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Review Article

Single and multiple respiratory virus infections and severity of respiratory disease: A systematic review

Edward Anthony Goka [1,*], Pamela J. Vallely [1], Kenneth J. Mutton [1,2], Paul E. Klapper [1,2]

[1] Institute of Inflammation and Repair, Faculty of Medical and Human Sciences, University of Manchester
[2] Department of Clinical Virology, Central Manchester Universities NHS Trust

EDUCATIONAL AIMS

- To inform scientists on the role of co-infection in acute respiratory tract infection (ARI) leading to hospitalization to a general ward or the ICU, bronchiolitis or pneumonia.
- To highlight the problems of confounding and bias when crude analysis is applied and the importance or need of conducting stratified analysis in research on respiratory virus co-infections.
- To present evidence for multiple testing of respiratory virus infections in patients presenting with influenza like illness.

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admission to a general ward
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disease severity

ABSTRACT

Introduction: There are suggestions that virus co-infections may influence the clinical outcome of respiratory virus illness. We performed a systematic review of the literature to summarise the evidence.
Methods: MEDLINE, EMBASE, Ovid and WEB of Science databases, major organisation websites and reference lists of published studies were searched. The quality of studies was assessed using the STROBE tool (von Elm et al., 1) Individual study data was analyzed using odds ratios and 95% confidence intervals as a measure of association between exposure (co-infection), patient outcome and results summarised using forest plots and tables
Results: Nineteen (19) studies from all over the world were identified and included in the review. Most of the studies 73.7% (14/19) recruited children ≤6 years old. Evidence on the role of co-infection in increasing disease severity was inconclusive. In five out of eight studies, co-infection significantly increased risk of admission to general ward (OR: 2.4, 95% CI: 1.3 - 4.4, p = 0.005; OR: 2.4, 95% CI: 1.1 - 7.7, P = 0.04; OR: 3.1, 95% CI: 2.0 - 5.1, p = <0.001; OR: 2.4, 95% CI: 1.7-3.4, p = <0.0001 and OR: 2.3, 95% CI: 1.1 - 5.1, p = 0.34), one found it did not (OR: 0.59, 95% CI: 0.4 - 0.9, p = 0.02) and the other 2 had insignificant results. Similarly on risk of admission to ICU, some studies found that co-infection significantly increased risk of admission to ICU (OR: 2.9, 95% CI: 1.4 - 5.9, p = 0.004 and OR: 3.0, 95% CI: 1.7 - 5.6, p = <0.0001), whereas others did not (OR: 0.18, 95% CI: 0.05 - 0.75, p = 0.02 and OR: 0.3, 95% CI: 0.2 - 0.6, p = <0.0001). There was no evidence for or against respiratory virus co-infections and risk of bronchiolitis or pneumonia.
Conclusion: The influence of co-infections on severe viral respiratory disease is still unclear. The observed conflict in outcomes could be because they were conducted in different seasons and covered different years and periods. It could also be due to bias towards the null, especially in studies where only crude analysis was conducted. Future studies should employ stratified analysis.

INTRODUCTION

Respiratory viruses including; influenza virus types A and B (Flu A/B), respiratory syncytial virus (RSV), rhinovirus (RV), adenovirus (AdV), human metapneumovirus (hMPV), human coronavirus (hCoV), human bocavirus (hBoV) and human parainfluenza viruses type 1, 2 and 3 (hPIV1-3), have been singly or jointly detected from patients suffering from respiratory diseases [2–5]. Incidence studies have indicated that 15-38% of respiratory infections develop into acute lower respiratory infections (ARIs) with severe signs and symptoms including wheezing, bronchiolitis, croup, high fever and pneumonia with subsequent increases in hospitalization to a general ward (GW), admission to intensive care unit (ICU), or mortality [6–11]. A number of factors have been attributed to the

* Corresponding author.
E-mail address: edwardgoka@postgrad.manchester.ac.uk (E.A. Goka).

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severity of respiratory viral disease including; underlying chronic diseases such as chronic respiratory diseases, diabetes, chronic liver disease, chronic heart disease, chronic renal disease; and other factors such as immunodeficiency, old age, young age, pregnancy, viral genome mutations [11–14]. There are suggestions that the presence of more than one type of virus in the respiratory specimen may also affect the clinical presentation of respiratory tract infection [15–18]. However, the relationship between co-infection and severity of illness remains unclear. This review investigates the relation between co-infection in general and co-infection between influenza and other respiratory viruses and clinical outcome.

METHODOLOGY

We searched the electronic databases; MEDLINE, EMBASE and WEB of Science for primary epidemiological studies on the role of co-infections in causing severe clinical disease; i.e. risk of hospitalization to the GW, admission to ICU or death, and risk of developing bronchiolitis and pneumonia. We also searched websites of health organisations e.g. the World Health Organisation (WHO), United Kingdom's Health Protection Agency (HPA), United States of Americas Centre for Disease Control (CDC), World Influenza Network Centre for bibliography or any published reports on respiratory viruses' co-infections and patient outcome. The MEDLINE and EMBASE system have studies published from May, 1946 to date, whereas the Web of Science has studies published from 1945 to date. The search was refined to include studies related to medicine in general or to specific branches i.e. infectious diseases, virology, internal or respiratory system, pathology and critical care. Reference lists of good quality studies, were also manually searched to identify studies addressing the question under review.

For the electronic databases, the search technique involved combining a number of subject headings and keywords and the scoping of text words; words used included: Viruses, virus, virus diseases, virus infection, respiratory tract infections, respirovirus, respirovirus infections, lower respiratory tract infection(s), upper respiratory tract infection(s), orthomyxoviridae, orthomyxoviridae infections, orthomyxovirus, influenza human, influenza A virus, influenza A virus H1N1 subtype, 2009 H1N1 influenza, influenza A(H1N1)pdm09, influenza A virus H3N2 subtype, rhinovirus, human rhinovirus, rhinovirus infection, adenovirus, adenovirus infection(s), respiratory syncytial virus(es), respiratory syncytial virus infection(s), metapneumovirus, metapneumovirus human, parainfluenza virus 1 human, parainfluenza virus 2 human, parainfluenza virus 3 human, bocavirus, bocavirus infection, coronavirus, coronavirus infection, co-infection(s), mixed infection, dual infection(s), multiple infection(s), virulence, virus virulence, prognosis, pathogenicity, virus pneumonia, bronchiolitis, viral bronchiolitis, hospital, hospitalisation, hospitalization, hospital care, hospital admission, patient admission, length of stay, intensive care, critical care, intensive care unit, ICU admission, fatality, mortality, death.

Study quality assessment and selection criteria

The "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" tool for critical appraisal of epidemiological studies (von Elm et al., [1]), was used to assess the studies identified in the search. Only studies which measured co-infection as a risk factor for disease outcome and included the outcome measures; hospitalization to general ward, admission to ICU, bronchiolitis or pneumonia were included. Studies that investigated exposures other than those investigated in this review i.e. did not include influenza and $\geq$4 of the other respiratory viruses considered as exposures of interest in this study, did not give risk outcome in co-infections vs. single infections, did not report risk of hospitalization to ICU, or general ward, bronchiolitis and pneumonia, did not use PCR or RT-PCR as a diagnostic method, were conducted among patients with underlying chronic diseases or impaired immunostatus, were duplicates of other included studies or had data incompatible with odds ratios calculation, (i.e. with some cells having a zero) were excluded.

Statistical analysis

The exposure of interest was co-infection among eleven respiratory viruses i.e. Flu A/B, RSV, RV, AdV, hMPV, hCoV, hBoV and hPIV1-3. Association between co-infection and severe disease (admission to general ward or ICU, bronchiolitis or pneumonia) was assessed using odds ratios and 95% confidence intervals calculated using single infection(s) as the baseline, or single influenza A or B infection as the baseline, in the analysis of influenza co-infections and severity of respiratory disease. Results from individual studies were summarised using tables and all analyses were done using the Comprehensive Meta-Analysis software – version 2 (BIOSTAT, Englewood, NJ 07631 USA).

RESULTS

Characteristics of the studies included in this review

A summary of the number of studies that were retrieved from each database and the studies that were selected and included in this systematic review is provided in Figure 1. Out of the 3,391 papers identified through electronic and manual search, ninety two (92) papers were reviewed of which 19 were included.

Studies included in this review were from all over the world, i.e. 6 of the included studies were from Europe, 5 from North America, 3 from South America, 3 from Asia and 2 from Africa. The details of the included studies are provided in Table 1. A large number of the studies, 11/19 (57.9%), involved patients hospitalized to a general ward or the intensive care unit with acute respiratory disease, some (6/19; 31.6%) recruited in and outpatients and 2/19 (10.5%) were case-control studies recruiting hospitalized patients and healthy controls. The highest proportion of studies 52.6% (10/19) recruited children $<$6 years old, 6 (31.6%) studies included children $\leq$18 years old, 3 (15.9%) included both adults and children. Most of the studies 14/19 (73.7%) applied a prospective design covering periods ranging from 3 months to 4 years, and 5/19 (26.3%) analysed patients data retrospectively. Together all the studies recruited 12,320 people with 48 as the smallest sample size and 4,336 as the largest sample size, the majority recruiting between 200 and 900 patients.

Factors associated with positivity and co-infection rates

Positivity rates ranged from 30.9% to 96.1% (mean 68.2%) whereas co-infection ranged from 5.0% to 62.0% (mean 23.0%). Respiratory syncytial virus was the most predominant co-infecting virus with most of the studies reporting RSV being the most common among all the viruses involved in the co-infections (Supplementary Table S1). RSV was reported as the most frequent co-infecting with adenovirus by Huguenin et al., [19] and Martin et al., [20] co-infecting with bocavirus by Cilla et al., [21] and Franz et al., [22] and co-infecting with influenza A virus by Boivin et al., [23] and Kouni et al., [24] There was a weak negative correlation between age and high positivity/co-infection rate, such that studies that recruited young children were more likely to report high rates of infection and co-infection (correlation coefficients - 0.56 and 0.35 for infection and co-infection respectively). In studies that recruited both adults and