The role of respiratory co-infection with influenza or respiratory syncytial virus in the clinical severity of COVID-19 patients: a systematic review and meta-analysis

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Abstract

Aim: To understand the impact of influenza/RSV co-infection on clinical disease severity among COVID-19 patients. Methods: We conducted a systematic literature review of publications comparing the clinical severity between the co-infection group (i.e., influenza/RSV with SARS-CoV-2) and mono-infection group (i.e., SARS-CoV-2), using the following four outcomes: need or use of supplemental oxygen, intensive care unit (ICU) admission, mechanical ventilation and deaths. We summarized the results by clinical outcome and conducted random-effect meta-analyses, where applicable. Results: Twelve studies reporting a total of 7862 COVID-19 patients were included in the review. Influenza and SARS-CoV-2 co-infection was found to be associated with a higher risk of ICU admission (5 studies, OR: 2.09, 95% CI: 1.64-2.68) and mechanical ventilation (5 studies, OR: 2.31, 95% CI: 1.10-4.85). No significant association was found between influenza co-infection and need/use of supplemental oxygen or deaths among COVID-19 patients (4 studies, OR: 1.04, 95% CI: 0.37-2.95; 11 studies, OR: 1.41, 95% CI: 0.65-3.08, respectively). For RSV co-infection, data were only sufficient to allow for analyses for the outcome of deaths, and no significant association was found between RSV co-infection and deaths among COVID-19 patients (3 studies, OR: 5.27, 95% CI: 0.58-47.87). Conclusions: Existing evidence suggests that co-infection with influenza might be associated with a 2-fold increase in the risk for ICU admission and for mechanical ventilation among COVID-19 patients whereas evidence is limited on the role of RSV co-infection. Co-infection with influenza does not increase the risk of death in COVID-19 patients.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a global pandemic and public health concern [1]. Despite the rollout of vaccination programs and implementation of non-pharmaceutical interventions (NPIs), the number of infected cases kept rising rapidly particularly after the emergence of the delta variant and recently, the emergence of the omicron variant. Globally, as of March 17, 2022, there have been over 460 million COVID-19 cases and over 6 million deaths [2].

Both influenza and respiratory syncytial virus (RSV) are the most common respiratory viruses mainly affecting young children and older adults, especially in low and middle income countries (LMICs)[3–7]. Globally, it is estimated that in the year of 2016, influenza and RSV were associated with 39 and 25 million acute lower respiratory infection episodes, and 58,000 and 77,000 deaths, respectively [8]. In most temperate regions, influenza and RSV normally circulates in autumn and winter months[9]. During the COVID-19 pandemic, the activity of both viruses was low early on due to the large-scale implementation of NPIs but then the resurgence of RSV epidemic was observed in a number of countries globally since late 2020[10], followed by the resurgence of influenza epidemic in the winter of 2021 [11]. While there is no doubt that the comeback

of influenza and RSV will pose greater pressures on health-care providers who are already over-stretched in response to the COVID-19 pandemic, it is not yet known for individual COVID-19 patients, whether co-infection of influenza or RSV could further increase their clinical severity.

In the present study, we aimed to systematically and critically review the existing evidence on the impact of co-infection with influenza or RSV on disease severity in COVID-19 patients.

Methods

Search strategy and selection criteria

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Text S1) and Synthesis without meta-analysis in systematic reviews (SWiM) reporting guideline (Text S2). The protocol of this review was registered in International Prospective Register of Systematic Review (PROSEPRO) with registration number CRD42021283045. We searched the following electronic databases: MEDLINE, EMBASE, Web of Science, the WHO COVID-19 Global literature on coronavirus disease database, China National Knowledge Infrastructure (CNKI), WanFang, CqVip, and Sinomond for relevant publications from January 1, 2020 to December 31, 2021 using a tailored search strategy (Text S3). No restrictions on language were applied. The reference lists of eligible studies were also examined for eligibility. The following selection criteria were applied.

Inclusion criteria

Population-based studies reporting any laboratory-confirmed co-infections with influenza or RSV in COVID-19 patients; AND

At least one of the following outcomes should be reported separately in co-infection group (i.e., SARS-CoV-2 and influenza / RSV) and mono-infection group (i.e., SARS-CoV-2): need or use of supplemental oxygen, ICU admission, mechanical ventilation (including invasive and non-invasive ventilation) and deaths.

Exclusion criteria

- Studies that focused on reporting nosocomial infections; OR
- Studies that only included patients with comorbidities (e.g., patients with chronic obstructive pulmonary disease, or patients infected with human immunodeficiency virus) OR
- Reviews or studies reporting data that were previously reported by another study (in which case only the primary studies were considered for inclusion).

Systematic literature review

Two reviewers (BC and SD) independently screened titles, abstracts and full-texts of the retrieved records from the literature search, and extracted data using tailored data extraction template. The data extraction template consisted of two parts: the first part collected study-level characteristics such as the study location, period, number of subjects, age of subjects, statistical method, disease severity outcomes reported, clinical specimens, viral diagnostic techniques and so on; the second part collected data on the clinical outcomes by mono- infection group and co-infection group. Any discrepancies during data screening and extraction were resolved among YL, BC and SD.

Quality assessment

Quality assessment was conducted for all included studies independently by two reviewers (BC and SD). The questionnaire used for the quality assessment was modified based on the Critical Appraisal Skills Programme

(CASP) checklist for cohort studies[12]. The modified questionnaire contained the following seven questions: 1. Did the study address a clearly focused issue?, 2. Were the subjects recruited in an acceptable way?, 3. Was the exposure accurately measured to minimize bias?, 4. Was the outcome accurately measured to minimize bias?, 5. Have the authors used multivariable analysis method to adjust for confounders?, 6. Can the results be applied to the local population?, 7. Do the results of this study fit with other available evidence? The questionnaire contained seven questions and answer to each of the questions could be "Yes", "No", or "Can't tell", corresponding to 1, 0 and 0 points, respectively. We calculated the overall score for each study after assessing each criterion as listed above. Studies with 7, 5-6 and [?]4 points were defined as "high quality", "moderate quality" and "low quality", respectively. Any discrepancies during quality assessment were resolved among YL, BC and SD.

Data analysis

A narrative synthesis was conducted for all outcomes of interest. The outcomes were compared between the mono-infection group and the co-infection group. A random-effect meta-analysis of the corresponding odds ratios was conducted if three or more studies were available per comparison (i.e., influenza and SARS-CoV-2 co-infection vs SARS-CoV-2 mono-infection, and RSV and SARS-CoV-2 co-infection vs SARS-CoV-2 mono-infection). The choice of conducting a random-effect meta-analysis (rather than fixed-effect meta-analysis) was based on the anticipation that populations included in the studies differed by region, age, study period (in relation to the COVID-19 pandemic), clinical specimens and diagnostic methods. We applied a continuity correction of 0.5 if no one had severity outcomes in any group [13]. This allowed calculation of an OR for these instances, and enabled inclusion within subsequent meta–analyses. When odds ratios could be obtained both from univariate analysis and multivariate analysis in a report, the one from the multivariate analysis was included in the meta-analysis. For influenza and SARS-CoV-2 co-infection, the subgroup analysis was conducted by influenza type (i.e., influenza A and influenza B) if data allowed. Sensitivity analyses excluding studies with small sample sizes (defined as [?] 5 subjects in any of the mono-infection and co-infection groups) and excluding those low-quality studies were performed. Symmetry of funnel plot and Egger's regression method were used to evaluate the presence of small study effects [14]. Heterogeneity was evaluated by I^2 values; I^2 value of >50% and >75% suggested moderate and high heterogeneity, respectively [15]. All statistical analyses and data visualizations were performed with R version 4.1.0.

Results

Review process

After elimination of duplicates, 1591 records were assessed by title and abstract, of which 164 records were further assessed by full-text. Finally, a total of 12 studies were included (Figure 1).

Characteristics of included studies

Of the 12 studies included, eleven [16–26] investigated the role of influenza co-infection with SARS-CoV-2 in the outcomes of interest, and three [22,23,27] investigated the role of RSV co-infection with SARS-CoV-2. The included studies represented 955 laboratory-confirmed COVID-19 patients coinfected with influenza or RSV and 6907 patients infected with SARS-CoV-2 mono-infection. All studies reported deaths as one of the outcomes of interest; four, six and six studies reported the outcomes of need or use of supplemental oxygen, mechanical ventilation and ICU admission, respectively.

All studies were conducted in inpatient settings except one study [19] with mixed settings (i.e., inpatients, emergence department and outpatients). Subject age varied greatly across the included studies and was reported in various statistical forms (e.g., frequency by age group, mean and standard deviation, median, etc.). The total number of SARS-CoV-2 coinfected with influenza/RSV and mono-infected patients per

study ranged from 22 to 4501. The included studies were mainly conducted in Asia (9/10), among which six [16,17,21–23,25] were from China. For viral detection method, SARS-CoV-2 was detected using PCR for all studies whereas influenza and / or RSV co-infection was confirmed by PCR, serological testing or antigen assays. The quality assessment of included studies is provided in Table S1. Four studies [16,17,19,25] were assessed as high-quality and they used multivariate statistical methods to account for common confounders such as age, sex, and comorbidities. The basic characteristics of the included studies are available in Table 1.

Co-infection and risk of need or use of supplemental oxygen

Four studies[16,22,25,26] reported the need or use of supplemental oxygen as an outcome (four on influenza and one [22] on RSV co-infection).

Our meta-analysis results showed that SARS-CoV-2 co-infection with influenza did not seem to be associated with increased need or use of supplemental oxygen compared with SARS-CoV-2 mono-infections (OR=1.04, 95% CI: 0.37-2.95) (Figure 2, panel A). When excluding studies with small sample size or low-quality studies, the meta-estimates did not differ substantially from the main analyses (Figure S1, panel A; Figure S2, panel A). SARS-CoV-2 co-infection with influenza A virus was also not observed to be associated with increased need or use of supplemental oxygen (OR=1.28, 95% CI: 0.36-4.53) (Figure 2, panel B). Two high-quality studies showed contrasting findings: one study [16] showed SARS-CoV-2 co-infection with influenza A virus was associated with decreased need or use of supplemental oxygen (OR=0.61, 95% CI: 0.48-0.76) whereas no such difference was observed on SARS-CoV-2 co-infection with influenza B virus (OR=0.97, 95% CI: 0.56-1.67); the other study [25] showed that SARS-CoV-2 co-infection with influenza was associated with increased need or use of supplemental oxygen (OR=2.47, 95%CI: 1.04-5.86).

Only one study [22] had available data on SARS-CoV-2 co-infection with RSV; however, none of the included patients in that study required supplemental oxygen.

Co-infection and risk of mechanical ventilation

Six studies[17,19,22,24,25,27] reported mechanical ventilation as an outcome (all but one [27] on influenza and two studies [22,27] on RSV co-infection).

Based on the meta-analysis results, SARS-CoV-2 co-infection with influenza was found to be associated with a higher risk of mechanical ventilation as compared to SARS-CoV-2 mono-infection (OR=2.31, 95% CI: 1.10-4.85) (Figure 3, panel A). SARS-CoV-2 co-infection with influenza A virus was also associated with a higher risk mechanical ventilation (OR=5.04, 95% CI: 2.19-11.62) (Figure 3, panel B). After excluding low-quality studies, a similar meta-estimate was observed (Figure S2, panel B). Results from two high-quality studies [19,25]using multivariable models were consistent with our meta-estimates although another high-quality study [17] showed no significant difference in receiving mechanical ventilation between the two groups.

Regarding the SARS-CoV-2 co-infection with RSV, one moderate-quality study [27] indicated that the co-infection was not associated with increased risk of mechanical ventilation (OR=5.00, 95% CI: 0.27-93.96) in children under two years old. The other low-quality[22] study reported no patients receiving mechanical ventilation in either group.

Co-infection and risk of admission to intensive care unit (ICU)

Six studies[18,19,22,24,25,27]compared the utilisation of intensive care between mono-infection and co-infection (all but one[27] on influenza and two [22,27] on RSV co-infection).

Based on the meta-analysis results, SARS-CoV-2 co-infection with influenza was associated with a higher risk of ICU admission compared with SARS-CoV-2 mono-infection (OR=2.09, 95% CI: 1.64-2.68) (Figure 4,

panel A). Sensitivity analysis revealed a similar meta-estimate when excluding low-quality studies (Figure. S2, panel C). SARS-CoV-2 co-infection with influenza A virus was also associated with a higher risk of ICU admission (OR=2.11, 95% CI: 1.61-2.76) (Figure 4, panel B). Results from the two high-quality studies [19,25] were in accordance with the meta-analysis results.

Two studies [22,27] investigated the SARS-CoV-2 co-infection with RSV. One moderate-quality study [27]found no significant difference in ICU admission (OR: 2.40, 95% CI: 0.18-31.88) between mono- and co-infection groups. Another one low-quality study [22] reported no patients being admitted to ICU.

Co-infection and risk of death

All studies included in our review reported the proportion of deaths in mono- and co-infection groups (all but one [27] on influenza and three[22,23,27] on RSV co-infection).

For SARS-CoV-2 co-infection with influenza, the meta-analysis results showed that the co-infection was not associated with increased risk of death compared with SARS-CoV-2 mono-infection (OR=1.41, 95% CI: 0.65-3.08) (Figure 5, panel A). Sensitivity analyses that excluded studies with small sample size and low-quality studies showed similar meta-estimates (Figure S1, panel B; Figure S2, panel D). Similar results were also found in subgroup analysis by co-infection of influenza A and B virus (Figure 5, panel B, C). Findings from high-quality studies showed contrasting results: two studies [16,17] reported decreased risk of death in co-infection group (OR=0.51, 95% CI: 0.36-0.73; OR=0.26, 95% CI: 0.07-0.95, respectively) whereas another study [19] reported increased risk of death (OR: 2.27,95% CI: 1.23-4.19); in addition, another two studies[24,25] (moderate-quality and high-quality, respectively) reported no differences in risk of death between the two groups (OR=4.61,95% CI: 0.98-21.67; OR=21.09, 95% CI: 0.84-527.66, respectively).

With respect to SARS-CoV-2 co-infection with RSV, three lower-quality studies [22,23,27] reported very small number of coinfected patients (range: 1-6). Our meta-analysis results suggested that no significant association was found between the co-infection status and death (OR=5.27, 95% CI: 0.58-47.87) (Figure 5, panel D).

Discussion

In this systematic review and meta-analysis, we included 955 laboratory-confirmed COVID-19 patients coinfected with influenza or RSV and 6907 patients infected with SARS-CoV-2 alone from 12 retrospective observational studies. We found that co-infection with influenza was associated with a 2-fold increase in the risk for ICU admission and for mechanical ventilation among COVID-19 patients whereas evidence was limited on the role of RSV co-infection. Co-infection with influenza did not seem to increase the risk of death in COVID-19 patients.

The 2-fold increase in the risk of ICU admission and receiving mechanical ventilation in COVID-19 patients coinfected with influenza could have important implications for the clinical management. COVID-19 patients who received influenza positive tests before or upon admission might benefit from early interventions that could prevent or slow disease deterioration. This also highlights the importance of influenza vaccination program that might have been suspended because of the COVID-19 pandemic[28].

Earlier systematic reviews that compared co-infections of any viruses (rather than co-infection of influenza as used in this study) with mono-infection among COVID-19 patients did not observe any statistical differences in ICU admission between the co-infection and mono-infection groups [29–31]. This suggests that the increased risk of ICU admission in the co-infection group observed in our study was likely to be influenza-specific. One of the possible explanations is that influenza co-infection could predispose patients to secondary bacterial infections, which could lead to more severe clinical outcomes[32,33]. This explanation is supported by a recently published study in Israel that observed substantial reductions in pneumococcal diseases in young children

during the COVID-19 pandemic; the authors showed that the reductions in pneumococcal and pneumococcus-associated diseases were not predominantly related to reduced pneumococcal carriage and density but were strongly associated with the disappearance of specific respiratory viruses such as influenza[34]. The role of influenza co-infection in the increased severity of COVID-19 patients was also supported by influenza probe studies. In a large Brazilian cohort study of over 53,000 COVID-19 patients, those who received a recent influenza vaccine had 7% lower risks of requiring intensive care treatment (95% CI: 2% to 13%) and 17% lower risks of requiring invasive respiratory support (95% CI: 12% to 23%)[35]. Moreover, a recently published animal model study found that simultaneous or sequential co-infection by SARS-CoV-2 and the influenza A(H1N1)pdm09 strain caused more severe disease than mono-infection by either virus in hamsters [36].

However and interestingly, a systematic review and meta-analysis by Guan and colleagues reported that influenza co-infection lowered the risk for critical outcomes (composite outcomes including any of shock, being admitted to ICU and requiring ventilatory support), with the pooled OR of 0.64 (0.43 to 0.97) based on five studies [37]. As this was contrary to the findings of our study, we closely compared the methodology and the extractions between our study and that by Guan and colleagues; in addition to the use of the composite outcomes as mentioned above that differed from our study, the meta-estimate by Guan and colleagues was largely driven by a preprint that only had univariate OR available for extraction. Moreover, there seemed to be a discrepancy in the extracted OR in the study by Guan and colleagues — one of the included studies, by Stowe and colleagues, [19] reported that COVID-19 patients with influenza co-infection were around twice as likely to be ventilated (OR 2.15, 1.20 to 3.84) or to be admitted to ICU (OR 2.08, 1.17 to 3.70) through multivariate analysis whereas the OR was extracted as 0.91 (0.41 to 2.02) in the report by Guan and colleagues. After removing the preprint and correcting the extraction above from the included studies by Guan and colleagues, the updated OR in their study reversed — 1.76 (1.06 to 2.92), which re-confirmed the robustness of the meta-estimates in our study (details are provided in Figure S4).

Our meta-analysis revealed that co-infection with SARS-CoV-2 and influenza had no observable effects on the overall mortality in both the main and the two sensitivity analyses (i.e., excluding studies with small sample size and excluding low-quality studies). Nonetheless, these findings did not yet indicate that co-infection of influenza did not increase the risks of mortality. We could not rule out type II error (i.e., false negative) due to the limited statistical power; most studies had less than 50 COVID-19 patients with co-infections and the median number of deaths is 1 (IQR: 0-4). Moreover, the point estimates from the main and sensitivity analyses were consistently above 1, favouring the association between influenza co-infection and mortality.

Similar to influenza co-infection, no effects on the overall mortality were observed for RSV co-infection but this was only based on three small studies. Our review highlighted the gaps in the knowledge on the role of RSV co-infection in COVID-19 disease severity. A retrospective study among six children's hospitals in the United States revealed that one in six COVID-19 inpatients under 18 years old had viral co-infections, with two thirds of viral co-infections being RSV co-infections; the proportion of viral co-infections was even higher in infants under one year — one in three infants hospitalized for COVID-19 had viral co-infections, with almost three quarters of them having RSV co-infections [38]. The substantial proportion of RSV co-infection among paediatric COVID-19 patients calls for further research on the possible synergistic effects of the RSV and SARS-CoV-2 in this vulnerable age group.

At the time of writing of this manuscript, a large-scale study from the UK (including about 7000 COVID-19 patients) was published, which reported that that influenza co-infection was associated with increased odds of receiving invasive mechanical ventilation among COVID-19 patients (OR: 4.1, 2.0 to 8.5) in a multivariable regression analysis, further confirming the findings of our study[39]. The authors of that study did not find any significant associations for co-infection with other viruses including adenovirus and RSV, confirming our speculation that the association on viral co-infection and COVID-19 clinical severity is specific to influenza. Ad-hoc inclusion of the estimates from that study did not substantially change our meta-estimates (Table S2).

We acknowledge some limitations of this study. Several factors could contribute to heterogeneity in the findings of the studies, such as study population (including age and sex), case definition, laboratory method

and statistical method; we were unable to explicitly account for these variations. In the present review, there were only four studies applying multivariate analyses to adjust for common confounders between co-infections and severity outcomes. Although restricting to these high-quality studies did not substantially change any of our findings, this highlighted the lack of high-quality studies on the role of co-infections and COVID-19 disease severity. We were also unable to account for bacterial co-infection in the analysis due to the absence of data that had reliable laboratory confirmation on viral and bacterial infections. Compared with other outcomes, mortality as the proxy for disease severity was more likely to be affected by variations in clinical treatment, which could confound the estimates if treatment differed by status of co-infection. All of the included studies were conducted in 2020 when the activity of influenza and RSV was on the course to gradual reduction; it remains unknown whether the resurgence of influenza and RSV could modify the association reported in this review.

Despite these limitations, this systematic review and meta-analysis includes a comprehensive summary with extensive literature search, and critical appraisal and synthesis of existing evidence on the role of influenza and RSV co-infection in the clinical severity of COVID-19 patients. While our study highlights the gaps in research on this topic particularly for RSV, existing evidence suggests that influenza co-infection could increase the disease severity of COVID-19 patients, which could have important implications for clinical management as well as influenza vaccination campaign in the context of resurgence of influenza among other respiratory viruses in the post-COVID-19 era.

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REFERENCES

1. Yang J, Chen X, Deng X, et al. Disease burden and clinical severity of the first pandemic wave of COVID-19 in Wuhan, China. *Nat Commun* . 2020;11:5411. doi:10.1038/s41467-020-19238-2

2. WHO Coronavirus (COVID-19) Dashboard. Accessed March 18, 2022. https://covid19.who.int

3. Shi T, McLean K, Campbell H, Nair H. Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis. *J Glob Health* . 2015;5(1):122-131. doi:10.7189/jogh.05.010408

4. Shi T, Arnott A, Semogas I, et al. The Etiological Role of Common Respiratory Viruses in Acute Respiratory Infections in Older Adults: A Systematic Review and Meta-analysis. *J Infect Dis* . 2020;222(Supplement_7):S563-S569. doi:10.1093/infdis/jiy662

5. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *LANCET* . 2017;390(10098):946-958. doi:10.1016/S0140-6736(17)30938-8

6. Shi T, Denouel A, Tietjen AK, et al. Global Disease Burden Estimates of Respiratory Syncytial Virus–Associated Acute Respiratory Infection in Older Adults in 2015: A Systematic Review and Meta-Analysis. *J Infect Dis* . 2020;222(Supplement_7):S577-S583. doi:10.1093/infdis/jiz059

7. Wang X, Li Y, O'Brien KL, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. *LANCET Glob Health* . 2020;8(4):E497-E510. doi:10.1016/S2214-109X(19)30545-5

8. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis* . 2018;18(11):1191-1210. doi:10.1016/S1473-3099(18)30310-4

9. Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *Lancet Glob Health* . 2019;7(8):e1031-e1045. doi:10.1016/S2214-109X(19)30264-5

10. Li Y, Wang X, Cong B, Deng S, Feikin DR, Nair H. Understanding the potential drivers for respiratory syncytial virus rebound during the COVID-19 pandemic. *J Infect Dis* . Published online January 14, 2022:jiab606. doi:10.1093/infdis/jiab606

11. Project FluCov * 2021-2022 | Nivel. Accessed January 17, 2022. https://www.nivel.nl/en/nivel-zorgregistraties-eerste-lijn/project-flucov-2021-2022

12. Brice R. CASP CHECKLISTS. CASP - Critical Appraisal Skills Programme. Accessed April 2, 2022. https://casp-uk.net/casp-tools-checklists/

13. Sankey SS, Weissfeld LA, Fine MJ, Kapoor W. An assessment of the use of the continuity correction for sparse data in meta-analysis. *Commun Stat - Simul Comput* . 1996;25(4):1031-1056. doi:10.1080/03610919608813357

14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* . 1997;315(7109):629-634.

15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* . 2003;327(7414):557-560.

16. Wu P, Lu W, He L, et al. COVID-19 Patients with Recent Influenza A/B Infection: A Retrospective Study. *J Infect* . 2021;82(1):159-198. doi:10.1016/j.jinf.2020.05.050

17. Tong X, Xu X, Lv G, et al. Clinical characteristics and outcome of influenza virus infection among adults hospitalized with severe COVID-19: a retrospective cohort study from Wuhan, China. *BMC Infect Dis* . 2021;21:341. doi:10.1186/s12879-021-05975-2

18. Alosaimi B, Naeem A, Hamed ME, et al. Influenza co-infection associated with severity and mortality in COVID-19 patients. *Virol J* . 2021;18(1):127. doi:10.1186/s12985-021-01594-0

19. Stowe J, Tessier E, Zhao H, et al. Interactions between SARS-CoV-2 and influenza, and the impact of coinfection on disease severity: a test-negative design. *Int J Epidemiol* . 2021;50(4):1124-1133. doi:10.1093/ije/dyab081

20. Takahashi M, Egorova NN, Kuno T. COVID-19 and influenza testing in New York City. *J Med Virol* . 2021;93(2):698-701. doi:10.1002/jmv.26500

21. Zhu X, Ge Y, Wu T, et al. Co-infection with respiratory pathogens among COVID-2019 cases. *Virus Res* . 2020;285:198005. doi:10.1016/j.virusres.2020.198005

22. Zhang C, Gu J, Chen Q, et al. Clinical and epidemiological characteristics of pediatric SARS-CoV-2 infections in China: A multicenter case series. Persson LÅ, ed. *PLOS Med* . 2020;17(6):e1003130. doi:10.1371/journal.pmed.1003130

23. Li Y, Wang H, Wang F, et al. Co-infections of SARS-CoV-2 with multiple common respiratory pathogens in infected children.*Medicine (Baltimore)* . 2021;100(11):e24315. doi:10.1097/MD.0000000000024315

24. Agarwal A, Agarwal M, Sharma A, Jakhar R. Impact of influenza A co-infection with COVID-19. *Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis* . 2021;25(5):413-415. doi:10.5588/ijtld.21.0086

25. Zheng J, Chen F, Wu K, et al. Clinical and virological impact of single and dual infections with influenza A (H1N1) and SARS-CoV-2 in adult inpatients. *PLoS Negl Trop Dis* . 2021;15(11):e0009997. doi:10.1371/journal.pntd.0009997

26. Akhtar Z, Islam MA, Aleem MA, et al. SARS-CoV-2 and influenza virus coinfection among patients with severe acute respiratory infection during the first wave of COVID-19 pandemic in Bangladesh: a hospital-based descriptive study. *BMJ Open* . 2021;11(11):e053768. doi:10.1136/bmjopen-2021-053768

27. Alvares PA. SARS-CoV-2 and Respiratory Syncytial Virus Coinfection in Ho. . . : The Pediatric Infectious Disease Journal. *Pediatr Infect Dis J* . 2021;40(4):e164-e166. doi:10.1097/INF.0000000000003057

28. Wang X, Kulkarni D, Dozier M, et al. Influenza vaccination strategies for 2020-21 in the context of COVID-19. *J Glob Health* . 2020;10(2):021102. doi:10.7189/jogh.10.021102

29. Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect* . 2020;81(2):266-275. doi:10.1016/j.jinf.2020.05.046

30. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: A systematic review and meta-analysis. *PloS One* . 2021;16(5):e0251170. doi:10.1371/journal.pone.0251170

31. Alhumaid S, Al Mutair A, Al Alawi Z, et al. Coinfections with Bacteria, Fungi, and Respiratory Viruses in Patients with SARS-CoV-2: A Systematic Review and Meta-Analysis. *Pathog Basel Switz* . 2021;10(7):809. doi:10.3390/pathogens10070809

32. Li Y, Peterson ME, Campbell H, Nair H. Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies. *BMJ Open* . 2018;8(4):e019743. doi:10.1136/bmjopen-2017-019743

33. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. *Clin Infect Dis Off Publ Infect Dis Soc Am* . 2000;30(5):784-789. doi:10.1086/313772

34. Danino D, Ben-Shimol S, Van Der Beek BA, et al. Decline in Pneumococcal Disease in Young Children during the COVID-19 Pandemic in Israel Associated with Suppression of seasonal Respiratory Viruses, despite Persistent Pneumococcal Carriage: A Prospective Cohort Study.*Clin Infect Dis Off Publ Infect Dis Soc Am* . Published online December 14, 2021:ciab1014. doi:10.1093/cid/ciab1014

35. Fink G, Orlova-Fink N, Schindler T, et al. Inactivated trivalent influenza vaccination is associated with lower mortality among patients with COVID-19 in Brazil. *BMJ Evid-Based Med* . Published online December 11, 2020:bmjebm-2020-111549. doi:10.1136/bmjebm-2020-111549

36. Aj Z, Ac L, Jf C, et al. Coinfection by Severe Acute Respiratory Syndrome Coronavirus 2 and Influenza A(H1N1)pdm09 Virus Enhances the Severity of Pneumonia in Golden Syrian Hamsters. *Clin Infect Dis Off Publ Infect Dis Soc Am* . 2021;72(12). doi:10.1093/cid/ciaa1747

37. Guan Z, Chen C, Li Y, et al. Impact of Coinfection With SARS-CoV-2 and Influenza on Disease Severity: A Systematic Review and Meta-Analysis. *Front Public Health* . 2021;9:773130. doi:10.3389/fpubh.2021.773130

38. Wanga V, Gerdes ME, Shi DS, et al. Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19 - Six Hospitals, United States, July-August 2021. *MMWR Morb Mortal Wkly Rep* . 2021;70(5152):1766-1772. doi:10.15585/mmwr.mm705152a3

39. Swets MC, Russell CD, Harrison EM, et al. SARS-CoV-2 co-infection with influenza viruses, respiratory syncytial virus, or adenoviruses.*Lancet Lond Engl* . Published online March 25, 2022:S0140-6736(22)00383-X. doi:10.1016/S0140-6736(22)00383-X

Figures and Tables:

Figure 1. PRISMA diagram for selection of studies.

Figure 2. Comparison of risk for need or use of supplemental oxygen between SARS-CoV-2 co-infection with influenza and SARS-CoV-2 mono-infection. N-the total number of SARS-CoV-2 coinfected and mono-infected patients; QA-the score of quality assessment.

Figure 3. Comparison of risk for mechanical ventilation between SARS-CoV-2 co-infection with influenza and SARS-CoV-2 mono-infection. N-the total number of SARS-CoV-2 coinfected and mono-infected patients; QA-the score of quality assessment.

Figure 4. Comparison of risk for ICU admission between SARS-CoV-2 mono-infection and A) SARS-CoV-2 co-infection with influenza, B) SARS-CoV-2 co-infection with influenza A virus. N-the total number of SARS-CoV-2 coinfected and mono-infected patients; QA-the score of quality assessment.

Figure 5. Comparison of risk for death between SARS-CoV-2 mono-infection and A) SARS-CoV-2 co-infection with influenza, B) SARS-CoV-2 co-infection with influenza A virus, C) SARS-CoV-2 co-infection with influenza B virus, D) SARS-CoV-2 co-infection with RSV. N-the total number of SARS-CoV-2 coinfected and mono-infected patients; QA-the score of quality assessment.

Table 1. Characteristics of included studies.

ER = emergency room; IP = inpatient; OP = outpatient; NPS=Nasopharyngeal swab; OPS=Oropharyngeal swab; BLF=Bronchoalveolar lavage fluid; BAF=bronchial aspiration fluid; NPS=nasopharyngeal aspirate; NA= not available; RT-PCR = Reverse transcription polymerase chain reaction; DFA = direct immunofluorescence assay; IFA = indirect immunofluorescence assay; CL = chemiluminescence; CIA = chromatographic immunoassay; Number of subjects = the total number of SARS-CoV-2 coinfected with influenza/RSV and mono-infected patients; O2=oxygen; MV= mechanical ventilation; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation; y=years; m=month.

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