**Title**

**RSV disease burden in Primary Care in Italy: A Multi-Region Pediatric study, winter season 2022-23**

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**Abstract**

**Introduction:**

Human respiratory syncytial virus (RSV) is one of the most frequent causes of respiratory infections in children under five years of age, but its socio-economic impact and burden in primary care settings is still little studied.

**Methods:**

During the 2022/23 winter season, 55 pediatricians from five Italian regions participated in our community-based study. They collected a nasal swab for RSV molecular test from 650 patients under the age of 5 with Acute Respiratory Infections (ARIs) and performed a baseline questionnaire. The clinical and socio-economic burden of RSV disease in primary care was evaluated by two follow-up questionnaires completed by the parents of positive children, on day 14 and 30.

**Results:**

RSV laboratory-confirmed cases were 37.8% of the total recruited ARI cases, with RSV subtype B accounting for the majority (65.4%) of RSV-positive swabs. RSV-positive children were younger than RSV-negative ones (median 12.5 vs 16.5 months). The mean duration of symptoms for all children infected by RSV was 11.47 ± 6.27 days. We did not observe substantial differences in clinical severity between the two RSV subtypes, but RSV-A positive patients required more additional pediatric examinations than RSV-B cases. The socioeconomic impact of RSV infection was considerable, causing 53% of children to be absent from school, 46% of parents to lose working days and 25% of families to incur extra costs.

**Conclusions:**

Our findings describe a baseline of the RSV disease burden in primary care in Italy before the introduction of upcoming immunization strategies.

**Keywords**

RSV, Acute Respiratory Infections, Primary Care, Respiratory Infection Surveillance,

**BACKGROUND**

Respiratory syncytial virus (RSV) is a ubiquitous pathogen that affects individuals of all age groups, with a significant impact on pediatric populations.1 Understanding the epidemiology of RSV is essential in comprehending its burden on public health systems and devising effective preventive measures.2

RSV exhibits a seasonal pattern of circulation, typically characterized by annual epidemics during the colder months in temperate regions. In these areas, RSV infections tend to peak during late autumn through early spring, with a notable increase in cases during the winter months.3  
RSV is further distinguished by its antigenic diversity, primarily classified into two major subtypes: RSV-A and RSV-B. Understanding the significance of these antigenic subtypes is crucial in assessing their role in the disease burden, transmission dynamics, and vaccine development. 4 Both RSV groups usually co-circulate, even if RSV A is reported to be the predominant group during most seasons.  
An alternating trend in terms of prevalence of RSV-A and B in hospital-admitted cases was reported in a study conducted in Italy, in the Lazio region, between 2015 and 2018. 5 Most studies report no difference in clinical severity between children infected with RSV-A and RSV-B.6

The onset of symptoms in an RSV infection typically occurs following an incubation period of 4 to 6 days. The influenza-like symptoms caused by RSV may include shortness of breath, wheezing, cough, a sore throat, coryza, fever, and difficulties with feeding. 2 What is increasingly understood is that the impact of RSV extends beyond the acute phase. In particular, RSV infections that occur within the first year of life, even those not severe enough to warrant hospitalization, are linked to a higher likelihood of experiencing recurrent wheezing and an increased risk of developing asthma later on. 1,7, 8

Among pediatric populations, infants and young children are particularly susceptible to severe RSV infections, in fact this virus is a leading cause of bronchiolitis and pneumonia in children under the age of five, resulting in substantial morbidity and mortality worldwide.9

RSV is known as one of the most common causes of pediatric acute respiratory infections (ARIs), yet the global burden of the disease attributable to this virus is still unknown.10–12 Although the scientific community is globally focusing on the surveillance of RSV transmission and the related hospital admission rate, 13 14 the specific burden of RSV in primary care settings remains inadequately characterized, especially in Italy, making it critical to investigate the associated clinical and socio-economic impact.15

The epidemiology of RSV exhibits geographical and temporal variability. This variability is influenced by factors such as climate, population density, healthcare infrastructure, and the presence of risk factors within specific communities.3 Consequently, the burden of RSV may vary considerably between regions and even within different populations within the same country.16

The RSVComNet project,17 which started in the 2019-2020 season, has provided a platform aimed to assess the clinical and socio-economic burden of RSV, particularly among children under five years of age in primary care settings, across multiple European countries.18  
As suggested by Azzari et al.,2 a strengthening of community-based epidemiological surveillance of RSV infections in the Italian pediatric population was much needed.

Our study, originating from the Italian arm of the RSVComNet multi-country study, seeks to further explore the nature of the RSV disease burden in Italy’s primary care setting and   
to describe the differences in RSV circulation patterns, risk factors, and clinical impact on the pediatric population within five Italian regions, during the 2022-2023 winter season.

**METHODS**

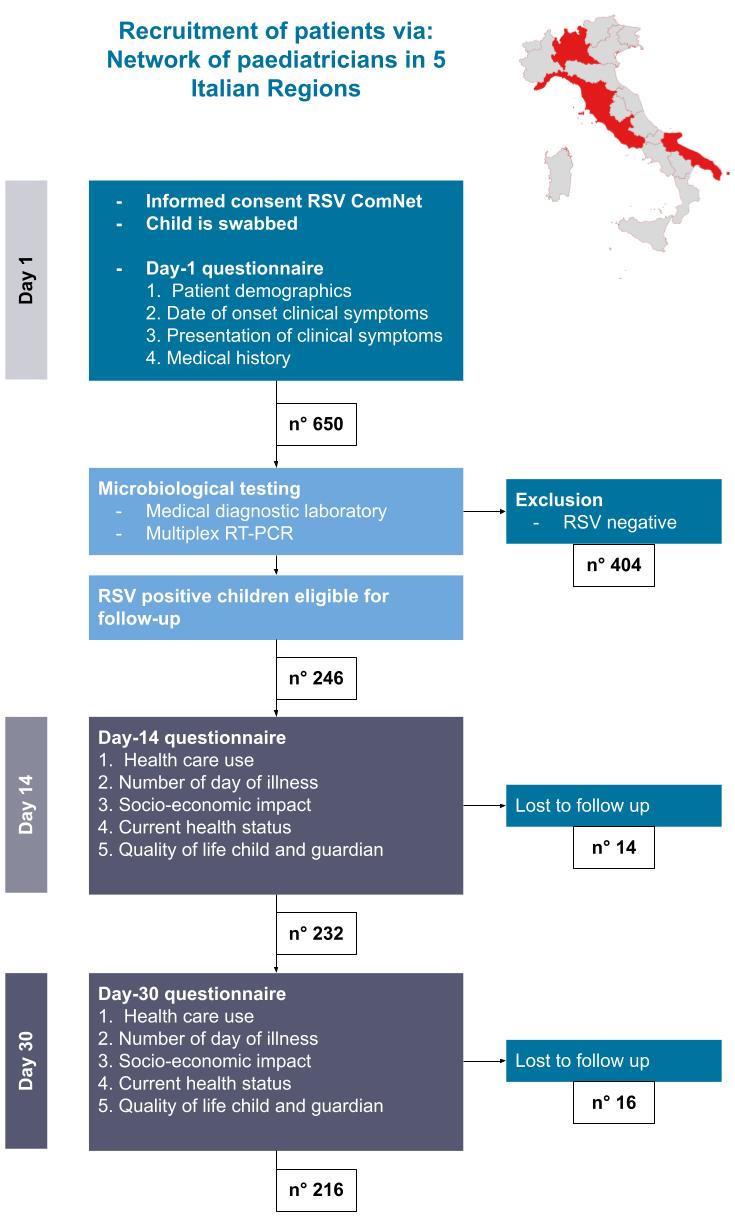
During the 2022-2023 winter season, 55 pediatricians from five Italian regions (Lazio, Liguria, Lombardy, Apulia and Tuscany) participated in the community-based surveillance of the RSVComNet-Italy study. These pediatricians were given specific instructions to carry out nasal swab tests on all patients under the age of 5 who exhibited ARIs between week 44 of 2022 and week 13 of 2023. An ARI case was defined following the WHO-ECDC Case Definition: “sudden onset of symptoms and at least one of the following four respiratory symptoms -cough, sore throat, shortness of breath, coryza- and a clinician’s judgment that the illness is due to an infection”.19

At the time of enrollment (referred to as T0), after obtaining informed consent from the participants, we collected detailed information about the clinical condition of each child and collected a nasopharyngeal swab. This swab was then analyzed to detect RSV genome by using multiplex RT-qPCR, which involved a panel capable of detecting 27 different respiratory viruses and bacteria. We also collected data regarding the child's flu vaccination status at T0.

The overall study design is illustrated in Figure 1 in the form of a flowchart. Subsequently, parents of children who tested positive for RSV were contacted via telephone and were requested to complete two follow-up questionnaires on day 14 and day 30 after diagnosis. These questionnaires gathered information on the clinical and socio-economic impact of the RSV infection (referred to as T14 and T30 questionnaires).

To represent RSV epidemiological trends in the five different regions, an epidemic curve was constructed using the R package EpiCurve. Socio-demographic and clinical differences between children testing positive for RSV and the one testing negative were analyzed using Welch two Sample t-test for continuous variables and chi-square test for categorical variables. Furthermore, we conducted ANOVA and chi-square tests to assess socio-demographic and clinical differences among RSV cases in the five regions.

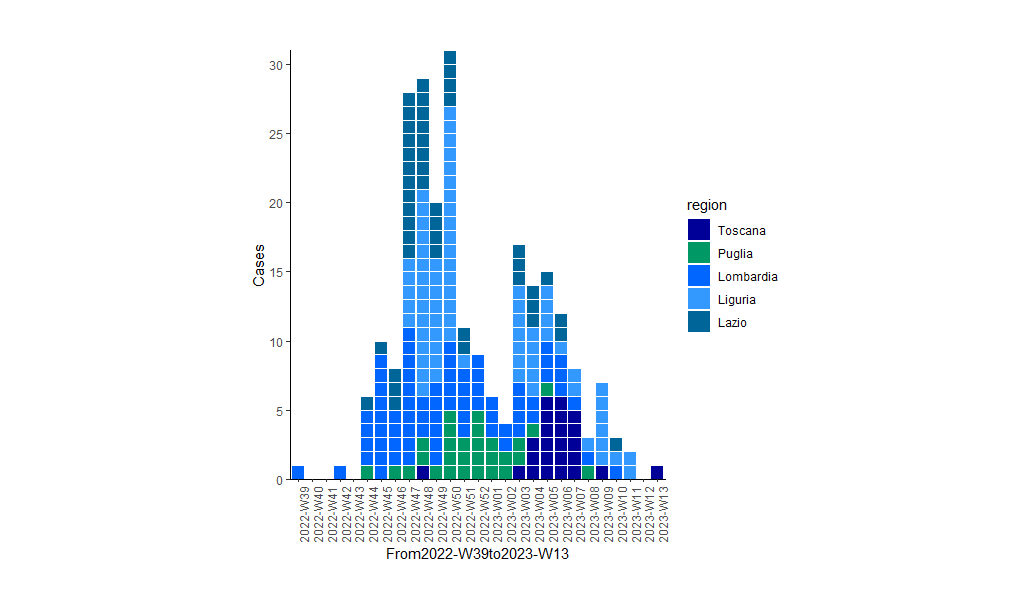
Only statistically significant results with a p-value<0.01 were considered for further investigations. All data analysis was conducted using R software.



***Figure 1.*** *Flowchart: Disease Burden Protocol used in Italy RSV ComNet III. Children are selected via a network of pediatricians.*

**RESULTS**The 55 pediatricians enrolled have an estimated 18.500 assisted population of children under 5 years of age, that corresponds to 2% of the total population < 5 years of age in the five regions. The total Italian population in this age group was around 2,2 million in 2022,20 and 40% of those children lived in the five regions included in our study.

650 (3.5% of the estimated assisted population under 5 years old) children were enrolled in the study, as they met the eligibility criteria for ARI. A total of 246 (37.8%) of the 650 children with ARI were RSV-positive. The peak in the epidemiological trend of RSV cases was reported in week 47-2022, as shown in Figure 2, with cases observed in Lazio, Lombardy, and Liguria.



***Figure 2****. Epidemiological trend of RSV in the winter season 2022-2023 among the five participating Italian Regions*

The demographic and clinical characteristics of the RSV-positive and negative children are described in Table 1.

RSV-positive children are younger than RSV-negative, this difference is statistically significant (Welch Two Sample t-test: t = -4.06, p < 0.00001).

|  |  |  |  |
| --- | --- | --- | --- |
| Patient characteristics | Number of RSV+ children (n = 246) | Number of RSV- (n = 404) | Total  (n = 650) |
| *Age in months\* (median, IQR)*  *(mean, SD)* | 12.5 (6 – 22) | 16.5 (8 – 30.25) | 15 (8 – 28) |
| 16.43 ± 13.53 | 21.32 ± 16.35 | 19.47 ± 15.52 |
| Age groups (n, %) |  |  |  |
| *0-5 months* | 52 (21.1%) | 67 (16.6%) | 119 (18.3%) |
| *6-11 months* | 61 (24.8%) | 71 (17.6%) | 132 (20.3%) |
| *0-11 months\** | 113 (46%) | 138 (34.1%) | 251 (38.6%) |
| *12-23 months* | 74 (30%) | 121 (30%) | 195 (30%) |
| *24-59 months\** | 59 (24%) | 145 (35.9%) | 204 (31.4%) |
| *Birth weight gr. (median, IQR)*  *(mean, SD)* | 3270 (3000 - 3555) | 3210 (2900 - 3506) | 3240 (2950 - 3548) |
| 3251 ± 547 | 3186 ± 547 | 3212 ± 548 |
| *Boys (n, %)* | 125 (50.8%) | 202 (50%) | 327 (50.3%) |
| *Prematurity (n, %)* | 14 (5.7%) | 38 (9.4%) | 66 (10.1%) |
| Presence of chronic condition (n, %) |  |  |  |
| *Respiratory disease* | 9 (3.7%) | 15 (3.7%) | 26 (4%) |
| *Congenital heart disease* | 4 (1.6%) | 1 (0.2%) | 5 (0.8%) |
| *Immunocompromised* | 1 (0.4%) | 1 (0.2%) | 2 (0.3%) |
| *Atopy* | 26 (10.6%) | 37(9.1%) | 63 (9.7%) |
| Vaccination status (n, %) |  |  |  |
| *Influenza vaccination this season (n, %)* | 48 (19.5%) | 97 (24%) | 145 (22.3%) |
| RSV type |  |  |  |
| *RSV A*  *RSV B*  *RSV A + B*  *NA* | 59 (24%)  161 (65.4%)  2 (0.8%)  24 (9.8%) | 0  0  0  0 | 59 (9.1%)  161 (24.7%)  2 (0.3%)  24 (3.7%) |

***Table 1.*** *Demographics, baseline characteristics of RSV+ and RSV- children. Variables with a \* have a statistically significant difference between RSV+ and RSV- groups.*

The antigenic subtype of RSV that caused an infection was more frequently the RSV B (65.4%), with statistically significant differences among the five regions (chi square statistics: X2= 35.24, p-value < 0.00001). The RSV B antigenic subtype was more prevalent than RSV A in every region in our study, except for Lombardy where RSV A and B were almost equally represented, with 56.4% for subtype A and 43.6% for subtype B.  
After performing chi square tests for categorical variables and ANOVA for age and birth weight, no statistically significant differences were observed in the basal characteristics of children infected by RSV among the five regions, except for atopy, which was most frequently observed among children in Apulia and Tuscany (X2= 12.4, p-value < 0,01). A comprehensive description of baseline patients’ characteristics divided per region is provided in Table 2.  
Differences in the rate of flu vaccination were observed comparing RSV-positive (19.5% vaccinated against flu) and RSV-negative children (24% vaccinated against flu), despite not being statistically significant. Similarly, the number of RSV-positive children that were vaccinated against flu varied comparing the five regions, but this result was not significant.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Number of subjects enrolled Lazio: 122 | Number of subjects enrolled Liguria: 203 | Number of subjects enrolled Lombardy: 164 | Number of subjects enrolled Apulia: 65 | Number of subjects enrolled Tuscany: 96 |
| Patient characteristics | **Number of RSV+ Lazio: 70**  **(57,3%)** | **Number of RSV+ Liguria:59**  **(29,1%)** | **Number of RSV+ Lombardy:55**  **(33,5%)** | **Number of RSV+ Apulia:38**  **(58%)** | **Number of RSV+ Tuscany: 24**  **(25%)** |
| *Age in months (median, IQR)*  *(mean, SD)* | 12 (6.25– 21.75) | 13 (8 – 29) | 14 (7.5 – 21) | 12 (5 – 23.5) | 9,5 (5.75 – 17.25) |
| 16.57 ± 13.64 | 18.74± 15.41 | 18.02 ± 11.92 | 16.24 ± 14.68 | 12 ± 8.95 |
| Age groups (n, %) |  |  |  |  |  |
| *0-5 months* | 16 (23.2%) | 9 (15.3%) | 8 (15.1 %) | 13 (34.2%) | 6 (25%) |
| *6-11 months* | 17 (23.2%) | 16 (27.1%) | 14 (26.4 %) | 6 (15.8%) | 8 (33.3%) |
| *0-11 months* | 33 (46.3%) | 25 (42.4%) | 22 (41.5%) | 19 (50%) | 14 (58.3%) |
| *12-23 months* | 21 (30.4%) | 16 (27.1%) | 22 (39.6 %) | 9 (23.7%) | 6 (25%) |
| *24-59 months* | 16 (23.2%) | 18 (30.5%) | 11 (18.9%) | 10 (26.3%) | 4 (16.7%) |
| *Birth weight (median, IQR)*  *(mean, SD)* | 3260 (3000 - 3447.5) | 3230(2900 - 3570) | 3385 (3045 - 3562.5) | 3262,5 (2925 - 3550) | 3448 (3007.5 - 3600) |
| 3266 ± 437 | 3127 ± 890 | 3354 ± 628 | 3242 ± 571 | 3295 ± 603 |
| *Boys (n, %)* | 39 (55.7%) | 27 (45.7%) | 27 (49.1%) | 18 (47.4%) | 14 (58.3%) |
| *Prematurity (n,%)* | 3 (4.3%) | 7 (11.9%) | 0 | 2 (5.3%) | 2 (8.3%) |
| Presence of chronic condition (n,%) |  |  |  |  |  |
| *Respiratory disease* | 6 (8.6%) | 2 (3.4%) | 0 | 1 (2.6%) | 0 |
| *Congenital heart disease* | 1(1.4%) | 3 (5%) | 0 | 0 | 0 |
| *Immunocompromised* | 0 | 1 (1.7%) | 0 | 0 | 0 |
| *Atopy\** | 6 (8.6%) | 4 (6.8%) | 0 | 11 (28.9%) | 5 (20.8%) |
| Vaccination status (n, %) |  |  |  |  |  |
| *Influenza vaccination this season (n, %)* | 16 (22.8%) | 17 (28.8 %) | 5 (9.1%) | 8 (21.1%) | 2 (8.3%) |
| RSV type |  |  |  |  |  |
| *RSV A\**  *RSV B\**  *RSV A + B*  *NA* | 9 (12.8%)  37 (52.9%)  0  22 (34.3%) | 8 (13.5%)  49 (83.1%)  2 (3.4%)  0 | 31 (56.4%)  24 (43.6%)  0  0 | 4 (10.5%)  34 (89.5%)  0  0 | 7 (29.2%)  17 (70.8%)  0  0 |

***Table 2.*** *Demographics and baseline characteristics of RSV+ children in five Italian regions. Variables with a \* have a statistically significant difference among regions.*

On Day 14, 115/232 children (49.6%) were still symptomatic, while on Day 30, 37/216 children (17.1%) had still persistent symptoms. The frequency of the various symptoms reported at different times is specified in Table 3.

The mean duration of symptoms for all children infected by RSV was 11.47 ± 6.27 days.

|  |  |  |  |
| --- | --- | --- | --- |
| *Clinical symptoms (n,%)* | Baseline  N=246 | Day-14  N=232 | Day-30  N=216 |
| *Shortness of breath* | 131 (53.2%) | 5 (2.1%) | 1 (0.4%) |
| *Wheezing* | 110 (44.7%) | 4 (1.7%) | 2 (0.9%) |
| *Cough with slime* | 142 (57.7%) | 39 (16.8%) | 9 (4.2%) |
| *Cough without slime* | 126 (51.2%) | 38 (16.4%) | 18 (8.3%) |
| *Sore throat* | 32 (13.0%) | 5 (2.1%) | 0 |
| *Coryza* | 200 (81.3%) | 56 (24.1%) | 18 (8.3%) |
| *Fever ≥ 38 °C* | 146 (59.3%) | 7 (3.0%) | 1 (0.5%) |
| *Feeding difficulties* | 90 (36.6%) | 14 (6.0%) | 2 (0.9%) |

***Table 3****. Clinical symptoms reported at baseline, T14 and T30.*

In the overall period between the day of diagnosis and day 30, 125/232 (53.8%) RSV positive children needed further pediatric medical examinations, with a mean number of 2.53 ± 2.84 examinations; 102 children (43.9%) needed extra phone/email pediatric consultations, with a mean number of 2.82 ± 2.76 consultations.

In the same period, 20/232 children (8.6%) needed to consult a different medical specialist, such as a pneumologist, a cardiologist, a dermatologist, a general practitioner, or a private pediatrician; 29/232 children (12.5%) had an Emergency Department access, with 7 of them (3%) hospitalized, for an average length of stay of 4.7± 2.2 days. One of them (0.4%) was admitted to the ICU.

A total of 123/232 children (53%) had an absence from day-care/school, for an average duration of 13.02 ± 7.58 days.

Moreover, 46.1% (107/232) of parents had to ask for days off because of their children’s illness, for a mean duration of 7.92 ± 5.25 days.

Extra costs were reported by 59/232 (25.4%) parents, which included babysitting costs in 9/59 cases (15.3%), purchase of medicines in 52/59 (88.1%), or purchase of medical devices in 4/59 (6.8%).  
  
In our study, we did not observe substantial differences in clinical severity between different RSV subtypes. However, it is worth noting a statistically significant result regarding the proportion of RSV-A patients requiring additional pediatric examination at T30. Specifically, 29% of RSV-A patients (11 out of 38) required further evaluation, whereas only 11% of RSV-B patients (16 out of 142) needed such examination. The statistical analysis using chi-square statistics yielded a value of X2= 7.35, with a p-value less than 0.01, indicating the significance of this difference. (Table 4)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Follow-up | RSV A  T14 n =53  T30 n= 38 | RSV B  T14 n =157  T30 n= 142 |
| Persistence of symptoms | T14 | 28 | 71 |
| T30 | 7 | 26 |
| Further pediatric examination\* | T14 | 36 | 109 |
| **T30\*** | **11** | **16** |
| Emergency Department access | T14 | 7 | 16 |
| T30 | 3 | 2 |
| Hospitalization | T14 | 2 | 2 |
| T30 | 2 | 0 |
| Complications | T30 | 4 | 9 |

***Table 4****. Severity outcomes at T14 and T30 for RSV A and RSV B subgroups. patients with missing subtype characterization and with positivity for both A and B subtypes were excluded. Variables with a \* have a statistically significant difference.*

RSV-positive children received drug treatment in 89.6% of cases (208/231). The most used drugs were bronchodilator inhalers (116/232, 50%), followed by corticosteroid inhalers (69/232, 29.7%), paracetamol (61/232, 26.3%) and antibiotics (54/232, 23.3%). Antibiotic consumption was reported to be different in the five regions (X2= 20.77, p-value <0.01). Liguria was the region that reported the highest antibiotic prescription rate among RSV positive children (22/56, 39.3%) followed by Tuscany (9/23, 39.1%), Apulia (11/38, 28,9%) Lazio (8/67, 11.9%) and Lombardy (4/47, 8.5%). There were no significant differences in the utilization of bronchodilator and corticosteroid inhalers across the five regions. Conversely, the utilization of paracetamol displayed significant variability (X2= 18.90, p-value < 0.001). Specifically, Tuscany had the lowest paracetamol usage, with only 4.3% (1/23) of cases receiving it. In contrast, Lombardy reported the highest paracetamol consumption, with 46.8% (22/47) of cases using this medication. Lazio followed closely with 29.9% (20/67) of cases using paracetamol, while Liguria reported 17.9% (10/56) usage. Apulia fell in between, with 21.1% (8/38) of cases receiving paracetamol.

Other therapies were also employed but were less often recommended, such as cortisone tablets (46/232, 19.8%), non-steroidal anti-inflammatory medications (20/232, 8.6%), nasal sprays (12/232, 5.2%), and cough syrups (2/232, 0.9%).

**Discussion**

The public health measures adopted against COVID-19 pandemic significantly influenced the epidemiology of RSV, 21,22,23  
This has been described in 2021, when Italy suffered a seasonal shift of RSV epidemic, with a beginning in August and a delayed peak in November.24

Therefore, the mitigation of restrictive measures in Italy during winter season 2022-2023 has been crucial to observe the characteristic of the RSV re-emergence, its transmission and seasonal trend. The epidemiological changes of RSV highlight the importance of seasonal surveillance and greater knowledge of the RSV burden in the community. This would allow the health-care services to face the challenge of an appropriate preparation that meets the demands of RSV infections.

Our findings show that the RSV season started in October (week 42-2022) and lasts 21 weeks in total, with a peak starting in late November between week 47 and 50 of 2022, that encloses almost 50% of RSV positive cases of the whole season. With little variation, the peak of cases occurs in this time frame in all regions (Lombardy and Lazio first, then Liguria, and lastly Apulia); due to logistical issues, the recruitment of patients was delayed in Tuscany, and as a result, the region's peak was postponed until week 5 of 2023.

Nevertheless, the results we obtained support the evidence of a change in the seasonal epidemic pattern that characterized the pre-Covid era in favor of an early peak in November. This data is in line with recent literature from Italy as well as from other European countries.25,26

The causes of the seasonal patterns and the changes in viral circulation throughout time are still unknown. Several theories have been postulated, contemplating the interaction and connection between multiple factors including seasonal variations in virus survival and transmissibility, physiology of the host and the social behavior that fluctuates with the seasons and, in particular, after the epidemic.27

Although seasonal and local variations in the preponderance of RSV subtypes A and B have been recorded, literature provides evidence about the seasonal co-circulation of both subtypes and about the usual predominance of one subgroup in each season. The pattern of predominance is yet unknown, although it is clear that RSV A and B alternately predominate, with a higher percentage of RSV B over RSV A infections over the past ten years. 4

Differences in the prevalence of RSV antigenic subtypes among regions confirm a different epidemiology of RSV in different areas of Italy, which is not associated with baseline patient demographic and clinical characteristics. Our study found that subtype B was predominant in Italy during the 2022-2023 season, being observed in 65.4% of positive cases, while subtype A was observed in 24% of cases. All the participating regions showed comparable proportions of both subtypes, with subtype B clearly dominating in all of them except for the Lombardy region, where there was roughly equal distribution of both subtypes. This is in line with other studies performed in the same season in other European countries, whereas the previous season showed the predominance of RSV-A subtype.28

Literature results are contradictory regarding the severity of the disease caused by the two subtypes of RSV. Due to the co-circulation of multiple different strains throughout any given RSV season, some studies might not achieve the statistical power to identify significant differences in illness severity.29 Our results showed a significant difference between subtypes in the clinical course of disease, with almost 30% of RSV-A patients requiring further medical evaluation during the 30 days after the diagnosis, against about the 10% of RSV-B patients who needed it. Literature reports that, in general, RSV-A viruses are detected more frequently among patients with ARIs compared to RSV-B viruses,30 regardless of age, prematurity, and other risk factors. In contrast, fewer researches have showed that subtype B infections were more severe than subtype A infections, and some studies were utterly unable to find any relevant correlation between subtype and disease severity. These contradictions of findings emphasize the need of a surveillance of the molecular evolution of RSV, as well as its temporal and geographic differences.31

Comparing the RSV ComNet data with the ones provided by Influnet, the national influenza like illness (ILI) surveillance system,32 it appears that the RSV ComNet study detected a comparable proportion of RSV infections, both in children under 2 years of age (41,9% for RSVComNet and 49,1% for Influnet) and in children between 2 and 4 years of age (32.9% for RSV ComNet and 22,3% for Influnet). The difference in RSV detection rate could be explained by the different case definition used by these two surveillance systems (ARI vs ILI).

Our study examined the presence of various socio-demographic risk factors within the enrolled patients, in particular those that are quite consistently reported in literature such as age, prematurity, preexisting health conditions (chronic lung disease, congenital heart disease and atopy), to explore the strength of an association with ARI diagnosis and RSV positivity.

Our data confirmed that younger children are those most at risk of infection by RSV. In fact, the age of RSV-positive children was lower than that of negative children (median age 12.5 vs 16.5 months)33

Unlike previous studies, 9,12 which focused mainly on the RSV associated morbidity, mortality and hospitalization burden. Our study represents a unique source of data for the evaluation of the RSV burden in primary care settings, after the pandemic. The questionnaires’ results showed that 71.4% of RSV-positive children needed further medical consultation by the pediatrician, either in person or via phone/email, and 20.8% consulted another medical specialist and/or had access to the Emergency Department, describing a significant impact on the primary care system.

Interestingly, our results highlighted a common issue regarding inappropriate antibiotic prescription, with almost a quarter of RSV positive children who have received antibiotic treatment. Our data confirms what has already been published in other studies regarding the wide over-prescription of antibiotics for respiratory disease in primary care,34 with about one-third of all antibiotic prescriptions for ARIs in children being inappropriate.35

The prescription of antibiotics was particularly high in the Tuscany and Liguria regions, with almost 40% RSV-positive children receiving at least one antibiotic at T14, while in Lazio and Lombardy approximately 10% of children reported antibiotic utilization. It’s worth noticing that the regions in which less antibiotics were consumed (Lombardy and Lazio) are the same that reported a higher utilization of paracetamol, respectively 46.8% and 29.9%.

This significant regional variation in antibiotic prescription merits further investigation to verify the appropriateness of prescription and to assess the antibiotic prescription policies existing in the various regions.

It is widely recognized that RSV infections place a significant burden on affected families.36 Through the questionnaires, our study also explored the socio-economic impact of RSV infection in families, with nearly a half of parents that reported the need for days off at work, with an average duration of about 8 days, and with one in 4 parents reporting extra costs. It is therefore fundamental to raise the level of RSV awareness regarding the disease, symptoms, treatment, and prevention strategies, among both healthcare professionals and parents.

Our study presents some limitations. One of these limitations is related to the community-based surveillance method we used, which may have led to an underestimation of the number of severe RSV cases, as patients with more serious infections might bypass visiting a pediatrician and necessitate direct hospitalization. In addition, the enrollment of children might have been affected by a selection bias, because pediatricians may have more likely enrolled patients who they believed had a higher chance of being RSV-cases.  
Our sample size was quite small, considering that the 5 regions participating in the study have a pediatric population aged less than 5 years that represents 40% of the Italian population in this age group. However, as previously reported, we only included the patients of 55 pediatricians willing to participate, thus limiting the number of possible ARI-cases.

Moreover, the Tuscany regional center began data collection in late January, beyond the peak of the epidemic season. This may represent an issue in comparing trends between Tuscany and the other four regions.

**Conclusions**

The characterization of RSV disease burden in primary care settings is essential to design vaccination campaigns to maximize the positive impact on pediatric health. (e.g. cost-effectiveness studies) It is also crucial for effective risk communication to healthcare professionals and parents, thus addressing vaccine hesitancy. The insights provided from this study could guide the development of future preventive strategies, underlining the need for further research and surveillance, especially in light of the new passive immunization strategies (monoclonal antibodies) and vaccines, that can be used to protect small children. 37–39

**Authors’ contributions**

MS, SB, EE, LDA and FB conceived the paper. MS, SB, EE, LDA and FB performed the literature search and drafted the manuscript.

LDA, FB, IC performed the data extraction and analysis. CR and BC provided expert insights and contributed manuscript revision. DP, MO, DL, MC, EP, LP, EP, EP and RSV ComNet Italy Study Group collected the data reported in the present manuscript, critically reviewed the drafts, and provided specific feedback. All the authors approved the final manuscript.

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**Conflict of Interest Statement**

LDA received travel reimbursement from Moderna. FB received an educational grant from AstraZeneca and travel reimbursement from Moderna. CR participated in Advisory Board and Expert scientific discussion for Seqirus, MSD, GlaxoSmithKline (GSK), Sanofi and AstraZeneca. The other authors have no conflict to disclose.

**Ethics**

The study was approved by the Ethical Committee “Comitato Etico di Area Vasta Nord Ovest (CEAVNO) per la Sperimentazione clinica” of the Tuscany Region, Italy (prot. 22871\_Dini on the 25/10/2022).

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