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SYSTEMATIC REVIEW-META-ANALYSIS

Infectious Disease

Viral and atypical respiratory co-infections in COVID-19: a systematic review and meta-analysis

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Abstract

Objectives: Respiratory co-infections have the potential to affect the diagnosis and treatment of COVID-19 patients. This meta-analysis was performed to analyze the prevalence of respiratory pathogens (viruses and atypical bacteria) in COVID-19 patients.

Methods: This review was consistent with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). Searched databases included: PubMed, EMBASE, Web of Science, Google Scholar, and grey literature. Studies with a series of SARS-CoV-2-positive patients with additional respiratory pathogen testing were included. Independently, 2 authors extracted data and assessed quality of evidence across all studies using Cochrane's Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and within each study using the Newcastle Ottawa scale. Data extraction and quality assessment disagreements were settled by a third author. Pooled prevalence of co-infections was calculated using a random-effects model with univariate meta-regression performed to assess the effect of study subsets on heterogeneity. Publication bias was evaluated using funnel plot inspection, Begg's correlation, and Egger's test.

Results: Eighteen retrospective cohorts and 1 prospective study were included. Pooling of data (1880 subjects) showed an 11.6% (95% confidence interval [CI] = 6.9–17.4, $I^2 = 0.92$) pooled prevalence of respiratory co-pathogens. Studies with 100% co-pathogen testing (1210 subjects) found a pooled prevalence of 16.8% (95% CI = 8.1–27.9, $I^2 = 0.95$) and studies using serum antibody tests (488 subjects) found a pooled prevalence of 26.8% (95%, CI = 7.9–51.9, $I^2 = 0.97$). Meta-regression found no moderators affecting heterogeneity.

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Conclusion: Co-infection with respiratory pathogens is a common and potentially important occurrence in patients with COVID-19. Knowledge of the prevalence and type of co-infections may have diagnostic and management implications.

KEYWORDS
COVID-19, influenza, human, mycoplasma, pneumonia, viral, respiratory tract infections

1 | BACKGROUND

A novel coronavirus, now called SARS-CoV-2, was identified as the cause of pneumonia in a cluster of patients in Wuhan, China in December of 2019.[1] Since this initial outbreak, the identified virus has spread across the globe with the World Health Organization (WHO) declaring a global pandemic on March 11, 2020.[2] As of May 3, 2020, there were over 3.3 million cases and 238,000 deaths reported worldwide.[3] Initially, experts including the Centers for Disease Control (CDC) and several state health departments recommended testing individuals with fever and lower respiratory tract infections for other viruses with instructions not to test for SARS-CoV-2 if alternate infections (eg, influenza) were present.[4–9] Early guidance from the WHO also recommended that clinicians only test for SARS-CoV-2 (formerly 2019-nCoV) once influenza had been ruled out.[10,11] Subsequent case reports indicate that co-infections may be an important reason for delayed diagnosis of COVID-19.[12,13] More recently, experts have recommended that individuals who undergo testing for SARS-CoV-2 should additionally be tested for other common respiratory pathogens besides influenza.[14]

2 | IMPORTANCE

Information about the type and rate of respiratory co-infections has potential diagnostic and treatment implications in COVID-19. Multiple studies have described typical presenting features for those with COVID-19 with markers that aid in predicting outcome.[14] It is unknown if co-infections alter the presentation, clinical course, or diagnostic markers (eg, laboratory or CT scan findings) used to assess prognosis in COVID-19. It is also possible that treatment of influenza with anti-virals and atypical bacteria with antibiotics might improve the outcome of patients co-infected with COVID-19. Alternately, individuals with co-infections may not respond to treatment in a manner similar to those without COVID-19. For these reasons, knowledge of the prevalence and type of respiratory co-infections has important management and outcome implications in COVID-19 patients.

3 | GOALS OF THIS INVESTIGATION

The purpose of this meta-analysis was to determine the prevalence and type of common respiratory co-infections including infections due to respiratory viruses and atypical bacteria in individuals who are SARS-CoV-2-positive.

4 | METHODS

This protocol was consistent with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) methodology (Supporting Information Table S1). The protocol was registered with the Center for Open Science's Open Science Framework: citation osf/io/x4q3z. Our study was performed to analyze the prevalence of respiratory virus and atypical bacteria (eg, Chlamydia, Legionella, and Mycoplasma) co-infections in patients infected with SARS-CoV-2.

4.1 | Data sources and search

We performed a comprehensive literature search of the National Library of Medicine's PubMed, EMBASE, Web of Science (version 5.34) and Google Scholar (top 1000 results for Google Scholar). A targeted grey literature search was performed using OpenGrey, Clinical Trials.gov, and the Clinical Trials Registry Platform/ICTRP (Supporting Information Table S2). Preliminary searches were initially performed on March 30 and 31, with repeated daily searches until April 11, 2020.

The database search strategy was developed by 2 study authors (SGR and PD) and adapted from published meta-analyses that evaluated respiratory co-infections.[15–17] When available, we used controlled indexing language or controlled vocabularies to conduct searches with databases. The following medical subject headings (MeSH) were used when searching PubMed: COVID-19, severe acute respiratory syndrome coronavirus 2, adenoviridae infection*, alphacoronavirus, betacoronavirus, bocavirus, *Bordetella pertussis*, *Chlamydophilia pneumoniae*, cytomegalovirus, enterovirus, influenza*, legionella, metapneumovirus, *Mycoplasma pneumoniae*, parainfluenza, respiratory syncytial virus, and rhinovirus. Non-MeSH terms added to the PubMed search included: 2019-nCoV, adenovirus, and Chlamydia pneumoniae. Emtree subject headings were used when searching EMBASE: adenoviridae, alphacoronavirus, betacoronavirus, bocavirus infection, bordetella, Chlamydia OR Chlamydiae, COVID-19 (candidate term), cytomegalovirus, enterovirus, human parainfluenza virus 1, human parainfluenza virus 2, human parainfluenza virus 3, human parainfluenza virus 4, metapneumovirus, Legionella, Mycoplasma, pertussis, pneumovirus, respiratory syncytial virus infection, and rhi-

novirus. The Web of Science search was limited to the Science Citation Index, Conference Proceedings Citation Index-Science and Social Sciences/Humanities, and the Emerging Sources Citation Index. Search limits included human studies and study dates (2019 to 2020) for all databases. No study design, language or age restrictions were included in any database searches (Supporting Information Table S2). Selected titles and abstracts from each search were downloaded into an Excel spreadsheet or a CSV file that was converted into an Excel spreadsheet.

4.2 | Study selection

Two board certified emergency physician study authors independently reviewed each title and abstract from the literature search to select the combined initial list of potential articles. The full text and references of each article or abstract that passed this initial screen of either reviewer were analyzed to further identify missed articles. Full text from each selected article obtained during the initial screen and from references within were read by each reviewer and selected based on pre-determined inclusion/exclusion criteria. At the full-text screening stage, 2 authors independently reviewed each article for final article inclusion and group consensus was used to resolve conflicts. Authors of articles or abstracts that appeared to collect but not publish data within our inclusion criteria were contacted by email on 2 occasions.

The PICO (population, intervention, comparison, outcomes) framework was used to devise our search strategy and inclusion criteria including:

- Patient/population/problem: patients who tested positive for SARS-CoV-2 and simultaneously had testing for other viral pathogens,
- Intervention: performance of viral pathogen or atypical bacterial tests,
- Comparison: none, and
- Outcome: number of viral and atypical bacterial pathogens including Mycoplasma, Chlamydia, Legionella, and Coxiella species.

Exclusion criteria included the following:

- Absence of total number of SARS-CoV-2 patients,
- Absence of simultaneous viral pathogen or atypical bacteria testing,
- Duplicate studies or studies using the same patient database during the same time period,
- Series with <20 patients with SARS-CoV-2, and
- Language other than English.

4.3 | Data extraction

Two reviewers independently extracted data from individual articles based on the Meta-analyses of Observational Studies in Epidemiology/MOOSE reporting checklist (Table S3). Extracted data from each article included a description of the study population study details (author, publication year, population country and province/state, design), and specific end point data (patient ages, number of SARS-CoV-2 positive patients, number of viral and atypical pathogen positive patients, specific viral and atypical pathogens tested, specific pathogens found, and type of assay used to test). Group consensus was used to resolve any conflicts regarding data extracted.

4.4 | Quality assessment

The quality of evidence across studies and risk of bias for individual studies was independently assessed by 2 study authors. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to assess quality of evidence across studies as high, moderate, low or very low.[18] The risk of bias was assessed for individual studies using the Newcastle-Ottawa Scale for observational studies. With the Newcastle-Ottawa Scale, studies received up to 9 points based on study subjects, study comparability, and outcome of interest assessment. A Newcastle-Ottawa Scale of 0–6 indicates a high risk of bias, and 7–9 indicates a low risk of bias.[19-21] For GRADE and Newcastle-Ottawa Scale assessments, any disagreement between the 2 independent reviewers was settled by a third reviewer.

Initial agreement between the 2 initial Newcastle-Ottawa Scale raters overall total points was assessed using Cohen's kappa. A kappa coefficient was considered almost perfect at 0.81–1, showed substantial agreement at 0.61–0.80, moderate agreement at 0.41–0.60, fair agreement at 0.21–0.40, slight agreement at 0.01–0.20, and less than chance at <0.

4.5 | Publication bias

Publication bias was evaluated using funnel plot inspection, Begg's test and Egger's test with a $P < 0.10$ considered evidence of bias.[22] If publication bias was found, the trim and fill approach was planned to estimate the number of missing studies due to suppression of extreme results to either side of the funnel plot.[23]

4.6 | Data synthesis and statistical analysis

The overall pooled prevalence and 95% confidence intervals (CIs) were estimated using a Freeman-Tukey (arcsine square root) transformation, random effects model to calculate a weighted summary. Subset analysis of studies that comprised only adults, serum studies for co-pathogens, reverse transcription polymerase chain reaction (RT-PCR) studies for co-pathogens, large studies (>100 SARS-CoV-2 positive patients), populations outside of Hubei province, published studies, studies graded as having low risk of bias, and populations with 100% co-pathogen investigations was planned. Observed heterogeneity for summary and subgroup analyses were measured using the I^2 statistic. I^2 <25% was considered low, 30%–60% moderate, 50%–90% substantial, and 75%–100% considerable based on

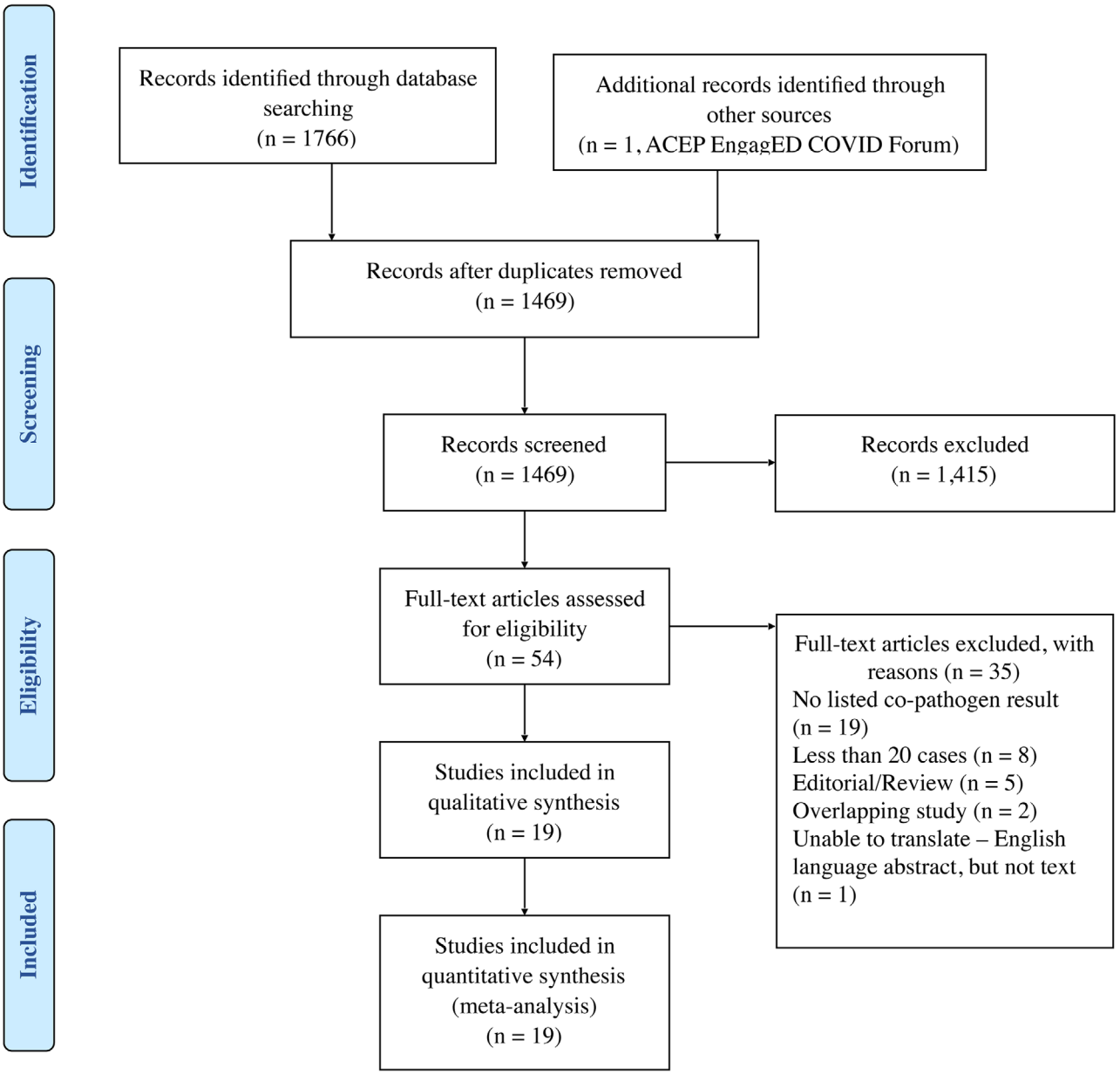

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

definitions from the Cochrane Collaborative and GRADE working group.[24,25]

Post hoc, univariate meta-regression was performed using a random effects model to assess the effect of subsets on heterogeneity. A multivariate meta-regression was planned using subset variables with $P < 0.05$ entered into a model.

Data synthesis and statistical analyses were performed using (1) MedCalc Statistical Software version 18.11 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018), (2) RevMan Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014), (3) Stata 16 StataCorp. 2019 Stata Statistical Software, Release 16 (StataCorp LLC, College Station, TX), and (4) Meta-essentials (Erasmus Research Institute of Management).[26]

5 | RESULTS

Initial database searches resulted in 1766 publications of potential relevance with 1000 identified via Google Scholar, 316 publications identified via Medline/PubMed, 324 publications identified via EMBASE, 89 publications identified via Web of Science, 34 publications identified via Wiley's Cochrane Library, and 3 publications identified via OpenGrey (Figure 1; Supporting Information Table S2) At the full article screening stage, 6 study authors were contacted by mail regarding possible unpublished data from their studies with 1 responding that the data were unavailable. After title/abstract review and full text article screening, 19 articles were included in the final meta-analysis with a total of 1880 patients[27–45] (Figure 2 and Table 1). Eleven included stud-

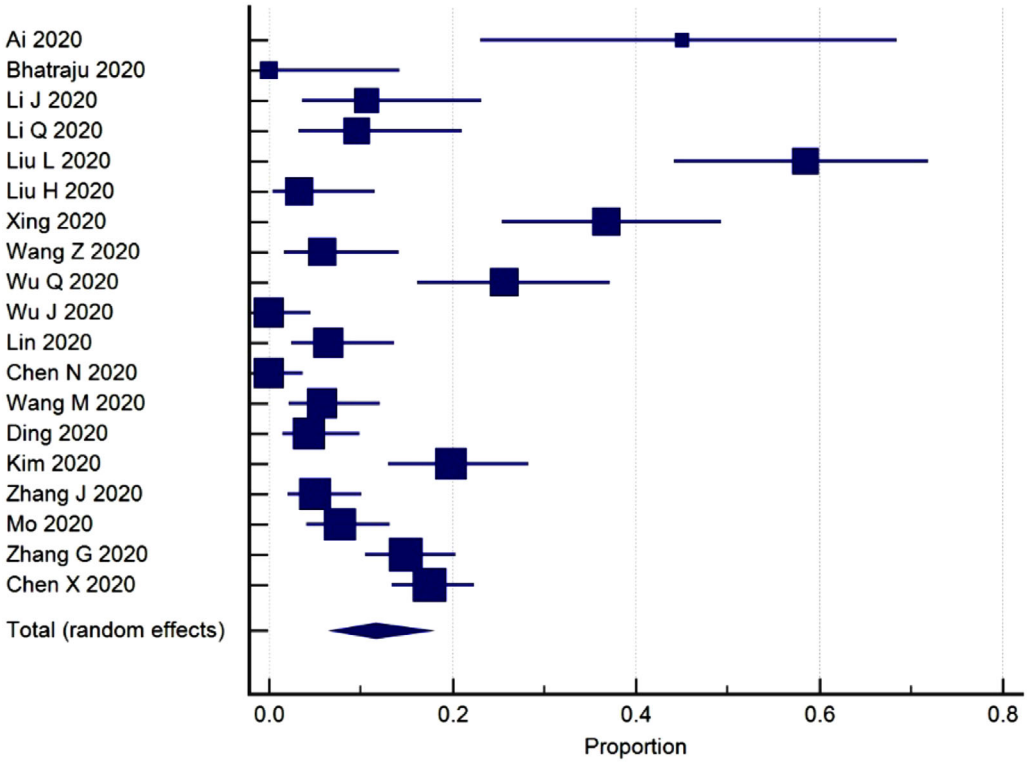

FIGURE 2 Forest diagram of included studies—prevalence of viral and atypical bacteria co-infections

ies were from peer reviewed journals.[28,29,31,34–38,40,41,45] Eight studies comprised articles located on a British Medical Journal's preprint server for health sciences (medRxiv) containing articles that had not yet been peer reviewed.[27,30,32,33,39,42,43,44]

Laboratory techniques for co-pathogen detection within studies included 8 that used respiratory samples and RT-PCR tests, 5 that used serologic tests (antibodies), 1 that tested both serology and RT-PCR, and 5 that did not specify their testing methods (Table 2). Seventeen studies examined patients for a combination of viruses and atypical bacterial infections although 3 of these 17 studies did not detail pathogens tested. One study only evaluated patients for the presence of influenza A and B and 1 study only evaluated for the presence of Chlamydia or Mycoplasma.

The Newcastle-Ottawa Scale for individual studies ranged from 6–7 with 12 studies (63%) rated as having high quality (Table 3; Supporting Information Figure S1). The interrater agreement for the total Newcastle-Ottawa Scale was substantial for the initial 2 raters (kappa = 0.77; 95% CI = 0.5–1) Based on GRADE, the overall quality of evidence across all studies was low (Table S4).

Pooling of data found an 11.6% co-infection rate (95% CI = 6.9–17.4) for all patients in all studies, and a 16.8% co-infection rate (95% CI = 8.1–27.9) for the subset of studies/subgroups where 100% of SARS-CoV-2 positive patients were tested for co-pathogens. Pooled prevalence for subgroups is listed (Table 4). A total of 159 viral co-pathogens were found in all studies with influenza found in 55 subjects (35% of viral pathogens). Mycoplasma comprised 86 (74%) of 116 atypical bacteria co-infections. At least 23 patients had >1 co-pathogen although the number of co-infections for each individual was not routinely documented (Table 2)

Heterogeneity was high (substantial) across all studies and all subsets (I^2) (Table 4). Univariate meta-regression found no moderators that had a significant effect on heterogeneity (Supporting Information Table S5). Thus, a multivariate meta-regression was not performed. Begg's correlation test (z = 1.2, $P = 0.23$) and Egger regression (intercept = 0.7; 95% CI = −1.4–2.9) revealed no publication bias (Figure 3).

6 | LIMITATIONS

The number of the cases within this meta-analysis, 1880, was small. Despite this finding, the lower limit of the 95% CI, 6.9%, still implies a meaningful rate of co-infections. It is likely that our study underestimated co-infections because many studies only tested for a subset of respiratory viruses and atypical bacteria.

We excluded studies with <20 patients. Our cutoff of 20 patients is consistent with other meta-analyses requiring populations with at least 20, 25, or 30 patients.[46–48] We chose to exclude smaller studies, because they have a higher risk of bias and are less likely than large studies to be published if results are negative. The potential for equal weighting of small and large studies in random effects meta-analyses tends to skew results toward smaller studies. Experts also have noted that underpowered/smaller studies often contribute little information.[49] We compared study size via subgroup analysis and meta-regression and found no effect on heterogeneity or outcome.

TABLE 1 Summary of included articles

Author, year, published	Region, state, country	Study, design, and date patients admitted	Median, age in years(range unless IQR or SD listed)[c]	Population studied	Total SARS-CoV-2 cases	Total SARS-CoV-2 tested for co-pathogens	Total number cases with viral or atypical pathogens
Ai	Multiple hospitals Eastern China	Prospective observational 1-22-20 to 2-9-20	37	Consecutive positive CT scans in patients with travel to or contact with individual from Hubei province or individual with COVID-19	20	20	5
Bhatraju	9 hospitals, Seattle, WA	Retrospective case series 2-24-20 to 3-9-20	64 – mean age (18 SD)	Consecutive admitted patients with COVID-19	24	23 (influenza tests) 21 (extended viral panel)	0
Chen N	Jinyintan hospital[a] Wuhan, China	Retrospective case series 1-1-20 to 1-20-20	55.5	Consecutive admitted pneumonia patients with COVID-19	99	99	0
Chen X	First Hospital Changsha, Loudi Central hospital, Hunan, China	Retrospective case series 1-23-20 to 2-14-20	46 (1–84)	Consecutive admitted patients with COVID-19 with and without pneumonia	291	84 (84 or fewer if no overlap of Mycoplasma/Chla testing)	51 (only tested 44 for Mycoplasma and 40 for Chlamydia)
Ding	Tongji hospital[b] Wuhan, China	Retrospective case series Admitted before March 8, 2020	49 (39–66) Only influenza cases described	Consecutive admitted patients with COVID-19	115	Not specified	5
Kim	Stanford, CA	Stanford Medical Center, Stanford, CA 3-3-20 to 3-25-20	Retrospective case series 48.8–mean age (1–98)	Symptomatic patients presenting to an outpatient clinic (n = 50) and emergency department/ED (n = 66) with 16 ED patients being admitted	116	116	23
Li J	Tongji hospital, Wuhan, China	Retrospective case series 2-8-20 to 2-11-20	62 (51–70 IQR)	Consecutive patients with severe COVID-19 pneumonia	47	47	5
Li Q	Wuhan Union hospital, Wuhan, China	Retrospective case series 2-3-20 to 2-7-20	57 (49–69 IQR)	Consecutive patients presenting to a fever clinic who were SARS-CoV-2-positive	52	Not specified	5
Lin	31	Retrospective case series 1-20-20 to 2-1-20	No median (80% were aged 18–65)	Consecutive admitted patients who were SARS-CoV-2 positive	92	92	6

(Continues)

TABLE 1 (Continued)

Author, year, published	Region, state, country	Study, design, and date patients admitted	Median, age in years(range unless IQR or SD listed)[c]	Population studied	Total SARS-CoV-2 cases	Total SARS-CoV-2 tested for co-pathogens	Total number cases with viral or atypical pathogens
Liu H	Xinhua hospital, Shanghai China, Maternal and Child Health hospital of Hubei, Wuhan China	Retrospective case series 1-27-20 to 2-14-20	Pregnancy SARS-CoV-2-positive: 30 (22–42) Pregnant SARS-CoV-2-negative: 31 Non-pregnant adults: 33.5 (27–58) Children: 3 (0.17–9)	14 non-pregnant adults, 16 pregnant women, 4 children who were SARS-CoV-2-positive and underwent CT of the chest 26 pregnant females were SARS-CoV-2-negative and diagnosed based on CT and clinically	60	Not specified	2 Within 60 patient group, Mycoplasma pneumonia (1) found and deleted from analysis Within the 34 SARS-positive cases, 1 viral infection
Liu L	Shiyan Renmin hospital, Shiyan, China	Retrospective case series 1-23-20 to 2-24-20	38 (28–47 IQR) 6 (11.3%) were <14 years	Consecutive SARS-CoV-2 cases admitted to hospital	53	53	25 Mycoplasma 6 viral
Mo	Zhongnan Hospital, Wuhan, China	Retrospective case series 1-1-20 to 2-5-20	54 (42–66 IQR)	Consecutive COVID-19 pneumonia admitted patients	155	Not specified	12
Wang M	Renmin hospital, Wuhan, China	Retrospective case series 1-20-20 to 2-9-20	56 (42–67 IQR)	Consecutive patients tested at Renmin hospital	104	104	6
Wang Z	Union hospital, Wuhan, China	Retrospective case series 1-16-20 to 1-29-20	42 (35–62 IQR)	Consecutive patients admitted to hospital who were positive for SARS-CoV02	69	28	4
Wu J	Three hospitals in Jiangsu province	Retrospective case series 1-22-20 to 2-14-20	46.1 (30.7–61.5)	Consecutive patients positive for SARS-CoV-2	80	80	0
Wu Q	Two hospitals in northern and southern china; Qingdao Women's and Children's Hospital, Wuhan Children's Hospital	Retrospective case series 1-20-20 to 2-27-20	6 (0.1–15.1)	Consecutive SARS-CoV-2-positive pediatric cases screened for respiratory pathogens (20 asymptomatic, 24 upper respiratory, 29 mild pneumonia, 1 severe pneumonia)	74	34	19 (only 34 tested for upper respiratory pathogens)
Xing	Renmin hospital, Wuhan, China; 3 Qingdao hospitals, Qingdao, China	Retrospective case series 1-17-20 to 1-16-20	Qingdao subset: 50 (37–59 IQR) Wuhan subset: 31 (28–38)	Consecutive SARS-CoV-2-positive patients tests at both hospitals	68	68	25

(Continues)

TABLE 1 (continued)

Author, year, published	Region, state, country	Study, design, and date patients admitted	Median, age in years(range unless IQR or SD listed)[c]	Population studied	Total SARS-CoV-2 cases	Total SARS-CoV-2 tested for co-pathogens	Total number cases with viral or atypical pathogens
Zhang G	Zhongnan hospital, Wuhan, China	Retrospective case series 1-2-20 to 2-10-20	55 (20–96)	55 severe cases (admitted to ED or ICU), 166 non-severe admitted cases	221	221	33 (email sent 3-30-20 to get breakdown of 17 bacteria can add them in if they are the atypicals)
Zhang JJ	Hospital #7, Wuhan, China	Retrospective case series 1-16-20 to 2-3-20	57 (25–87)	Consecutive hospitalized patients diagnosed with viral pneumonia	140	140	7

[a]This was the central hospital where all admitted cases were directed in Wuhan.
[b]Only those with SARS-CoV-2 plus influenza were described in the series.
[c]Median age unless otherwise specified. Range in parenthesis unless otherwise specified. IQR, interquartile range.

Our meta-analysis included 8 unpublished, non-peer-reviewed studies.[27,30,32,33,39,42,43,44] Prior studies found that most investigators and editors who evaluate meta-analyses believe that unpublished data should be included as long as the information undergoes the same methodological evaluation as published studies.[50–52] Exclusion of unpublished studies and grey literature potentially can lead to overestimation of treatment effects within meta-analyses.[53] The Cochrane collaborative allows for inclusion of unpublished studies within systematic review and meta-analyses to avoid publication bias with the caveat that unpublished studies may have lower methodological quality and may be sourced from entities with a biased "interest" in the study results.[51,52] To determine their effect on our meta-analysis, we included a subgroup analysis and meta-regression of published versus unpublished studies and found no effect on heterogeneity or outcome.

High variance between studies or heterogeneity in our and other meta-analyses can be due to clinical, methodological, or statistical reasons. Eighteen of 19 included studies were retrospective case series. The median number of subjects per study was small, 80, only 7 studies contained 100 or more patients each, and no 2 studies used the same testing methodology. These differences might partly explain the high heterogeneity (I^2) for the entire study and all studied subsets in our meta-analysis. The wide range of co-infections (0%–58.5%) in our study supports the concept that there were important differences between studies. Preferably, studies combined within a meta-analysis should have comparable designs, interventions or measurements, and patient populations. Thus, it should be expected that a meta-analysis that combines studies with different sizes, designs, participants, and testing methods would have high heterogeneity. Experts have stated that any amount of heterogeneity is expected and acceptable as long as predefined criteria for inclusion are sound and data is correct.[54]

The overall quality of evidence within our meta-analysis GRADE was designated as low indicating that the true prevalence of respiratory co-infections might be different from our estimation. The majority of Cochrane systematic reviews, WHO guidelines, and many online medical resources of medical interventions also are based on low or very low quality of evidence.[55–57] As an example, Alexander et al.[57] found that the WHO made strong recommendations in over 56% of instances in which the quality of evidence was rated low or very low. Multiple reasons exist for this disparity including the known benefit of a treatment, the magnitude of benefit, potential (or lack of potential) for catastrophic harm, confidence in similar alternative options, and overall risk related to recommendations.[58,59] Thus, low GRADE quality of evidence is not a reason to ignore that evidence and GRADE is not the only determinant regarding the importance of recommendations or systematic reviews. Instead, it indicates that future research is likely to "have an important impact on our confidence in the estimate of effect and is likely to change that estimate."[60] Because the current pandemic began and rapidly expanded over the past 4 months, many studies describing co-infections are small, retrospective, and currently, unpublished. Until large prospective studies are completed, it will be difficult to conduct meta-analyses based on moderate or high-quality evidence.

TABLE 2 Description of testing methods and results

Author	SARS-CoV-2 testing method	Other viruses and atypical bacteria testing method	Type of co-pathogens tested	Total patients with co-pathogens and total organisms found
Ai	RT-PCR[a] via nasopharyngeal swab	RT-PCR via nasopharyngeal swab and Metagenomic sequencing of RNA	Adenovirus, Bordetella pertussis, Chlamydia, Coronavirus (229E, HKU1, NL63, OC43), Influenza A, Influenza AHI, Influenza A H3, Influenza A H1N1/pdm09, Influenza B, Metapneumovirus, A + B, Mycoplasma, Parainfluenza (1,2,3,4), Rhinovirus/enterovirus, RSV A + B	5 total patients: 2 Rhino/enterovirus 1 Influenza H3N2 1 Influenza B 1 RSV 4 *Haemophilus parainfluenza*, 1 Klebsiella, 1 Candida not counted in total as co-respiratory pathogen
Bhatraiu	RT-PCR via CDC testing guidelines which include either nasopharyngeal, oropharyngeal, nasal mid-turbinate, anterior nares swab; nasal or nasopharyngeal wash/aspirate	RT-PCR via nasopharyngeal swab	University Washington subset: Adenovirus, Bocavirus, Coronavirus (not SARS-CoV-2), Influenza A, Influenza B, Metapneumovirus, Parainfluenza (1,2,3,4), RSV, Rhinovirus Swedish Med. Center: Adenovirus, Bordetella, Chlamydia, Coronavirus (229E, HKU1, NL63, OC43), Influenza A (H1, 2009 H1, H3), Influenza B, Metapneumovirus, Mycoplasma, Parainfluenza (1,2,3,4), Rhinovirus, RSV Virginia Mason Med. Center: Adenovirus, Coronavirus (not SARS-CoV-2), Influenza A, Influenza B, Metapneumovirus, Parainfluenza (no subtype specified), RSV	None
Chen N	RT-PCR via throat swab	RT-PCR via throat swab	Adenovirus, Coronavirus (MERS-CoV, SARS-CoV-2) Influenza A (H1N1, H3N2, H7N9), Influenza B, Parainfluenza, RSV	None
Chen X	RT-PCR via throat swab	Serum antibody test – (IgM, IgG)	Chlamydia, Mycoplasma	51 total patients: 22 Chlamydia, 29 Mycoplasma
Ding	Not documented	Influenza serology	Influenza A, Influenza B	3 Influenza A, 2 Influenza B
Kim	RT-PCR—site for collection (nasopharyngeal vs throat) not documented	RT-PCR via nasopharyngeal swab	Adenovirus, Chlamydia, Coronavirus (non SARS, non MERS), Influenza A, Influenza B, Rhinovirus/enterovirus, Metapneumovirus, Mycoplasma, Parainfluenza 1,2,3,4, RSV	23 total patients: 8 Rhinovirus 6 RSV 5 Coronavirus (non SARS, non MERS) 2 Metapneumovirus 1 Parainfluenza 1 1 Parainfluenza 3 1 Parainfluenza 4 1 Influenza A

(Continues)

TABLE 2 (Continued)

Author	SARS-CoV-2 testing method	Other viruses and atypical bacteria testing method	Type of co-pathogens tested	Total patients with co-pathogens and total organisms found
Li J	RT-PCR via throat swab	RT-PCR via throat swab (within results influenza antibody tests are described)	Adenovirus, Coronavirus (SARS-CoV-1, MERS), Influenza A (H1N1, H3N2, H7N9), Influenza B, RSV, Parainfluenza,	5 total patients: 5 Influenza A (within table–results state 5 antibody tests positive)
Li Q	RT-PCR via nasopharyngeal swab	Not specified	Adenovirus, Chlamydia, Coxsackie B, Influenza (no sub-types specified), Mycoplasma, RSV	5 total patients: 5 with respiratory pathogen not specified
Lin	RT-PCR–site for collection (nasopharyngeal vs throat) not documented	RT-PCR of respiratory tract specimen (naso- vs oropharyngeal source not specified)	Adenovirus, Bocavirus, Coronavirus NL63, Coronavirus 229E, Coronavirus HKU1, Coronavirus OC43, Influenza A, Influenza B, Metapneumovirus, Parainfluenza 1, 2, and 3, Rhinovirus, RSV	6 total patients: 1 with HKU1+ metapneumovirus, 1 with HKU1+RSV 1 with RSV+parainfluenza 2 1 with RSV+rhinovirus 1 with Metapneumovirus 1 with Rhinovirus
Liu H	RT-PCR via throat swab Subset diagnosed by clinical features plus CT scan of chest	Not specified	Adenovirus, Chlamydia, Coxsackie virus B, Influenza A, Influenza B, Mycoplasma, Parainfluenza (no types specified) RSV	2 total patients: 1 Mycoplasma 1 RSV
Liu L	RT-PCR—site for collection listed as respiratory tract	Serum antibody test (IgM, IgG)	Adenovirus, Chlamydia, Coxiella, Influenza A, Influenza B, Legionella, Mycoplasma, Parainfluenza (1,2,3), RSV	25 Mycoplasma 6 viruses (Influenza A, Influenza B, RSV)
Mo	RT-PCR via throat swab	Not specified	Adenovirus, Influenza A, Influenza B, Mycoplasma, Parainfluenza, RSV	12 total patients: 3 Parainfluenza (no type specified) 3 RSV 3 Adenovirus 2 Mycoplasma 2 Influenza A 2 Influenza
Wang M	RT-PCR – via nasopharyngeal swab or sputum sample	Respiratory electrophoresis fragment analysis with PCR	Adenovirus, Bocavirus, Chlamydia, Coronavirus, Influenza A (H1N1, H3N2), Influenza B, Metapneumovirus, Mycoplasma, Parainfluenza, Rhinovirus, RSV	6 total patients: 3 Coronavirus (non-SARS, non-MERS) 2 Influenza A, 2 Rhinovirus, 1 Influenza A type H3N2 (it was assumed 2 patients had 2 additional infections in addition to SARS-CoV-2)

(Continues)

TABLE 2 (Continued)

Author	SARS-CoV-2 testing method	Other viruses and atypical bacteria testing method	Type of co-pathogens tested	Total patients with co-pathogens and total organisms found
Wang Z	RT-PCR via throat swab	Serum Antibody test (IgM, IgG)	Not specified	2 Chlamydia 1 RSV 1 Adenovirus
Wu J	RT-PCR via nasal or throat swab	Not specified	9 respiratory pathogens including Influenza A, Influenza B, with the other 7 pathogens not specified	None
Wu Q	RT-PCR via nasopharyngeal swab	Not specified	Not specified	16 Mycoplasma 3 RSV 3 Epstein-Barr 3 Cytomegalovirus 1 Influenza (type not specified)
Xing	RT-PCR via throat swab	Serum antibody test (IgM, IgG)—serum for Qingdao and Wuhan subsets RT-PCR throat swab for Wuhan subset	Antibody test— Adenovirus, Chlamydia, Coxiella, Influenza A, Influenza B, Legionella, Mycoplasma, Parainfluenza, RT-PCR test (Wuhan)—Adenovirus, Bocavirus, Chlamydia, Coronavirus (SARS-CoV-1), Influenza A, Influenza B, Influenza subtypes (H1N1, H3N2), Mycoplasma, Parainfluenza, RSV, Metapneumovirus, Rhinovirus,	25 total patients: 18 Influenza A 16 Influenza B 8 Mycoplasma 6 Legionella 1 RSV
Zhang G	RT-PCR via pharyngeal swab	RT-PCR via pharyngeal swab, bronchoalveolar lavage, sputum, or bronchial aspirate	Adenovirus, Chlamydia, Influenza A (H1N1, H7N9), Influenza B, Legionella, Mycoplasma, Parainfluenza, RSV	33 viral co-infections There were also 17 bacterial co-infections not counted in this number although some may have been Mycoplasma, Chlamydia, or Legionella
Zhang J	RT-PCR via pharyngeal swab	Serum antibody test (IgM, IgG)	Adenovirus, Chlamydia, Coxsackie B, Cytomegalovirus, Echovirus, Epstein-Barr, Influenza A, Influenza B, Mycoplasma, Parainfluenza (sub types not specified), RSV	5 Mycoplasma 1 RSV1 Epstein-Barr

[a] RT-PCR, reverse transcription, polymerase chain reaction.

TABLE 3 Newcastle Ottawa Scale for risk of bias in cohort or cross-sectional studies

Items	Ai	Bhatraju	Chen N	Chen X	Ding	Kim	Li J	Li Q	Lin	Liu H	Liu L	Mo	Wang M	Wang Z	Wu J	Wu Q	Xing	Zhang G	Zhang JJ
Selection																			
Exposed truly representative of average[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Selection of non-exposed from the same community as exposed	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Exposure ascertained by secure record or interview	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Demonstration of outcome of interest (coinfection) not present at start of the study[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Comparability of those with versus without co-infection																			
Comparable groups based on major factor (age)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Comparable groups based on minor factor (Gender)	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗
Outcome (0 or 1 point each)																			
Adequate assessment of outcome	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Follow-up long enough for outcome to occur	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adequacy of follow-up: subjects lost to follow-up unlikely to introduce bias[b]	✓	✗	✓	✗	✓	✗	✓	✓	✗	✓	✓	✓	✗	✗	✓	✗	✓	✓	✓
Total score	7	6	7	6	7	6	7	7	6	7	7	7	6	6	7	6	7	7	7

✓, present; ✗, absent.

[a] In general, consecutive admissions or consecutively screened patients were felt to be representative of average patient with SARS-CoV-2 in that clinic or hospital.

[b] Newcastle-Ottawa Scale instructions state that the disease and not mortality should be the major outcome of interest. For COVID-19, if infections were new, this criterion was met.

TABLE 4 Pooled prevalence for all studies and subsets

Study subsets	Studies(n)	Subjects(n)	Pooled prevalence[a] (95% CI)	Heterogeneity I^2 statistic(95% CI)
All Studies	19	1880	11.6 (6.9–17.4)	0.92 (0.89–0.94)
Adults only	15	1577	8.9 (4.9–13.9)	0.9 (0.85–0.93)
Viral co-pathogens	16	1469	7 (3.8–11.1)	0.86 (0.80–0.91)
100% of subjects tested for co-pathogens	15	1210	16.8 (8.1–27.9)	0.95 (0.94–0.97)
Atypical bacterial co-pathogens	11	1150	7.9 (2.3–16.5)	0.95 (0.93–0.97)
Low risk of bias studies	12	1110	12.3 (5.5–21.3)	0.94 (0.91–0.96)
Published studies	11	1107	7.2 (2.8–13.5)	0.92 (0.88–0.95)
RT-PCR testing[b]	9	761	9.1 (3.8–16.4)	0.88 (0.80–0.93)
Large (>100 patients with SARS-CoV-2)	7	1142	10.5 (6.3–15.5)	0.84 (0.70–0.92)
Outside Hubei province	6	561	21 (6–41.9)	0.96 (0.93–0.97)
Serum antibody testing	6	488	26.8 (7.9–51.9)	0.97 (0.95–0.98)

CI, confidence interval.
[a]Pooled prevalence for viral or atypical co-pathogen co-infection.
[b]Five studies did not specify type of testing and were not included in subset.

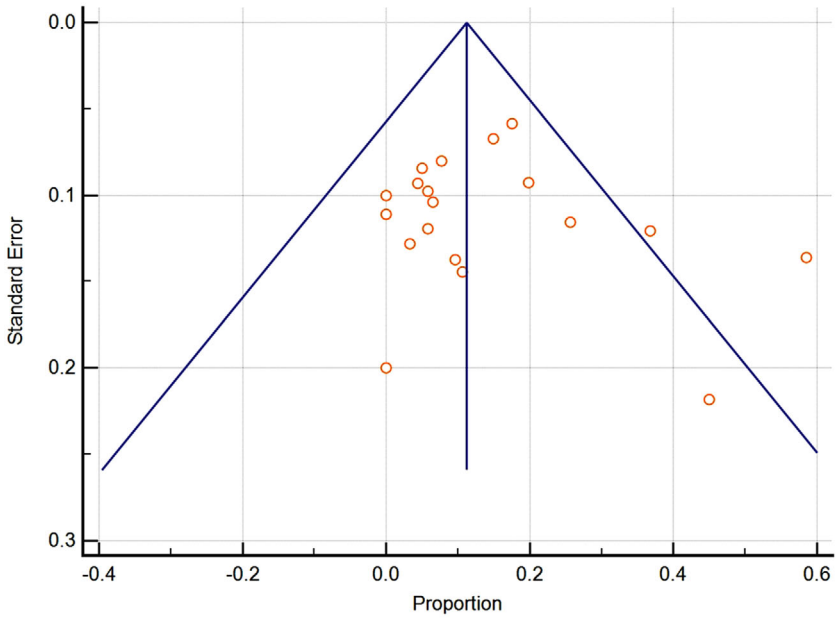

FIGURE 3 Funnel plot of included studies—viral and atypical bacteria co-infections

7 | DISCUSSION

We found a pooled prevalence of 11.6% for viral and atypical pathogens in 1880 patients who were SARS-CoV-2-positive when all subjects within studies were included and 16.8% when patients with 100% co-pathogen testing were analyzed. Viral co-pathogens comprised 159 and atypical bacteria comprised 116 infections. Subset analysis of studies comprised of adults only found a pooled prevalence of 8.9% co-infections. Subset analysis of viral and atypical bacterial co-pathogens found a pooled prevalence of 7% and 7.9%, respectively. These results indicate that co-infections with both respiratory viruses and atypical bacteria are a common and potentially important factor in patients with COVID-19.

The majority of individuals within included studies were symptomatic and were admitted to the hospital. It is possible that co-infection rates are higher in these patients and co-infection contributed to symptoms, disease severity, and hospitalization. Testing of relatively asymptomatic SARS-CoV-2 positive patients for other pathogens will be required to determine if a similar rate of co-infections exists in a less ill population of SARS-CoV-2-positive outpatients.

All studies contained patients enrolled from January to March 2020. It is likely that the presence and timing of viral respiratory outbreaks (especially influenza) influenced the prevalence of co-pathogens. Although influenza virus infections are detected year-round, peak activity in the northern hemisphere is typically December through March.[61] This time frame coincides with the current SARS-

CoV-2 outbreak. Because of this phenomenon, co-infection rates during other "non-flu" months within the southern hemisphere, and during local co-pathogen outbreaks, are likely to differ.

Only 6 studies evaluated serum antibody tests with this method detecting co-infections in a 26.8% of COVID-19 patients. It is possible that application of this testing method across all studies would reveal an even higher overall co-infection rate than found in our study. Alternately, it is possible that positive serology indicated recent and not acute infection in included patients. Positive RT-PCR tests also might indicate recently resolved infection or colonization. Byington et al[62] found that 16% of children with respiratory viruses had positive PCR tests for 3 or more weeks after an initial infection. Tests for bocavirus and rhinoviruses stayed positive for a longer period than other respiratory viruses although symptomatic viral infections lasting over 3 weeks occurred with most tested viruses (adenovirus, coronavirus [all subtypes 229E, HKU1, NL63, OC43], influenza, human metapneumovirus, parainfluenza, and respiratory syncytial virus).[62] It is uncertain if prolonged viral test positivity without infection also applies to adults.

Although RT-PCR was used to detect viruses in 17 included studies, these tests have not shown a consistent level of accuracy in detecting viral pathogens. Basile et al[63] reviewed point-of-care diagnostic tests including RT-PCR for respiratory infections and found that sensitivity for viral pathogens varied from 20%–94% depending on the type of test, the individual viruses analyzed, the manufacturer, and the specific technique used. Zhang et al[64] combined serology (antibody testing) with RT-PCR to analyze the additive diagnostic yield with a combined testing approach. In their study, antibody testing increased detection of viral pathogens between 12%–49% depending upon the virus studied.[64] Only a subset of 1 study in our meta-analysis combined serology and RT-PCR in their population.[43]

Separate from issues with testing, co-infection with other respiratory pathogens has important implications for diagnosis and prognosis. It is possible that the clinical presentation, laboratory results, radiological findings, and outcome differ between SARS-CoV-2 positive patients with and without co-infections. Burk et al[65] found that coexisting viral and bacterial pathogens increased mortality in community-acquired pneumonia. Other studies conflict on whether or not co-infection with *Chlamydia pneumonia* in individuals with SARS-CoV-1 is associated with increased disease severity and mortality.[66] Prospective studies detailing presenting historic, physical examination, and laboratory/radiological features will be needed to determine how patients with respiratory pathogens differ from those without co-pathogens.

Medical management might differ for COVID-19 patients with and without co-infections. Although there are no currently approved treatments for COVID-19, anti-virals for influenza and antibiotics for atypical bacteria would likely benefit individuals with those co-infections. When treatments are developed for COVID-19, clinicians will need to understand the interactions of medicines and side effects of combining medicines when treating individuals with COVID-19 and co-pathogens.

In summary, we found an 11.6% pooled prevalence for co-infection with viruses and atypical bacteria in studies of SARS-CoV-2-positive patients. Pooled prevalence was even higher, 16.8%, in studies that tested 100% of patients for co-pathogens. These results indicate that clinicians should not rely on positive tests for these co-infections when considering whether or not to test patients for SARS-CoV-2. Further study is needed to determine if co-infections alter clinical features, laboratory and radiological examinations, and outcomes for patients with COVID-19.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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