on contrasting results about the efficacy and cost-effectiveness of palivizumab found in several studies, following the influence of the Italian Society of Neonatology and patient associations, in 2017 AIFA revoked the 2016 limitations [24]. At the moment, reimbursement criteria for palivizumab include:

- Infants born at ≤ 35 WGA and who are < 6 months old at the beginning of RSV season;
- Children with BPD that required medical treatment within the previous 6 months and who are < 2 years old at the beginning of RSV season;
- Children born with CHD who are < 2 years old at the beginning of RSV season;
- Children born with severe congenital malformations (eg, neuromuscular, tracheo-bronchial) and who are ≤1 year old at the beginning of RSV season;
- Children with primitive or secondary immunodeficiencies and who are ≤2 years old at the beginning of RSV season.

Recently, studies investigating the effect of 2014 APP recommendations about palivizumab prescription, reported contrasting results about RSV hospitalization rate of infants born at 30-35 WGA. In particular, in Belleudi 2018 and 2021, reimbursement criteria changes were not associated with higher RSV hospitalizations rate, despite a significant reduction in palivizumab used was

detected [25,26] and previous studies support these findings [27,28,29]. On the contrary, a retrospective observational study involving 3 neonatal intensive care units in northern Italy, found a significant increase of RSV hospitalizations following restriction of palivizumab reimbursement [30] and similar findings were claimed in a systematic review focused on Italian reports [31].

According to these findings, there is a current urgent need of real world studies that may shed light on the use of palivizumab in Italy as the only approved preventive treatment against RSV for high-risk infants. In this context, the Lazio region seems to be a suitable area for real word studies. Indeed, among the Italian regions, Lazio is one of the most populated, with around 40.000 newborns per year, where palivizumab prophylaxis is frequently adopted to protect also infants born at 30-35 WGA. Both the contrasting results found over years about cost-effectiveness of palivizumab and the ascertained clinical burden of RSV infection worldwide, make further investigations in this field warranted.

2. OBJECTIVES OF THE STUDY

The overall objective of this retrospective study is to analyze children at high-risk for RSV severe infection. The analysis, focused on children with BPD, children born with CHD and children born preterm (≤29 and 30-35 WGA), has the following main objectives:

I) To investigate palivizumab utilization (e.g., presence or absence of palivizumab prophylaxis, number of prescriptions, adherence, etc..);

II) In BPD, CHD and preterm populations, describe the HCRU up to 24 months after birth related to:

- LRT infection hospitalizations (due to RSV or undetermined respiratory agents (URA)) and related hospital procedures (i.e., intensive care unit (ICU), oxygen therapy, mechanical ventilation);
- Hospitalizations related to respiratory events (e.g. wheezing and bronchospasm)
- Drug consumption from primary and secondary care related to respiratory anomalies (e.g. oral systemic antibiotics, oral corticosteroids, inhaled beta-agonists, inhaled glucocorticoids).

In addition, total number of high-risk infants on total newborns in the study period will be calculated.

3. METHODS

3.1 STUDY DESIGN AND DATA SOURCE

This is a retrospective longitudinal and record-linkage population-based cohort study. The study will be conducted in infants born between January 2017 and December 2020 in Lazio region. Specifically, three different cohorts will be identified: infants in whom BPD has been established, infants born with CHD and infants born preterm (≤29 and 30-35 WGA). Data used for the analyses will be extracted from six main regional administrative health databases:

- Certificate of Delivery Care (CEDAP up to 2020). This national registry, is the primary source of information about newborns, including WGA, birth weight, sex and date of birth. In addition, information about sociodemographic of parents, health status of mothers, and health status of the newborns, including, when applicable, causes of stillbirth and presence of congenital malformations (according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)), are available.
- Hospital Information System (HIS). This database collects information on all hospital admissions and discharges registered in regional hospitals, including the dates of admission and discharge, diagnoses and procedures (primary and secondary) (according to the ICD-9-CM) and internal transfer (such as admission to an ICU).
- Inhabitant Registry (IR). This registry includes information about the date of birth, gender, date of registration in the regional healthcare system, and where applicable, date of deregistration.
- Drug Claims Registry. This registry collects information on drug prescriptions reimbursed by the healthcare system, including drugs dispensed by private, public and hospital pharmacies and by local health units. For each drug prescription, the following details are available: patient code, date of prescription, drug substance, marketing authorization code and number of packages. All drugs are identified through the international Anatomical Therapeutic Chemical (ATC) classification system.
- Co-payment Exemption Registry. This registry collects information on persons who benefit from co-payment of health care services requested for disease specific or income related exemptions.
- Healthcare Emergency Information System (HEIS) collects all Emergency Department (ED) visit records and includes information on patient diagnosis at discharge, according to ICD-9-CM codes, as well as admission hour and vital status.

Record-linkage among these administrative databases will be managed by DEP. The main objective of this institution is to conduct epidemiological studies aimed at improving the quality and effectiveness of healthcare and reducing the health effects of environmental exposures.

3.2 STUDY POPULATION

All infants born between January 2017 and December 2020, born alive, resident in Lazio region and covered by the regional healthcare system, will be selected using CEDAP, HIS (discharged after birth hospitalization) and IR. Infants will be categorized into 3 high-risk groups with the following priority: BPD, CHD, prematurity. As such, the following three cohorts will be obtained:

- Infants in whom BPD has been established (Cohort 1): among infants born between January 2017 and December 2019, infants in whom presence of BPD has been established, regardless of infants' WGA and diagnosis of CHD, will be extracted (ICD-9 codes used for infants' identification are describe in table 1 of appendix);
- Infants born with CHD (Cohort 2): among infants born between January 2017 and December 2019, infants in whom presence of CHD has been reported, regardless of infants' WGA, will be extracted (ICD-9 codes used for infants' identification are described in table 2 of appendix);
- Infants born preterm (Cohort 3): among infants born between January 2017 and December 2020, those born at ≤ 29 and 30-35 WGA will be extracted.

According to risk priority categorization for severe RSV disease, each infant will be exclusively included in one of the 3 groups.

3.3 PALIVIZUMAB PROPHYLAXIS

Through record-linkage with Drug Claims Registry, palivizumab prophylaxis (ATC: J06BB16) will be recorded for each RSV season. Overall, three completed RSV seasons (from 1 October to 30 April) have been defined (2017–2018; 2018–2019; 2019-2020).

For each cohort and for each RSV season, infants will be defined as eligible for palivizumab prophylaxis based on the following criteria:

- Infants in whom BPD has been established and who and are < 2 years old at the start of RSV season (cohort 1);
- Infants with CHD who are < 2 years old at the start of RSV season (cohort 2);
- Infants born preterm at 30-35 WGA who are < 6 months old at the start of RSV season or born during the RSV season and infants born preterm at ≤29 WGA who are < 12 months old at the start of RSV season or born during the RSV season (cohort 3).

In each study cohort, for each RSV season, infants will be stratified in: infants who received and infants who did not received palivizumab prophylaxis. For infants who received palivizumab, drug

utilization will be described using the following variables: age when receiving first palivizumab dose, number of palivizumab administrations, adherence (compliance with the recommended administration schedule). Palivizumab utilization will be stratified by WGA (≤29 and 30-35) according to data availability. In table 3 are reported more details concerning measure of palivizumab prophylaxis.

3.4 VARIABLES COLLECTED AT BASELINE AND EVENTS RECORDED AT FOLLOW-UP

At baseline (at birth), specific infants' characteristics (sex, date of birth, birth weight) and mothers' characteristics (age, education, and occupation) will be retrieved by linkage among administrative health databases. As further sociodemographic information, a sensitivity analysis on mothers' co-payment exemptions will be performed at baseline.

Each study cohort will be followed up for a maximum period of 24 months after birth date and the registration of specific events will be performed. In particular, three different groups of events will be considered:

- Hospitalizations for LRT infections (hospitalizations with a diagnosis of RSV or URA infection): frequency and duration of hospitalizations will be recorded and utilization of specific hospital procedures during hospitalization, such as intensive care unit (ICU), oxygen therapy, mechanical ventilation will be identified (ICD-9 codes used for identification hospitalizations and hospital procedures are described in table 4 of appendix).
- Respiratory events: hospitalizations and ED access with diagnosis of a series of respiratory events, such as bronchiectasis, chronic airway obstruction, acute bronchospasm, dyspnea and respiratory abnormalities (ICD-9 codes used for identification of respiratory events are described in table 5 of the appendix).
- Drug consumption: prescription of drugs from primary and secondary care, will be recorded (ATC codes used to track drug consumption are described in table 5 of appendix).

Investigation of LRT infections hospitalizations will be performed during RSV season (October-April) over a follow-up period of 24 months after birth date for cohort 1 (BPD) and cohort 2 (CHD), while for cohort 3 (preterm infants) the observational time window will be of 12 months after birth date. Observation of respiratory events and drug consumption will pertain a period of 24 months after birth date for both three study cohorts (for this analysis cohort 3 will be restricted to 31 December 2019). The time of onset of each event will be taken into account.

Results will be stratified by palivizumab prophylaxis (palivizumab use defined as presence: at least one palivizumab dispensation during follow-up; and absence: without any palivizumab dispensation

during follow up). A further analysis based on the number of palivizumab doses administered will be performed. In addition, results will be also stratified by WGA (≤29 and 30-35) according to data availability.

3.5 STATISTICAL CONSIDERATIONS

The whole eligible population present in the databases will be included. Since descriptive methods will be applied, no sample size calculation is applicable.

Descriptive analysis will be performed on three different cohorts of high-risk children for RSV severe infection (children with BPD, children born with CHD and children born preterm (≤29 and 30-35 WGA).

All infants will be observed from index date (date of birth will be defined as index date) until the end of follow-up (maximum 24 months after index date), end of study (31/12/2021). Descriptive statistics will be defined by cohort and per year of birth and stratified by palivizumab use and WGA (according to data availability). Categorial variables will be presented as counts and percentages; while continuous variables will be presented as mean and standard deviation or median and interquartile range according to data distribution. Incidence and prevalence of hospitalizations for each RSV season will be calculated. At follow-up, infants who leave the regional healthcare system or die will be excluded from the study.

4. STUDY SPONSORSHIP AND FINANCING

The present study will be managed by Dipartimento di Epidemiologia del S.S.R – ASL Roma 1 – Regione Lazio. This study is promoted by IQVIA Solutions Italy S.r.l.. IQVIA Solutions S.r.l. will only receive aggregated, non-identifiable data, through a final study report.

The present study was designed on the basis of an existing Agreement stipulated between IQVIA and DEP. This agreement establishes collaboration between parties in the design and management of studies focused on research topics that DEP conducts autonomously and independently from IQVIA. DEP, as institution belonging to the Lazio regional healthcare system, conducts epidemiological studies aimed at improving the available scientific knowledge of Key Opinion Leaders and plan interventions to improve the quality and effectiveness of health care resources.

5. ETHICAL CONSIDERATIONS AND DATA PROTECTION

The present study protocol in accordance with national legislation regarding observational study, will be notified to the local ethical committee (Ethical Committee of ASL Roma 1). Data processing and

management will be performed in accordance with the General Data Protection Regulation (GDPR) EU Regulation n. 2016/679 and the D.Lgs. 101/18. The present study has a retrospective observational design and is based on administrative data routinely collected and available in the regional health databases. As such, written informed consents for subjects involved in the study will be not required. Data of health database are anonymized and under the responsibility of appointed regional data managers. Researchers conducting the present study do not have access to data allowing to identify the individual subject. Data linkage is performed using a unique anonymous key.
The analysis planned for the study will be conducted considering an anonymous identifier of the event (hospital code, number of records, admission and discharge date).

6. REFERENCES

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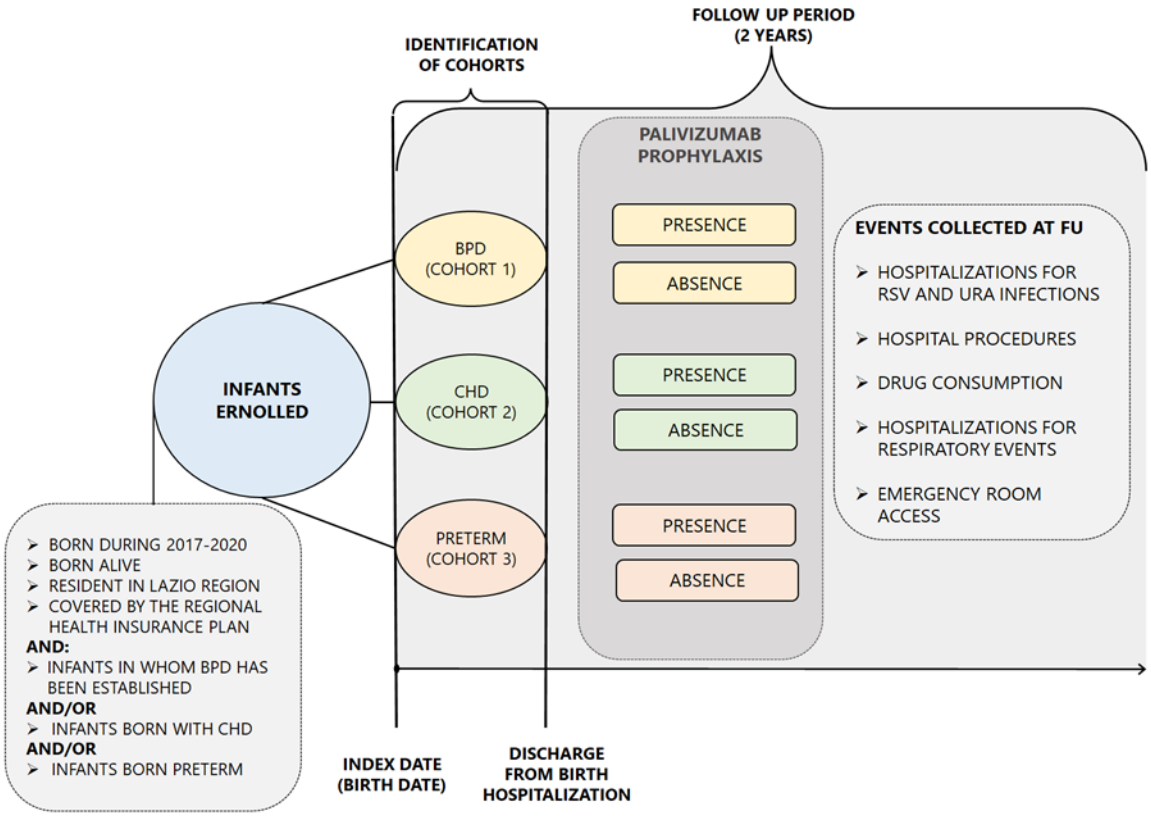
7.APPENDIX

Figure 1. Representation of cohorts according to risk priority and subcohorts



BPD= infants in whom BPD has been established regardless of their WGA and CHD diagnosis;
CHD= infants born with CHD regardless of their WGA;
PRETERM= infants born preterm (≤29 and 30-35 WGA).

PRESENCE= infants eligible for palivizumab prophylaxis who received treatment (at least once during the selected follow up period)
ABSENCE= infants eligible for palivizumab prophylaxis who not received treatment

Table 1. Diagnosis codes used for identification of cohort 1

Description	ICD-9-CM code
Chronic respiratory disease arising in the perinatal period	770.7
Respiratory distress syndrome in newborn	769

Table 2. Diagnosis codes used for identification of cohort 2

Description	ICD-9-CM code
Congenital heart diseases	745*; 746*; 747*

* Includes all diagnostic subcodes.

Table 3. Palivizumab prophylaxis

Drug	Outcome	Code
	Palivizumab	ATC J06BB16
Prophylaxis	Variables	
	Age when receiving first palivizumab dose	
	Number of palivizumab administrations	
	Adherence	

Table 4. Diagnosis codes and procedural codes used for identification of hospitalizations related to LRT infections (RSV and URA infections)

Hospitalizations	Outcome	Code
RSV	Respiratory syncytial virus Infection	ICD-9-CM 079.6
	Pneumonia due to respiratory syncytial virus	ICD-9-CM 480.1
	Bronchiolitis due to respiratory syncytial virus	ICD-9-CM 466.11
URA	Acute bronchitis and bronchiolitis	ICD-9-CM 466[$]
	Bronchitis (unspecified if chronic or acute)	ICD-9-CM 490.1
	Viral pneumonia	ICD-9-CM 480[§]
	Bronchopneumonia, organism unspecified	ICD-9-CM 485
	Pneumonia, organism unspecified	ICD-9-CM 486
Hospital procedures	Non-invasive mechanical ventilation	ICD-9-CM 93.90
	Intermittent positive pressure breathing [IPPB]	ICD-9-CM 93.91
	Other continuous invasive mechanical ventilation	ICD-9-CM 96.7*
	Ventilatory support (mechanical ventilation and/or continuous positive airway pressure [CPAP] ventilators)	ICD-9-CM 96.01 ICD-9-CM 96.05 ICD-9-CM 96.7*

$Includes 466.0, 466.1 and 466.19
[§]Includes 480.8 and 480.9
*Includes all procedures codes

Table 5. Codes for identification of respiratory events and drug consumption

Hospitalizations	Outcome	Code
Respiratory events	Bronchiectasis	ICD-9-CM 494
	Chronic airway obstruction, not elsewhere classified	ICD-9-CM 496
	Acute bronchospasm	ICD-9-CM 519.11
	Dyspnea and respiratory abnormalities	ICD-9-CM 786.0*
Drug consumption	Outcome	Code
	Antibacterials for systemic use	ATC J01
	Adrenergics, inhalants (Beta2-agonists)	ATC R03A
	Selective beta-2-adrenoreceptor agonists	ATC R03AC
	Glucocorticoids	ATC R03BA
	Corticosteroids for systemic use, plain	ATC H02A

*Includes all diagnostic subcodes.