

Research article

Actual data regarding the impact of viral respiratory co-infection (Covid-19 and flu/Respiratory Syncytial Virus-RSV)- A systematic review

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Abstract: Background. The impact of SARS-CoV-2 infection alongside with influenza and RSV, the major viral agents in pediatric disorders, may be an important concern to the healthcare system. Clinical outcomes of the interaction are unknown. The aim of this systematic review is to contribute at establishing the prevalence of the co-infection, its clinical outcomes and potential risk factors. Methods. A systematic literature search was performed for papers published in PubMed, Scopus, Web of Science, Pedro and Cochrane Library, from January 2020 - the beginning of the COVID 19 pandemic - to June 2023. Our review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methods. Studies were eligible for inclusion if they approached the co-infection COVID 19 and influenza or RSV, and were available in English. Due to the fact that studies conducted on pediatric population are scarce, we included patients of all ages. Results. Out of 159 articles found, 12 were eligible for inclusion. The prevalence of co-infection was between 5% and 12 % for influenza viruses and 10% for RSV. The most common symptoms were high-grade fever, cough, headache, and shortness of breath and the most frequent complications were pneumonia and respiratory distress. In terms of laboratory findings, co-infected patients presented with significant lymphopenia and pronounced inflammatory response, as well as a progressive tendency towards pneumonia and respiratory distress. Regarding the clinical outcomes of co-infection, the majority of articles indicated that simultaneous infection with SARS-CoV-2 and influenza predisposes to a more severe course of the disease(s), with a longer length of hospital stay and an increased risk of death. Conclusion. Our study underlines that the frequency of such co-infections, although not very high, predisposes to more frequent hospitalisations and a longer length of stay, complications including admission to intensive care and more severe outcomes, including life-threatening events. It is therefore essential to determine the epidemiological impact of such an interaction nowadays, in order to inform and adjust treatment and control and prevention strategies, for limiting co-infection between major respiratory viruses. Due to the lack of studies on children, we were unable to identify specific features of co-infections in this population. Therefore, more studies are needed to evaluate the paediatric population and consequently, our doctoral research endeavour is warranted.

Keywords: COVID-19, SARS-CoV-2, Influenza, Co-infection, RSV

Introduction

In December 2019, an outbreak of viral pneumonia caused by a new coronavirus with a high similarity to an acute respiratory syndrome virus (SARS-CoV-2) emerged and was subsequently named SARS-CoV-2 by the World Health Organization (WHO). In 2020, the ongoing pandemic (COVID-19) presented a major challenge to health systems globally and was therefore recognized as a critical public health emergency of international concern.

To date, WHO has reported 702 million confirmed cases and 6 981 064 deaths worldwide.[1] As SARS-CoV-2 continues to spread globally, it overlaps with other respiratory infections, in particular influenza viruses and respiratory syncytial virus (RSV). Influenza virus and SARS-CoV-2 infection share similar symptoms of respiratory illness, including fever, cough, sore throat and fatigue[2], while the hallmarks that differentiate COVID-19 from influenza infection are lacking. Seasonal outbreaks of respiratory syncytial virus (RSV) and influenza virus caused significant morbidity and mortality among young children worldwide.[3] The highest number of hospitalizations due to RSV were reported in children <1 year of age, which traditionally tended to peak in the winter months.[4,5]

Each year, seasonal influenza viruses are estimated to cause >100 million illnesses and 870,000 hospitalizations globally for acute lower respiratory tract infections among children under 5 years of age.[6–8]

During the 2019 coronavirus disease pandemic (COVID-19), the epidemiology of these viruses changed dramatically. Initially, RSV and influenza A/B were low in circulation in 2020. Restrictive measures applied globally, such as social distancing, lockdowns and wearing masks, have limited the transmission of all respiratory viruses. [9,10]

During the 2021/2022 cold season, cases of RSV and influenza have increased and their characteristics have changed, although published data are not yet available on either increased numbers or other changes in the characteristics of these infections. Countries report peaks in incidence at different times, in contrast to trends in previous years before the COVID-19 pandemic[11]. COVID-19 and other respiratory pathogens co-infections may complicate disease course and prognosis.

The effect of COVID 19 - influenza co-infection is a topic of interest in the medical world, there are several studies in the literature on its most important aspects . However, the effects of co-infection with SARS-CoV-2 and influenza virus on the severity of the disease, in terms of mortality, incidence of shock, admission to intensive care units or need for ventilator support are not yet fully understood. In addition, knowledge of pathogenic interactions between SARS-CoV-2 and influenza virus is also limited to date.

It is therefore essential to determine the epidemiological impact of such an interaction to inform and adjust treatment, control and prevention strategies. The current study performed a systematic review to compare clinical features, laboratory findings and the outcome of co-infection with COVID-19 and influenza in patients of all ages.

2. Materials and Methods

The present study was a systematic review which was conducted according to the instruction of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

For this systematic review, a hand-search of published literature was performed in PubMed, Scopus, Pedro, Cochrane Library and Web of Science - to check whether the words identified have been published in Institute for Scientific Information (ISI) indexed journals, to identify all relevant articles from the beginning of the COVID-19 pandemic, January 2020 to 16th of June, 2023. These searches were conducted using a set of key words such as: "influenza", "Sars-CoV-2", "respiratory syncytial virus", "co-infection". Details of search strategy in each database are available in **Table 1**.

Cuvinte cheie	Medline	Scopus	Cochrane	Pedro	Total
"influenza" + "SARS-CoV-2" + "co-infection"	0	0	33	0	33
"Influenza or flu" + "SARS-CoV-2 or covid-19 or coronavirus" + "rsv" + "co-infection"	0	116	0	0	116
"Influenza" + "SARS-CoV-2" + "co-infection" + "treatment" + "rehabilitation"	10	0	0	0	10
Total	10	116	33	0	159

Table 1 Key Words used in the search strategy

We restricted our search to studies published in English. Eligible articles that were included were also those open access, found in journals indexed in ISI/Web of Science. No additional limits such as species or article types were placed during the search process. In the next step, we performed the indirect qualitative filtering process by applying an adapted version of the Pedro classification (the basic criteria being the weighted average number of citations per year). As a result of this weighted average calculation, we classified papers according to the Pedro classification principles. We reported this average on the Pedro scale: 0-10 points.

Inclusion and Exclusion Criteria

1. Studies included in this systematic review were those that satisfied the following criteria: Study subjects were confirmed COVID-19 patients that were positive for influenza virus during their infection of SARS-CoV-2 (detected by PCR or rapid antigenic tests)
2. Studies included a clear description of the disease progress including, shock, being admitted to ICU, requiring ventilatory support and outcomes.

Studies reporting no co-infections or without a clear description of disease outcomes, were excluded.

The screening of the title and abstract were done by two authors, independently. If there were any differences between them, a third author decided if the paper should be included. We conducted a second screening of the full texts of the eligible papers.

3. Results

We interrogated the following databases: PubMed, Scopus, Pedro, Cochrane and Web of Science - to check whether the (initially) found articles were published in ISI indexed journals—ISI (Institute for Scientific Information—ex Thomson Reuters—currently administered by Clarivate Analytics).[12]

Eligible articles were those in written English, open access, published in ISI/Web of Science indexed journals between January 2020 and 16th of June 2023. Contextually, we used a series of key words combination, "syntaxes": "influenza" + "human" + "SARS-CoV2" + "co-infection", "influenza"/ "flu" + "SARS-CoV-2"/ "COVID-19"/ "coronavirus" + "co-infection", "Influenza" + "SARS-CoV-2" + "co-infection" + "treatment" + "rehabilitation". The articles found in these search methods were afterwards filtered in 5 steps (without meta-analysis) on the standardized base of the PRISMA inspired selection methodology. [13]

An initial total of 156 articles were found using the key words. The second step was to remove the duplicates. A total of 12 duplicates were removed, with 147 articles remaining to be reviewed.

Subsequently, of the 147 papers, those that were not found in ISI/Web of science indexed journals were removed. On the remaining 106 items, we implemented a customized Pedro

inspired algorithm for indirect quality classification.[14] As a result of this weighted average calculation we classified according to the Pedro classification principles. We reported this average on the Pedro scale: 0-10 points. Only the papers with a score greater than 4 on Pedro scale were included.

Full text screening was applied to the remaining 26 articles, those with a Pedro score greater than 4. The reasons for excluding 14 articles were various: the lack of co-infection or the co-infection of Covid-19 and bacterial/ fungal infection or the consecutive-infections of these two. The screening process was conducted by two reviewers who applied the eligible criteria and selected studies independently, using the Rayyan software. If there were any disagreements between individual judgements, there was a discussion in order to re-evaluate the paper. If the disagreement was still not resolved, a third author would be asked for an opinion. He made the ultimate decision.

Furthermore, two individuals extracted and received data independently (one extracted and the other one checked the extracted data). The data was recorded using Excel application. If there was unreported data, the study would not be considered eligible.

The main variables that were included were: the incidence of co-infection, age, gender, history of medical conditions, history of vaccination for SARS-CoV-2 and influenza, the need for admission to the intensive care unit (yes/no), the need of oxygen therapy and the period of time, the need for ventilator support and the period of time for using the ventilator, length of hospital and ICU stay, risk of death.

The detailing article selection process is illustrated in **fig 1** - PRISMA CHART

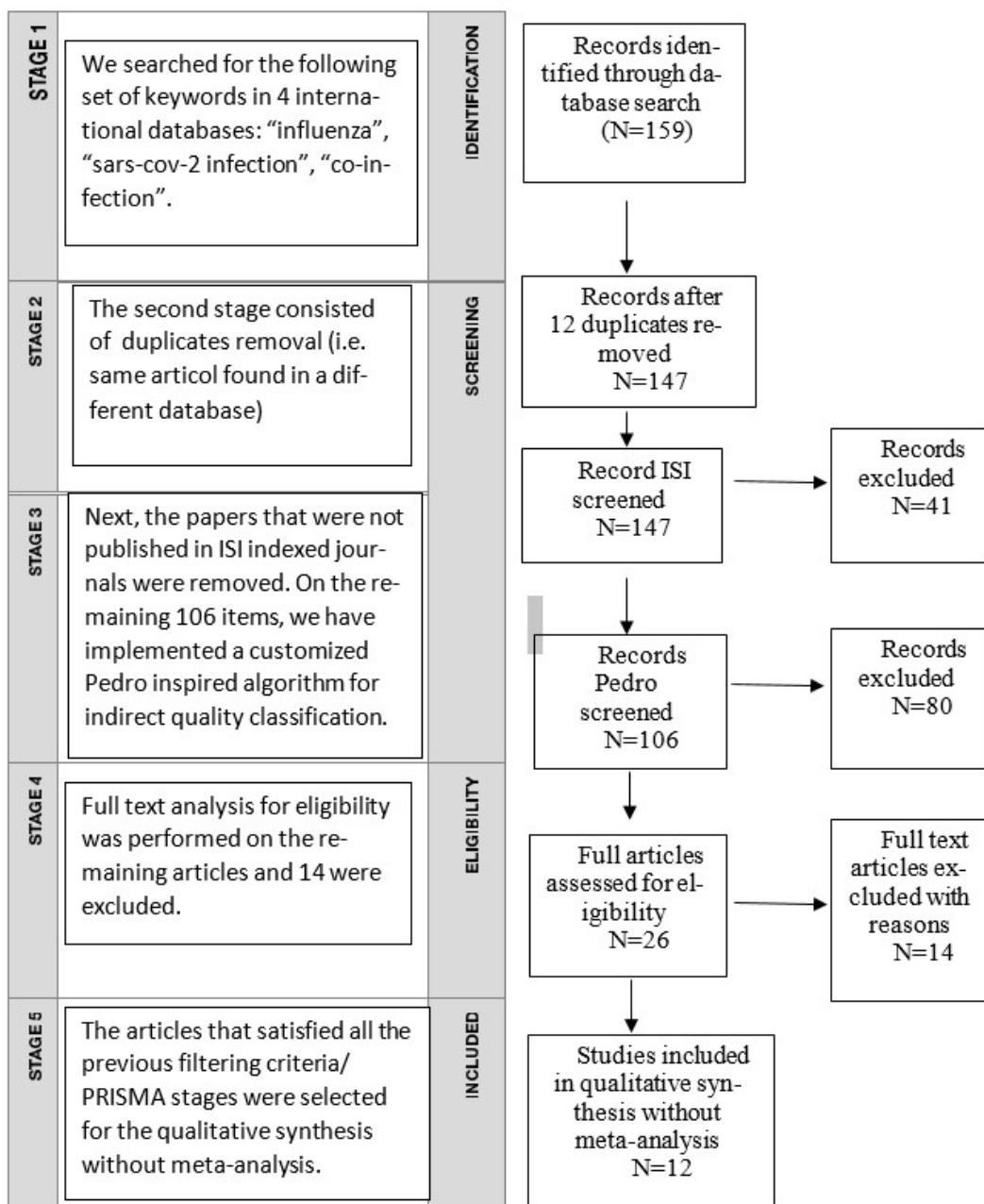


Figure 1. PRISMA guideline flowchart detailing article selection process

In the end, a total of 12 papers were selected [3,15–25] (**Table 2**): 2 case reports, one case series, 2 systematic reviews, one cross-sectional study, one cohort study, one observational study, 2 letters, 2 reviews.

Due to the small number of articles included, no meta-analyses was performed.

Table 2. The articles resulting from our search

No	Article	Year	Cited by	Citation per year	PEDro score
1	Stowe J, Tessier E, Zhao H, Guy R, et al. Interactions between SARS-CoV-2-2 and influenza, and the impact of co-infection on disease severity: a test-negative design. <i>International Journal of Epidemiology</i> . 2021;(4):1124-1133. doi:10.1093/ije/dyab081	2021	63	21	10
2	Tsabouri S, Makis A, Kosmeri C, Siomou E. Risk Factors for Severity in Children with Coronavirus Disease 2019. <i>Pediatric Clinics of North America</i> . 2021;68(1):321-338. doi:10.1016/j.pcl.2020.07.014	2021	70	23.33	10
3	Cuadrado-Payán E, Montagud-Marrahi E, Torres-Elorza M, Bodro M, et al. SARS-CoV-2-2 and influenza virus co-infection. <i>The Lancet</i> . 2020;395(10236):e84. doi:10.1016/S0140-6736(20)31052-7	2020	124	31	10
4	Swets MC, Russell CD, Harrison EM, et al. SARS-CoV-2-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses. <i>The Lancet</i> . 2022;399(10334):1463-1464. doi:10.1016/S0140-6736(22)00383-X	2022	75	37.5	10
5	Yue H, Zhang M, Xing L, Wang K, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. <i>J Med Virol</i> . 2020;92(11):2870-2873. doi:10.1002/jmv.26163	2020	90	22.5	10
6	Khorramdelazad H, Kazemi MH, Najafi A, Keykhaee M, et al. Immunopathological similarities between COVID-19 and influenza: Investigating the consequences of Co-infection. <i>Microbial Pathogenesis</i> . 2021;152:104554. doi:10.1016/j.micpath.2020.104554	2021	53	17.66	8
7	Alosaimi B, Naeem A, Hamed ME, Alkadi HS, et al. Influenza co-infection associated with severity and mortality in COVID-19 patients. <i>Virology</i> . 2021;18(1):127. doi:10.1186/s12985-021-01594-0	2021	46	15.33	7
8	Chotpitayasunondh T, Fischer TK, Heraud J, et al. Influenza and COVID-19: What does co-existence mean? <i>Influenza Other Respi Viruses</i> . 2021;15(3):407-412. doi:10.1111/irv.12824	2021	39	13	6
9	Jiang S, Liu P, Xiong G, Yang Z, et al. Co-infection of SARS-CoV-2-2 and multiple respiratory pathogens in children. <i>Clinical Chemistry and Laboratory Medicine (CCLM)</i> . 2020;58(7):1160-1161. doi:10.1515/cclm-2020-0434	2020	43	10.75	5
10	Pinky L, Dobrovolny HM. SARS-CoV-2 co-infections: Could influenza and the common cold be beneficial? <i>J Med Virol</i> . 2020;92(11):2623-2630. doi:10.1002/jmv.26098	2020	48	12	5
11	Aghbash PS, Eslami N, Shirvaliloo M, Baghi HB. Viral co-infections in COVID-19. <i>Journal of Medical Virology</i> . 2021;93(9):5310-5322. doi:10.1002/jmv.27102	2021	31	10.33	5
12	Krumbein H, Kümmel LS, Fragkou PC, Thölken C, et al. Respiratory viral co-infections in patients with COVID-19 and associated outcomes: A systematic review and meta-analysis. <i>Reviews in Medical Virology</i> . 2023;33(1). doi:10.1002/rmv.2365	2023	8	8	4

With respect to clinical features of co-infection, the majority of articles indicated that simultaneous infection with SARS-CoV-2 and influenza predisposed to a more severe course of disease, with longer hospitalisation and an increased risk of death.[18,19,26]. Moreover, SARS-CoV-2 and flu co-infection was symptomatically prone to dyspnoea as the main symptom, and patients present with significant lymphopenia and pronounced inflammatory response, as well as a progressive tendency towards pneumonia and respiratory distress.[16]

4. Discussion

The extremely contagious SARS-CoV-2 has caused thousands of deaths globally, especially with adults, and presented a serious challenge to healthcare systems worldwide [15]. As a result, numerous studies have been conducted to determine the mechanism of infection, its signs and short and long term consequences, and the causes contributing to its severity and risk of death. The infection is still being studied. One factor that may contribute to the disease's worsening is the co-occurrence of infections.

A systematic review and meta-analysis which assessed the general viral respiratory co-infection in patients with COVID-19, described a rate of co-infection of 5 to 12% with influenza viruses and 10 % with RSV in patients of all ages. [15,26] With the exception of one papers which described the incidence of the co-infection between SARS-CoV2 and RSV, none of the remaining 11 papers analysed this interaction.

According to the findings of prevalence studies that identified the type of influenza virus responsible for the development of illness in individuals with COVID-19, the prevalence of type A influenza virus was found to be significantly higher than type B. This was expected, due to the fact that influenza virus type A is more common than type B overall.[8],[24]

The incidence of the co-infection of SARS-CoV-2 and influenza viruses is controversial and yet not determined. A 2020 study from England, aimed to determine the interaction between these two viruses. Results showed that adults that tested positive for influenza had a 58% lower risk of testing positive for SARS-CoV-2.[27]. At that moment in time, the lower risk of co-infection suggested a pathogenic competition between those two viruses. [28] . Another possible explanation could be the fact that the immune system was somehow stimulated and thus reactive to a viral respiratory co-infection. However, restrictive measures taken to prevent further spreading of the disease, during the early stages of the pandemic, determined a change in the epidemiology of all respiratory infections; therefore, cases of influenza severely decreased that year globally. It is yet to be determined whether there is a the pathogenic competition between SARS-CoV-2 and influenza virus.

COVID-19 frequently presents with respiratory symptoms similar to influenza. The clinical features, mode of transmission, and seasonal synchronicity of influenza virus infection are believed to bear similarities to COVID-19. SARS-CoV2 and influenza co-infection can cause problems for patient diagnosis and treatment; furthermore, this co-infection may worsen the disease's symptoms and consequences, particularly in high risk patients.

Along with the common respiratory symptoms of influenza and SARS-CoV-2 viruses, which include high-grade fever, cough, headache, and dyspnoea, SARS-CoV-2's seasonality overlaps with influenza during winter, thus increasing the number of people with undetected co-infection.[7,16,29].

In the studies that analysed viral respiratory co-infections, clinically, the main symptom described in flu and COVID 19 co-infection, was dyspnoea. [16,19]. Another clinical situation that can lead us to the idea of co-infection, was the presence of acute respiratory distress syndrome (ARDS), which was uncommon in the outbreak of influenza, but was reported more often in COVID-19.[30]

Moreover, hyper inflammation, which is seen in disorders such as ARDS, myocarditis, acute kidney injury, and dysfunction of other organs are found in the co-infection of influenza and COVID 19 patients [10,21,31], owing to the stronger and more frequent activation of the cytokine cascade. [27,32,33]. Therefore, we aimed to evaluate if the co-infection had a clinical specific pattern, which could be easily ignored, and assumed to be the effect of either of the viral infections. But as shown previously, identifying SARS-CoV-2 influenza co-infection is important because early specific antiviral treatment can provide effective care and improve outcomes. [8,34,35]

In terms of laboratory findings, patients with SARS CoV-2 and influenza co-infection presented significant lymphopenia and pronounced inflammatory response, as well as a progressive imagistic tendency towards pneumonia. Various studies concluded that lymphopenia, prolonged prothrombin time (PT), high levels of Lactate dehydrogenase (LDH), aspartate transaminase (AST), alanine transaminase (ALT), C-reactive protein (CRP), along with high procalcitonin and D-dimer levels, may be specific to co-infection, more than to mono-infection alone.[15,30,31] However, patients with high levels of procalcitonin could have had bacterial co-infection. Based on currently available data, it is not possible to identify laboratory values associated with increased disease severity. Further studies need to be undertaken in order to determine the laboratory pattern of the viral co-infection.[6,25,36]

In terms of the prognosis, the co-infection of Sars-CoV-2 and influenza viruses had a higher risk of poorer outcomes – need for ventilatory support and intensive care unit admission and death. [15,21,30,31]

Finally, one limitation of our study is the lack of information from all regions of the world. Secondly, the majority of studies addressed the adult population, with little information about paediatric population. Further studies are needed to evaluate the effect of co-infection in children.

As, like we have appointed, the literature resources approaching this subject matter in children contain, by now, few works and conditioning our quest and filtering only to studies published in English and those published in journals that were indexed ISI Web of Science, this may cause some important studies to be missed.

5. Conclusions

The three viral respiratory infections with major public health impact are SARS-CoV-2, influenza and RSV.

Viral co-infections, although not very frequent, are associated with increased length of hospital and ICU stay and more severe, even life-threatening outcomes.

The incidence of viral co-infections, although not very high, predisposes to more frequent hospitalisations and length of stay, complications including increased need for oxygen therapy, admission to intensive care and more severe outcomes, of life-threatening type.

It is therefore essential to determine the epidemiological impact of such an interaction nowadays, to document and adjust treatment and prevention strategies, in order to limit co-infection between major respiratory viruses, especially in pediatric population. Due to the lack of studies done on children, we were unable to establish the main features of the co-infection in this population. Therefore, more studies are needed to evaluate the paediatric population.

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