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Journal of Clinical Virology Plus 1 (2021) 100036

Contents lists available at ScienceDirect

Journal of Clinical Virology Plus

journal homepage: www.elsevier.com/locate/jcvp

Co-infection of SARS-CoV-2 and influenza viruses: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
COVID-19
SARS-CoV-2
Influenza
Co-infection
Molecular

ABSTRACT

We conducted this meta-analysis to determine the proportion of co-infection with influenza viruses in SARS-CoV-2 positive patients and to investigate the severity of COVID-19 in these patients. We included studies with SARS-CoV-2 infection confirmed by qRT-PCR and influenza virus infection (A and/or B) by nucleic acid tests. The proportion of co-infection was compared between children and adults, and between critically ill or deceased patients compared to overall patients. Fifty-four articles were included. The overall proportion of co-infection was 0.7%, 95%CI = [0.4 – 1.3]. Most influenza co-infections were due to the influenza A virus (74.4%). The proportion of co-infection with influenza viruses among children (3.2%, 95% CI = [0.9 – 10.9]) was significantly higher than that in adult patients (0.3%, 95% CI = [0.1 – 1.2]), p-value <0.01. The proportion of co-infection with influenza viruses among critically ill patients tended to be higher than that in overall patients (2.2%, 95% CI = [0.3 – 22.4] versus 0.6%, 95% CI = [0.3 – 1.2], respectively, p-value = 0.22). Screening for pathogens in co-infection, particularly influenza viruses in patients infected with SARS-CoV-2, is necessary. This warrants close surveillance and investigation of the co-incidences and interactions of SARS-CoV-2 and other respiratory viruses, which is facilitated by the expansion of syndromic diagnosis approaches through the use of multiplex PCR assays.

1. Introduction

At the end of 2019, an epidemic of severe respiratory infections and pneumonia (known as COVID-19) due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China. The World Health Organization (WHO) declared the global pandemic on 11 March 2020, less than three months after it first appeared (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen). To date, the pandemic has not yet been controlled on a global scale.

Bacterial and viral co-infections have been described as a factor associated with more severe outcomes during pandemic and seasonal influenza outbreaks [1]. COVID-19 may be overlooked or diagnosed late, due to co-infections with other respiratory pathogens [2,3]. Since the onset of the SARS-CoV-2 pandemic, several studies have reported influenza virus and SARS-CoV-2 co-infection, with most data based on case reports or case series [4].

The transmissibility, clinical course, and prognosis in patients co-infected with SARS-CoV-2 and influenza viruses remain unclear. It has been hypothesised that treatment of influenza with antivirals might improve the outcome of patients co-infected with SARS-CoV-2, although response to treatment against influenza may differ between patients with and without co-infection with COVID-19 [3]. Therefore, greater knowledge on morbidity and mortality in COVID-19 patients co-infected with influenza viruses is needed.

We conducted this meta-analysis to determine the proportion of co-infection with SARS-CoV-2 and influenza viruses and investigate the severity of COVID-19 in these patients.

2. Methods

2.1. Protocol and research strategy

The protocol of this review follows the recommendations established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (http://www.prisma-statement.org).

The following databases were investigated in an attempt to identify all relevant studies published on

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https://doi.org/10.1016/j.jcvp.2021.100036
Received 15 April 2021; Received in revised form 20 July 2021; Accepted 6 August 2021

Google Scholar (http://scholar.google.fr/), Web of Science (https://www.webofknowledge.com/) and PubMed (http://www.ncbi.nlm.nih.gov/pubmed). The most recent search was conducted on 15 July 2021. The topic search terms used were the following:

#1: "SARS-CoV-2" OR "COVID-19"
#2: "influenza virus" OR "influenza viruses"
#3: "co-infection" OR "co-detection"
#4: #1 AND #2 AND #3

2.2. Eligibility criteria

We included published articles that reported the proportion of SARS-CoV-2 and influenza virus co-infection. Preprints were also included. Only studies published in English, reporting SARS-CoV-2 infection confirmed by real-time reverse transcription-polymerase chain reaction (qRT-PCR) were included. Only studies reporting influenza virus infection (A and/or B) by nucleic acid tests were included. . Case reports, case series, review articles, opinion articles and letters which did not present original data were excluded, but reference lists were screened to identify studies that might have been missed by the search.

To compare influenza co-infection in children and adults with SARS-CoV-2, we separated the included studies into two groups: one involving children only (≤14 years of age) and the other adults only. In studies conducted both in children and adults, subgroups were individualised.

To evaluate the co-infection effect on the severity of COVID-19, we separated the included studies into two groups: one conducted on critically ill or deceased patients only, and the other on all patients, regardless of the severity of the disease. In studies conducted in both non-severe and severe patients, subgroups were individualised.

2.3. Study selection

After manually removing duplicates, the articles identified through the initial search were first screened by title and abstract by three independent researchers (TLD, HVT and GP). The full texts of relevant articles were examined for inclusion and exclusion criteria (Fig. 1). In addition, articles without an abstract were included for full-text screening and assessed at this stage. After screening the abstracts, the full texts of the articles were assessed for eligibility by the same three researchers and were selected or rejected for inclusion in the systematic review. Any discordant results were discussed in a consensus meeting.

2.4. Data collection process and data items

Data extraction forms included information on the type of publication, the country where patients were sampled, the time period of the study, the number of patients tested for both SARS-CoV-2 and influenza viruses, the number of patients who tested positive for SARS-CoV-2, the number of COVID-19 patients with a co-infection with influenza viruses, type of sample, and influenza type, if available. A fourth researcher (PC) checked the article list and data extractions to ensure there were no duplicate articles or duplicate information on the same patient and also resolved discrepancies about study inclusion.

2.5. Assessment of risk for publication bias and statistical approach

We did not evaluate publication bias with funnel plots and statistical test in this review, as the usefulness of a standard publication bias test for a meta-analysis has been questioned. Although publication bias may cause inflated estimates in meta-analyses for studies of treatment effect, this is an unlikely scenario in this context, because we only reported the proportion of COVID-19 patients co-infected with influenza viruses.

The meta-analysis was performed using the open-source software R [R Core team. R: A language and environment for statistical computing. R foundation for statistical computing, Vienna, Australia, 2020. URL: [http://www.r-project.org]. and using a random effects model. This software made it possible to include dichotomous outcomes (number of events out of the total). We performed subgroup analyses by group of patients (adult versus children) and by severity of the studied population (critically ill patients or deceased patients versus overall infected patients with COVID-19). A p-value <0.05 was considered significant.

3. Results

3.1. Study selection and characteristics

The study selection process is presented in the flow-diagram (Fig. 1). The search algorithm produced 1248 articles from the Google Scholar, Web of Science and PubMed databases. Nineteen articles were added from other sources. After removing duplicates, 426 articles were scanned, based on their title and abstract. A total of 169 articles were processed for full text screening. Fifty-four articles met the inclusion criteria and were included in the qualitative synthesis of the systematic review and meta-analysis (Fig. 1) [5-58].

Of the 54 included articles (Table 1), all were peer-reviewed papiers. Most studies were conducted in China (n= 15), followed by the USA (12), France (7), Spain (3), Switzerland (2), Saudi Arabia (2), the UK (1), Singapore (1), Iran (1), Japan (1), Russia (1), Finland (1), Italy (1), Taiwan (1), Brazil (1), Canada (1), Korea (1), India (1) and Thailand (1). All studies were conducted in 2020 with the majority before May 2020, corresponding to the first phase of the COVID-19 pandemic. Forty-nine articles reported the study dates (Table 1). Of these, 28 (51.9%) were conducted during the descending phase of the influenza season and 11 (20.4%) were conducted at the end of the influenza season in the related countries (Supplementary data). Eleven studies lasted ≤ two weeks, 15, 15 and eight lasted respectively from three to five weeks, from six to ten week and >ten weeks (Table 1). Fifteen studies were conducted in adults only, nine in children only and one compared the co-infection in adults and children. Thirty studies were conducted in any classes of age or did not reported the age of the studied population. Most studies were conducted on patients at various stages of disease severity, while five studies were limited to critically ill patients or patients who died. No eligible study that compared severe versus non-severe COVID-19 co-infected patients was available.

3.2. Proportion of co-infection with influenza viruses in COVID-19 patients

The proportion of co-infection with influenza viruses in COVID-19 patients varied according to period of study and to countries where studies were conducted. Table 1 shows the proportion of co-infection with influenza viruses and SARS-CoV-2 and influenza surveillance information related to countries, respectively. This review included 18,021 patients infected with SARS-CoV-2 who were tested for influenza viruses. Of them, 143 patients were co-infected. Hence, the overall proportion of co-infection was 0.7%, 95%CI = [0.4 – 1.3] and heterogeneity (I^2) was 87.4%. Most of 143 influenza co-infections were due to the influenza A virus (106, 74.1%) and 29 cases (20.3%) involved the influenza B virus. One patient was coinfected with three viruses (SARS-CoV-2, influenza A virus and influenza B virus). The type of influenza virus was not identified in nine patients. Influenza A virus subtypes were identified in 23 cases, with H1N1 being the most frequent (38, 77.6%) and H3N2 in 11 cases, (22.4%).

3.3. Proportion of co-infection with influenza viruses in child and adult COVID-19 patients

The proportion of co-infection in children was 3.2%, 95% CI = [0.9 – 10.9] and that among adult patients was 0.3%, 95% CI = [0.1 – 1.2] (Fig. 2). The difference was significant with a p-value <0.01 and heterogeneity (I^2) was 54.0% and 26.0%, respectively.

Table 1
Characteristics of included studies.

Reference	Type of study	Country	Period of study	Duration of study (week)	Number of patients tested	Number of patients positive for SARS-CoV-2	Number (proportion, %) of co-infected patients	Type of sample	Age	Number (proportion) of critically ill patients, and mortality rate
Influenza co-infection in all COVID-19 patients										
[5]	Cross-sectional	France	1 March to 30 April 2020	9	4,222 patients were tested for both SARS-CoV-2 and influenza viruses	643	4 (0.6%) (IAV = 2, IBV = 2)	Nasopharyngeal swabs	Adults and children	NA
[6]	Cross-sectional	France	25 January to 29 March 2020	9	1,423	301	5 (1.7%) type of influenza was not reported	Upper and lower respiratory tract samples	Adults and children	Critically ill = 20% in overall patients
[7]	Retrospective analysis	USA	10 March to 23 March 2020	2	500	51, but only 46 patients were tested for influenza by qPCR	1 (2.2%) (IAV)	Nasopharyngeal swabs	Adults and children	ND
[8]	Retrospective cohort	China	1 January to 20 January 2020	3	-	99	0 (0%)	-	Adults	Critically ill (23%), mortality (11%)
[9]	Cross-sectional	France	7 February to 22 February 2020	2	-	13	1 (7.7%) (IAV H1N1)	Nasopharyngeal swabs	Adults and children	ND
[10]	Cross-sectional	USA	12 March to 15 April 2020	5	2,458	459	3 (0.7%) (IAV)	Nasopharyngeal swabs	ND	ND
[11]	Cross-sectional	Japan	10 March to 7 May 2020	8	191	8	0 (0%)	Nasopharyngeal swabs	ND	ND
[12]	Retrospective study	UK	20 February to 30 April 2020	10	-	836, but only 250 were tested for influenza viruses	0 (0%)	Sputum or bronchoalveolar	Adults	Mortality (262/836, 31.3%)
[13]	Cross-sectional	China	24 January to 29 February2020	5	164	3	0 (0%)	Oropharyngeal swabs	ND	ND
[14]	Retrospective	China	1 December 2019 to 16 January 2020	7	161	2	0 (0%)	Nasopharyngeal swab, sputum or bronchoalveolar lavage fluid	Children	ND
[15]	Cross-sectional	USA	3 March to 25 March 2020	3	1,206	115	1 (0.9%) (IAV)	Nasopharyngeal swabs	Adults and children	ND
[16]	prospective cohort	Switzerland	1 January to 29 March 2020	13	7,663 but 1816 were tested for influenza viruses	309/1,816	2 (0.6%) (IAV)	Nasopharyngeal/ oropharyngeal swabs	Adults and children	Critically ill (67/1966 hospitalized patients, 3.4%)
[14]	Retrospective cohort	China	1 January to 1 March 2020	9	-	32	0 (0%)	Sputum	Adults	Critically ill (10/32, 31.3%)
[18]	Cross-sectional	China	20 January to 1 February 2020	2	186	92	0 (0%)	Sputum, nasal or throat swab	Adults and children	ND
[19]	Retrospective cohort	China	4-28 February 2020	3	-	354 hospitalised patients, but only 76 were tested for influenza viruses	0 (0%)	Sputum	Adults	Critically ill (84/354, 23.7%), mortality (11/354, 3.1%)
[20]	Cross-sectional	China	19 January to 26 February 2020	5	-	250	3 (1.2%) (IAV = 2, IBV = 1)	Sputum or nasopharyngeal swabs	ND	Critically ill (8/11 co-infected patients with respiratory viruses, 72.7%)
[21]	Cross-sectional	USA	25 March to 22 April 2020	4	12,075	1,690	0 (0%)	Nasopharyngeal swabs	Adults and children	ND
[22]	Retrospective cohort	USA	16 March to 20 April 2020	5	10,194	8,990, but only 1,204 patients were tested for influenza virus	1 (0.1%) (IAV)	-	ND	ND
[23]	Cross-sectional	Thailand	8-31 January 2020	3	-	11 hospitalised patients	1 (9.1%) (IAV)	Nasopharyngeal, oropharyngeal swabs and sputum	Adults	Critically ill (0%), mortality (0%)

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Table 1 (*continued*)

[21]	Retrospective cohort	USA	1 March to 4 April 2020	5	-	5700, but only 1,996 patients were tested for influenza virus	1 (0.1%) (IAV)	Nasopharyngeal swabs	Adults and children	2,634 patients with available clinical data, Critically ill (373/2,634, 14.2%), mortality (553/2,634, 21%)
[25]	Retrospective cohort	USA	3 February to 31 March 2020	8	316. Of whom, 270 were tested for influenza virus by qPCR and 97 patients were tested by mNGS	33	0 (0%)	oropharyngeal and/or nasopharyngeal swab	Adults	186 were hospitalised, Critically ill (53/186, 28.5%), mortality (16/186, 8.6%)
[26]	Retrospective cohort	Russia	2 March to 30 April 2020 (set 1) and 5 May to 20 June 2020 (set 2)	16	7,864 (set 1) and 4,458 (set 2)	455 were tested for influenza viruses	0 (0%)	Nasopharyngeal swabs	Adults and children	ICU (1.4%), mortality (1%) in overall patients
[24]	Retrospective cohort	China	21 January to 29 February 2020	6	2,188	24	0 (0%)	Nasopharyngeal swabs	ND	ND
[28]	Cross-sectional	Singapore	5 February to 15 April 2020	10	736	431	0 (0%)	oropharyngeal and/or nasopharyngeal swab	ND	Critically ill (16/736, 2.2%)
[29]	Retrospective cohort	China	20 January to 27 February 2020	5	-	74 infected children. But only 34 were screened for influenza viruses	1 (2.9%) (IAV and IBV)	Nasopharyngeal swabs	Children	Critically ill (0%)
[30]	Retrospective cohort	France	26 February to 14 March, 2020	2	-	70	0 (0%)	Respiratory samples	Adults	Critically ill (11/70, 15.7%), mortality (4/70, 5.7%)
[31]	Retrospective cohort	USA	9 March to 30 April2020	7	3,669 ill children. But only 767 patients were tested for both SARS-CoV-2 and influenza virus	101/767	1 (1.0%) (IAV)	-	Children	ND
[32]	Retrospective cohort	China	27 January to 23 February2020	4	57 children	34	9 (26.5%) (IAV = 3, IBV = 6)	Nasopharyngeal or throat swabs	Children	Mortality (0%)
[33]	Cross-sectional	China	22 January to 2 February 2020	2	-	257	7 (2.7%) (IAV = 2, IBV = 5)	Throat samples	Adults and children	Critically ill (17/257, 6.6%), mortality (0%)
[34]	-	China	-	-	-	162	3 (1.9%) (IVA H3N2)	Nasopharynx swabs and sputum	ND	ND
[5]	Cross-sectional	China	23 January to 8 February 2020	2	-	20	3 (15.0%) (IAV = 1, IBV = 2)	Pharyngeal swabs	Children	Mortality (0%)
[36]	Retrospective	Spain	2-16 March 2020	2	365	41	2 (4.9%) (IBV)	-	Children	Critically ill (22/365, 6.0%)
[37]	Retrospective	China	1-10 February 2020	1	-	25	2 (8.0%) (IBV)	Nasopharyngeal and throat swabs	Children	Critically ill (2/25, 8.0%)
[38]	Cross-sectional	Reunion Island, France	18 March to 15 April 2020	4	-	36, but only 31 patients were tested for influenza viruses	1 (3.2%) (H1N1)	Nasopharyngeal swab or tracheal aspirate	ND	Critically ill (10/36, 27.8%)
[39]	Prospective cohort	Finland	2 December 2019 to 30 April 2020	21	213	28, but only 21 were tested for influenza viruses	0 (0%)	Respiratory samples	Adults	ND
[40]	Retrospective	Taiwan	February to August 2020	-	205	55	0 (0%)	Nasopharyngeal swabs	Adults and children	ND
[41]	Cross-sectional	Italia	21 January to 7 February 2020	2	126	3	0 (0%)	Nasopharyngeal swabs	ND	ND
[42]	Cross-sectional	Spain	28 February to 22 April 2020	8	-	989	5 (0.5%) (IAV = 4, IBV = 1)	Respiratory samples	ND	ND
[43]	Cross-sectional	Switzerland	-	-	-	71	0 (0%)	Nasopharyngeal swabs	Adults (41), children (30)	ND

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Table 1 (*continued*)

[44]	Retrospective	USA	25 March to 15 May 2020	7	-	54	0 (0%)	Nasopharyngeal swabs	Children	ND
[45]	Cross-sectional	Spain	4-28 March 2020			183 but 103 were tested for influenza viruses	1 (1.0%) (IAV H1)	Nasopharyngeal swabs	Adults	ND
[46]	Cross-sectional	USA	1 February to 31 May 2020		17,4746	3,757	15 (%) (IAV = 12, IBV = 3)		ND	Mortality (512/3,757, 13.6%)
[47]	Retrospective cohort	India	1 August 2020 to 31 December 2020		-	101	9 (H3N2 = 8, H1N1 = 1)	Upper respiratory tract samples	ND	Mortality (9/92 (9.8%) in COVID-19 only patients and 3/9 (33.3%) in co-infected patients)
[48]	Retrospective cohort	Saudi Arabia	-	-	-	48	17 (35.4%) (H1N1)	Respiratory tract samples	Adult and Children (1-92 years)	14 ICU (6 co-infected) patients and 34 mild (11 co-infected) patients
[49]	Retrospective cohort	China	11 January 2020 to 1 March 2020		-	408 but only 348 patients were tested for influenza viruses	4 (1.1%) (Influenza A = 1, Influenza B = 3)	Nasopharyngeal swabs	ND	Mortality (3, 0.7%)
[50]	Observational study	Brazil	March to December, 2020		987	418	6 (1.4%) (Influenza A)	Respiratory tract samples	Adults and children	ND
[51]	Cross-sectional study	France	25 January to 30 April, 2020		3768	806	4 (0.5%)	Respiratory tract samples	Adults	Mortality (19.1%)
[52]	Retrospective cohort	Korea	7 to 23 February, 2020		20,054	342	3 (0.9%) (Influenza A)	Respiratory tract samples	ND	ND
[54]	Retrospective study	Canada	7 March to 28 May, 2020		255627	6717, but only 1020 patients were tested for influenza viruses	1 (0.1%) (Influenza A)	Respiratory tract samples	ND	ND
Influenza co-infection in critically ill or died COVID-19 patients										
[54]	Retrospective cohort	USA	-	-	-	8	1 (12.5%) (IBV)	Upper and lower respiratory tract samples	Adults	Mortality was not available
[55]	Retrospective cohort	KSA	20 March to 31 May 2020	10	-	352	0 (0%)	Nasopharyngeal swabs	Adults	Mortality (32.1%)
[56]	Retrospective cohort	France	13 March to 16 April 2020	5	-	92 but only 82 were tested for influenza viruses	0 (0%)	Nasopharyngeal swabs	Adults	Mortality (48.9%)
[57]	Cross-sectional	USA	20 February to 5 March 2020	2	-	21	2 (9.5%) (IAV)	Nasopharyngeal swabs	Adults	Mortality (52.4%)
[58]	Retrospective	Iran	2 March to 20 April 2020	7		105 died patients	23 (21.9%) IAV H1N1 = 18, IAV non-H1N1 = 5, IBV = 0)	Nasopharyngeal and throat swabs	Adults and children	Mortality (100%)

ND: not documented, IAV: influenza A virus, IBV: influenza B virus, ICU: intensive care unit

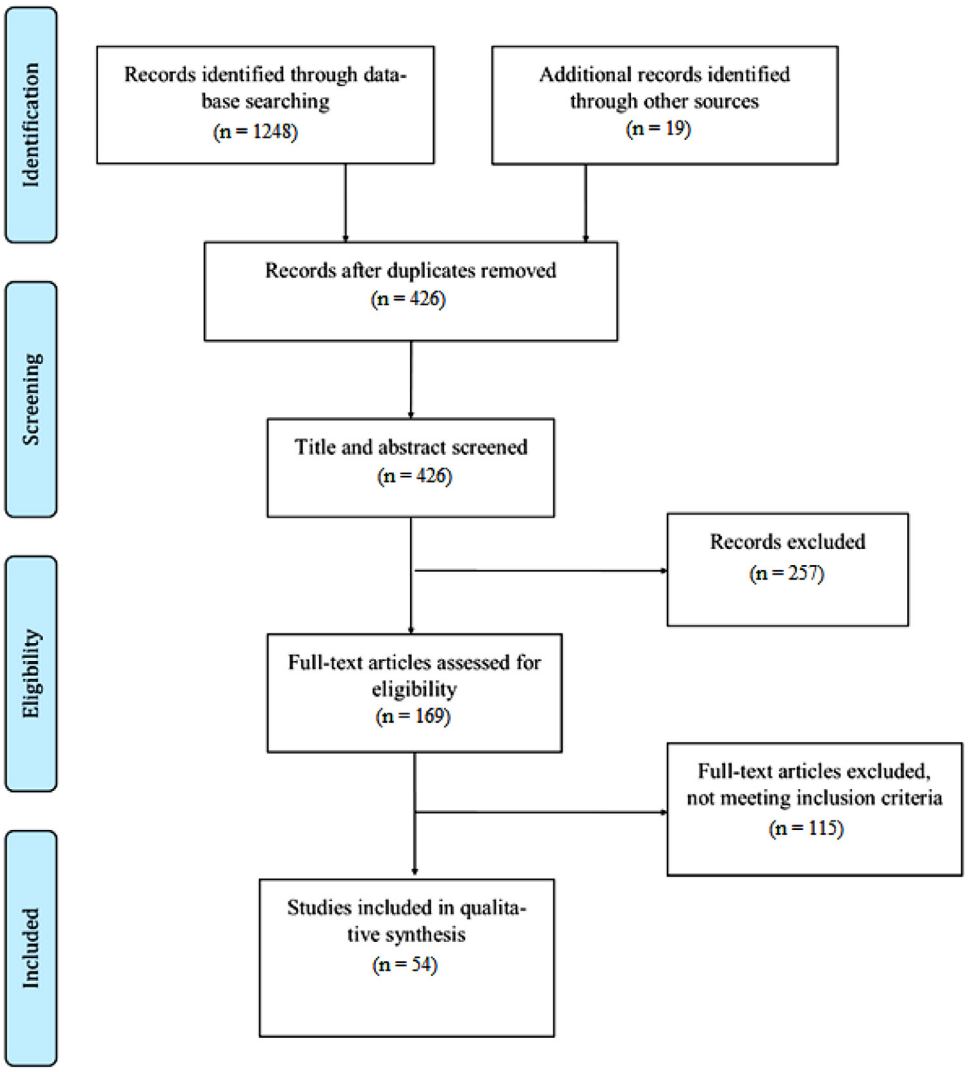

Fig. 1. Flow chart.

3.4. Effect of co-infection with influenza viruses on the severity of COVID-19

The proportion of co-infection in critically ill or deceased patients was 2.2%, 95% CI = [0.3 – 22.4] and among overall population of co-infected patients was 0.6%, 95% CI = [0.3 – 1.2] (Fig. 3). The difference was not significant with a p-value = 0.22 and heterogeneity (I^2) was 0% and 85%, respectively.

4. Discussion

The co-infection rate varied according to country and period of study. Influenza viruses circulate all over the world. In temperate regions, influenza is seasonal epidemic disease, occurring typically in the winter season: from November to April in the northern hemisphere and from April to September in the southern hemisphere (https://www.who.int/ith/diseases/influenza_seasonal/en/). In tropical territories, there is no clear seasonal pattern and influenza circulates year-round, albeit typically with several peaks during rainy seasons (https://www.who.int/ith/diseases/influenza_seasonal/en/). In addition, the number of COVID-19 cases also varies widely between countries around the world (https://www.worldometers.info/coronavirus/). Consequently, the proportion of SARS-CoV-2 and influenza co-infection varies from country to country. Also because of the seasonal pattern of influenza, the reported rate of co-infected patients depends on the time when the study was conducted. Our analysis shows that the actual proportion of co-infections may have been underestimated, because over 70% of included studies were conducted during descending and late phases of the influenza season in the relevant countries (Supplementary data).

On other hand, the detection of co-infection with influenza virus (or other viruses) and SARS-CoV-2 depends on the dynamic of infection of each pathogen. This adds to the challenge of diagnosing COVID-19, especially when the patient may test negative for SARS-CoV-2 but positive for other viruses, and very shortly thereafter turns SARS-CoV-2 positive. In this case, COVID-19 may be under-estimated, and medical treatment could be delayed [2,59]. In fact, influenza viruses have shorter mean incubation and viral shedding times than SARS-CoV-2 virus (two days vs. six days and three days vs. 17 days, respectively) [60-62]. It is likely that in some patients getting infected with the two viruses simultaneously, the influenza virus is no longer detectable at the time the SARS-CoV-2 infection is diagnosed and the time window of co-detectability may be too short to adequately identify all co-infections with influenza and SARS-CoV-2 using molecular tests.

Our analysis shows that the proportion of co-infections with influenza virus in COVID-19 children was significantly higher than in infected adults. In a comparative study by Pigny *et al.*, viral co-infection (with any viruses) was more frequent in SARS-CoV-2 children than in adults living in the same household [43]. Although no cases of influenza virus infection have been found, possibly due to the study being con-

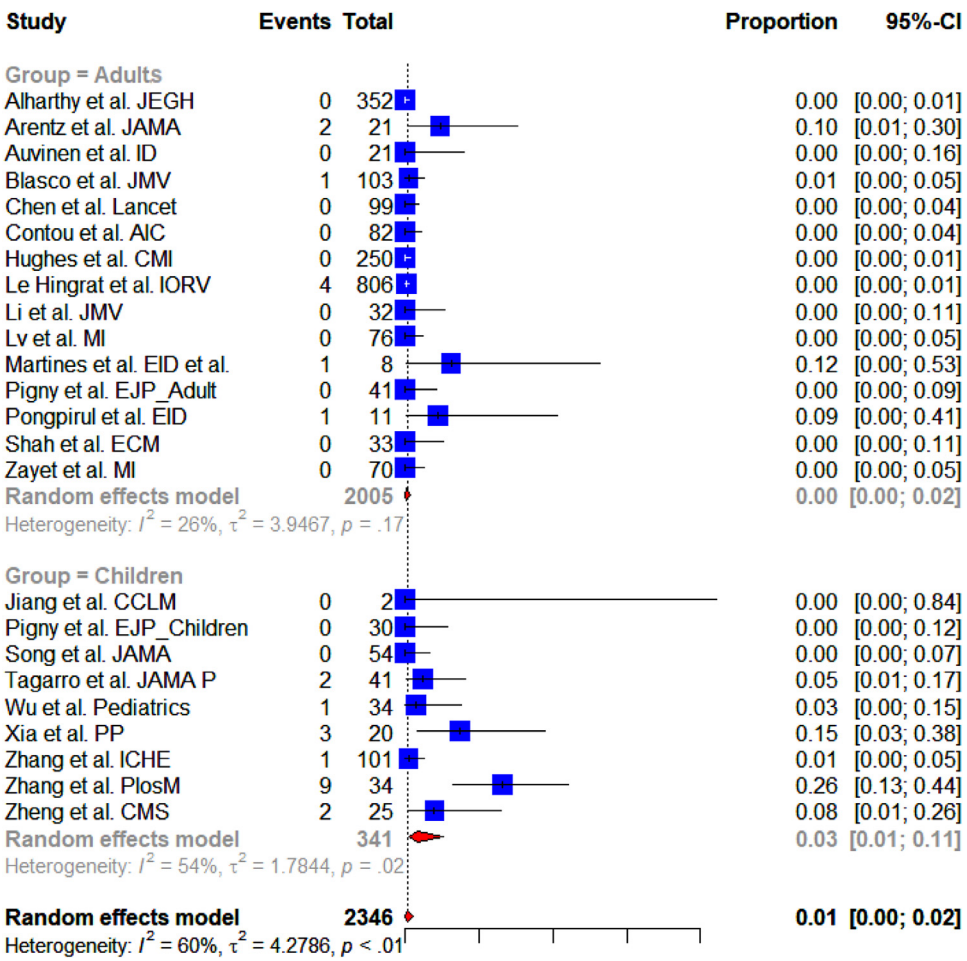

Fig. 2. Rates of co-infection with SARS-CoV-2 and influenza virus in COVID-19 children and adult patients.

ducted during the recession phase of the influenza epidemic in the USA, this study showed that COVID-19 paediatric patients are at a higher risk of viral co-infection. Interestingly, despite partial lockdowns with creches and schools being closed, COVID-19 children were co-infected with other respiratory viruses while their families were not [43]. In addition, a higher frequency of viral respiratory co-infections in children than in adults had been shown in the pre-COVID-19 pandemic [63]. This suggests that the pathogen infection and co-infection also depend on the host body.

Although the difference was not statistically significant, the proportion of co-infection in severe COVID-19 patients was three times higher than in the total population of patients in our analysis. In previous studies, the clinical presentation in COVID-19 patients coinfected with influenza viruses was not different to that of patients with a single SARS-CoV-2 infection, but the clinical outcome was more severe among co-infected patients [64-67]. In a comparative study by Ma *et al.*, conducted on 93 critically ill COVID-19 patients and including 44 deaths, no significant difference was observed in the proportion of co-infection with influenza virus and SARS-CoV-2 between the two groups: survivors and non-survivors [64]. However, in patients who died, the incidence of acute cardiac injury was significantly higher in patients who were co-infected with influenza viruses than in those with SARS-CoV-2 mono-infection (86.4% versus 54.5% respectively, p <0.05) [64]. In another study, Yue *et al.* showed that patients coinfected with SARS-CoV-2 and influenza B virus were more likely to develop poor outcomes, compared with those with a single SARS-CoV-2 infection and SARS-CoV-2-influenza A virus co-infection [65]. Stowe *et al.* analysed the risk of mortality among individuals with COVID-19 and influenza virus co-infection [67]. Of the 19,256 patients tested, 4,500 were positive for SARS-CoV-2, of whom 58 were co-infected. Their analysis showed that co-infected patients had a two-fold higher risk of dying than patients only infected with SARS-CoV-2. The lake of a significant difference in the co-infection rate according to COVID-19 severity in our analysis can be explained by the limited number of studies conducted on patients with severe forms of the disease (only five). Interestingly, the proportion of influenza virus co-infections was proportional to the mortality rate in the four studies with available mortality data. In fact, the proportion of co-infections was 0.1%, 0.6%, 9.5% and 21.9% in studies reporting a mortality rate of 32.1%, 48.9%, 52.4% and 100%, respectively [55-58].

In addition, Zhang *et al.* conducted an animal model study on simultaneous or sequential co-infection with influenza A(H1N1)pdm09 and SARS-CoV-2 [68]. Their results showed that co-infected hamsters had a more severe disease than hamsters infected with a single virus. Simultaneous co-infection lowered SARS-CoV-2 loads in the respiratory tract but was associated with delayed resolution of lung damage. Moreover, co-infected hamsters had lower levels of the SARS-CoV-2 neutralising antibody in the serum and longer SARS-CoV-2 shedding in oral swabs [68]. These results suggest an interaction effect between the two viruses compared to mono-infection with SARS-CoV-2.

Our study has some limitations. First, seven out of 54 studies were conducted on fewer than 20 patients. Furthermore, a high heterogeneity was also observed across all studies and all subgroup analyses (divided by age of the population studied or severity of patients). The high variance between studies in our meta-analysis may be due to methodological factors, clinical factors, sample size, and particularly to the period of time when the studies were conducted, as the rate of co-infection depends on the rate of epidemiological co-incidence of the viruses [5]. This is important, because influenza is a seasonal infection in many regions.

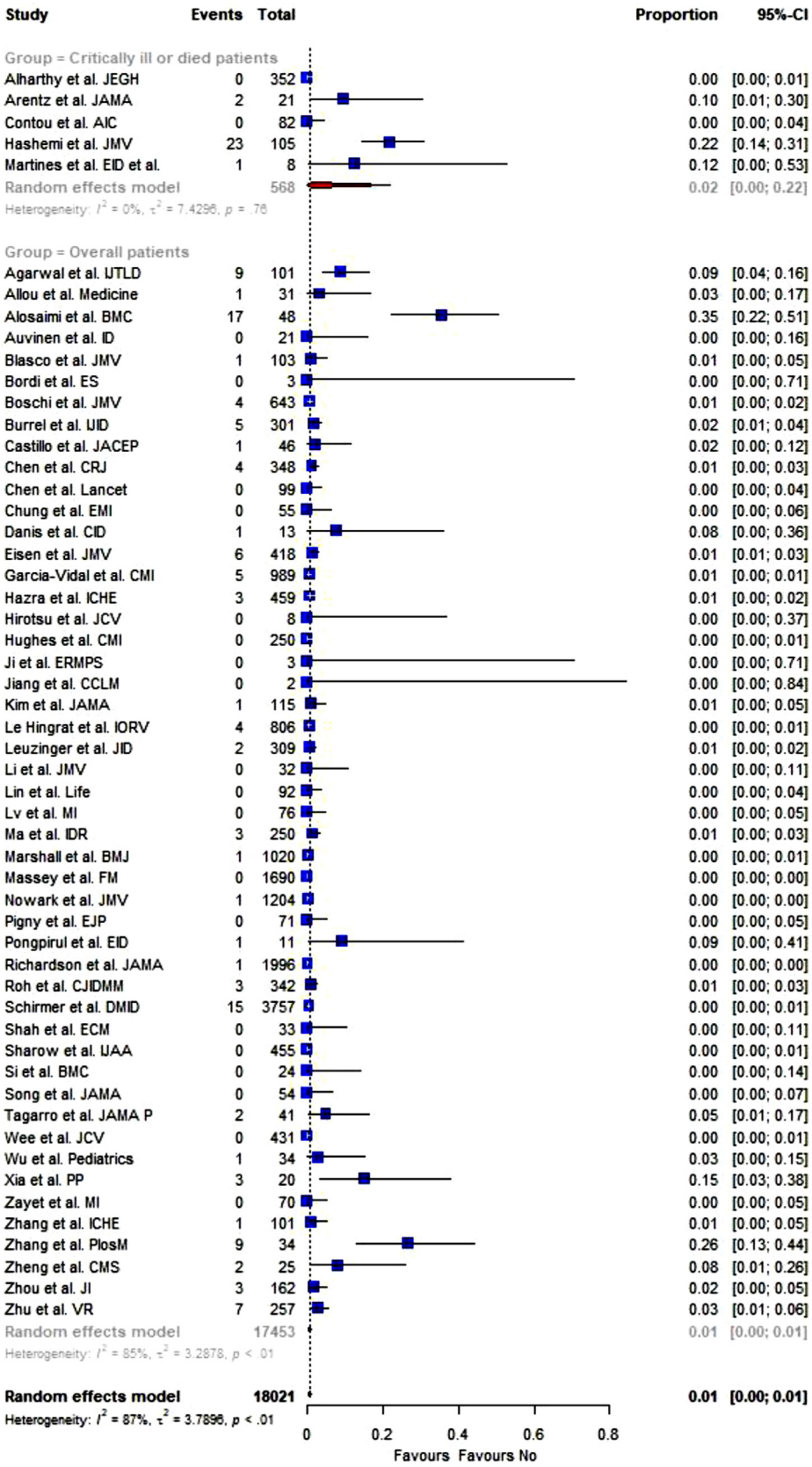

Fig. 3. Rates of co-infection with SARS-CoV-2 and influenza virus in total population of patients and in critically ill or deceased patients.

While there are more than 108 vaccines in clinical development for COVID-19 (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), only a few vaccines have been licensed by WHO. After 20 months of the pandemic, the value of therapeutics against COVID-19 remains controversial. In contrast, antivirals and vaccines are available for influenza. Influenza vaccines reduce not only hospitalisation due to influenza infections but may possibly also reduce their subsequent impact on COVID- 19 mortality. However, access to influenza vaccination as well as to COVID-19 vaccination is not identical around the world. In any case, individual non-pharmaceutical preventive measures should be improved. It is noteworthy that cases of the influenza decreased dramatically following the application of control measures against COVID-19 [69,70], as confirmed by the national surveillance data presented here (Supplementary data). It is very difficult to confirm whether this decrease is related to the interaction between pathogens or to the effectiveness of preventive measures against COVID-19. Since the future of the epidemics is unpredictable, close surveillance and investigation of the co-incidences and interactions of SARS-CoV-2 and other respiratory viruses, including influenza viruses is needed. An expansion of syndromic diagnosis approaches through the use of multiplex PCR assays is definitely also required [71].

Ethical approval

NA.

Consent to participate

NA.

Consent to publish

NA.

Authors' contribution

Conceptualisation: Thi Loi Dao, Van Thuan Hoang, Philippe Gautret

Methodology: Thi Loi Dao, Van Thuan Hoang, Matthieu Million, Philippe Gautret

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Supervision: Philippe Gautret

Funding

No funding.

Availability of data and materials

The datasets generated during and/or analysed during the current study are available in the manuscript.

Declarations of interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcvp.2021.100036.

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