

# Impact of hospitalizations for bronchiolitis in preterm infants on long-term health care costs in Italy: a retrospective case-control study

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**Purpose:** Bronchiolitis is an acute inflammatory injury of the bronchioles, and is the most frequent cause of hospitalization for lower respiratory tract infections in preterm infants. This was a retrospective, observational, case-control study conducted in Italy, based on administrative database analysis. The aim of this study was to evaluate differences in health care costs of preterm infants with and without early hospitalization for bronchiolitis.

**Patients and methods:** Preterm infants born in the period between January 1, 2009 and December 31, 2010 and hospitalized for bronchiolitis in the first year of life were selected from the ARNO Observatory database and observed for the first 4 years of life. These preterm infants were compared (paired 1–3) with preterm infants who were not hospitalized for bronchiolitis in the first year of life and with similar characteristics. Only direct health care costs reimbursed by the Italian National Health Service were considered for this study (drugs, hospitalizations, and diagnostic/therapeutic procedures).

**Results:** Of 40,823 newborns in the accrual period, 863 were preterm with no evidence of prophylaxis, and 22 preterm infants were hospitalized for bronchiolitis (cases) and paired with 62 controls. Overall, cases had 74% higher average cost per infant in the first 4 years of life than controls (18,624€ versus 10,189€, respectively). The major cost drivers were hospitalizations, accounting for >90% in both the populations. The increase in total yearly health care cost between cases and controls remained substantial even in the fourth year of life for all cost items. A relevant increase in hospitalizations and drug consumption linked to respiratory tract diseases was noted in infants hospitalized for bronchiolitis during the entire follow-up period.

**Conclusion:** Preterm infants hospitalized for bronchiolitis in the first year of life were associated with increased resource consumption and costs throughout the entire period of observation; even in the fourth year, the difference versus paired controls was relevant.

**Keywords:** bronchiolitis, cost, preterm, hospitalizations

## Introduction

Bronchiolitis is an acute respiratory illness that affects young children and infants, causing obstruction in the small airways (bronchioles) of the lung, and represents the most frequent cause of hospitalization due to lower respiratory tract infection (LRTI) in preterm infants in the US.<sup>1–4</sup> A hospitalization due to bronchiolitis occurs in ~3% of all infants younger than 1 year in the US and Europe<sup>5</sup> and hospitalizations usually occur during the epidemic season; in Italy, a recent study<sup>6</sup> found a 5.4% rate of hospitalization for bronchiolitis in preterm infants in the first 12 months of life.

Bronchiolitis is a distressing, potentially life-threatening respiratory condition that affects young babies. Its initial symptoms could be similar to those of a common cold,

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but in a few days, they can progress to cough, wheezing, and difficulty in breathing. The vast majority of affected children get better with home care, but a very small percentage of them require hospitalization.<sup>5,7</sup> The most frequent cause of bronchiolitis is a viral infection, mainly represented by respiratory syncytial virus (RSV) which is responsible for ~70% of bronchiolitis during the epidemic season.<sup>8</sup> During childhood, infants with an early episode of severe LRTIs (like bronchiolitis requiring hospitalization) are frequently affected by wheezing, asthma, and allergy.<sup>9,10</sup> These conditions characterize this population even in adulthood, as reported by a study conducted by Sigurs et al<sup>11</sup> in a cohort of 47 subjects with hospitalization for an RSV infection in the first year of life compared with 92 controls followed until 18 years of age; this study reveals a higher frequency of asthma, allergy, and allergic sensitization persisting in early adulthood in the RSV cohort. Hospitalizations for RSV bronchiolitis were the only significant risk factor for the presence of these pathologies in these young adults. Similar findings were reported by Backman et al<sup>12</sup> regarding the increased risk of asthma and use of asthma medication in adults aged 28–31 years who suffered from bronchiolitis or an LRTI caused by RSV with wheezing in early childhood.

The aim of the present study was to evaluate resource consumption and costs reimbursed by the Italian National Health Service (INHS) (drugs, hospitalizations, diagnostic and therapeutic procedures) in the first 4 years of life for the management of preterm infants without prophylaxis for RSV with at least one hospitalization for bronchiolitis in the first year of life; these costs were compared with those associated with the treatment of a cohort of preterm infants with similar characteristics without any hospitalization for bronchiolitis in the first year of life.

## Materials and methods

The present study is a retrospective, observational, noninterventional, case-control study performed from the perspective of the INHS based on the administrative databases from ARNO Observatory (provided by CINECA Interuniversity Consortium).<sup>13</sup> Population-based, health care-related data (from several local health units across Italy) are reported in the ARNO Observatory, an online, multicenter, observational database. For each subject, the data are combined and aggregated through epidemiological methods. Data reported in the ARNO Observatory database include demographic characteristics, drug consumption, hospitalizations, and diagnostic and therapeutic procedures. In the present study, we analyzed data starting from a population of ~2.4 million inhabitants from five local health units, of whom 40,823 were newborns in 2009 and

2010 (58.8% came from northern regions, 28.8% from central regions, and 12.3% from southern regions of the country). For the purpose of the present study, all preterm infants (gestational age  $\leq 36$  weeks) born in the period between January 1, 2009 and December 31, 2010 and hospitalized at least once due to bronchiolitis in the first year of life were selected and observed for the first 4 years of life. In the same selection period, this population (cases) was paired with three preterm infants (controls, extracted from the preterm infant population) who were not hospitalized for bronchiolitis in the first year of life and of the same sex, gestational age, and season of birth.

Prematurity status at birth was defined through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM)<sup>14</sup> codes 765.21–765.28 (<24 completed weeks of gestation to 35–36 completed weeks of gestation).

Hospitalizations for bronchiolitis were identified through the following ICD9-CM codes: 466.1 (acute bronchiolitis), 466.11 (acute bronchiolitis due to RSV), and/or 466.19 (acute bronchiolitis due to other infectious organisms).

Newborns with known RSV prophylaxis with palivizumab in the first year of life were excluded from the present analysis.

As the present study assumed the perspective of the INHS, the following health care resources were evaluated: drugs reimbursed by the INHS (prices reimbursed by INHS), diagnostic and therapeutic procedures (Italian national tariffs), and hospital admissions (Italian national tariffs for the provision of hospital care).

## Statistical analysis

Direct health care costs of the two cohorts were described by mean and standard deviation. Differences between cases and controls in costs per infant per year were assessed by Wilcoxon–Mann–Whitney nonparametric tests. Two-sided *P*-values <0.05 were considered statistically significant.

## Ethics

As the study was retrospective, observational, noninterventional, and data were extracted from the administrative database of Arno Observatory in an anonymous way, the ethical committee's evaluation was not necessary.

## Results

Out of a total analyzed population of 2,400,227 subjects, there were 40,823 newborns in the accrual period; among them, 863 were preterm infants not treated with RSV prophylaxis, and 22 (41% females) were hospitalized for bronchiolitis in the first year of life. Sixty-two paired controls with similar

**Table 1** Direct health care costs in the 4 years of follow-up (per infant)

Health care resources	First year		Second year		Third year		Fourth year	
	Cases (n=22) (mean ± SD)	Controls (n=62) (mean ± SD)	Cases (n=22) (mean ± SD)	Controls (n=62) (mean ± SD)	Cases (n=22) (mean ± SD)	Controls (n=62) (mean ± SD)	Cases (n=22) (mean ± SD)	Controls (n=62) (mean ± SD)
Drugs	€58±64	€72±31	€153±455	€44±69	€50±75	€33±62	€65±360	€26±66
Hospitalizations	€16,410±9,367*	€9,384±5,701	€505±1,076	€186±746	€331±1,313	€96±389	€422±1,922	€0
Therapeutic and diagnostic procedures	€282±328	€238±412	€206±312 <sup>§</sup>	€77±90	€106±176	€52±96	€36±117	€29±55
Total	€16,750±9,410 <sup>#</sup>	€9,645±5,706	€864±1,157	€307±774	€487±1,332	€182±408	€523±2,269	€55±65

Notes: \*P=0.0003 versus controls; <sup>#</sup>P=0.0485 versus controls; <sup>§</sup>P=0.0003 versus controls.

Abbreviation: SD, standard deviation.

characteristics and who were not hospitalized for bronchiolitis were identified. Among infants hospitalized for bronchiolitis, 9.1% had bronchopulmonary dysplasia, and 4.5% had cardiovascular pathologies.

On average, preterm infants hospitalized for bronchiolitis (cases) had 83% higher average cost per infant over 4 years than those not hospitalized for bronchiolitis (controls) (18,624€ versus 10,189€, respectively). As a whole, during the 4 years of follow-up, the major cost driver was hospitalizations, accounting for >90% in both the populations.

Detailed costs per year of life are reported in Table 1.

Cases were associated with higher total costs compared to controls in each year of life in all the considered cost components. Health care costs related to the treatment of cases remained substantially higher than those of controls even in the fourth year of life (523€/infant versus 55€/infant, respectively), although data referring to year three and four should be interpreted considering the limited sample size; the most important drivers of this difference were hospital admissions and drug consumption.

The increased expenditure associated with infants hospitalized for bronchiolitis was consistent over all the weeks of gestational ages and over the entire follow-up of 4 years as detailed in Table 2.

Considering hospitalizations for major diagnostic category 04 (diseases and disorders of the respiratory system), as detailed in Table 3, cases were associated with substantially higher costs (4,455€/infant versus 138€/infant over 4 years, respectively) and percentage of admitted infants versus controls; moreover, although among the controls only 1.6% of patients were hospitalized with a diagnosis belonging to major diagnostic category 04 after the first year of life, among cases, in the same period, 18.2% of infants were hospitalized with this diagnosis.

Over the 4 years of observation, infants hospitalized for bronchiolitis were associated with higher costs for the use of drugs for obstructive airway diseases (+258%), systemic antibiotics (+33%), and systemic corticosteroids (+247%). Major anatomical therapeutic chemical drug classes in terms of per capita expenditure are reported in Table 4.

**Table 2** Direct health care costs in the 4 years of follow-up by gestational age (per infant)

wGA	Four years of follow-up costs per infant	
	Cases (n=22) (mean ± SD)	Controls (n=62) (mean ± SD)
≤28	€23,689±9,757	€16,194±5,434
29–30	€19,340±3,973	€17,088±4,149
31–34	€15,430±6,038	€8,708±4,813
35–36	€18,073±17,567	€7,009±3,739

Abbreviations: wGA, weeks of gestational age; SD, standard deviation.

**Table 3** Costs per infant for hospitalizations due to diseases and disorders of the respiratory system in the 4 years of follow-up

Populations	First year of follow-up		Second to fourth year of follow-up	
	Hospitalization cost per infant (MDC04) (mean ± SD)	Percentage of hospitalized infants	Hospitalization cost per infant (MDC04) (mean ± SD)	Percentage of hospitalized infants
Cases (n=22)	€3,703±12,875	86.4	€752±4,598	18.2
Controls (n=62)	€81±8,924	3.2	€57±2,521	1.6

Abbreviations: MDC, major diagnostic category; SD, standard deviation.

**Table 4** Drug expenditure per infant in the 4 years of follow-up

ATC classes	ATC description	First year		Second year		Third year		Fourth year	
		Cases (n=22)	Controls (n=62)	Cases (n=22)	Controls (n=62)	Cases (n=22)	Controls (n=62)	Cases (n=22)	Controls (n=62)
R03	Drugs for obstructive airway diseases	€31.5	€7.0	€53.3	€23.1	€26.7	€19.4	€41.7	€9.8
J01	Antibacterials for systemic use	€11.8	€8.4	€14.4	€16.5	€20.6	€12.0	€21.2	€14.4
A02	Drugs for acid-related disorders	€6.1	€1.9	€1.6	€1.2	€0	€0.2	€0	€0
B03	Antianemic preparations	€3.9	€2.3	€0	€0.5	€0	€0.3	€0	€0.2
A11	Vitamins	€2.3	€1.8	€0	€0.9	€0	€0.3	€0.3	€0.3
H02	Corticosteroids for systemic use	€1.6	€0.6	€0.8	€0.6	€1.4	€0.4	€0.9	€0.3

Abbreviation: ATC, anatomical therapeutic chemical classification system.

Among diagnostic and therapeutic procedures, outpatient visits were the major cost driver; in the first 4 years of life, cases were associated with an average expenditure for outpatient visits of 311€/infant versus 202€/infant of controls (+54%).

## Discussion

This study highlights that preterm infants hospitalized for bronchiolitis in the first year of life are associated with substantially higher health care resource consumption and related costs than preterm infants not hospitalized for bronchiolitis in the first year of life; these differences are maintained at least over a period of 4 years.

A few studies on the costs and resource consumption of patients with severe bronchiolitis, particularly focused only on the costs of bronchiolitis hospitalization<sup>15–17</sup> or with short observational period,<sup>18–20</sup> are currently available at an international level; for this reason, due to differences in the types of cost items considered, study structure/period of observation, and health care reimbursement setting, a comparison with this analysis could not be deemed suitable.

In recent years, administrative database analyses are considered valuable tools to observe the real-world practice and some relevant clinical/economic consequences in large populations observed for long periods of time, particularly regarding low-incidence clinical events and outcomes. Administrative data sets could be considered

an interesting source of “real-world” health care data on a large population of unselected patients.<sup>21</sup> Moreover, as data reported in the administrative databases are reliable and associated with standardized coding systems (ie, ICD9-CM), they can be used for health care utilization purposes and cost estimation.<sup>22</sup>

A major limitation to the use of administrative databases is that they were created for health care policy purposes<sup>22–24</sup> and could therefore be lacking information that could be valuable for research purposes.

A major limitation of this study is that, as hospitalizations for bronchiolitis are not so frequent, even in preterm infants, the observed population, as expected, is small, although the reference population from which the preterm infants were extracted is wide (>2,400,000 subjects, over 40,000 newborns). In the evaluation of the selection criteria/timing, it should be considered that, in Italy, ICD9-CM 2007 version,<sup>25</sup> which allows the identification of the specific gestational ages, was adopted in the year 2009; for this reason, it was not possible to enlarge the selection period (and consequently the observed populations) maintaining the observational period of 4 years.

It should also be considered that, as data were extracted from administrative databases, there were no specific data regarding the severity of the pathology and on comorbidities, which can allow an estimate of the detailed clinical characteristics of the patients.

The most important strengths of this analysis are linked to the administrative database structure in which data for each patient were systematically collected and recorded, given the possibility to longitudinally observe a specific cohort of subjects for long periods of time. In our case, as far as we know, this is the first Italian study with real-world evidence on bronchiolitis-related costs with a relatively long observational period. Moreover, the presence of a control group of preterm infants with similar characteristics as that of the cases and without bronchiolitis allows the estimation of the differences in resource consumption between the two populations.

This study, despite having several limitations linked to the data source and limited sample size, highlights the economic relevance of early hospitalization for bronchiolitis in preterm infants. The wide increase in the economic cost of these populations compared with preterm infants without severe bronchiolitis is maintained over the entire observational period of 4 years, supporting the possibility that babies with an acute and severe case of bronchiolitis in the first year of life could have long-lasting clinical consequences,<sup>11,12</sup> as also highlighted in literature, and pose a related important economic burden on health care services.

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## Author contributions

DPR, AR, and ER conceived the study, and prepared the protocol and the analysis plan. ER and SC performed the analysis. DPR, AR, ER, and NM critically revised the data. DPR, AR, and ER wrote the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they have no conflict of interest regarding this work.

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