Coinfections in Covid-19 patients in India: A Systematic Review

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Abstract

Objectives

To determine the rate of coinfections and its subsequent impact on hospitalization and mortality rate in Indian COVID-19 patients.

Method

Systematic literature search was performed on PubMed, Cochrane, WHO-COVID-19 database, and Google Scholar. The studies were retrieved and included based on JBI's CoCoPop framework. Meta-analysis was not performed due to limited number of studies and high heterogeneity. Hence, descriptive statistics was summarized based on the retrieved coinfections data. The protocol was registered with PROSPERO – CRD42021275644.

Results

Eight studies included 2418 patients. The prevalence of coinfections ranged from 4%-46%. Pathogen-specific data showed the highest prevalence of bacterial (57.3%) coinfections, followed by parasitic (21.1.%), viral (14.6%), and fungal coinfection (6.9%). About 60–80% of the patients with coinfections required ICU admissions with an average length of stay of 13.67 ± 3.51 days. The mortality rate of COVID-19 patients with coinfections ranged from 9%-65%.

Conclusion

The prevalence of bacterial coinfections was highest among COVID-19 patients, consistent with previous literature. A causal relationship between coinfections and mortality rate in COVID-19 patients remained unexplored. This brings up the need for comprehensive data recording practices and meticulous reporting. Further, large-scale epidemiologic studies are needed to determine the nationwide burden of coinfections in the COVID-19 pandemic.

Introduction

Infection prevention and control (IPC) has become one of the public health priorities as advocated by organizations such as World Health Organization (WHO), the Centre for Disease Prevention and Control (CDC) for decades.[1,2] It has become a global health concern demanding stringent IPC practices during coronavirus disease (COVID-19).[3,4] As of 01 Mar2022, global statistics revealed 0.43 billion Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) cases and 5.9 million deaths due to COVID-19.[5] The burden of COVID-19 became heftier due to coinfections of concurrently evolved other non-COVID respiratory pathogens.[6] Recent studies report the coinfection rate from 7% to as high as 50% in COVID-19 patients.[7–9] Global vaccination drives have flattened the COVID-19 curve however, the risk of coinfections remains intact due to upcoming strains of COVID-19 and this requires attention.[10]

Coinfections refer to infections occurring simultaneously or concurrent with the initial infection whereas secondary infections occur during or after the treatment[11]. Although its mechanism is not clear, the contributing factors include prolonged hospital stays [especially in intensive care units (ICUs), cardiovascular disorders (CVD), diabetes mellitus (DM), and other immunocompromising conditions], predisposing the patients to other infections.[12,13] Literature showed worsened outcomes, increased disease severity, and higher ICU admissions of COVID-19 patients with coinfections.[14–19] Additionally, coinfected patients had higher odds of death compared to non-coinfected COVID-19 patients.[7,8] Likewise, hospital- or healthcare-associated infections (HAIs), especially in low resource settings, pose an additional challenge prolonging hospital stays[20] thereby warranting an urgent need for actionable evidence.

Despite comprehensive global guidelines on the management of coinfections, data on the COVID-19 coinfection epidemiology is sparse.[21–23] While there are focused studies on the prevalence of coinfections in past pandemics like influenza, Middle East Respiratory Syndrome Coronavirus (MERS CoV), and Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1)[24–27], research studies or practice guidelines in low and low middle income countries (LMICs) on COVID-19 associated coinfections is sparse. In

India, an evidence-based guideline is available exclusively for coinfection with seasonal diseases, but its evidence strength is questionable. This can be attributed to poor evidence synthesis methodology.[23] Reporting-related inconsistencies and the know-do gaps in the context of coinfections observed amongst Indian infection control practitioners impelled us to conduct this review.

Objective

The objective of the present study was to consolidate the existing literature on the rate of coinfection(s) and its subsequent impact on the mortality rate in Indian COVID-19 patients.

Methods

Protocol registration

The protocol for this systematic review (SR) was registered with PROSPERO – CRD42021275644.

Study selection criteria

The present SR was carried out in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[28]

Study design:

We included prospective and retrospective cohorts, case-control studies, case series, and cross-sectional studies to corroborate high-quality evidence. Studies such as reviews, randomized controlled trials (RCTs), case reports, commentaries, and editorials were excluded.

Eligibility criteria:

The studies were retrieved and selected based on CoCoPop (Condition, Context, Population) framework.[29]

Population– We included studies on, COVID-19 patients with manifestation of co-infection(s) (irrespective of the type).

Condition – We included studies containing information on the rate of co-infections in COVID-19 patients. India has a high prevalence of seasonal epidemics; therefore, studies assessing the rate of infection with malaria, dengue, and leptospirosis were also included.

Context– Studies within India were included and those from other regions were excluded.

Search filters – Studies published in the English language were included.

Search strategy

A preliminary search was carried out in PubMed to retrieve relevant key terms, these formed the basis for detailed search strategy. An exhaustive literature search was conducted in PubMed, the Cochrane library, Google Scholar, and the WHO COVID-19 database. The PubMed-based search and article shortlisting was carried out by a state-of-the-art AI-powered tool - MaiA (Genpro Research Inc.). Epidemiology and infection journals were searched manually to retrieve additional records. The search strategy used in the PubMed database is supplied in supplementary file -1.

Data extraction

The data extraction was performed independently by two reviewers (DP and VC). The data extraction template was prepared using three articles and was modified in accordance with the type of available data. The data extraction items included: the author's name and year of publication, evidence type, demographic details of patients, comorbidities, the proportion of patients admitted to ICU, proportion of patients with co-infections – subcategorized to bacterial, fungal, and viral, infectious species, site involved, symptoms, and the proportion of patients who died. The extracted data was cross verified by (KK and SS). Any disagreements were resolved mutually or by consenting to a third reviewer (KK).

Data synthesis

The primary outcome of interest was the prevalence of coinfections in COVID-19 patients. Patients were further stratified into those admitted to ICU and those in the ward. We also performed a subgroup analysis based on the coinfecting pathogen (bacterial, viral, or fungal). Due to limited studies and high heterogeneity (I^2>97%), we could not perform a meta-analysis. Hence, we performed descriptive analyses based on the proportion data for coinfections. The sub-group's (based on causative organisms) data were presented in graphical format. The data was extracted and synthesized in Excel (version 16.0.1). Further, descriptive statistics including mean$\pm$standard deviation (SD) were calculated for the average length of stay (LOS) using R software (version 4.1.2).

Risk of bias assessment

Risk of bias (RoB) among the included studies was assessed using the Jonna Briggs Institute (JBI) critical appraisal tools – checklist for prevalence studies and case series, wherever applicable.[30] The RoB data from individual studies were presented in a graphical format.

Results

Study selection

Our search retrieved 4438 results. After de-duplication and removal of 3141 irrelevant records via first-level screening, eligibility screening was performed on full-text 97 articles. Of these, 90 articles were excluded due to their study design, representative population, or/and outcome. Finally, an additional article was found and cross-referenced in previously included articles -totaling eight articles eligible for analysis. The detailed study selection process is depicted in Figure 1.

We analyzed data from 2418 COVID-19 patients from the eight studies included.[31–38] Equal number of studies were found in both prospective (N = 4) and retrospective designs (N = 4). Seven studies had patients belonging to the age group $\geq$17 years and one study involved children only [median age = 4.5 years; interquartile range (IQR) = 0.4-7.5].[37]; one study included on pregnant women[31] (see Table 1). Five studies (adult and pediatric) reported comorbidity-related data. Two of the seven studies (on adults) reported malaria or dengue coinfections in healthcare workers (HCWs).[32,33] Studies focusing on bacterial (N=4/8) coinfections were higher than those on and viral (N = 3/8), parasitic (N = 3/8), and fungal (N = 2/8) coinfections.

Coinfections

We found the overall prevalence of coinfections ranged from 4% to 46%[31–38]. Bacterial coinfections showed the highest prevalence (57.3%) followed by parasitic (21.1%), and viral coinfections (14.6%); fungal coinfections were the least (6.9%). *Klebsiella Pneumoniae* and *Staphylococcus Aureus* were most the prominent bacterial species (28.57%) (Figure 2). Amongst viruses, *dengue virus* (26.47%) and *human rhinovirus (HRV)* (11.76%) (Figure 3) were prevalent; *Mucormycosis* and *Pseudomonas Jirovecii* prevailed in fungal coinfections.[34,36]

Comorbidities

Comorbidity(ies) were noted in COVID-19 patients with and without coinfections. They included DM, hypertension (HTN), congestive heart disease (CHD), chronic kidney disease (CKD), asthma, malignancy, neurological disorder, and other renal and cardiac diseases in

both adult and pediatric patients.[32,33,35–37] Mahajan et al. studied co-occurrence of pre-eclampsia in a pregnant patient. Patients with a history of chronic liver disease (CLD) and thrombocytopenia were also reported.[31]

Interestingly, neurological complications were significantly more common among patients with SARS-CoV-2 and *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* coinfections than those with only SARS-CoV-2 infection (35.7% Vs 3.4%, p<0.001), as reported by Chaudhry et al.[35] In addition, adults coinfected with *M. pneumoniae* or *C. pneumoniae* were more likely to develop acute respiratory distress syndrome (ARDS) (76.5% vs. 46.9%, p = 0.023) than patients with only SARS-CoV-2,[35] implying the effect of coinfection on the severity of COVID-19 infection.

Clinical presentation/symptoms

As per our analysis, the commonly manifested symptoms in COVID-19 patients included fever, cough, confusion, myalgia, dyspnea, and headache.[31,32,35,36] A higher prevalence of confusion and headache was observed in the *M. pneumoniae* or *C. pneumoniae* coinfected group (41.2% and 29.4%, respectively), than those with only SARS-CoV-2 infection (16.4% and 5.6%, respectively).[35] Among pediatrics, fever duration was significantly higher in the coinfected group compared to non-coinfected [6 days (3–10) vs. 3.5 days (1–7), p=0.012].[37] However, respiratory distress was reported more frequently in children with moderate to severe COVID-19 infection (45.7%, N = 27/59) than those presenting with coinfections (32.5%, N = 14/43).[37]

Amongst HCWs, except for 3 asymptomatic cases, the remaining reported symptoms of malaria or dengue along with COVID-19 symptoms. The difference in viral clearance was statistically significant (11 days [IQR 8–15] vs. 7 days [IQR 5-11] (p < 0.001).[32]

Intensive Care Unit Length of Stay

The proportion of COVID-19 patients with coinfections requiring ICU admissions ranged from 60% to >80%[32,35–37] and the average length of hospital stay was 13.67±3.51 days. A higher rate of ICU admission was observed in adults with coinfections compared to those without coinfections (77.7% vs. 68.3%, p=0.143), as reported by Sreenath et al.[36] Similarly among children, coinfected patients required longer pediatric ICU (PICU) stay than those without coinfections (8 vs 6.5 days, p=0.02).[37] Also, coinfected children required mechanical ventilator support in a higher proportion compared to the non-coinfected children (34.8% vs. 15.2%, p=0.03).[37]

Mortality

The mortality rate in COVID-19 patients with coinfections ranged from 9% to 65%.[35–37] According to Sharma et al. coinfected patients had a significantly higher mortality rate than the non-coinfected patients (53.4% vs. 24%, p<0.00001). A similar finding was reported by Chaudhry et al., 64.7% of patients died in the *M. pneumoniae* or *C. pneumoniae* co-infection group compared to 32.8% in non-coinfected group (p = 0.029). Patients of older age with comorbidities were more likely to die.[35]

Raychaudhri et al. noticed a higher mortality rate in coinfected children than the non-coinfected group (9.3% vs. 1.7%) however, this was non-significant.[37] Amongst the four patients, one with malarial coinfection suffered an intrauterine fetal demise.[31]

Surprisingly, one study found that adults with malarial coinfection had faster recovery with respect to virus clearance (mean 7.7 days) compared to those without malarial coinfection (mean 11.5 days) (p < .005).[32]

Quality assessment

We used the "*JBI checklist for prevalence studies"* to assess the risk of bias among the included studies. The overall assessment showed a low risk of bias. The study design and statistical analysis-based requirements were majorly fulfilled by all studies (Figure 4). However, a few questions such as adequate sample size, standard methods used for identification, and measuring the condition were marked "unclear".

Our review involved two cases series[31,34] which were subjected to "*JBI checklist for case series"* (Figure 5).

Discussion

We performed an epidemiological literature review to assess coinfection rate in COVID-19 patients in India. The study is unique due to the unavailability of systematic literature review (SLR) data on COVID-19 patients with coinfections in the Indian context. To serve this purpose, we utilized a standard framework for prevalence studies (recommended by JBI) known as the CoCoPop framework. We studied eight studies comprising of a total of 2418 Indian patients with COVID-19.[31–38] The prevalence of coinfections ranged from 4% to 46% with a higher prevalence of bacterial coinfecting pathogens compared to viruses. Our analysis shows a slightly higher prevalence compared to that reported in previous literature (8-20%)[7,8,39]; this might be attributed to the geographic variation, publication year, and the number of studies included. Notably, our findings tally with previous reviews which suggest a higher prevalence of bacterial coinfections followed by viral and lowest of fungal coinfections.[7,8]

Species-wide findings suggested that among bacterial coinfections, *S. aureus* & *K. pneumoniae* were present in high proportion; a study by Musuuza et al. showed similar results. A review by Lansbury et al. reported that *M. Pneumoniae, Pseudomonas aeruginosa,* and *haemophilus influenzae* were the frequently detected bacterial species.

In our study, *dengue* and *rhinovirus* were the commonly presented viral coinfections. Our findings did not coincide with recent reviews reporting *respiratory syncytial virus* and *Influenza A* in large proportions.[7] Fungal coinfections, on the other hand, were in the lowest proportion as noted by our study and previous literature reviews; this warrants further attention. Apart from bacterial, viral, and fungal infections we also included seasonal infections like malaria and dengue. Surprisingly, the malaria parasite was the second highest coinfection after bacteria and the dengue virus was found in the highest proportion (26.74%) among the virus species. The findings recommend that a higher level of awareness of seasonal infections is needed among health care practitioners (HCPs) and the public; this would curb its negative implications in COVID-19 patients.

Coinfections associated with COVID-19 affect the severity of the latter and prolong hospital stays.[14–19] Our analysis found that more than half of patients with coinfections required ICU admission. Few studies reported similarly stating that coinfections were responsible for higher ICU admissions and fatal outcomes in COVID-19 patients.[7,40] On the contrary, Musuuza et al. reported a higher prevalence of coinfection in non-ICU patients.[8] The study demonstrated higher prevalence of superinfections and not coinfections among ICU patients.[8]

Another aspect discussed in our analysis was the impact of coinfections on mortality. Two studies (on adults) reported a mortality rate of >40% in the coinfected group. Previous studies also reported a higher likelihood of death in presence of coinfections along with COVID-19.[7,8,39,40] Moreover, we found that compared to adults, children had a higher death rate (65%). Interestingly, one of the studies analyzed pregnant women; one patient with malarial coinfection suffered intrauterine fetal demise. These findings are suggestive of mother-to-child transmission and highlight the need for vigilance in the diagnosis and management of coinfections among vulnerable patients.

From a statistical viewpoint, we could not perform a meta-analysis due to high heterogeneity across the included studies and the non-poolable nature of the data. Nonetheless, previous studies by Lansbury et al. and Musuuza et al. performed meta-analysis despite I^2>80%,[7,8] which can raise bias and reliability concerns. Besides, there were a few challenges faced with respect to data interpretation such as the unavailability of data on SD accompanying mean, and unspecified IQR for median data. Such statistical errors could cause serious interpretation issues and provide misleading results. Adding to that, the ICU data in our review was representative of patients with COVID-19 infections rather than the coinfected population which hindered the possibility to establish a causal relationship between COVID-19 severity and coinfections. Last but not the least, COVID-19 variant-related information was out of scope, implying cautious interpretation of our findings before their generalization across COVID strains.

This study has several strengths such as the findings of our study could be used as a precursor for further large-scale studies. Secondly, the methodological framework distinguishes our study from the previously published studies in a similar domain.[7,8,39] For example, we utilized the CoCoPop framework which brought clarity to eligibility-based screening. Further, only observational studies (retrospective and prospective) and case series were included, while other study designs including randomized controlled trials, case reports, and reviews and these were excluded as they does not provide appropriate data on disease occurrence patterns.[41] Apart from the methodological concerns, it is noteworthy that there is an absence of proper policy evidence or guidelines for COVID-19 coinfections. The Ministry of Health and Family Welfare (MoHFW), Government of India- has released guidelines covering the

management of seasonal infections and coinfections including dengue, malaria, influenza, and leptospirosis.[23] However, it does not state any management protocols for coinfection by other respiratory viruses and fungi. From a policy viewpoint, the findings of our study could serve as a useful resource to plan clinical strategies with a realistic understanding of the burden of coinfection. This can prevent misdiagnosis of coinfection(s) in the presence of SARS-CoV-2 infection and aid in the construction of appropriate antibiotic strategies for timely management of coinfections. This may in turn help lower the morbidity and mortality rates.

Conclusion And Recommendation

We studied COVID-19 patients with a coinfection of three major species – bacteria, viruses, and parasites. As our study focused exclusively on the Indian population, it can greatly impact the existing infection control practices, if implemented with clinical acumen. Although it is based on heterogenous studies, our review presents a realistic range of coinfection prevalence- consistent with previously published literature, making it a reliable source given the paucity of such data. While the causal relationship between coinfections and mortality remains unexplored, a convergent approach including inputs from both patients and providers is recommended to strengthen the data quality.

Furthermore, efforts are required to carry out more large-scale epidemiological studies to determine the disease burden of COVID-19 coinfections on a national level. Our findings provide further implications for practice. Being the first evidence synthesis report on coinfections, the review findings could be utilized to inform and develop antibiotic stewardship strategies. On the other hand, there is an urgent need for clinical and diagnostic guidelines for COVID-19 coinfected patients, especially in LMICs. Researchers, clinicians, and industry could collaboratively work and build a consensus on the management of COVID-19 patients with coinfections. Our review also spotlights the need for robust reporting practices at patient and hospital levels to reinforce infection control practices. Lastly, we observed a lack of bioinformatic/genomic data to assess a causal relationship between specific strains of causative organisms[42]. Hence, bioinformatic analysis could be an engaging future research area.

Declarations

Funding Statement

This research did not receive funding.

Declaration of Competing Interest

The authors declare no conflict of interest.

Author contributions

Divya Patel: Conceptualization, Methodology, Visualization, Writing – Original draft

Vatsal Chhaya: Conceptualization, Methodology, Visualization, Writing – Original draft

Sonal Sekhar: Writing – Review & Editing

Kapil Khambholja: Writing – Review & Editing, Project Administration

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Table

Table 1 is available in the Supplementary Files section

Figures

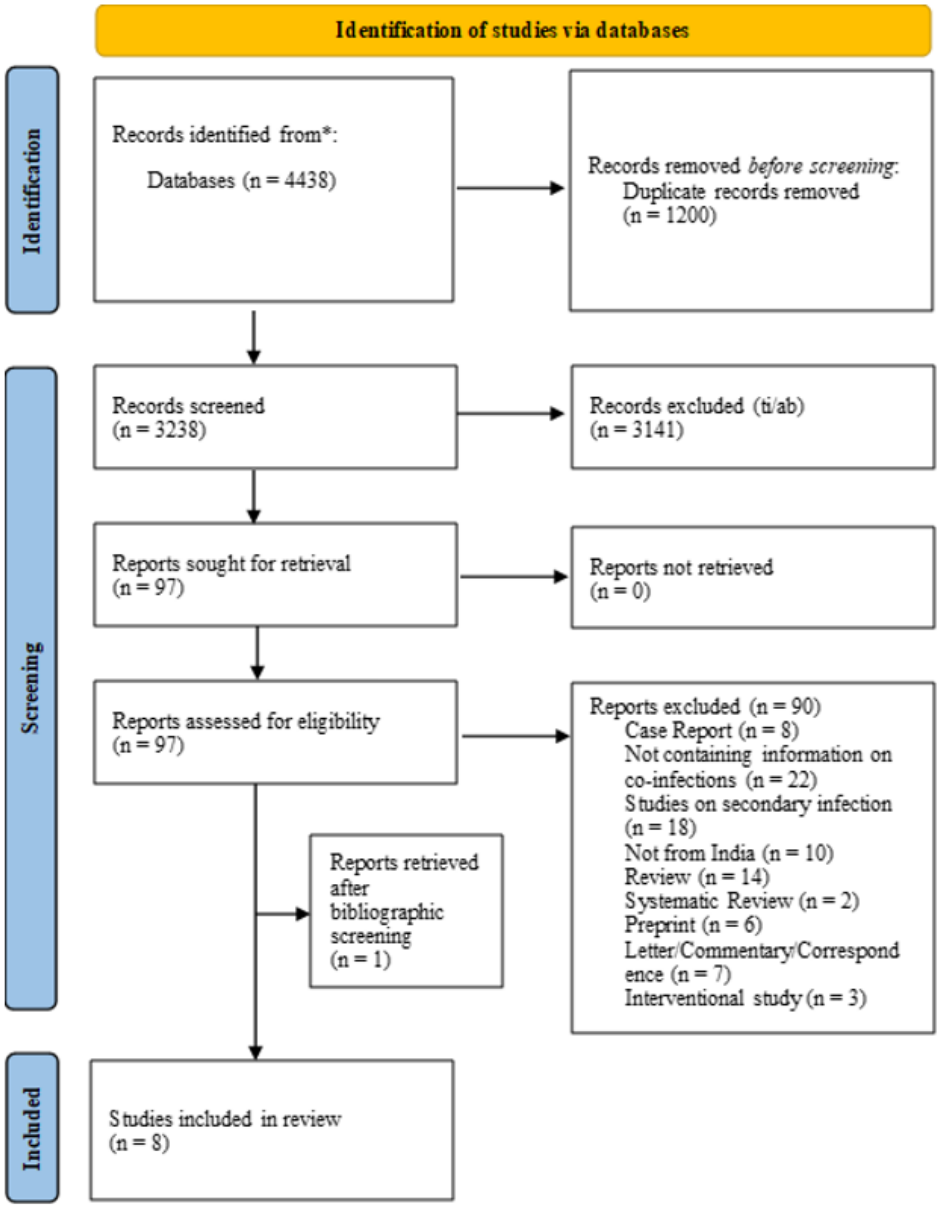

Figure 1

PRISMA flow diagram

**PubMed:1365; Cochrane:43; WHO COVID-19 database:2830; Google Scholar:200*

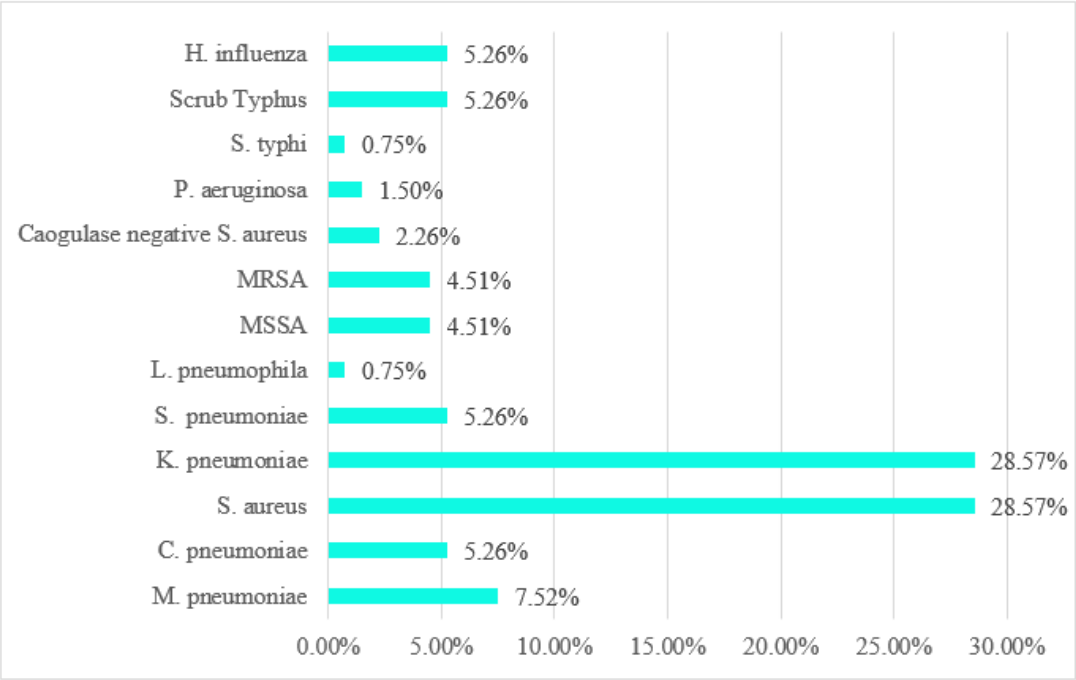

Figure 2

Bacterial pathogens as a proportion of total number of organisms per pathogen (%)

Abbreviations: MSSA: methicillin sensitive staphylococcus auerus, MRSA: methicillin resistant staphylococcus auerus, P. aeruginosa: pseudomonas aeruginosa, S. typhi: salmonella typhi, M. pneumoniae: mycoplasma pneumoniae, C. pneumoniae: chlamydia pneumoniae, S. aureus: staphylococcus aureus, S. pneumoniae: streptococcus pneumoniae, K. pneumoniae: klebsiella pneumoniae, L. pneumophilia: legionella pneumophilia, H. influenzae: haemophilus influenzae

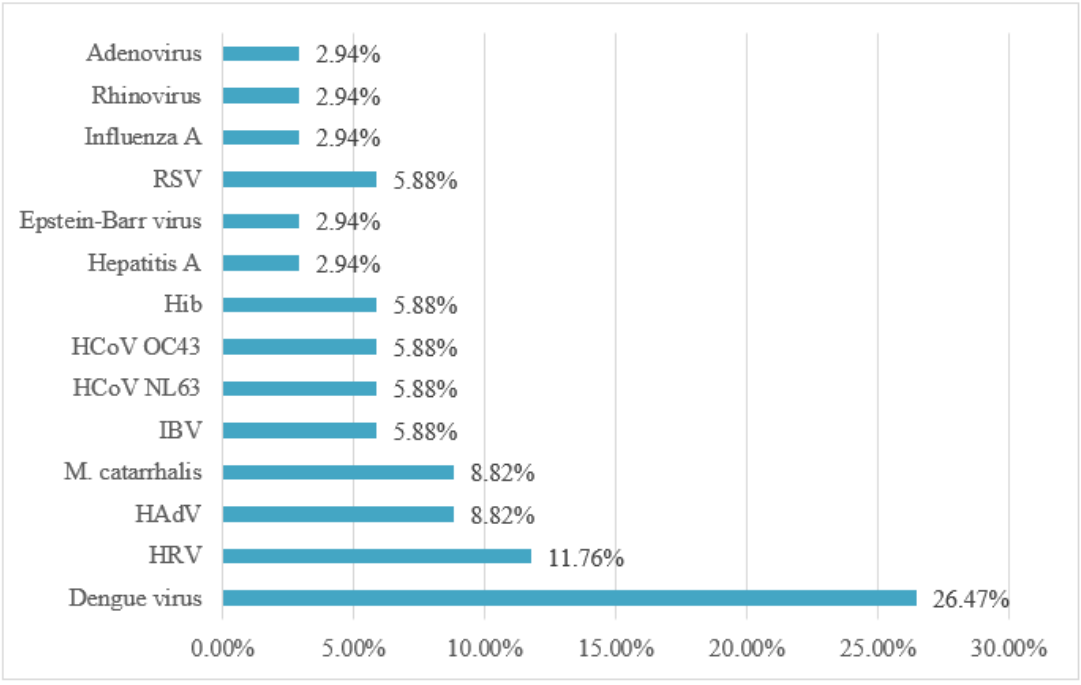

Figure 3

Viral pathogens as a proportion of total number of organisms per pathogen (%)

Abbreviations: RSV: respiratory syncytial virus, HAdV: human adenovirus, HRV: human rhinovirus, M. catarrhalis: Moraxella catarrhalis, IBV: infectious bronchitis virus, HCoV: human coronavirus, Hib: haemophilus influenzae type b

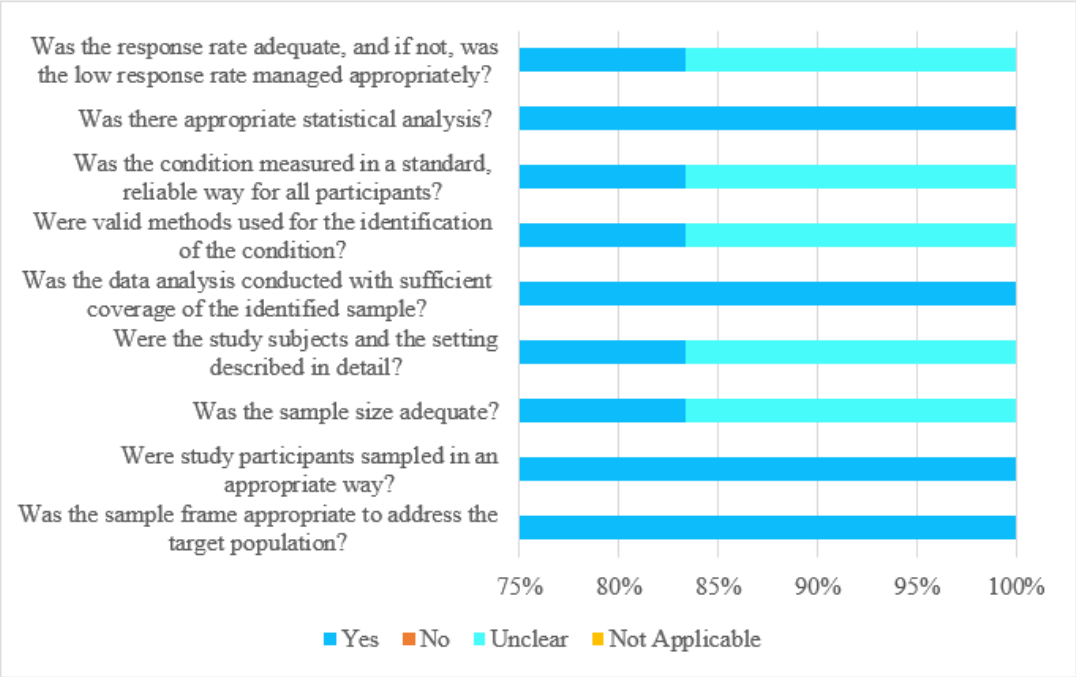

Figure 4

Risk of Bias assessment of the included studies (JBI checklist for prevalence studies)

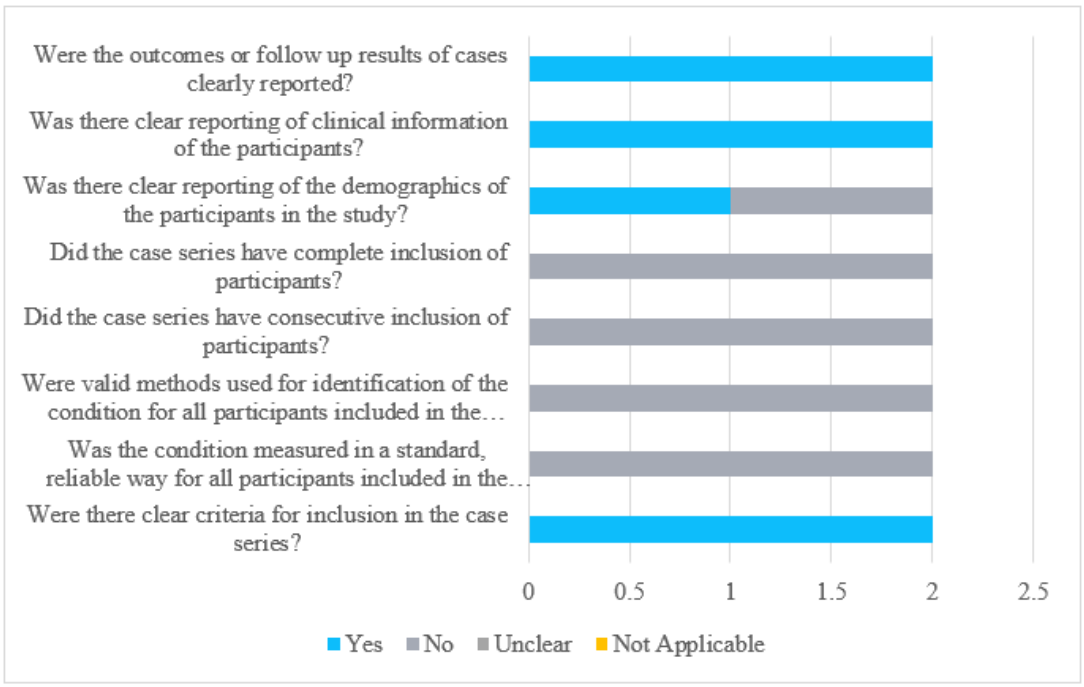

Figure 5

Risk of bias assessment (JBI checklist for case series)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFile1.docx
- Table1.docx