vaccines

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Review

Rate of Hospitalizations and Mortality of Respiratory Syncytial Virus Infection compared to Influenza in Older People: a Systematic Review and Meta-Analysis

Stefania Maggi [1], Nicola Veronese [2,*], Marianna Burgio [2], Giorgia Cammarata [2], Maria Elena Ciuppa [2], Stefano Ciriminna [2], Francesco Di Gennaro [3], Lee Smith [4], Mike Trott [5], Ligia J. Dominguez [1,6], Giovanni M. Giammanco [2], Simona De Grazia [2], Claudio Costantino [2], Francesco Vitale [2] and Mario Barbagallo [2]

[1] Consiglio Nazionale delle Ricerche, Neuroscience Institute, Padova, 35100, Italy.
[2] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University of Palermo, 90127 Palermo, Italy.
[3] Department of Biomedical Sciences and Human Oncology, Clinic of Infectious Diseases, University of Bari "Aldo Moro", 70121 Bari, Italy.
[4] Centre for Health Performance and Wellbeing, Anglia Ruskin University, Cambridge, UK.
[5] Centre for Public Health, Queen's University Belfast, Belfast, UK
[6] School of Medicine and Surgery, University of Enna "Kore", 94100, Enna, Italy;
* Correspondence: Nicola Veronese, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University of Palermo, 90127 Palermo, Italy. Email: nicola.veronese@unipa.it

Abstract: Respiratory Syncytial Virus (RSV) is commonly regarded as an infection typical of children, but increasing literature is showing its importance in older people. Since the data regarding the impact of RSV are still limited for older people, the aim of this systematic review and meta-analysis is to compare the rate of hospitalization and mortality between RSV and influenza in this population. A systematic literature search until 15th June 2022 was done across several databases and including studies reporting incidence rate and cumulative incidence of hospitalization and mortality in RSV and influenza affecting older people. Among 2,295 records initially screened, 16 studies including 762,084 older participants were included. Compared to older patients having influenza, patients with RSV did not show any significant different risk in hospitalization (either cumulative or incidence rate). Similar results were evident for mortality. The quality of the studies was in general good. In conclusion, our systematic review and meta-analysis showed that the rate of hospitalization and mortality was similar between RSV and influenza in older adults, suggesting the importance of vaccination for RSV in older people for preventing negative outcomes, such as mortality and hospitalization.

Keywords: Respiratory Syncytial Virus; influenza; meta-analysis; hospitalization; mortality

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1. Introduction

Respiratory Syncytial Virus (RSV) is commonly regarded as an infection typical of children.[1,2] Unlike influenza, for which the epidemiological importance has been widely recognized for years, the epidemiological impact of RSV infection in middle-age and older adults has only recently gained importance [3,4]. In children, primary RSV infections may result in severe disease, subsequent infections that are often comparatively mild. [1] Sometimes, a state of incomplete immunity has been reported, that can predispose to a continued susceptibility to reinfection during the life [5].

Such as for influenza, older adults may have a greater incidence of negative outcomes when affected by RSV, since they are affected more frequently from respiratory and cardiovascular conditions [6], such as chronic obstructive pulmonary disease [7] or heart

failure [8], than can further increase hospitalization and mortality rates and other negative outcomes.[9] In this regard, it was reported in the USA that each year, between 60,000–120,000 older adults are hospitalized and 6,000–10,000 of them die due to RSV infection.[10,11] In particular, RSV is an important risk factor for hospitalization in frailer subjects, such as those living in nursing home.[12] In particular, some systematic reviews with meta-analyses have reported that RSV could be associated to a high case fatality rate in nursing home.[13,14]

Because of these findings, and the known role of influenza in causing hospitalization and mortality, studies of RSV in older adults have often used influenza as comparison group, also considering that it is often hard to distinguish between symptoms of severe RSV or severe influenza. In older people, it was reported that RSV infections present less frequently with fever but more frequently with wheezing **[15]** for example, but otherwise it can be difficult to distinguish it clinically from influenza without appropriate diagnostic tests.

Since the data regarding the impact of RSV are still limited for older people, the aim of this systematic review and meta-analysis is to compare the rate of hospitalization and mortality between RSV and influenza in older people including observational studies available.

2. Materials and Methods

This systematic review adhered to the PRISMA statement (checklist available in the Supplementary Material). [16] The protocol was registered on 02nd December 2022 on PROSPERO (CRD42018381040).

2.1. Data sources and searches

Four investigators (MEC, GC, SC, MB) by couples, independently, conducted a literature search using several databases including Embase, Web of Science from database inception until 15th June 2022, including observational studies investigating the rate of hospitalization and/or mortality in older people affected by RSV infection.

The search strategy run in Pubmed was: "(Respiratory Syncytial Virus OR RSV OR Respiratory Syncytial Viruses [mh]) AND ("Mortality"[Mesh] OR "mortality" [Subheading] OR "Mortality" OR "Mortalities" OR "Case Fatality Rate" OR "Case Fatality Rates" OR "Death Rate" OR "Death Rates" OR "survival" OR "Hospital" OR "Acute care" OR "Hospitalized older adults" OR "Hospital medicine" OR "Older inpatients" OR "Inpatient" OR "Acute geriatric ward" OR "Clinical ward" OR "Medical units" OR "Geriatric units" OR "Hospitalization" OR "Length of Stay") AND ((("elderly population"[Title/Abstract] OR elderly[Title/Abstract] OR elders[Title/Abstract] OR "elderly patient"[Title/Abstract] OR "elderly patients"[Title/Abstract] OR "elderly people"[Title/Abstract] OR "aged 70"[Title/Abstract] OR "aged 80"[Title/Abstract] OR "aged >65"[Title/Abstract] OR ">65 years old"[Title/Abstract]) OR ("70 years old"[Title/Abstract] OR ">70 years old"[Title/Abstract] OR "older person*"[Title/Abstract] OR "older persons"[Title/Abstract] OR "Older Adult*"[Title/Abstract] OR "Older Adults"[Title/Abstract] OR "Oldest Old"[Title/Abstract] OR Nonagenarians[Title/Abstract] OR Octogenarians[Title/Abstract] OR Centenarians[Title/Abstract])) OR ("aged over 80"[Title] OR "aged over 90"[Title]))" Any inconsistencies were resolved by consensus with a senior author (NV).

The search strategy was adapted using OVID for the other databases searched.

2.2. Study selection

Following the PICOS question, we considered eligible studies that included older participants (defined as age ≥ 60 years) (P), affected by RSV (I) versus influenza (C) including the incidence of hospitalization and/or mortality as outcomes (O). Therefore, prospective and retrospective studies were considered (S). We also included conference abstracts, if sufficient data were available for the meta-analysis. We excluded studies made

in people younger than 60 years, considering outcomes (such as disability or intensive care unit admission) other than those mentioned above, and cross-sectional studies. Moreover, studies were excluded if data could not be meta-analyzable.

2.3. Data extraction

Four independent investigators (MEC, GC, SC, MB) extracted key data from the included articles in a standardized Excel spread sheet and a third independent investigator (NV) checked the data. For each article, we extracted data on author names, year of publication, country/continent, study design (retrospective or prospective), demographic information, follow-up duration (in months).

2.4. Outcomes

The primary outcomes were the incidence rates of hospitalization and mortality. The incidence could be reported as overall cumulative incidence or as standardized incidence rates with their 95% confidence intervals (CIs). In this latter case, we used the formulas reported in the Cochrane handbook of systematic reviews of interventions [17]. All the data were reported as per 100,000 persons-year for hospitalization and per 1,000 persons-year for mortality.

2.5. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the study quality/risk of bias [18]. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome. The evaluation was made by four independent investigators (MEC, GC, SC, MB) and checked by another (NV), independently. The risk of bias was then categorized as high (<5/9 points), moderate (6-7), or low (8-9) *[19]*.

2.6. Data synthesis and analysis

All analyses were performed using STATA version 14.0 (StataCorp).

The primary analysis investigated the incidence rates of hospitalization/mortality between patients affected by RSV and influenza. We calculated the risk ratios (RRs) with their 95% confidence intervals (CIs), applying a random-effect model **[20].** Similarly, we considered the mean difference (MD) with 95%CI in the incidence rate RSV and influenza standardized as indicated before. The results were reported by the method used for the diagnosis of RSV/influenza.

Heterogeneity across studies was assessed by the I^2 metric and χ^2 statistics and significant heterogeneity was placed in case of an $I^2 \geq 50\%$ or the correspondent p-value <0.05.

Publication bias was assessed by visually inspecting funnel plots and using the Egger's bias test.[21] The trim-and-fill analysis was planned for addressing this issue, but not used.[22]

For all analyses, a P-value less than 0.05 was considered statistically significant.

3. Results

3.1. Search results

As shown in Figure 1, among 2295 records initially screened, 74 were retrieved as full texts. After excluding some works, mainly because data were not meta-analyzable (Table S1 reports the references and the reason of the exclusion), 16 papers were finally included [23-38].

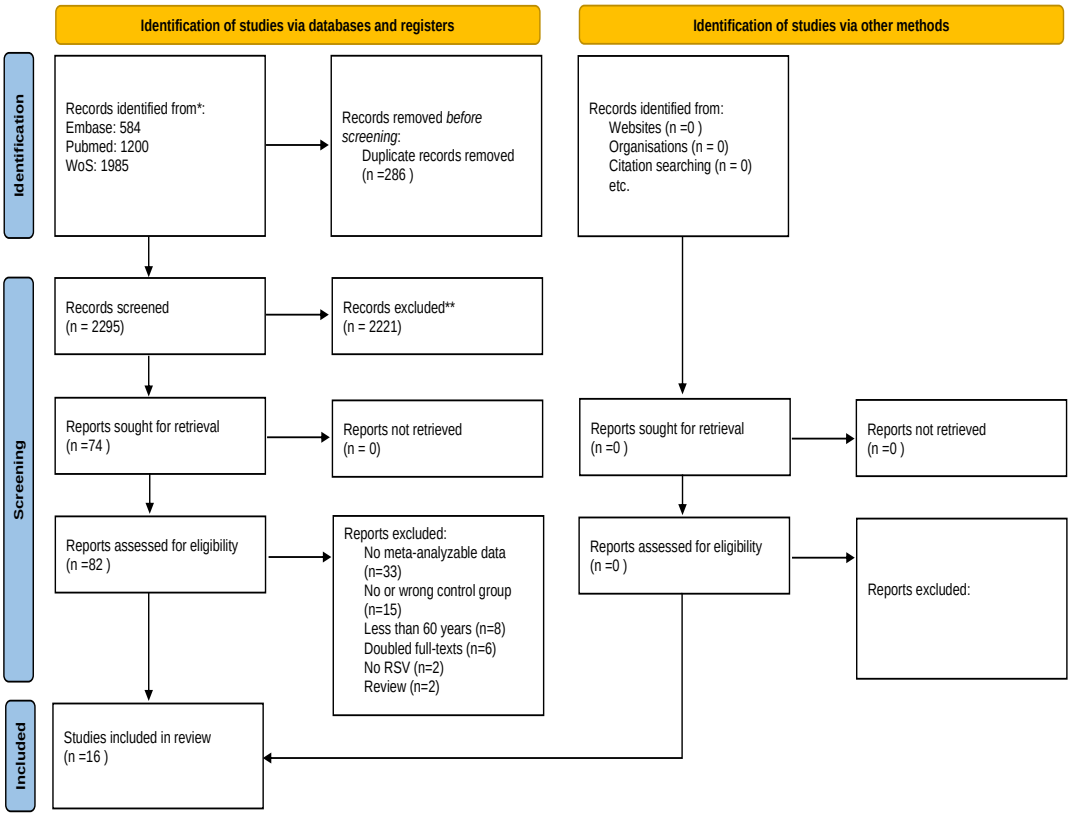

Figure 1. PRISMA flow-chart.

3.2. Study and patient characteristics

Full details regarding the descriptive findings are reported in Table 1. The 16 studies included 762,084 older participants (range: 29 to 551,633 participants), with a median for each study of 1,246 older people. The mean age was 73.4 years. The majority of studies were conducted in North America (n=9), five in Europe, one in Africa and another one in twelve different countries. No study was made in Asia. Overall, nine studies had a prospective design and the remaining seven retrospective. The diagnosis of RSV/influenza was mainly made using polymerase chain reaction (PCR) (n=9), sometimes in combination with other methods. The median follow-up time was 48 months, with a range between 3 and 84 months.

Table 1. Descriptive characteristics.

Author, year	Type of study	Sample size	Mean age	Diagnosis of RSV and influenza	Follow-up (months)	NOS
Ackerson, 2019	Retrospective	2523	78	PCR and culture	12	8
Auvinen, 2021	Prospective	974	76	PCR	48	8
Ellis, 2003	Retrospective	10581	65+	Antigent tests and cultures	48	7
Falsey, 2005	Prospective	146	72	RT-PCR, Serologic test, viral culture	48	8
Falsey, 2021	Prospective	604	65.6	PCR	3	8

Author, year	Type of study	Sample size	Mean age	Diagnosis of RSV and influenza	Follow-up (months)	NOS
Gilca, 2014	Prospective	210		Luminex RVP FAST assay	48	7
Gonçalo Matias, 2017	Retrospective	64456	65+	Weekly influenza update	144	7
Korsten,2020	Prospective	1040	75	PCR	48	8
Loubet, 2016	Prospective	1452	74	PCR	12	8
Malosh, 2017	Prospective	426		PCR	24	8
Muller-Pebody, 2006	Prospective	551633	65+	ICD-10	36	7
Rabarison, 2019	Retrospective	375		PCR	60	8
Schanzer., 2008	Retrospecitve	103262		Hospitalization Morbidity Database (HMDB)14	60	7
Sharp, 2021	Retrospective	21787	65-74	Antigene detection, culture, and genomic/pcr/lcr detection	84	8
Tseng ,2017	Prospective	2586	60+	PCR	48	8
Widemer 2012	Prospective	29	65+	PCR	36	8
Total	**9 studies: prospective; 7 studies: retrospective**	**762,084**	**73.4**	**9 studies: PCR; 7 studies: others**	**48 (range: 3-84)**	

3.3. Rate of hospitalizations and mortality in RSV vs. influenza: meta-analysis

As reported in Table 1, compared to patients having influenza, patients with RSV did not show any significant different risk in hospitalization. When considering cumulative incidence, the RR was 0.93 (95%CI: 0.53-1.62; p=0.80; I^2=0%; k=5) (Figure 1A). The Egger's test suggests the absence of any publication bias as confirmed in Figure A5. Similarly, when including ten studies reporting data as incidence rate per 100,000 persons-year, we did not observe any difference in hospitalization rate (MD=-262; 95%CI: -755; 229), even if this outcome was characterized by a high heterogeneity (I^2=99%), mainly driven by the study of Goncalo **[30]** that shows a reduced risk of hospitalization in RSV compared to influenza (Figure 2A). No publication bias was evident.

When considering mortality as outcome, the results remained similar. Compared to influenza, RSV did not carry any significant increased risk in mortality (RR=1.19; 95%CI: 0.98-1.45; p=0.08; I^2=0%; k=4) (Figure 3A). No publication bias was present (Figure A6). Finally, when using incidence rate, instead of cumulative incidence, RSV did not differ in terms of mortality compared to influenza (MD=15 per 1,000 persons-year; 95%CI: -133 to 162; p=0.85; I^2=0%) (Figure 4A). Again, no evidence of publication bias was present.

Table 2. Meta-analysis of hospitalization and mortality rate between RSV and influenza.

	Cumulative incidence						Incidence rate (per 100,000 persons-year)					
Outcome	**N of studies (participants)**	**RR**	**95%CI**	**p-value**	**I²**	**Egger's test (p-value)**	**N of studies**	**MD**	**95%CI**	**p-value**	**I²**	**Egger's test (p-value)**
Hospitalization	5	0.93	0.53-1.62	0.80	0	-0.73 (p=0.08)	10	-262	-755; 229	0.30	99	-6.57 (p=0.20)
Mortality	4	1.19	0.98-1.45	0.08	0	0.57 (p=0.10)	2	15	-133; 162	0.85	0	Not possible

3.4 Sensitivity analyses

We have categorized the incidence of mortality and hospitalization according to the diagnostic method of RSV. Regarding the cumulative incidence of death, all the studies included used the PCR; when using the incidence rate, no significant differences between studies using the Weekly influenza update and antigenic methods were found (p for interaction=0.613). Regarding the cumulative incidence of hospitalization, no significant differences between PCR, administrative data and luminex RVP FAST assay (p for interaction= 0.706), while the mean difference between RSV and influenza reported that the incidence rate collected using administrative data (weekly influenza update, ICD-10, HMDB-14) was statistically lower than PCR and antigen tests (p for interaction < 0.0001).

3.5. Risk of bias

The Newcastle-Ottawa Scale overall indicated a good quality of the studies included, without any study at high risk of bias. The most common sources of bias were the ascertainment of exposure (that was not accurate in five studies and the comparability of cohorts on the basis of the design or analysis that was not of high quality since the propensity score was missing in all the studies included (Table 1; Table S2).

4. Discussion

In this systematic review with meta-analysis including 16 observational studies and a total of 762,084 older participants, we found that the incidence of hospitalizations and mortality was similar between RSV and influenza, overall reinforcing the importance of identifying RSV in older people.

In previous works, an important effort was dedicated to compare the clinical severity and presentation of RSV with influenza [8,25,27,38,39]. In agreement with the previous studies, also included in this systematic review, we found that the hospitalization and the mortality rate attributable to RSV in older people was like that of influenza. Regarding the possible differences between RSV and influenza infections, one study reported that older individuals with RSV were admitted later in their illness, on average, than individuals with influenza [39]. These findings may indicate a slower overall progression to acute illness for RSV versus influenza, as confirmed in other studies [40]. Similarly, another important study reported that the diagnosis of RSV infection in hospitalized older adults is often delayed and this may further affect clinical management and outcomes [41]. All these findings, in our opinion, indicate the urgent need for a stricter surveillance, also using molecular approaches for individuating RSV [42].

In this regard, it is important to remember that influenza represents a major cause of morbidity and mortality in older people [43]. Moreover, influenza is an important cause of other medical conditions in older subjects such as stroke and cardiovascular diseases [44], disability [45], pneumonia [46], and finally mortality. Vaccination against influenza in older people is highly effective in preventing all these conditions and therefore highly

recommended [47]. Therefore to report that the incidence rate of hospitalization and mortality is similar between RSV and influenza is of epidemiological importance, also considering the likely increased susceptibility observed during COVID-19 pandemic.[48]

Based on the epidemiological findings confirmed by our systematic review with meta-analysis, current vaccine development efforts have identified prevention of severe RSV-associated illness. To the best of our knowledge, 33 respiratory syncytial virus prevention candidates are in clinical development using different approaches, including recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines, and monoclonal antibodies [49,50]. Nine candidates are in phase 3 clinical trials [49]. Of interest, a phase 3 trial reported that a single dose of an adjuvant vaccine was highly efficacious against RSV-confirmed lower respiratory tract diseases and RSV-confirmed acute respiratory infections in older adults, regardless of RSV disease severity, RSV subtype, baseline comorbidity and presence of frailty [51].

The findings of this systematic review must be interpreted within its limitations. First, some outcomes were characterized by a high heterogeneity. Second, about half of the studies had a retrospective design, possibly introducing a bias in these findings. Third, no study was made in Asia, limiting the generalization of our findings in these countries. Finally, the admission rate in ICU was not available for almost all studies included in our systematic review, but the admission in ICU represents an important risk factor for mortality, as shown in pediatric population. [52] However, it has been reported that ICU admission rate is similar for RSV and influenza older patients [25].

5. Conclusions

Our systematic review and meta-analysis showed that the rate of hospitalization and mortality was similar between RSV and influenza in older adults, suggesting the importance of vaccination for RSV in older people for preventing the negative outcomes, such as hospitalization and mortality. Since RSV is highly prevalent in older people and associated with negative outcomes, our systematic review supports the need of increasing awareness before vaccines availability. Future studies confirming our findings in the light of public health interventions are needed.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Conceptualization, N.V. and S.M.; methodology, M.B., N.V.; formal analysis, N.V.; data curation, M.B., G.C., M.E.C., S.C.; writing—original draft preparation, N.V., F.D.G., L.S., M.T.; writing—review and editing, L.J.D., G.G., S.D.G., C.C., F.V.; supervision, M.B., S.M.; funding acquisition, S.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Ethical review and approval were waived for this study since no patients were directly involved.

Informed Consent Statement: Patient consent was waived since no patients were directly involved.

Data Availability Statement: The data are available upon reasonable request to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix B

Table S1. List of excluded references with reason.

Author, year	Reason of exclusion
Abu Seir, 2021	Younger than 60 years
Ackerson, 2020	No meta-analyzable data
Ali, 2019	No meta-analyzable data
Amand, 2018	Younger than 60 years
Barnes, 2018	No meta-analyzable data
Beran, 2021	No meta-analyzable data
Berginc, 2015	No meta-analyzable data
Blackburn, 2017	No meta-analyzable data
Boattini, 2020	No meta-analyzable data
Boattini, 2021	No meta-analyzable data
Bosco, 2021	No meta-analyzable data
Branche, 2018	No meta-analyzable data
Branche, 2021	No or wrong control group
D.Sieling, 2021	Younger than 60 years
Falsey, 1995	Younger than 60 years
Falsey, 2013	No or wrong control group
Fleming, 2015	No meta-analyzable data
Fu Tseng, 2020	No or wrong control group
Goldestein, 2015	No meta-analyzable data
Gomez, 2021	Review
Green, 2013	No RSV diagnosis
Hansen, 2022	No meta-analyzable data
Hartnett, 2022	No meta-analyzable data
Karstaedt, 2009	No meta-analyzable data
Katsurada, 2017	No meta-analyzable data
Kieke, 2020	No meta-analyzable data
Kim, 2018	No meta-analyzable data
Kujawski, 2022	No meta-analyzable data
Kumar, 2021	No meta-analyzable data
Kurai, 2021	No meta-analyzable data
Kyeyagalire, 2014	No meta-analyzable data
Leaver, 2021	Younger than 60 years
Lee, 2013	No meta-analyzable data
Lee, 2019	No or wrong control group
Lucero-Obusan, 2019	No meta-analyzable data
Matias, 2016	No meta-analyzable data
Mila M, Prill, 2021	No or wrong control group
Mizumoto, 2019	Younger than 60 years
Mullooly, 2006	No meta-analyzable data
Newall, 2008	No RSV diagnosis
Nicholson, 1997	No meta-analyzable data
Pangesti,2019	No meta-analyzable data
Saravanos, 2019	No or wrong control group
Schmidt, 2019	Younger than 60 years
Staadegaard, 2021	No or wrong control group
Stephens, 2021	Review
Sundaram, 2014	No or wrong control group
Tempia, 2021	Younger than 60 years

Author, year	Reason of exclusion
Thompson, 2003	No or wrong control group
Ting Shi, 2019	No meta-analyzable data
Tong, 2020	No or wrong control group
van Asten, 2012	No meta-analyzable data
Walsh, 2004	No or wrong control group
Widmer, 2013	No meta-analyzable data
Wyffles, 2017	No or wrong control group
Wyffles, 2017	No or wrong control group
Yoon, 2020	No or wrong control group
Zheng, 2022	No or wrong control group
Zhou, 2012	No meta-analyzable data

Table S2. Quality of the studies included.

Study, year	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of
Ackerson, 2019	*	*	*	*	*-	*	*	*
Auvinen, 2021	*	*	*	*	*-	*	*	*
Ellis, 2003	*	*	-	*	*-	*	*	*
Falsey, 2005	*	*	*	*	*-	*	*	*
Falsey, 2021	*	*	*	*	*-	*	*	*
Gilca, 2014	*	*	-	*	*-	*	*	*
Gonçalo Matias,	*	*	-	*	*-	*	*	*
Korsten, 2020	*	*	*	*	*-	*	*	*
Loubet, 2016	*	*	*	*	*-	*	*	*
Malosh, 2017	*	*	*	*	*-	*	*	*
Muller-Pebody,	*	*	-	*	*-	*	*	*
Rabarison, 2019	*	*	*	*	*-	*	*	*
Schanzer., 2008	*	*	-	*	*-	*	*	*
Sharp, 2021	*	*	*	*	*-	*	*	*
Tseng, 2017	*	*	*	*	*-	*	*	*
Widmer, 2012	*	*	*	*	*-	*	*	*

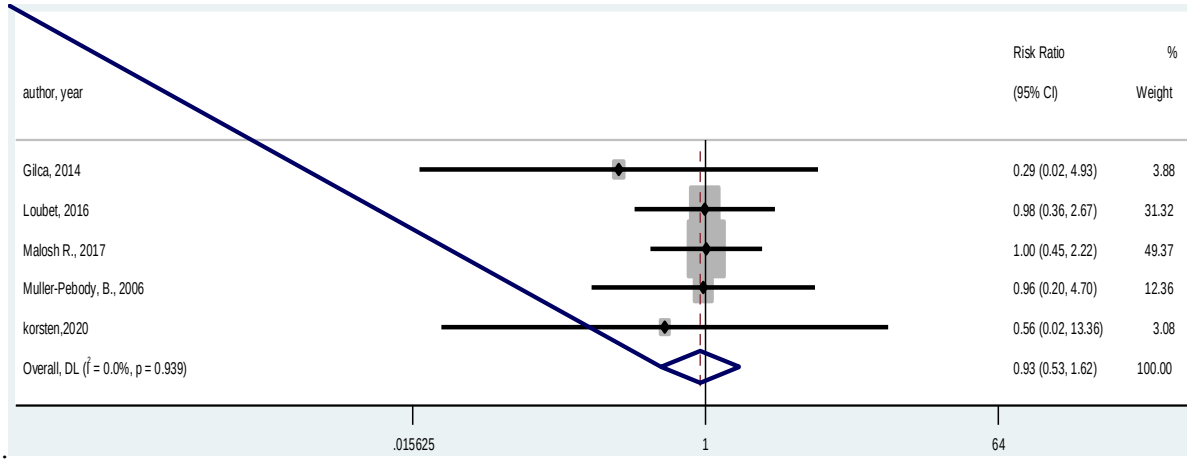


Figure A1. Hospitalization cumulative incidence between RSV and influenza.

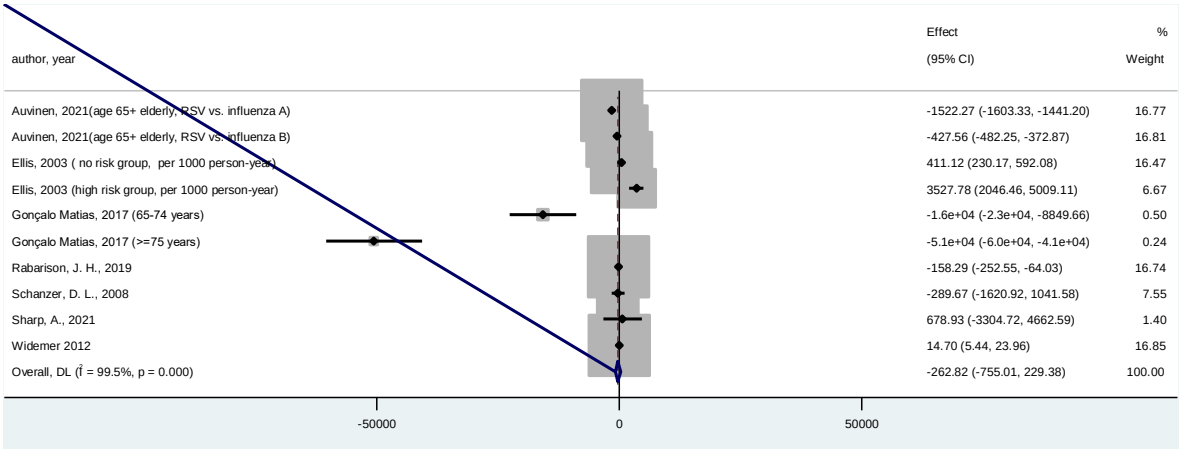


Figure A2. A. Hospitalization incidence rate (per 100,000 persons-year) between RSV and influenza.

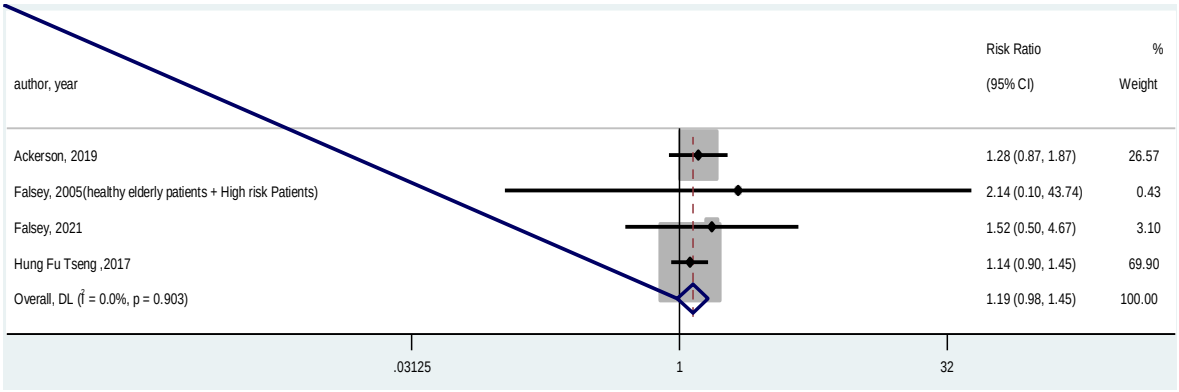


Figure A3. A. Mortality cumulative incidence between RSV and influenza.

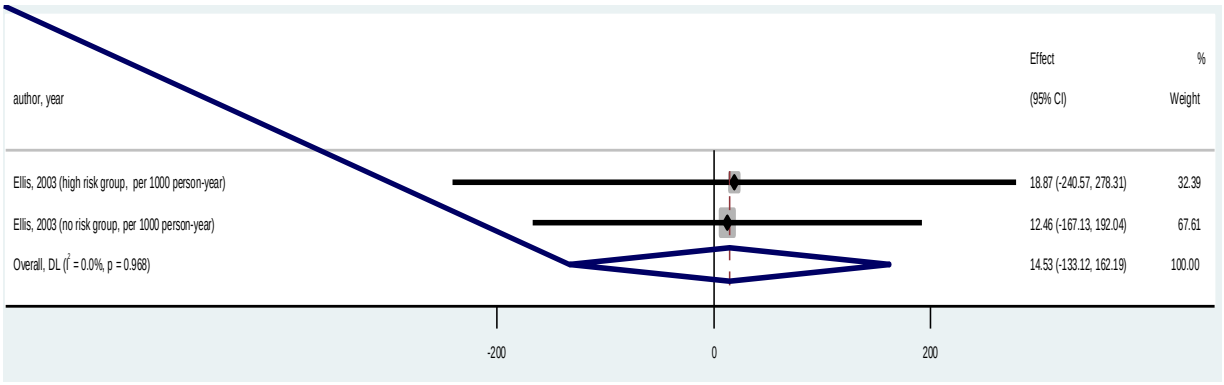
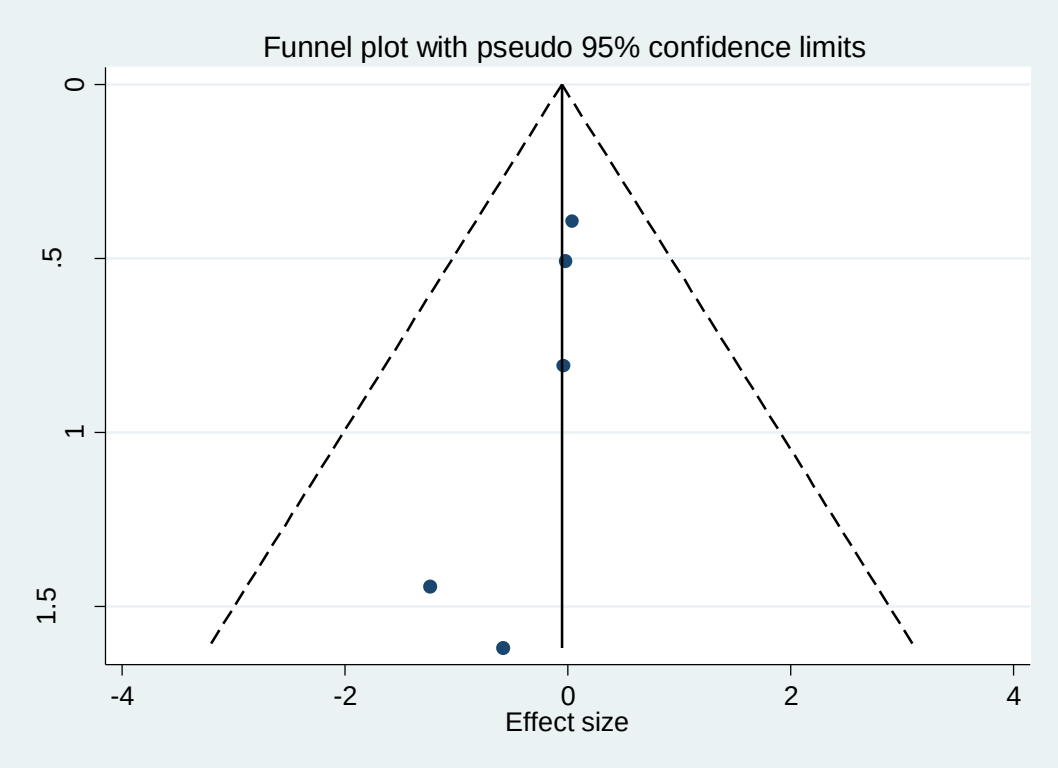


Figure A4. A. Mortality incidence rate (per 100,000 persons-year) between RSV and influenza.



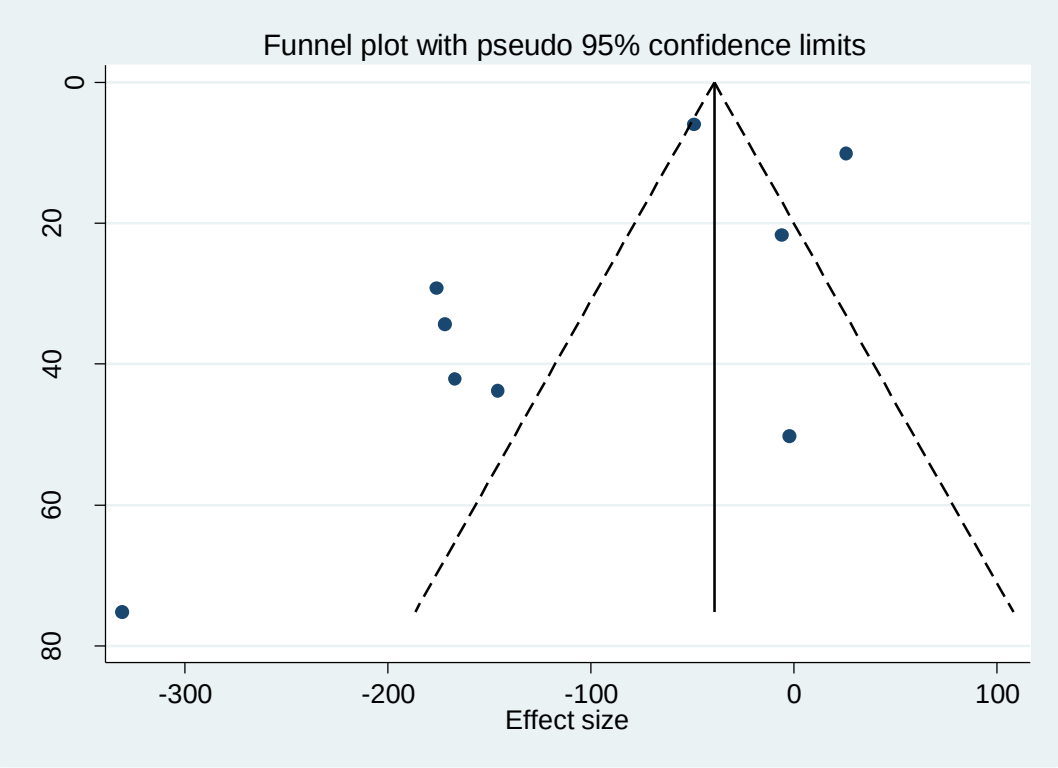
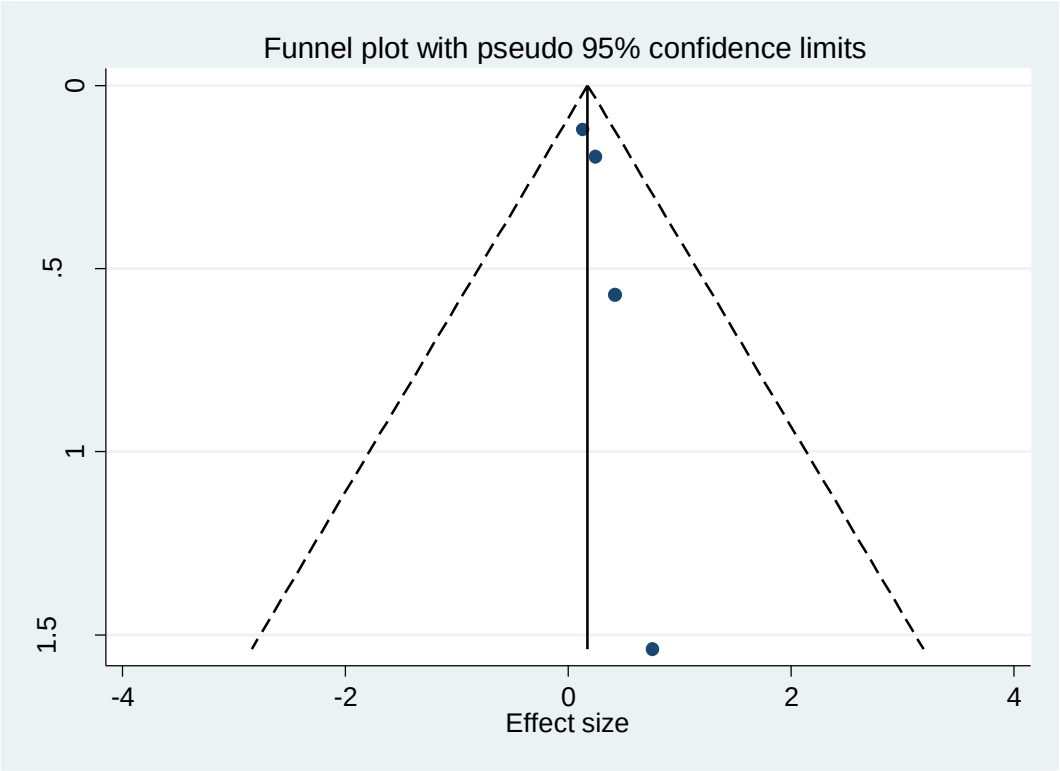


Figure A5. Funnel plots of total cumulative incidence (A) and incidence rate (B) of hospitalization.



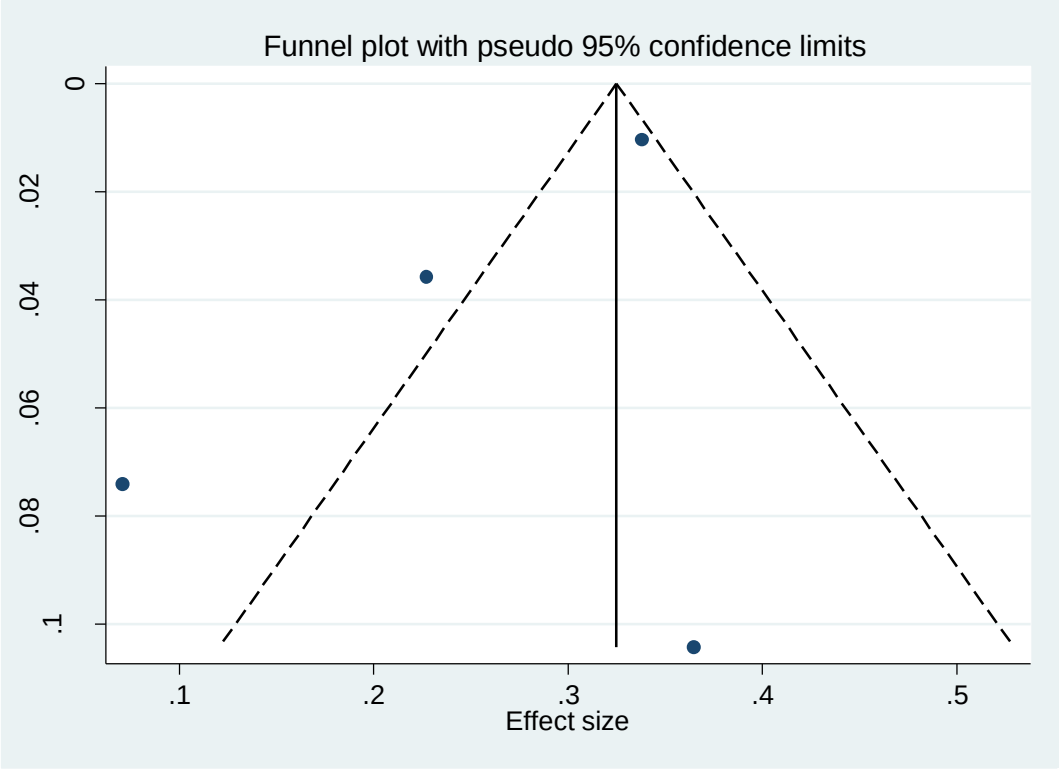


Figure A6. Funnel plots of total cumulative incidence (A) and incidence rate (B) of mortality.

PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2-3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	none

Topic	No.	Item	Location where item is reported
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	none
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	none
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	none
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	8-9
Study characteristics	17	Cite each included study and present its characteristics.	3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	4-5

Topic	No.	Item	Location where item is reported
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5-6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	none
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	none
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6-7
	23b	Discuss any limitations of the evidence included in the review.	7
	23c	Discuss any limitations of the review processes used.	7
	23d	Discuss implications of the results for practice, policy, and future research.	7
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	none
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	7
Competing interests	26	Declare any competing interests of review authors.	7

Topic	No.	Item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	7

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