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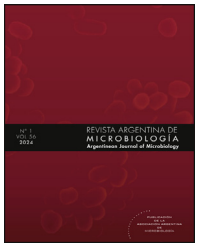

SPECIAL ARTICLE

Are *Mycoplasma pneumoniae* coinfections frequent in COVID-19 patients? A systematic review☆

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KEYWORDS
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Abstract Understanding the proportion of SARS-CoV-2 patients with *Mycoplasma pneumoniae* coinfection is crucial for treating patients suffering from coronavirus disease (COVID-19), help to ensure responsible use of antibiotics and minimize the negative consequences of overuse. In addition, this knowledge could have an impact on empirical antibiotic management guidelines for patients with COVID-19. This systematic review aimed to identify the prevalence of *M. pneumoniae* in patients with coronavirus disease 2019 (COVID-19).

A bibliographic search of studies published in Spanish or English was conducted using the PubMed search engine. Fourteen articles from different continents (America, Asia and Europe) were included, involving a total of 5855 patients in these studies. The mean age of COVID-19 patients with *M. pneumoniae* was 48 years old (range 1–107), most of whom were male. The detection of laboratory-confirmed *M. pneumoniae* infection varied between 0 and 33.3%. Most of patients referred fever, cough, and dyspnea, and received empirical antibiotic treatment. Bacterial coinfection was not associated with increased ICU admission and mortality. The prevalence of coinfection showed extremely dissimilar figures according to the population studied

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and diagnostic criteria. However, it is important to develop Latin American studies, given the heterogeneity observed in the studies conducted in different countries. Standardized definitions should be developed in order to be able to assess the impact of coinfections in patients with a diagnosis of COVID-19.

PALABRAS CLAVE
Infección por SARS-CoV-2;
COVID-19;
Mycoplasma pneumoniae;
Coinfección

¿Son frecuentes las coinfecciones con *Mycoplasma pneumoniae* en pacientes con COVID-19? Una revisión sistemática

Resumen Comprender la proporción de coinfección por coronavirus (COVID-19) y *Mycoplasma pneumoniae* es crucial para tratar a los pacientes con COVID-19, garantizando el empleo responsable de antibióticos y minimizando las consecuencias negativas del uso excesivo. Además, este conocimiento podría tener un impacto en las pautas de manejo empírico de antibióticos en pacientes con COVID-19. Esta revisión sistemática tuvo como objetivo identificar la prevalencia de *M. pneumoniae* en pacientes con COVID-19. Para ello se realizó una búsqueda bibliográfica de estudios publicados en español o inglés utilizando el buscador PubMed. Se incluyeron 14 artículos de diferentes continentes (América, Asia y Europa), con un total de 5855 pacientes estudiados. La media de edad de los pacientes COVID-19 con *M. pneumoniae* fue de 48 años (intervalo: 1 a 107 años) y la mayoría de ellos fueron varones. La detección de *M. pneumoniae* confirmada por laboratorio en pacientes con COVID-19 varió del 0 al 33,3%. La mayoría de los pacientes refirieron fiebre, tos y disnea, y recibieron antibióticos empíricos. La coinfección bacteriana no se asoció con un aumento de la admisión en UCI ni de la mortalidad. La prevalencia de coinfección fue muy disímil según la población estudiada y los criterios diagnósticos empleados. Dada la heterogeneidad de resultados en los diferentes países, es importante desarrollar estudios en América Latina, como así también establecer definiciones estandarizadas para poder evaluar el impacto real de las coinfecciones en pacientes con COVID-19.

Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) commonly causes infections of the respiratory system among all age groups[42]. This microorganism is one of the leading causes of community-acquired pneumonia (CAP), especially in children. Most pneumonia cases are benign, whereas some of them may develop into severe pneumonia and refractory pneumonia with pleural effusion, multi-organ dysfunction, and serious long-term sequelae, including bronchiolitis obliterans and bronchiectasis[16]. Airborne droplets containing *M. pneumoniae* can be transmitted and spread among people through coughing and sneezing. In most cases, clinical symptoms are non-specific and cough is the main symptom, which is usually paroxysmal and often persistent[43]. Coinfection of *M. pneumoniae* has been identified in viral pneumonia[40]. At present, coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 virus has spread to almost every part of the world. The combination of SARS-CoV-2 infection and other respiratory pathogens is a challenge for health care systems in terms of diagnosis, treatment, and management. Although viral infection and bacterial infection are essentially different in terms of pathogenesis, the clinical manifestations of COVID-19 and CAP, such as fever, dry cough, fatigue, all-over ache and chest tightness[46], are similar. Clinical practice indicates that reactive lymphocytes are frequently observed in COVID-19 infection, while in *M. pneumoniae* infection cold agglutination is common[20]. There are only subtle differences in radiographic features between these two infections[17].

Several studies have reported a wide range of coinfection rates in SARS-CoV-2 patients, with rates ranging from 3% to more than 20% being reported[24]. Therefore, studies that identify the pathogens coinfecting COVID-19 patients and the evaluation of their impact on the clinical outcome are crucial. These data may guide clinicians to establish a directed antimicrobial therapy, decrease the irrational use of antibiotics and improve the clinical outcome.

The objective was to assess the molecular prevalence of coinfection with this atypical bacterium in COVID-19 patients and describe the clinical features, laboratory parameters, complications, clinical outcomes of such coinfections, to determine the importance of detecting *M. pneumoniae* in patients with COVID 19 and establishing an adequate treatment.

Materials and methods

A systematic review of the literature was performed focusing on the identification of *M. pneumoniae* coinfections in SARS-CoV-2 patients. PubMed was searched using a combination of key terms such as COVID-19 and *M. pneumoniae*,

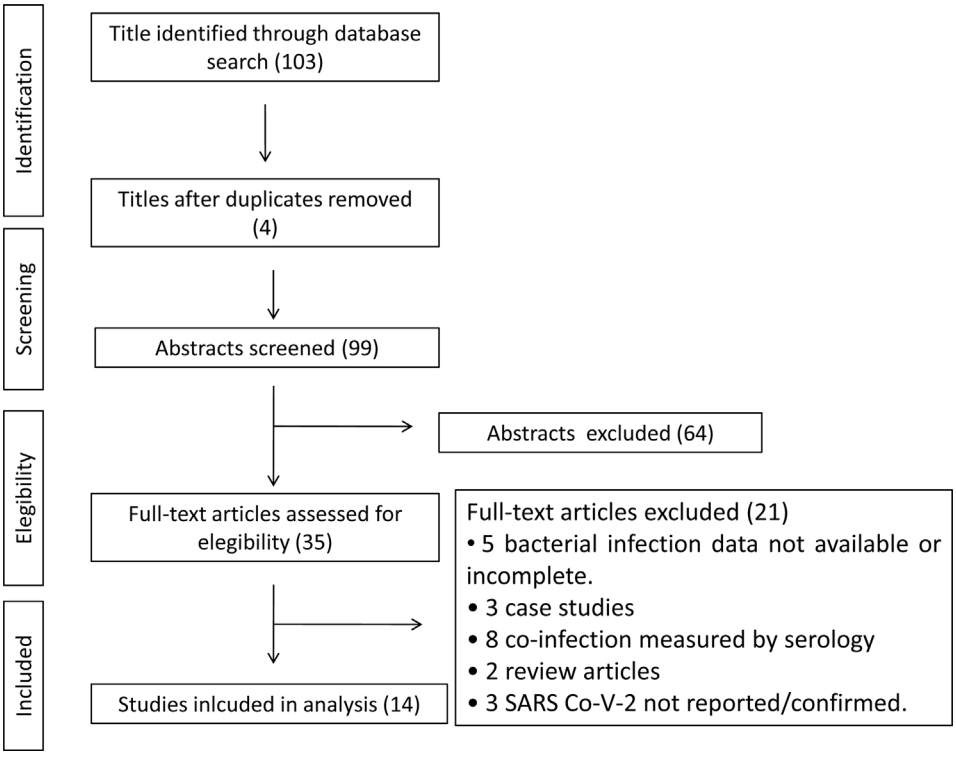

Figure 1 PRISMA flow-chart.

SARS-COV-2 and *M. pneumoniae*, bacterial coinfections and COVID-19, pneumonia and SARS-COV-2, pneumonia and COVID-19. We also used the same terms in Spanish and included articles written in English and Spanish (the primary languages of the investigators). We also reviewed the reference lists for the articles identified by our search, as well as those of any included studies. We only included those studies using molecular methods for *M. pneumoniae* detection and excluded all studies employing culture or serology techniques for *M. pneumoniae* identification.

Data abstraction

Each abstract and the articles selected for full review were evaluated by all investigators. For each included article, the study characteristics and data regarding detection were abstracted by the authors. For detection data, defined cases were included and possible cases were excluded. For each report, the type of surveillance used, number of cases reported and total population studies were documented. This review was conducted and reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-charts (Fig. 1).

Results and discussion

The literature search yielded 103 studies. After a first screening, 64 were excluded because they were not related to the subject and 4 were duplicate. After full text reading, 14 studies were included (Fig. 1). Specifically, four of the studies were retrospective and ten were prospective. Most studies were from the USA, Brazil, China and France and the remaining ones from the United Kingdom, Spain, India, Turkey, Peru and Iran. A total of 5855 COVID-19 patients were identified and included in our review (Table 1).

Concerns regarding coinfections during viral pandemics, specifically coinfections with respiratory bacterial pathogens, are borne from the experience in H1N1 influenza A, Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS)[1,22,33]. In these outbreaks, as in the COVID-19 pandemic, much lower coinfection rates with *M. pneumoniae* were reported[5,11,36,39,45]. The prevalence of reported *M. pneumoniae* infections in COVID-19 patients ranged from 0–33.3% in the retrospective studies and 0–28.1% in the prospective studies. These differences in the proportion of coinfection may be attributable to the selection of case-patients (adults or children), geographic factors, season and the clinical condition[9,10,25,27]. High prevalence of coinfection between *M. pneumoniae* and SARS CoV-2 was described using serological methods[18,28,47]. However, these methods are not highly specific tests and may result in an overestimation of infections[37]. In general, the bacterium less frequently found in coinfection with SARS-COV-2 is *M. pneumoniae*[13,15,16]. Many of the most recent studies showed that coinfections appeared to be relatively rare. However, due to the variability between countries and the limited country/region representation in the few studies published, the results shown cannot be extrapolated to Latin America. That is why it is important to generate local evidence to support decision-making. In Argentina, only one multicenter study reported the presence of *M. pneumoniae* in 12.3% (24/187) of COVID-19 patients, using nested-PCR[14].

Table 1 Summary of studies reporting the incidence of *M. pneumoniae* co- and secondary infection among COVID-19 patients.

Authors	Country	Type of study	Age[a]	Overall rate of coinfection (%)	*M. pneumomiae*/ SARS-CoV-2 (%)	Diagnostic methods	Treatment	Outcomes of COVID19/*M. pneumoniae* patients (%)
Blasco et al., 2020[2]	Spain	Retrospective	64	3/103 (2.9)	1/3 (33.3)	Multiplex PCR assay	NR	NR
Boschiero et al., 2022[3]	Brazil	Prospective	NR	84/1503 (5.6)	2/84 (2.38)	RT-PCR (respiratory pathogen panel)	NR	NR
Chaudry et al., 2022[5]	India	Prospective	50	17/194 (8.7)	3/17 (17.6)	RT-PCR (CARDS toxin gene)	Azithromycin, or fluoro-quinolones, or doxycycline	NR
Chi et al., 2020[6]	China	Retrospective	53.5	0/17 (0.0)	0/0 (0.0)	Multiplex PCR	NR	NA
Contou et al., 2020[8]	France	Retrospective	61	26/92 (28.0)	0/26 (0.0)	RT-PCR (respiratory pathogen panel)	NR	NA
Easom et al., 2020[12]	United Kingdom	Prospective	42.4	29/67 (43.3)	1/67 (1.5)	Multiplex PCR	Doxycycline and monofloxacin	0
Hazra et al., 2020[19]	USA	Prospective	NR	15/459 (3.0)	0/459 (0.0)	RT-PCR (respiratory pathogen panel)	NR	NA
Husain et al., 2022[21]	France	Retrospective	69	22/784 (2.8)	2/22 (9.1)	Multiplex PCR	NR	NR
Karaaslan et al., 2021[23]	Turkey	Retrospective	10	7/93 (7.5)	1/93 (1.07)	PCR	Azithromycin	0
Kim et al., 2020[24]	USA	Prospective	49	23/115 (20.0)	0/116 (0.0)	RT-PCR (respiratory pathogen panel)	NR	NA
Pérez-Lazo et al., 2021[30]	Peru	Prospective	58	154/295 (52.2)	83/295 (28.1)	PCR	Azithromycin	15 (18.1) died
Richardson et al. 2020[34]	USA	Prospective	63	42/1996 (2.1%)	1/42 (2.4)	RT-PCR (respiratory pathogen panel)	NR	NR
Soltani et al., 2021[38]	Iran	Prospective	52	10/40 (25.0)	9/40 (22.5)	PCR (P1 adhesion gene)	NR	NR
Varela et al., 2022[41]	Brazil	Prospective	5	31/97 (31.9)	0/31 (0.0)	RT-PCR (respiratory pathogen panel)	Azithromycin	NA

[a] Years (mean). NR: not reported. NA: not applicable. *M. pneumoniae*: *Mycoplasma pneumoniae*.

In two studies (Table 1), most patients who had contracted a bacterial respiratory infection did not test positive for COVID-19[3,4,24]. The median age of COVID-19 patients studied for *M. pneumoniae* was 48 years old (range 1–107), most of whom were male[2,5,8,21,23,30,34,38]. This observation is not consistent with the established literature that indicates that community-acquired viral coinfections are more common in younger populations[35].

The most common clinical symptoms in COVID-19 coinfected patients were fever, cough and dyspnea[5,6,12,21,23,30,38]. However, these symptoms are similar among COVID-19 monoinfections and coinfections with other pathogens, which made the clinical differentiation difficult. Thus, laboratory confirmation is required.

The clinical presentations of *M. pneumoniae* range from mild infections affecting the upper respiratory tract to pneumonia that needs hospital admission[43]. It has been proposed that pathogens such as *M. pneumoniae* can exacerbate clinical symptoms, increase morbidity and prolong the stay in the intensive care unit (ICU) in COVID-19 patients[5,13,23,30,34]. Boschiero et al., 2022[3] did not find an association between coinfections and more severe COVID-19-related outcomes in Brazil, while Perez-Lazo et al., 2021[30] reported a high rate of mortality in Peru (18.1%). The authors described an elevated development of sepsis in the group with *M. pneumoniae* coinfections (37.4%); however, they found that mortality was similar among coinfected and monoinfected groups[30]. In two studies included in this review a lower mortality rate was found[12,23], whereas the remaining studies did not report any mortality rates[2,3,5,21,34,38]. Lower rates of comorbidities, such as hypertension, diabetes mellitus, renal disease and obesity[5,30] were described in coinfected patients.

Antibiotic use was reported in five studies[5,12,23,30,41], with >50% of patients receiving empirical antibiotics[30]. This is particularly important in Latin America, where the abuse of antibiotics in COVID-19 patients has reached alarming levels[7,32]. The finding that there was a low number of patients with bacterial infections, such as *M. pneumoniae*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, highlights the fact that the empirical use of antibiotics in patients with COVID-19 should not be recommended[26,29,31,44]. The COVID-19 pandemic exacerbated the known challenges to optimal antibiotic administration, representing a direct threat to patient safety and public health through antibiotic overprescription and promotion of bacterial resistance.

Unfortunately, there were no specific data on clinical information and therapeutic interventions. Due to the diversity of studies and the low number of patients with detected coinfection with *M. pneumoniae*, it was difficult to find symptoms indicating coinfection with *M. pneumoniae* and SARS-CoV-2 in the studies included in our review.

Despite the fact that *M. pneumoniae* coinfections were searched and infrequently documented in patients with COVID-19 pneumonia, routine testing for respiratory pathogens should be advised, since agents for which specific therapy can be prescribed may be detected and may have a beneficial impact on patient outcomes.

Ethical approval

Not required.

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Conflict of interests

The authors declare that they have no conflicts of interest.

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