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Respiratory viral coinfection and disease severity in children: A systematic review and meta-analysis

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ABSTRACT

Background: With advent of molecular diagnostic technologies, studies have reported detection of two or more respiratory viruses in about 30% of children with respiratory infections. However, prognostic role of coinfection remains unclear.
Objective: Evaluate relation between respiratory viral confection and illness severity in children.
Study design: MEDLINE (through PUBMED), EMBASE, EBSCO, LILACS databases were searched up to March 2015 by two independent reviewers. Studies assessing severity of viral coinfection in patients aged less than 18 years were included. Standardized forms were used for data extraction of population, study design, clinical syndromes, virus combinations compared and severity outcomes. Risk of bias and quality of evidence were assessed through EPHPP and GRADE. Subgroup analysis was performed according to age and viral combinations.
Results: Of 5218 records screened, 43 were included in analysis. Viral coinfection did not influence risks of all outcomes assessed: length of stay (mean difference in days in coinfection, −0.10 [95% confidence interval: −0.51 to 0.31]), length of supplemental oxygen (−0.42 [−1.05 to 0.20]), need of hospitalization (odds ratio of coinfection, 0.96 [95% confidence interval: 0.61–1.51]), supplemental oxygen (0.94 [0.66 to 1.34]), need of intensive care (0.99 [0.64 to 1.54]), mechanical ventilation (0.81 [0.33 to 2.01]) and death (2.22 [0.83 to 5.95]). Sub-analyses according to age and viral combinations have not shown influence of these factors in outcomes.
Conclusions: Respiratory viral coinfection did not increase severity in all outcomes assessed. Further studies are necessary to confirm this finding, especially regarding role of specific viral interactions.

1. Background

Acute respiratory infections (ARI) are a major cause of hospital admission in young children and viruses are the most frequent etiological agents involved in such cases [1,2]. Viral detection techniques have greatly improved in recent years, as the use of molecular diagnostic tests has importantly increased the ability to identify respiratory viruses in children with ARI [3]. Until recently, infection by two or more viral agents concomitantly, in infants and toddlers, was considered an unusual event. However, as these new diagnostic techniques became more readily available in clinical settings, studies have been showing a much higher prevalence of respiratory coinfection [4]. In most of reports, detection of two or more respiratory virus simultaneously ranges from 10 to 30% in pediatric patients [5–7]. In reports that analyzed respiratory infections by nucleic acid amplification techniques assessing a large number of viruses, such prevalence is higher than 40% [8–10].

Abbreviations: ARI, acute respiratory infections; EPHPP, Effective Public Health Practice Project; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; OR, odds ratio; CI, confidence interval; MD, mean difference; SD, standard deviation; IQ, interquartile range.

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The relationship between detection of multiple respiratory viral infections and severity of disease in children has not been well established. Several studies have reported longer length of stay in hospital, an increased risk of hospitalizations, of admission to pediatric intensive care unit (PICU), of need for mechanical ventilation and even higher mortality, when two or more respiratory viruses were detected [11–17].

On the other hand, other reports have not found an association between viral coinfection and such outcomes, even in centers with high prevalence of respiratory viral coinfection [4,8,18,19]. Furthermore, an Italian study found that coinfection of respiratory syncytial virus (RSV) and metapneumovirus was a protection factor for length of hospital stay and hypoxia, when compared to RSV infection alone [20]. A French study also found shorter length of hospitalization in infants with concomitant RSV and rhinovirus coinfection comparing to single RSV infection [21].

2. Objectives

Due to the lack of consensus regarding whether mixed viral infection in children with ARI contributes to the severity of the disease, the aim of this study is to evaluate the prognostic role of respiratory viral coinfection in children.

3. Study design

The protocol of this systematic review was registered *a priori* in International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42014007250 (http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007250).

3.1. Eligibility criteria

Observational studies involving patients aged less than 18 years or with a subgroup analysis of patients within this aged group with ARI diagnosed by biology molecular assays in whose comparison of severity between those with one and two or more virus detected was possible. The following severity outcomes were selected for inclusion: need and length of hospitalization, use of supplemental oxygen, admission to PICU, mechanical ventilation and death. Only studies including the following viruses through biology molecular assays: RSV, influenza, adenovirus, parainfluenza, rhinovirus and metapneumovirus were included in main meta-analysis. Studies reporting only patients with specific comorbidities were excluded, as well as studies, which included only outpatients.

3.2. Information sources

Literature search was done through subject headings and words throughout the text related to respiratory viral coinfection and severity outcomes in the following databases: MEDLINE (through PUBMED), EMBASE, EBSCO, LILACS up to 24 March 2015. Search was performed from reference lists from selected articles, printed journals, abstracts and citations of selected articles from ISI Web of Science. Attempt to contact study authors for additional information was done whenever necessary. There were no language restrictions. When reviewers considered potential for inclusion in screened studies published in languages other than English, Spanish or Portuguese, a specific technical translation was asked.

MEDLINE search strategy: (coinfection*) OR "co-infection" OR co-detection* OR codetection*)) OR coinfection[MeSH Terms]) OR "dual infection*") OR 'mixed infections' AND (((((sever* OR death*) OR "mechanical ventilation") OR "respiratory insufficiency") OR "oxygen therapy") OR hospitalization*)) OR artificial respiration[MeSH Terms]) OR oxygen inhalation therapy[MeSH Terms]) OR respiratory insufficiency[MeSH Terms]) OR death[MeSH Terms]) AND ((((neonate*) OR newborn*) OR infant*) OR child*)) AND virus*))).

3.3. Study selection

Two independent reviewers assessed titles and abstracts. Studies which potentially met inclusion criteria were selected for full text reading and eligibility evaluation. A third reviewer assessed eligibility when discrepancies occurred.

3.4. Data collection process and data items

Data were extracted in duplicate from each eligible study to an Excel table according to a standardized template, specific for this review. It comprised the following items: first author, title, year of publication, country, design, patients age, number of viruses search using biology molecular assays, place of hospitalization (ward/PICU), level of quality, total number of included patients, number of positive samples, specific viral combinations compared, number of samples with coinfection, outcome(s), odds ratio (OR) or relative risk, statistics tests, confounding factors, and significant factors.

3.5. Risk of bias in individual studies and quality of evidence

Two authors independently assessed risk of bias and quality of evidence of included studies. Risk of bias was assessed using Quality Assessment Tool for Quantitative Studies of Effective Public Health Practice Project (EPHPP). According to this tool, studies are classified into three categories of quality: Strong, Moderate and Weak. Main aspects considered for classification are selection bias, study design, confounders, blinding, data collection methods and withdrawals and drop-outs. Overall quality of evidence for all outcomes assessed was done according to GRADE guidelines (Grading of Recommendations Assessment, Development and Evaluation) [22]. As interventional studies to evaluate severity of viral coinfection are not possible, observational studies were considered the highest level of evidence for all outcomes. The overall levels were downgraded according detection of risk of bias, inconsistency, indirectness and imprecision. Inconsistency was considered serious when substantial heterogeneity was detected (I^2 greater than 50% or $P < 0.01$). Serious indirectness was detected when most of studies compared a specific viral combination rather than all coinfections versus all single infections. Imprecision was considered when optimal information size was not met and/or a wide 95% confidence interval (CI) was detected. Disagreements between the review authors over the quality of evidence and risk of bias were resolved by a third reviewer.

3.6. Summary measures and synthesis of results

Statistical analysis was performed using *Review Manager* 5.3. The contribution of coinfection to severity was assessed using risk ratio and 95% (CI) for categorical variables and mean difference (MD) and 95% CI for continuous variables. For studies reporting multiple comparisons of virus combinations, all patients and events were joined if such procedure did not carry risk of including the same patients twice. For situations in which such risk was detected and for continuous outcomes, only combination with the largest number of patients was included in meta-analysis. Statistical heterogeneity was measured using I^2 test. Although serious heterogeneity was regarded as a sign of low quality of evidence, additional sub-groups analysis was considered necessary *a priori* regardless of heterogeneity. Random effect model were used

Table 1
Characteristics of studies included in main analysis.

First author	Year	Country	Number of patients compared	Prevalence of coinfection (%)	Age	Design	Clinical Syndrome/Comorbitidies (%)	Setting	Viruses tested with biology molecular assays	Comparison	Outcome included
Ahn	2013	South Korea	187	57.2	<18 y	Prospective	ARI/No	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	HBoV coinfection vs HBoV single infection	LOS
Aramburo	2011	USA	80	15	<9 y	Prospective	LRTI/76.3	PICU	RSV, Flu, PIV, AdV, HRV, hMPV, EV	Coinfection vs single infection	Death
Arruda	2014	Brazil	34	50	<2 y	Prospective	LRTI/100 (Preterm)	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	RSV coinfection vs RSV single infection	LOS
Asner	2015	Canada	472	17.1	<18 y	Retrospective	ARI/33	ER, PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	NH, NPICU and Death
Brand	2011	Netherlands	104	41.3	<2 y	Prospective	Bronchiolitis/19	ER, PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV coinfection vs RSV single infection	NMV
Calvo	2008	Spain	172	86	<2 y	Prospective	LRTI/15	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, EV	Coinfection vs RSV single infection	LOS
Cilla	2008	Spain	226	26.9	<3 y	Prospective	Pneumonia/4	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	Coinfection vs single infection	NH
Costa	2013	Brazil	337	31.4	<5 y	Retrospective	ARI/16.3	ER	RSV, Flu, PIV, AdV, HRV, hMPV	RSV + HRV vs RSV HRV coinfection vs HRV	LOS
da Silva	2013	Brazil	215	10.2	<3 y	Prospective	LRTI/24	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	RSV + HRV vs. HRV and RSV single infection	LOS and LO2
Do	2011	Vietnam	222	27.2	<15 y	Prospective	LRTI/Not mentioned	PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	LOS, NO2 and NPICU
Franz	2010	Germany	303	32	<16 y	Prospective	LRTI/48	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV coinfection vs RSV, HRV coinfection vs HRV, HBoV coinfection vs HBoV, AdV coinfection vs AdV	LOS, NO2
Frobert	2011	France	37	37.8	<2 y	Retrospective	Bhonchiolitis/ pneumonia/58	PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV coinfection vs RSV	NMV

Table 1 (*Continued*)

First author	Year	Country	Number of patients compared	Prevalence of coinfection (%)	Age	Design	Clinical Syndrome/Comorbitidies (%)	Setting	Viruses tested with biology molecular assays	Comparison	Outcome included
Gagliardi	2013	Brazil	70	25.7	<5 y	Prospective	ARI/Not mentioned	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV coinfection vs RSV	LOS, NMV
García-García	2007	Spain	52	75	<14 y	Prospective	ARI/21	ER, PW	RSV, Flu, PIV, AdV, HRV, hMPV, HBoV	HBoV coinfection vs HBoV single infection	LOS, NO2
Gerna	2008	Italy	47	31.9	<3 y	Prospective	LRTI/Not mentioned	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV coinfection vs RSV	LOS
Goka	2012	United Kingdom	2157	6.7	<5 y	Retrospective	ARI/Not mentioned	OUT, ER, PW	RSV, Flu, PIV, AdV, HRV, hMPV	Flu A (H1N1) and A (H3N2) single infections vs coinfection between both and Flu B, RSV, AdV, HRV (vs (H1N1 only), hMPV (vs H3N2 only)	NH
Goka	2014	United Kingdom	6065	16.7	<5 y	Retrospective	ARI/Not mentioned	OUT, ER, PW	RSV, Flu, PIV, AdV, HRV, hMPV	Coinfection vs single infection	NH
Guerrier	2013	Cambodja	551	10.8	<5 y	Prospective	LRTI/2	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	LOS and Death
Huguenin	2012	France	126	67.4	<1 y	Prospective	Bronchiolitis/Not mentioned	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	LOS, LO2, NO2 and NPICU
Kouni	2013	Greece	397	42.5	<14 y	Prospective	ARI/15.2	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	Coinfection vs single infection	NH
Kristoffersen	2011	Norway	130	10.7	<16 y	Prospective	ARI/33	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV + HCoV vs RSV, HCoV OC43 and HCoV NL63	LOS
Lees	2014	United Kingdom	448	10.4	<16 y	Retrospective	ARI/65.5	ER,PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV	Coinfection vs single infection	NO2 and NPICU
Marguet	2009	France	141	21.2	<1 y	Prospective	Bronchiolitis/No	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, EV	RSV + HRV vs RSV and HRV	LOS, LO2 and NO2

Martinez	2012	Chile	110	37.2	<18 y	Prospective	ARI/No	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	LOS and LO2
Martinez-Roig	2014	Spain	385	61.8	<15 y	Prospective	ARI/No	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	NO2, NPICU and NMV
Midulla	2009	Italy	98	15.3	<1 y	Prospective	Bronchiolitis/ No	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	RSV + HBoV vs RSV, HRV and HBoV	LOS
Miyaji	2013	Japan	151	12.5	<18 y	Prospective	ARI/Not mentioned	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HBoV, EV	Coinfection vs single infection	LOS, LO2, NH and NO2
Nascimento	2010	Brazil	72	47.2	<2 y	Prospective	Bronchiolitis/19%	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection, RSV coinfection vs RSV	NPICU and NH
Papenburg	2012	Canada	918	17.1	<3 y	Prospective	ARI/14	Out, ER, PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, EV	Coinfection vs single infection, RSV coinfection vs RSV, hMPV coinfection vs Hmpv	NH
Rajatonirina	2013	Madagascar	273	70.3	<5 y	Prospective	LRTI/17.8	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	Coinfection vs single infection	Death
Rhedin	2012	Sweden	83	14.4	<17 y	Retrospective	ARI/48.5	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Flu A (H1N1) coinfections vs Flu A (H1N1)	LOS, NPICU and Death
Richard	2008	France	180	24.4	<1 y	Retrospective	Bronchiolitis/43.9	PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, EV	Coinfection vs single infection	NPICU
Spaeder	2015	USA	511	12.7	<18 y	Retrospective	ARI/26.2	PICU	RSV, Flu, PIV, AdV, HRV, hMPV, EV	HRV coinfection vs HRV	Death

Table 1 (*Continued*)

First author	Year	Country	Number of patients compared	Prevalence of coinfection (%)	Age	Design	Clinical Syndrome/Comorbitidies (%)	Setting	Viruses tested with biology molecular assays	Comparison	Outcome included
Suryadevara	2011	USA	187	27.8	<2 y	Prospective	ARI/17.9	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, EV	Coinfection vs single infection	LOS, NO2 and NPICU
Tran	2013	Vietnam	257	22.9	<14 y	Prospective	ARI/No	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	RSV coinfection vs RSV	LOS
Tran	2014	Vietnam	78	66.6	<14 y	Prospective	ARI/No	ER	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	HBoV coinfection vs HBoV	LOS
Venter	2011	South Africa	510	54.7	<5 y	Prospective	ARI/61.1	ER, PW, PICU	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	Coinfection vs single infections of RSV, PIV-3, Flu A, AdV, HRV, hMPV, HBoV, HCoV	NH, NPICU and Death
Xiang	2010	China	69	46.3	<13 y	Prospective	Pneumonia/32.3	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	RSV + HRV A vs HRV A, RSV + HRV B vs HRV B	LOS and NO2
Xiao	2010	China	45	55.5	<14 y	Prospective	ARI/2.2	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	hMPV coinfection vs hMPV	NH
Xiao	2013	China	76	57.9	<13 y	Prospective	LRTI/18.4	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	hMPV vs hMPV coinfection, hMPV + HBoV and hMPV + RSV	LOS
Zeng	2014	China	202	52.9	<13 y	Prospective	LRTI/3.9	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	HRV coinfection vs HRV	NO2
Zhang	2010	China	327	40	<14 y	Prospective	ARI/7.9	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV	RSV coinfection vs RSV	LOS and NH
Zhang	2012	China	129	37.9	<3 y	Prospective	ARI/No	PW	RSV, Flu, PIV, AdV, HRV, hMPV, HCoV, HBoV, EV	Coinfection vs single infection	NPICU

Abbreviations: AdV = Adenovirus, ARI = Acute respiratory infections, EV = Enterovirus, ER = Emergency room, Flu = Influenza, HBoV = Human Bocavirus, HCoV = Human Coronavirus, hMPV = Human Metapneumovirus, HRV = Human Rhinovirus, LOS = Length of stay, LO2 = Length of supplemental oxygen, LRTI = Lower respiratory tract infection, NH = Need of Hospitalization, NMV = Need of mechanical ventilation, NO2 = Need of supplemental oxygen, NPICU = Need of pediatric intensive care unit, OUT = outpatient, PIV = Parainfluenza virus, PW = Pediatric ward, RSV = Respiratory Syncytial Virus.

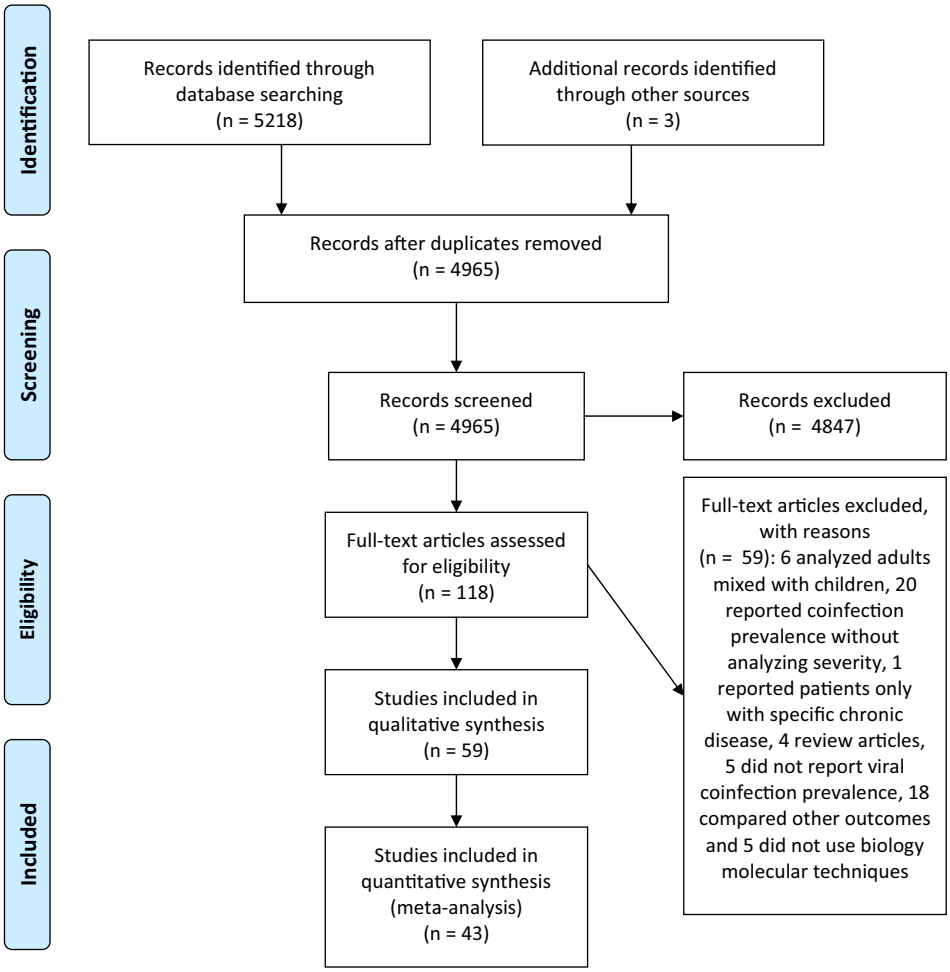

Fig. 1. Flow diagram of study selection process.

for pooled OR and MD calculations. If basic required data on results were not presented (e.g.: measures of central tendency) and attempt to contact authors were not successful, the study was excluded from analysis. For articles that presented continuous variable as median, the standard deviation (SD) was calculated from interquartile range (IQ) dividing it by 1.35 if the sample size was considered large and the distribution of the outcome was similar to the normal distribution. In conditions above were not met, study was excluded from meta-analysis [23]. After preliminary analysis considering all included articles, main analysis was performed with studies including minimal set of viruses mentioned above. Analysis was stratified by age in order to assess possible differences in severity in studies including only infants (0–23 months), preschool children (0–59 months) and all children (0–18 years).

3.7. Risk of bias across studies

Publication bias was assessed by visual inspection of funnel plot graphic.

3.8. Additional analysis

A sensitivity analysis excluding weak quality studies according to EPHPP tool was also performed. Specific combinations of viruses were analyzed if there was sufficient data to permit performing statistical analysis. A *post hoc* analysis was performed excluding studies based mainly on bocavirus and adenovirus combinations, as single or coinfection, due to possibility of persistent asymptomatic shedding of these viruses.

4. Results

4.1. Study selection

As shown in Fig. 1, 5218 articles were identified and the title and abstracts were screened and other 3 articles were identified through grey literature. After removing duplicates, 4965 articles were assessed for eligibility. Of those, 118 studies were included for full-text reading (three translated from Chinese), 59 were included for preliminary analysis and 43 of those selected for main analysis according to criteria described above. Among these, 41 were published in English and two in Spanish. An attempt of contact was done with 33 authors, of which 16 provided additional information.

4.2. Study characteristics

Table 1 summarizes the characteristics of the studies included in the main analysis, such as age, prevalence of coinfection, setting of enrollment, viruses tested through molecular biology techniques, specific combinations of viruses compared and outcomes assessed. Forty-three studies with 17234 patients were included [6,8–10,12–19,21,24–53]. Final analyses included the following outcomes: length of stay (24 studies, 3548 patients), need of hospitalization (11 studies, 9637 patients), need of supplemental oxygen (12 studies, 2285 patients) and length of supplemental oxygen (5

Table 2
Summary of findings and quality of evidence for severity of viral coinfections versus single infections in children.

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Single infection	Risk difference with viral coinfection (95% CI)
Length of stay	3548 (24 studies)	⊕⊕⊕⊖ **MODERATE**[a,b,c,d,e] due to indirectness			The mean length of stay in viral coinfection group was **0.1 lower** (0.51 lower to 0.31 higher)
Death	2296 (7 studies)	⊕⊖⊖⊖ **VERY LOW**[e,f,g,h,i] due to risk of bias, inconsistency, imprecision	**OR 2.22** (0.83–5.95)	**26 per 1000**	**30 more per 1000** (from 4 fewer to 111 more)
Need of hospitalization	9637 (11 studies)	⊕⊕⊕⊖ **MODERATE**[e,g,j,k,l] due to inconsistency	**OR 0.96** (0.61–1.51)	**749 per 1000**	**8 fewer per 1000** (from 104 fewer to 69 more)
Need of mechanical ventilation	492 (3 studies)	⊕⊕⊖⊖ **LOW**[b,e,i,m,n] due to indirectness, imprecision	**OR 0.81** (0.33–2.01)	**63 per 1000**	**11 fewer per 1000** (from 41 fewer to 56 more)
Length of supplemental oxygen	674 (5 studies)	⊕⊕⊕⊖ **MODERATE**[c,d,e,o,p] due to risk of bias			The mean length of supplemental oxygen in viral coinfection group was **0.42 lower** (1.05 lower to 0.2 higher)
Need of supplemental oxygen	2285 (12 studies)	⊕⊕⊖⊖ **LOW**[e,g,l,q,r] due to inconsistency, indirectness	**OR 0.94** (0.66–1.34)	**512 per 1000**	**15 fewer per 1000** (from 103 fewer to 72 more)
Need of PICU	2630 (11 studies)	⊕⊕⊕⊖ **MODERATE**[e,g,l,s,t] due to inconsistency	**OR 0.99** (0.64–1.54)	**220 per 1000**	**2 fewer per 1000** (from 67 fewer to 83 more)

Note: CI: Confidence interval; OR: Odds ratio;
GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Sixteen of twenty four included studies have no substantial risk of bias. The remaining eight have problems due to potential selection bias and/or failures to report or control of confounders.
[b] No serious inconsistency was found.
[c] In sixteen included studies, comparison was based upon specific viral combinations.
[d] Optimal sample size for detecting a difference of 1 day (alpha 0.05 and power of 80%) was met and null hypothesis, which was considered the most plausible, was met.
[e] No substantial publications bias was detected.
[f] Four of included studies have failures to report or control of confounders.
[g] High statistical heterogeneity ($p < 0.01$ and/or $I2 > 50\%$) was found.
[h] In four included studies, comparison was based upon all viral coinfections and all single infections.
[i] Optimal information size was not achieved and 95% confidence interval was wide.
[j] Eight included studies have no substantial risk of bias. The remaining three have failure to report or control of confounders.
[k] In seven included studies, comparison was based upon all viral coinfections and all single infections.
[l] Optimal sample size was met and 95% confidence interval was narrow and included null effect, which was considered most plausible hypothesis.
[m] No serious risk of bias was found in most of bias domains of included studies.
[n] In two included studies, comparison was based upon specific viral combinations.
[o] Three included studies have a substantial risk of bias due to selection bias and/or failure to report or control of confounders.
[p] In three included studies, comparison was based upon all viral coinfections and all single infections.
[q] Eight studies have no substantial risk of bias. The remaining four have failure to report or control of confounders.
[r] In half of included studies, comparison was based upon specific viral combinations.
[s] Six included studies have no substantial risk of bias. The remaining five have failure to report or control of confounders.
[t] In nine included studies, comparison was based upon all viral coinfections and all single infections.

studies, 674 patients), need of PICU (11 studies, 2630 patients) and mechanical ventilation (3 studies, 492 patients, after sensitivity analysis) and death (7 studies, 2296 patients); none study analyzing length of mechanical ventilation and length of PICU stay was included because none searched all viruses required.

4.3. Risk of bias within studies and quality of evidence

As shown in Supplemental Table 1, of 43 studies included, quality according to EPHPP tool was classified as strong in 13, moderate in 22 and weak in 8. The overall quality of evidence found was very low for risk of death, low for need of supplemental oxygen and need of mechanical ventilation and moderate for the remaining outcomes, as described in Table 2.

4.4. Results of individual studies and synthesis of results

For most outcomes assessed, as shown in Figs. 2–4 and Supplemental Figs. 1, 2 and 3, the severity of single and multiple infections were not different, both in the whole group and in the age sub-

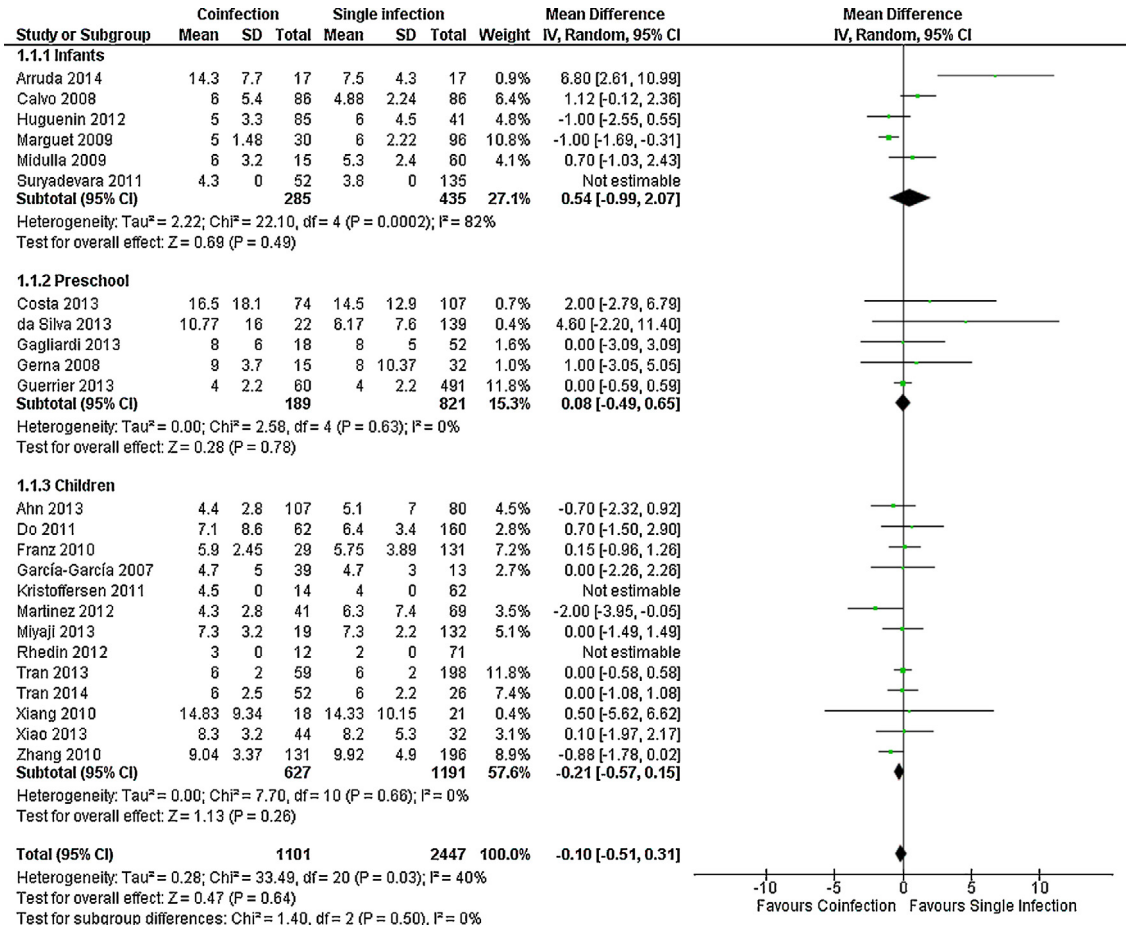

Fig. 2. Meta-analysis for length of stay comparing patients with viral coinfections and single infections in three age groups. Negative value indicates shorter time in patients with coinfections.

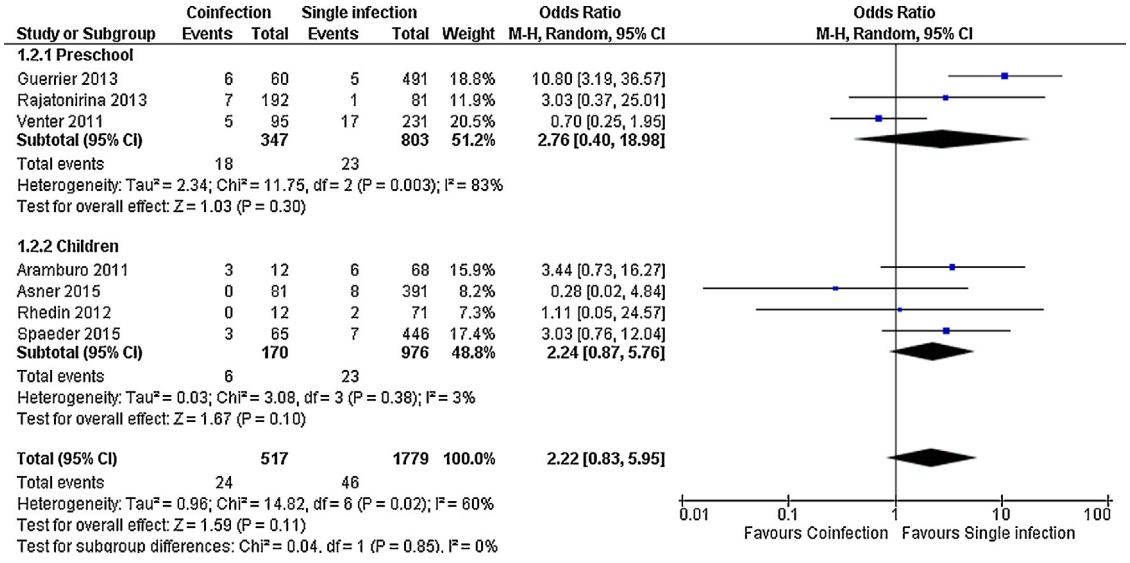

Fig. 3. Meta-analysis for risk of death comparing patients with viral coinfections and single infections in three age groups. Value higher than one indicates higher risk in patients with coinfections.

groups, as for length of stay, MD in days −0.10 (−0.51, 0.31), death, OR 2.22 (0.83, 5.95), need of hospitalization, OR 0.96 (0.61, 1.51), length of supplemental oxygen, MD −0.42 (−1.05, 0.20), need of supplemental oxygen, OR 0.94 (0.66, 1.34) and need of PICU, OR 0.99 (0.64, 1.54). Need of mechanical ventilation was not significant in the overall analysis, but had a trend to occur more often in children with single infection (OR 0.51 (0.26, 1.00)); in infants, however, it was significant (OR 0.34 (0.14, 0.83)) (Supplemental Fig. 4). Preliminary analysis for all outcomes including studies with less complete viral panels had similar results but with higher heterogeneity (data not shown).

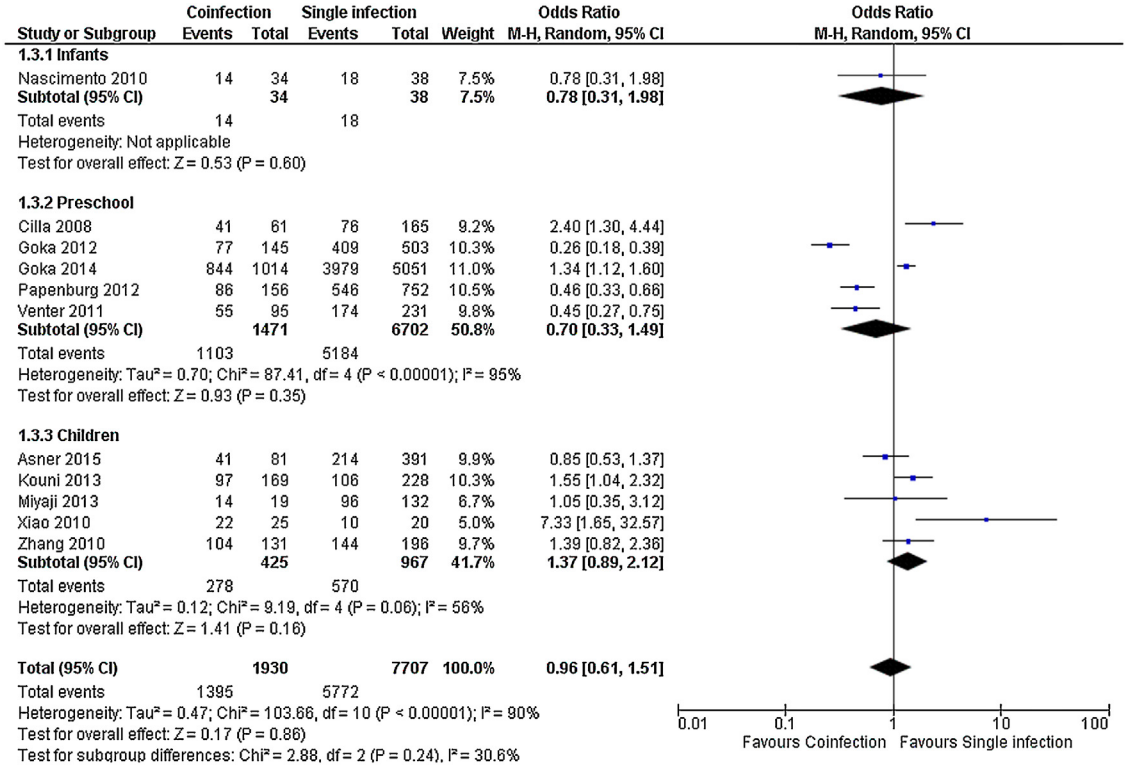

Fig. 4. Meta-analysis for risk of hospitalization comparing patients with viral coinfections and single infections in three age groups. Value less than one indicates less risk in patients with coinfections.

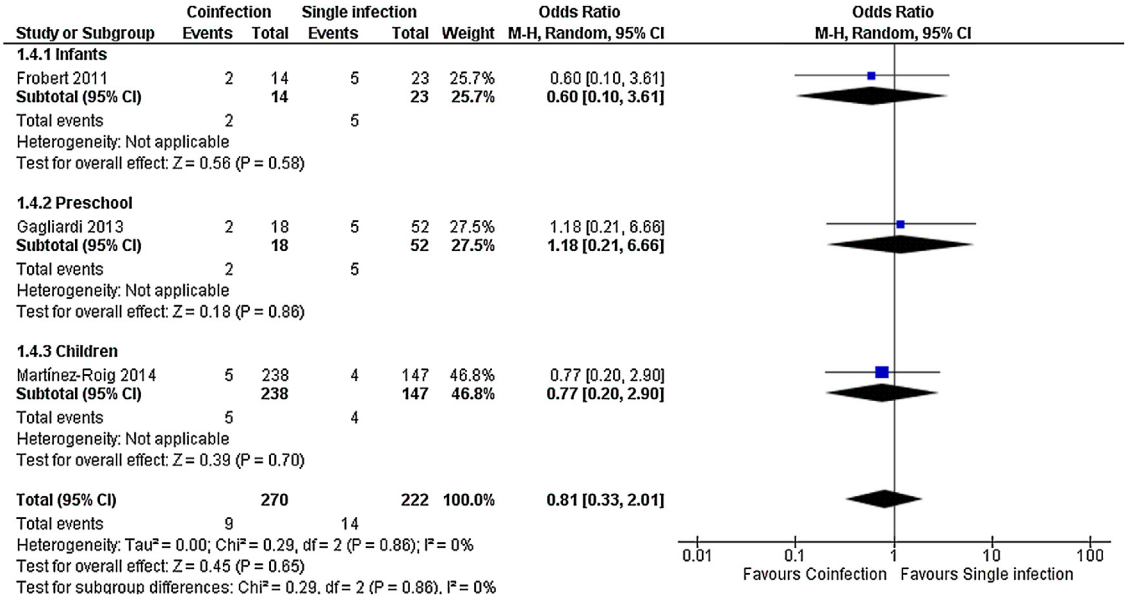

Fig. 5. Meta-analysis for risk of mechanical ventilation comparing patients with viral coinfections and single infections in three age groups. Value less than one indicates less risk in patients with coinfections.

Risk of bias across studies and additional analysis: Higher risk of mechanical ventilation found in studies including only infants was not sustained once a sensitivity analysis excluding weak quality studies was done (Fig. 5). In studies analyzing all other outcomes, findings were not changed after exclusion of weak quality studies (data not shown). None of seven outcomes was changed after exclusion of studies based on bocavirus and adenovirus and after comparing only studies with the same combinations, such as RSV plus others versus only RSV, for example (data not shown). Funnel plot of all outcomes is shown in Supplemental Fig. 5 and was not considered suggestive of an important publication bias for all outcomes, excepting need of mechanical ventilation before sensitivity analysis, which is changed after exclusion of weak quality studies.

5. Discussion

Viral coinfection did not increase severity of any outcome assessed in this systematic review and meta-analysis. From an empirical point of view, it might be logical to expect that the detec-

tion of two or more viruses could enhance illness severity; however, our results did not confirm this.

A few reasons might contribute to our findings. First, the use of molecular biology techniques has demonstrated that viruses may be excreted for a prolonged period, with few or no symptoms [54,55]. Therefore, some patients labeled as having coinfection may actually be subject of co-detection. Studies assessing viral load in attempt to make such distinction have not shown consistent differences between groups for most viruses [6,30,56]. On the other hand, some of these viruses, excreted in otherwise asymptomatic hosts, could enhance overall virulence if another viral infection was to occur. Consequently, it is difficult to rule out the role of even a co-detection in disease severity. Second, the limited possibilities of confirming bacterial etiology in lower respiratory tract infections and, consequently, bacterial-virus coinfection, is still an important challenge in clinical practice [57,58]. Third, the prognosis of respiratory infections may be modified, to better or worse, by specific viral interactions and virus combinations, as some studies have suggested [9]. Nonetheless, sub-analyses with viruses that may have persistent shedding, bocavirus and adenovirus, and attempt to assess role of especific viral combinations did not change our findings. This analysis was particularly difficult not only because report and comparison of several different combinations across studies. As shown in Table 1, since many combinations are reported as, for example, "RSV coinfections", including all different viruses detected with RSV into a single group, evaluation of specific viral interactions was hampered for most outcomes.

There are two previous systematic review and meta-analyses on this topic [59,60]. Both included a mixed population of adults and children, included less studies and had a smaller number of outcomes. The first one included 21 studies and subjects from different age groups and included a subgroup analysis in children; risk of hospitalization was not assessed. They found no association between viral coinfection and length of stay, oxygen requirements, admission to PICU and need of mechanical ventilation [59]. They found a higher mortality risk in preschool children, which was not consistent with our results and previous studies [41,46]. The second systematic review with mixed adult-children population included 19 studies, and reported an overall increase in risk of hospitalization in patients with two or more viruses detected, but there was not a subgroup analysis only with children for this outcome [60]. Besides of a search that ended more than two years later, some methodological reasons seem to account for the differences of those two studies with ours. First, they used less strict criteria for inclusion in meta-analysis and analysis was done including studies with a smaller number of viruses than those we assessed. We pooled studies including at least RSV, influenza, adenovirus, parainfluenza, rhinovirus and metapneumovirus, due to their virulence and prevalence, in an attempt to avoid a measurement bias.

Our study has limitations. Many studies did not measure, report or adjust severity for other confounding factors and interventions that could affect outcomes, such as how fast supportive actions are initiated and presence of comorbidities. Still, this is a broad systematic review and meta-analysis with a considerable number of studies and subjects, and with no language restriction; we also included additional sensitivity analyses excluding weak quality studies and stratified analysis of age groups. We believe that these measures rendered consistent results that can contribute to what is known on this important issue.

The results of this systematic review and meta-analysis suggest that the overall detection of two or more viruses has no impact on disease severity in children with respiratory infections for most clinically important outcomes, despite a relatively high prevalence of codetection or coinfection of respiratory viruses. Further studies are necessary, particularly to clarify the prognostic role of viral combinations.

Authors' contribution

Dr. Scotta conceptualized and designed the study, acted as third reviewer when necessary, extracted data from studies, made initial interpretation of data, drafted the initial manuscript, and approved the final manuscript as submitted.

Drs. Chakr, de Souza, Jones, Pinto, Pitrez and Stein acted in study's conception and design, analysis and interpretation of data, critically revised the manuscript, and approved the final manuscript as submitted.

Drs. de Moura and Becker acted in study's conception and design, acquisition of data as two independent reviewers and interpretation of data, critically revised the manuscript, and approved the final manuscript as submitted.

Dr. Mattiello and Dr Sarria conceptualized and designed the study, supervised data extraction data from studies, performed statistical analysis and interpretation of data, critically revised the manuscript and approved the final manuscript as submitted.

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Competing interests

None declared.

Ethical approval

Not required.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcv.2016.04.019.

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