Appendix S1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix pp 3-5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 and Appendix p6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5 and Appendix pp 7-8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix p9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-6 and Appendix p10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix S2. Search Strategy

MEDLINE

1. *respiratory syncytial viruses/ or *respiratory syncytial virus, human/ or RSV.mp. or respiratory syncytial virus*.mp.

2. *Respiratory Syncytial Virus Infections/

3. Influenza, Human/ or influenza.mp. or flu.mp.

4. exp influenzavirus a/ or exp influenzavirus b/ or exp influenzavirus c/

5. 1 or 2 or 3 or 4

6. coinfection*.mp. or exp Coinfection/ or mixed infection*.mp.

7. superinfection*.mp. or exp Superinfection/

8. 6 or 7

9. exp morbidity/ or exp mortality/ or exp death/

10. exp critical care/ or exp hospitalization/

11. *Hypoxia/

12. exp oxygen inhalation therapy/ or exp respiration, artificial/

13. 9 or 10 or 11 or 12

14. 5 and 8 and 13

341 Results by 26th Mar 2019 (first search)

389 Results by 31st Dec 2019

EMBASE

1. *respiratory syncytial viruses/ or *respiratory syncytial virus, human/ or RSV.mp. or respiratory syncytial virus*.mp.

2. *Respiratory Syncytial Virus Infections/

3. Influenza, Human/ or influenza.mp. or flu.mp.

4. exp influenzavirus a/ or exp influenzavirus b/ or exp influenzavirus c/

5. 1 or 2 or 3 or 4

6. coinfection*.mp. or exp Coinfection/ or mixed infection*.mp.

7. superinfection*.mp. or exp Superinfection/

8. 6 or 7

9. exp morbidity/ or exp mortality/ or exp death/

10. exp critical care/ or exp hospitalization/

11. *Hypoxia/

12. exp oxygen inhalation therapy/ or exp respiration, artificial/

13. 9 or 10 or 11 or 12

14. 5 and 8 and 13

1300 Results by 26th Mar 2019 (first search)

1439 Results by 31st Dec 2019

13. 6 and 10 and 12

Sample forms used for data cataloguing and extraction

Sample data cataloguing form

Study ID	
Author	
Year of publication	
Study period: from	
Study period: to	
Region	
Country	
Setting (community/hospital)	
Wards (inpatient/outpatient/emergency room)	
Age	
Number of subjects	
Diagnosis or symptoms	
Specimen for virus detection	
Diagnostic method for virus detection	
Hospitalisation (available or not)	
Length of stay (available or not)	
ICU admission (available or not)	
Mechanical ventilation (available or not)	
Use of supplemental oxygen (available or not)	

Mortality (available or not)	
Other_outcomes_reported (yes or no)	
Other_outcomes (free texts)	
Baseline variables compared between mono-infection and co-infection (e.g. age, sex, etc.)	
Any baseline variables balanced between the two groups	

Appendix S3. Sample data extraction form

Questions	*RSV Mono-infection*	*RSV Coinfection*
Study ID		
Virus		
Number of cases		
Results on proportion of hospitalisation		
Results on length of stay		
Results on ICU admission		
Results on mechanical ventilation		
Results on use of supplemental oxygen		
Results on mortality		
Other results reported (free texts)		

Appendix S4. Characteristics of included studies

Author	Year of Publication	Study Period	Country	Age	Diagnostic method	Clinical diagnosis	Setting(s)	Hospital admission	Length of hospital stay	Use of supplemental oxygen	ICU admission	Mechanical ventilation	Deaths
Aberle	2005	OCT 2010–JUL 2014	Austria	<1y	PCR	ALRI	IP	No	Yes	Yes	No	No	No
Ali	2010	JAN 2007–MAR 2007	Jordan	<5y	PCR	ARI	IP	No	Yes	Yes	Yes	Yes	Yes
Brand	2012	NOV 2006–APR 2009	Netherlands	<2y	PCR	Bronchiolitis	ER + IP	No	No	No	No	Yes	No
Caracciolo	2008	OCT 2005–APR 2007	Italy	<5y	PCR	ARI	IP	No	Yes	Yes	No	No	No
da Silva	2013	APR 2007–NOV 2007	Brazil	<3y	PCR	ALRI	ER + IP	No	Yes	No	No	No	No
De Paulis	2011	FEB 2005–NOV 2005	Brazil	<2y	PCR	ARI	IP	No	Yes	No	Yes	Yes	No
Espinola	2012	MAY 2010–OCT 2011	Paraguay	<2y	PCR	ARI	IP	No	Yes	No	Yes	No	No
Falkenstein-Hagander	2014	SEP 2006–MAY 2007	Sweden	<1y	PCR/IFA	ALRI	IP	No	Yes	Yes	No	Yes	No
Foulongne	2006	NOV 2003–OCT 2004	France	<5y	PCR/DFA	RTD	IP	No	Yes	Yes	No	No	No
Frobert	2011	DEC 2008–MAR 2009	France	<2y	PCR	RTD	ICU	No	No	No	No	Yes	No
Gagliardi	2013	JAN 2005–DEC 2005	Brazil	<5y	PCR/DFA	ARI	IP + OP + ICU	No	Yes	Yes	No	Yes	No
Gokce	2018	JAN 2013–OCT 2016	Turkey	<2y	PCR	Bronchiolitis	IP	No	Yes	Yes	No	No	No
Janahi	2017	JAN 2010–DEC 2011	Qatar	2w–2y	PCR	Bronchiolitis	IP	No	Yes	No	No	Yes	No
Kelly	2015	APR 2012–AUG 2014	Botswana	<2y	PCR	Pneumonia	IP	No	Yes	No	No	No	Yes
Kwon	2019	OCT 2014–APR 2017	South Korea	<5y	PCR	ARI	IP	No	Yes	Yes	No	Yes	No

Lim	2017	JAN 2008 – DEC 2012	Australia	6–59m	PCR/ culture	ARI	ER + IP	Yes	No	No	No	No	No
Lu	2015	JAN 2010– DEC 2014	China	<1m	PCR/DFA	ALRI	IP	No	No	No	Yes	No	No
Macao	2011	NOV 2009– MAR 2009	Portugal	<2y	PCR/DFA	Bronchiolitis	ER + IP	Yes	No	No	No	No	No
Mansbach	2012	NOV 2007– MAR 2010	US	<2y	PCR	Bronchiolitis	ER + IP	No	Yes	No	Yes	Yes	No
Marguet	2009	NOV 2002– MAR 2004	France	1m–1y	PCR/DFA	Bronchiolitis	ER + IP	No	Yes	No	No	No	No
Matsuno	2019	JUN 2008– MAY 2009	Brazil	<3y	PCR/DFA/ IFA	ALRI	IP	No	No	No	Yes	No	Yes
Mazur	2017	FEB 2009– DEC 2013	South Africa	<5y	PCR	SARI	IP + ICU	No	No	No	Yes*	No	No
Petrarca	2018	OCT 2004– MAY 2016	Italy	<1y	PCR	Bronchiolitis	IP	No	Yes	Yes	Yes	No	No
Richard	2008	SEP 2003– APR 2005	France	<1y	PCR/ culture	Bronchiolitis	IP + ICU	No	No	No	Yes	No	No
Semple	2005	NOV 2001– MAR 2002	UK	<2y	EIA/PCR	Bronchiolitis	IP + ICU	No	No	No	Yes	No	No
Venter	2011	JAN 2006– DEC 2007	South Africa	<5y	PCR/DFA/ EIA	ARI	IP + OP	Yes	No	No	Yes	No	Yes
Yu	2010	Winter 2006– Winter 2008	China	1–30m	PCR	Bronchiolitis	IP	No	Yes	No	Yes	No	No

*The authors used a composite outcome of mechanical ventilation, ICU admission and death.

PCR = polymerase chain reaction; DFA = direct immunofluorescence assay; IFA = indirect immunofluorescence assay; EIA = enzyme-linked immunosorbent assay; ALRI = acute lower respiratory infection; ARI = acute respiratory infection; RTD = respiratory tract disease; SARI = severe acute respiratory infection; ER = emergency room; IP = inpatient; OP = outpatient; ICU = intensive care unit.

Quality assessment

Author	Year of Publication	Did the study address a clearly focused issue?	Were the subjects recruited in an acceptable	Was the exposure accurately measured to minimise	Was the outcome accurately measured to minimise	Have the authors taken account of any confounding factors in the design and/or	Can the results be applied to the local population?	Do the results of this study fit with other available evidence?

			way?	bias?	bias?	analysis?		
Aberle	2005	yes	yes	yes	yes	no	can't tell	yes
Ali	2010	yes	yes	yes	yes	no	yes	yes
Brand	2012	yes	yes	yes	yes	no	yes	yes
Caracciolo	2008	yes	yes	yes	yes	no	yes	yes
da Silva	2013	yes	yes	yes	yes	no	can't tell	yes
De Paulis	2011	yes	yes	yes	yes	yes	yes	yes
Espinola	2012	yes	yes	yes	yes	no	yes	yes
Falkenstein-Hagander	2014	yes	yes	yes	yes	no	yes	yes
Foulongne	2006	yes	yes	yes	yes	no	yes	yes
Frobert	2011	yes	yes	yes	yes	no	yes	yes
Gagliardi	2013	yes	yes	yes	yes	no	yes	yes
Gokce	2018	yes	yes	yes	yes	no	yes	yes
Janahi	2017	yes	yes	yes	yes	yes	yes	yes
Kelly	2015	yes	yes	yes	yes	yes	yes	yes
Kwon	2019	yes	yes	yes	yes	yes	yes	yes
Lim	2017	yes	yes	yes	yes	yes	yes	yes
Lu	2015	yes	yes	yes	yes	yes	yes	yes
Macao	2011	yes	yes	yes	yes	no	yes	yes
Mansbach	2012	yes	yes	yes	yes	no	yes	yes
Marguet	2009	yes	yes	yes	yes	yes	yes	yes
Matsuno	2019	yes	yes	yes	yes	no	yes	yes
Mazur	2017	yes	yes	yes	yes	yes	no	yes
Petrarca	2018	yes	yes	yes	yes	no	yes	yes
Richard	2008	yes	yes	yes	yes	no	yes	yes
Semple	2005	yes	yes	yes	yes	no	yes	yes
Venter	2011	yes	yes	yes	yes	no	yes	yes
Yu	2010	yes	yes	yes	yes	no	yes	yes

Global Health

237 results by 26th Mar 2019 (first search)

289 results by 31st Dec 2019

Table S1. Summary of studies reporting both unadjusted and adjusted results

Study	Virus co-infected, Outcome	Unadjusted OR	Adjusted OR
De Paulis, 2011	Any viruses, mechanical ventilation	1.36 (95% CI: 0.90–2.05)	1.05 (95% CI: 0.29–3.85)
Lu, 2015	Any viruses, ICU admission	4.03 (95% CI: 1.76–9.24)	2.72 (95% CI: 1.05–7.07)
Mazur, 2017	Adenovirus, ICU admission	2.4 (95% CI: 1.2–4.8)	3.4 (95% CI: 1.6–7.2)

OR=odds ratio; CI=confidence interval; ICU=intensive care unit

Table S2. Summary of results on hospitalisations

Study	Virus co-infected	Results	Notes
Lim, 2017	Influenza virus	Probability of hospitalisation Mono: 43% (95% CI: 36–51) Co: 55% (95% CI: 35–73)	Marginal model fit from multivariable logistic regression model
Macao, 2011	Bocavirus	OR: 2.67 (95% CI: 1.71–4.18)	—
Venter, 2011	Any viruses	OR: 0.42 (95% CI: 0.30–0.59)	—

CI=confidence interval; Mono=mono-infection; Co=co-infection; OR=odds ratio

Table S3. Additional results on ICU admission

Study	Virus co-infected	Results	
Mazur, 2017	Adenovirus	Mono: 19/1306 (1.5%) Co: 11/340 (3.2%)	OR: 2.3 (95% CI: 1.6–3.3)

Richard, 2008	Adenovirus	Mono: 41/94 (43.6%) Co: 1/1 (100%)	—
Mazur, 2017	Enterovirus	Mono: 19/1306 (1.5%) Co: 3/186 (3.2%)	OR: 1.1 (95% CI: 0.6–2.1)
Richard, 2008	Enterovirus	Mono: 41/94 (43.6%) Co: 1/5 (20.0%)	OR: 0.3 (95% CI: 0.1–0.9)
Richard, 2008	Human coronavirus-NL63	Mono: 41/94 (43.6%) Co: 4/4 (100%)	—
Mazur, 2017	Influenza virus	Mono: 19/1306 (1.5%) Co: 0/29 (0%)	—
Richard, 2008	Influenza virus	Mono: 41/94 (43.6%) Co: 2/4 (50.0%)	OR: 1.3 (95% CI: 0.6–2.7)
Mazur, 2017	Parainfluenza virus	Mono: 19/1306 (1.5%) Co: 2/43 (4.7%)	OR: 3.3 (95% CI: 1.6–6.9)
Richard, 2008	Parainfluenza virus	Mono: 41/94 (43.6%) Co: 4/4 (100%)	—

Mono=mono-infection; Co=co-infection; CI=confidence interval; OR=odds ratio

Table S4. Summary of results on deaths

Study	Virus co-infected	Results	
Ali, 2010	hMPV	Mono: 3/341 (0.9%) Co: 0/8 (0%)	—
Kelly, 2015	Any viruses	Mono: 3/89 (3.4%) Co: 0/18 (0%)	—
Matsuno, 2019	Rhinovirus	Mono: 0/23 (0%) Co: 3/118 (2.5%)	—

Venter, 2011	Any viruses	Mono: 6/60 (10.0%) Co: 2/70 (2.9%)	OR: 0.26 (95% CI: 0.11–0.59)

hMPV=human metapneumovirus; Mono=mono-infection; Co=co-infection; CI=confidence interval; OR=odds ratio