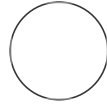




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# Burden of RSV in Italian adults: Protocol for a systematic review and meta-analysis

Giovanna Elisa

Alexander Domnich<sup>1</sup>, Calabrò<sup>2</sup><sup>1</sup>IRCCS Ospedale Policlinico San Martino;<sup>2</sup>Section of Hygiene, Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome, Italy

Alexander Domnich

IRCCS Ospedale Policlinico San Martino

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## ABSTRACT

Globally, respiratory syncytial virus (RSV) is a leading cause of respiratory infections and is responsible for a significant socioeconomic burden in all age groups, including adults. To date, no review systematically appraised the burden of RSV in Italian adults. Understanding country-specific burden of disease is a key driver for policy decisions on the introduction of new vaccines. In fact, two vaccines have been recently authorized to prevent lower respiratory tract disease caused by RSV in adults. In this protocol for a systematic review, we aim to collect and analyze data on the clinical burden of RSV in Italian adults with the goal of informing and supporting National and local decision makers on the planification and implementation of future vaccination strategies.

## ATTACHMENTS

[Prot\\_SRMA\\_RSV\\_Ita\\_v13112013.pdf](#)

## Introduction

### 1

Together with seasonal influenza, respiratory syncytial virus (RSV) is a leading cause of respiratory infections and is responsible for a significant socioeconomic burden in all age groups, especially at the extremes of age [McLaughlin, 2022; Rafferty, 2022]. Indeed, a recent modelling study [Osei-Yeboah, 2023] has estimated that on average, a total of 158,229 RSV-associated hospitalizations among European adults occur annually and 92% of these concern older adults aged  $\geq 65$  years. Contrary to young children, in the last 20 years mortality attributable to RSV increased in both working-age and older adults [Du, 2023].

Several systematic reviews [Shi, 2020; Tin Tin Htar, 2020; Nguyen-Van-Tam, 2022; Shi, 2022; Maggi, 2022; Li, 2023] have investigated global epidemiology and burden of RSV in (older) adults. These reviews have confirmed significant RSV attack rates, hospitalization, mortality and case-fatality rates [Shi, 2020; Tin Tin Htar, 2020; Nguyen-Van-Tam, 2022; Shi, 2022; Maggi, 2022; Li, 2023], which seem similar to seasonal influenza [Maggi, 2022], and noted a substantial case under-ascertainment [Li, 2023]. Moreover, there was a large between-country variation in burden estimates [Tin Tin Htar, 2020], which is driven by numerous factors, from climatic conditions [Haynes, 2013] to case definitions and efficiency of the surveillance system in place [Staadegaard, 2021]. Notably, the available systematic reviews [Shi, 2020; Tin Tin Htar, 2020; Nguyen-Van-Tam, 2022; Shi, 2022; Maggi, 2022; Li, 2023] have identified only up to six primary studies conducted in Italy.

Two vaccines have been recently authorized to prevent lower respiratory tract disease (LRTD) caused by RSV in adults aged  $\geq 60$  years [Kotton, 2023]. This age indication will be likely extended to younger adults in the upcoming years. In the United States (US), a single dose of RSV vaccine is recommended to adults  $\geq 60$  years, as a part of shared clinical decision-making between patient and healthcare provider [CDC, 2023]. In the United Kingdom (UK), RSV vaccination is recommended for older adults aged  $\geq 75$  years, being the most cost-effective option [United Kingdom Department of Health & Social Care, 2023]. By contrast, as of November 2023, no recommendations have been issued in Italy.

Understanding country-specific burden of disease (BoD) is a key driver for policy decisions on the introduction of new vaccines [Levine, 1997]. A systematic appraisal of the burden of RSV enables policy makers, health professionals and other relevant stakeholders to make informed decisions regarding the recently available vaccines. In this regard, systematic reviews on the frequency of different BoD indicators are important in the description of the spatiotemporal distribution and the variation between population subgroups potentially targeted by the novel preventive measures [Munn 2018; Barker, 2021]. Country-specific BoD indicators are also essential for all types of pharmacoeconomic models.

In Italy, a recent systematic review [Boccalini, 2023] has assessed RSV BoD in pediatric outpatients. By including six studies, the authors found that 18–41% of children with respiratory infections were positive for RSV. Conversely, no review systematically appraised the burden of RSV in Italian adults. Indeed, RSV epidemiology is highly age-dependent, which hinders transferability of pediatric estimates to other target population groups. Furthermore, as we mentioned earlier, the available global reviews on (older) adults [Shi, 2020; Tin Tin Htar, 2020; Nguyen-Van-Tam, 2022; Shi, 2022; Maggi, 2022; Li, 2023] were able to identify only a limited number of Italian studies. In this systematic review, we aim to comprehensively collect and analyze available data on the BoD of RSV in Italian adults in both primary care and hospital settings with the ultimate goal of informing and supporting National and local decision makers on the planification and implementation of vaccination strategies.

## 2

### **Methods**

### **Reporting standards**

PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement [Page, 2021] will be adopted as a reporting standard. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data developed by the Joanna Briggs Institute (JBI) [Zachary, 2015] will be also consulted.

## **Eligibility criteria**

All types of observational studies (e.g., surveillance, cross-sectional, cohort, case-series) and published in any modality (i.e., peer-reviewed article, preprint, conference abstract, official report and other forms of grey literature) will be eligible. The CoCoPop (condition, context, and population) approach [Munn, 2015] will be used to formulate the inclusion criteria. In particular, the condition of interest will be RSV infection detected by any laboratory technique, including reverse-transcription polymerase chain reaction (RT-PCR), cell culture, immunofluorescence assay (IFA) and rapid antigen detection test (RADT). Moreover, RSV-specific International Statistical Classification of Diseases and Related Health Problems (ICD) diagnosis codes will be also considered a good proxy for the true RSV infection. Indeed, specificity of the RSV-specific codes is 99.6–99.8% [Pisesky, 2016; Cai, 2020].

For the context, we will consider studies conducted in Italy, in any setting (outpatient, inpatient or mixed) and calendar period. For this latter, it is important to distinguish between year-around studies and those conducted during a typical RSV season, in which the probability of RSV detection is much higher [Rozenbaum, 2023]. We will define RSV epidemic season as a period between October and April [Hamid, 2023].

Population will consist of adults defined as individuals aged  $\geq 14/18$  years. When possible, we will consider estimates for different age subgroups (e.g., working-age and older

adults) reported by single studies. Any clinical entity [e.g., influenza-like illness (ILI), acute respiratory infection (ARI), severe ARI (SARI)] that triggers swab collection will be eligible.

The following will be the exclusion criteria: (i) modeling, pharmaco-economic and similar studies with no original data; (ii) records with insufficient data on RSV; (iii) studies on general population with no separate data for adults; (iii) multi-country studies with no separate information for Italy; (iv) redundant publications.

## **Study endpoints**

RSV attack rate (cumulative incidence) will be defined as the occurrence of laboratory-confirmed RSV detections in a population (symptomatic/medically attended, asymptomatic or both) in a specific period (e.g., RSV season). RSV prevalence (overall, by subtype and genotype) will be defined as proportion of RSV detections to the total number of subjects tested. Prevalence of co-detections will be described as number of samples tested positive for both RSV and any other respiratory pathogen to the total number of samples tested positive for RSV. Case complication rate will be defined as proportion of subjects tested positive for RSV and who developed at least one complication, such as pneumonia, exacerbation of chronic obstructive pulmonary disease, asthma, or congestive heart failure. As for drug use indicators, we will consider frequency of drug prescriptions among subjects who was diagnosed with RSV. For what concerns inpatient outcomes, crude hospitalization (per 100,000), case hospitalization (i.e., proportion of RSV-positive individuals who were hospitalized) rates, length of stay, frequency of admission to intensive care units will be of interest. Analogously, crude, in-hospital, 30-day mortality and case-fatality rates will be eligible. For these indicators, we will consider only RSV-specific codes for RSV pneumonia (ICD-9-CM: 480.1; ICD-10-CM: J12.1), acute bronchiolitis due to RSV (ICD-9-CM: 466.11; ICD-10-CM: J21.0), acute bronchitis due to RSV (ICD-10-CM: J20.5), and RSV as the cause of diseases classified elsewhere (ICD-9-CM: 079.6; ICD-10-CM: B97.4).

When possible, all study endpoints will be described overall, by age group (working-age and older adults) and RSV season. Additional not prespecified endpoints will be also eligible for exploratory purposes.

## **Search strategy**

The automatic search will be performed in the following: PubMed/Medline, Biological Abstracts, Global Health through Ovid and Scopus. In order to increase sensitivity, the number of selection criteria will be minimized to the condition and population of interest and no filters or other restrictions (e.g., language or publication year) will be applied. The search following script, which will be adapted to each citation database, will be used: ("Respiratory Syncytial Viruses"[MeSH Terms] OR "Respiratory Syncytial Virus, Human"[MeSH Terms] OR "Respiratory Syncytial Virus Infections" [MeSH Terms] OR "respiratory syncytial" OR "RSV") AND ("Adult" [MeSH Terms] OR "Aging"[MeSH Terms] OR "Men"[MeSH Terms] OR "Women"[MeSH Terms] OR "Retirement"[MeSH Terms] OR "Long-term care"[MeSH Terms] OR "Nursing care"[MeSH Terms] OR "Palliative care"[MeSH Terms] OR pension\* OR retire\* OR adult\* OR aged OR elderly OR senior\* OR geriatric\* OR nursing home\*) AND ("Italy"[MeSH Terms] OR Italy OR Italian\*).

We will then perform a manual search through several two modalities. First, the reference lists of the available systematic reviews will be checked. Second, a backward cross-reference checking of the included studies will be carried out. Third, a forward citation search by using Google Scholar (<https://scholar.google.com/>) will be performed, as this search engine is better suited for identifying grey literature sources [Haddaway, 2015]. Fourth, periodic reports of the Italian surveillance reports on influenza and other respiratory viruses (<https://respivirnet.iss.it>) will be examined. Finally, we will screen abstract books and proceedings of some relevant conferences, including ECCMID (European Society of Clinical Microbiology and Infectious Diseases), ESWI (European Scientific Working Group on Influenza) and ReSViNET.

## **Study selection**

Results of the automatic search will be merged into a single spreadsheet and duplicates will be removed in a semi-automatic modality. The resulting list of unique records will undergo the process of screening by assessing titles and/or abstracts and clearly irrelevant citations will be discarded. Full texts of potentially pertinent publications records will be then downloaded and assessed for the eligibility criteria described earlier. Selection will be finalized by performing the manual search, as described above. The entire process of study selection will be performed by two reviewers, each working independently, and eventual disagreements will be solved by consensus.

## **Data extraction and coding**

The following data will be extracted into a spreadsheet: (i) full citation record; (ii) location (region); (iii) period; (iv) design; (v) setting; (vi) population; (vii) sample size; (viii) funding source; (ix) definition of the clinical entity that triggered swab collection; (x) methods used for RSV case ascertainment; (xi) numerators and denominators used to compute the endpoints of interest described above. On the basis of period, studies will be dichotomized on whether they overlapped with the COVID-19 pandemic, which had a significant impact on circulation of RSV and many other respiratory viruses. In particular, the northern hemisphere winter season 2020/21 was characterized by the absence of very limited circulation of

RSV [Hamid, 2023; Boccalini, 2023; Gomez, 2021]. Estimates for that season will be extracted and reported, but not included in the quantitative synthesis. Starting from the 2021/22 season, RSV returned to the epidemiological scene [Hamid, 2023] and therefore estimates from 2021/22 will be fully considered. Multi-season studies that reported separate seasonal estimates will be considered as distinct estimates [Bergeri, 2022]. On the basis of sample size, studies will be median split. Regions will be categorized into three macro-areas of North (Aosta Valley, Liguria, Lombardy, Piedmont, Emilia-Romagna, Friuli-Venezia Giulia, Trentino-South Tyrol, and Veneto), Center (Lazio, Marche, Tuscany, and Umbria), and South (Abruzzo, Apulia, Basilicata, Calabria, Campania, Molise, Sicily, and Sardinia).

Missing data on relevant numerators and/or denominators will be handled as follows. First, the corresponding author will be contacted by email for clarification. In case of no reply, these data will be imputed from the available percentages and/or by extracting data from figures using WebPlotDigitizer v.4.6 (<https://automeris.io/WebPlotDigitizer>). Data will be extracted by AD and then validated by GEC.

## **Critical appraisal**

The JBI checklist for prevalence/incidence studies [Zachary, 2015] will be used to assess quality of the included studies. Critical appraisal will be performed independently by two reviewers and eventual conflicts will be solved by consensus.

## **Data synthesis**



Tabulated data will be first appraised qualitatively and by visualizing forest plots. For quantitative synthesis, a proportional meta-analysis will be undertaken according to the available recommendations [Zachary, 2015; Barker, 2021]. As heterogeneity is expected to be high, random-effects models with double arcsine transformation to stabilize variances will be used. Pooled estimates will be expressed as proportions with both 95% Clopper-Pearson exact confidence intervals (CIs) and 95% prediction intervals (PIs).

Heterogeneity will be quantified by means of the  $I^2$  statistic. Notably, high  $I^2$  values do not necessarily mean

that data are inconsistent since true heterogeneity is expected in prevalence estimates due to spatiotemporal differences [Barker, 2021]. As recommended, publication bias will be not formally assessed (i.e., by funnel plots or statistical tests), since there is no consensus about what a positive result in a meta-analysis of proportions is [Barker, 2021].

To investigate the sources of heterogeneity across studies, both subgroup and meta-regression analyses will be performed. In particular, the subgroup analysis will be performed by age group (working-age and older adults), setting (outpatient, inpatient and mixed) and study period in relation to the COVID-19 pandemic (before and after the 2020/21 season). The meta-regression modeling will be then conducted to examine the influence of study characteristics on the RSV-related endpoints. This latter will be performed only when at least 10 estimates are available [The Cochrane Collaboration, 2011].

Meta-analysis will be performed in R (R Foundation for Statistical Computing; Vienna, Austria) package "Meta" v. 6.5-0.