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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