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The Association between Helicobacter Pylori Infection and Community-Acquired Pneumonia: A Systematic Review

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Abstract

Background: Community-acquired pneumonia (CAP) remains a leading cause of morbidity and mortality worldwide. While Helicobacter pylori is primarily a gastric pathogen, emerging evidence suggests potential extra-gastric manifestations, including possible links to respiratory diseases. However, the association between H. pylori infection and CAP remains poorly characterized. ***Objective:*** This systematic review aimed to critically evaluate and synthesize the available evidence regarding the association between Helicobacter pylori infection and community-acquired pneumonia. ***Methods:*** A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science for publications from January 2021 to January 2026. Studies investigating direct or indirect associations between H. pylori infection and CAP were included. Eight studies met eligibility criteria, encompassing diverse designs including cohort, case-control, cross-sectional, and randomized controlled trials. Quality assessment was performed using appropriate tools (Newcastle-Ottawa Scale, JBI Checklist, Cochrane RoB 2). ***Results:*** Direct evidence for an H. pylori-CAP association was limited, with only three studies providing direct seroepidemiological or immunological data. These demonstrated that H. pylori infection may modulate systemic inflammatory responses (elevated CXCL10 and IL-10; reduced IL-1β and IL-6) and showed non-significant associations with respiratory pathogen co-exposure. Indirect evidence highlighted that proton pump inhibitor use—commonly prescribed for H. pylori-related conditions—was associated with significantly increased pneumonia risk (adjusted hazard ratio: 1.882 for long-term use). Studies in peptic ulcer patients reported postoperative pneumonia rates of 5–12%. Overall evidence quality was moderate, with significant heterogeneity precluding meta-analysis. ***Conclusion:*** Direct evidence linking H. pylori infection to community-acquired pneumonia is remarkably limited and inconclusive. The available data suggest that any association may operate through immunomodulatory mechanisms or indirect pathways, particularly proton pump inhibitor use. Well-designed prospective cohort studies with validated H. pylori diagnostics and adequate confounder adjustment are urgently needed to clarify this relationship.

Keywords: Helicobacter pylori; community-acquired pneumonia; respiratory infection; systematic review; proton pump inhibitors; gut-lung axis; extra-gastric manifestations.

INTRODUCTION

Community-acquired pneumonia (CAP) remains one of the leading causes of morbidity and mortality worldwide, imposing a substantial burden on healthcare systems and accounting for approximately 1.4 million emergency department visits and over 50,000 deaths annually in the United States alone [1]. The global incidence of CAP is estimated to range from 1.5 to 14 cases per 1,000 person-years, with the highest rates observed among older adults and individuals with underlying comorbidities [2]. Despite advances in vaccination strategies and antimicrobial therapy, CAP continues to rank as the fourth leading cause of death globally, with mortality rates reaching up to 30% in hospitalized elderly patients and those requiring intensive care unit admission [3]. The etiological landscape of CAP is diverse, encompassing bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and atypical organisms like *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, with an increasing recognition of viral etiologies including influenza and respiratory syncytial virus [4]. However, in up to 50% of cases, no specific pathogen is identified, suggesting that host factors and pre-existing chronic

conditions play critical roles in disease susceptibility and severity [2].

Helicobacter pylori is a gram-negative, microaerophilic bacterium that colonizes the gastric mucosa of approximately 50% of the world's population, with prevalence rates exceeding 70% in developing countries and ranging from 20% to 40% in developed nations [5]. The bacterium is well-established as the primary etiological agent of chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma, leading to its classification as a Group I carcinogen by the World Health Organization [6]. Beyond its established role in gastric pathology, *H. pylori* has been implicated in a growing list of extra-gastric manifestations, including cardiovascular diseases, autoimmune conditions such as immune thrombocytopenia, and neurological disorders like Parkinson's disease [7]. The proposed mechanisms for these systemic effects include chronic low-grade inflammation, molecular mimicry, and modulation of systemic immune responses, suggesting that the influence of *H. pylori* extends far beyond the gastric niche.

The potential link between *H. pylori* infection and respiratory diseases, including CAP, has garnered increasing attention over the past two decades. Several biological mechanisms have been proposed to explain how a gastric pathogen might influence pulmonary health. First, chronic *H. pylori* infection induces a persistent systemic inflammatory state characterized by elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), which may impair pulmonary host defenses and predispose to respiratory infections [8]. Second, *H. pylori* infection has been shown to modulate regulatory T-cell responses, potentially altering the balance between Th1 and Th2 immunity in ways that could affect susceptibility to both infectious and allergic respiratory diseases [9]. Third, the bacterium may exert indirect effects through its impact on gastric acid secretion, which in turn influences the gastric and oropharyngeal microbiota, potentially facilitating aspiration of pathogenic microorganisms into the lower respiratory tract [8]. Additionally, the widespread use of proton pump inhibitors (PPIs) for the management of *H. pylori*-related peptic ulcer disease has been independently associated with an increased risk of pneumonia, raising the possibility that the treatment of *H. pylori* rather than the infection itself may contribute to respiratory risk [9].

Despite these plausible mechanistic pathways, the clinical evidence for an association between *H. pylori* infection and CAP remains fragmented and inconclusive. Previous studies have yielded conflicting results, with some suggesting an increased risk of pneumonia among *H. pylori*-seropositive individuals, while others have found no significant association. A meta-analysis by Roussos *et al.,*[7] examining the relationship between *H. pylori* and chronic obstructive pulmonary disease found no consistent association, highlighting the need for a focused evaluation of CAP specifically. Furthermore, the majority of existing research has been limited by cross-sectional designs, small sample sizes, inadequate control for confounding variables, and reliance on serological markers that cannot distinguish between active and past infection. The role of *H. pylori*in CAP is further complicated by the bacterium's declining prevalence in Western populations, which coincides with epidemiological shifts in respiratory disease patterns, raising questions about the potential protective or pathogenic roles of this longstanding human commensal [5].

Given the substantial global burden of both CAP and *H. pylori* infection, clarifying the nature of their relationship has important clinical and public health implications. If a causal association exists, it would suggest that *H. pylori* eradication strategies might offer benefits beyond gastric disease prevention, potentially reducing the risk of CAP in susceptible populations. Conversely, if the association is primarily driven by confounding factors or the adverse effects of therapies used to manage *H. pylori*-related conditions, then clinical practices such as PPI prescribing patterns warrant scrutiny. To date, no comprehensive systematic review has specifically synthesized the evidence regarding the direct and indirect associations between *H. pylori* infection and CAP. Therefore, this systematic review was conducted to critically evaluate the available literature, synthesize the findings from studies examining this relationship, assess the quality of the evidence, and identify gaps in knowledge that should inform future research directions.

METHODOLOGY

Study Design and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility [10]. The review protocol was not prospectively registered, but the methodology was predefined to minimize bias. The aim of this review was to systematically identify, evaluate, and synthesize the available evidence regarding the association between *Helicobacter pylori*infection and community-acquired pneumonia (CAP) in adult and pediatric populations.

Search Strategy

A comprehensive literature search was performed across major electronic databases, including PubMed, Scopus, and Web of Science, covering publications from January 2018 to December 2023, ensuring a five-year capture of recent evidence. The search strategy was developed using a combination of Medical Subject Headings (MeSH) and free-text terms

related to the exposure (*Helicobacter pylori*, *H. pylori*) and the outcome (community-acquired pneumonia, pneumonia, respiratory infection). Boolean operators (AND, OR) were used to combine terms. The specific search string was adapted for each database. Additionally, the reference lists of included studies and relevant review articles were manually screened to identify any additional eligible studies not captured by the electronic search. No language restrictions were applied, but only studies with available English abstracts were considered for initial screening.

Eligibility Criteria

Studies were considered eligible for inclusion if they met the following predefined criteria: (1) the study design was either a randomized controlled trial, cohort study, case-control study, cross-sectional study, or *in vitro* mechanistic study; (2) the study directly or indirectly investigated the association between *H. pylori* infection (assessed by serology, stool antigen test, urea breath test, or histopathology) and CAP or pneumonia-related outcomes; (3) the study population included humans of any age (for clinical studies) or relevant bacterial strains (for *in vitro* studies); and (4) the study reported original data. Exclusion criteria were: (1) studies not published in peer-reviewed journals; (2) case reports, case series with fewer than 10 patients, editorials, or conference abstracts; (3) studies focusing exclusively on hospital-acquired pneumonia, ventilator-associated pneumonia, or aspiration pneumonia without a clear distinction from CAP; and (4) studies that did not provide sufficient data to assess the association of interest.

Study Selection Process

The study selection process was conducted using Rayyan, a web-based systematic review software designed to streamline the screening and collaboration process [11]. After removing duplicate records, two independent reviewers (initials withheld) screened the titles and abstracts of all retrieved citations against the eligibility criteria. Full texts of potentially eligible studies were then retrieved and assessed independently by the same two reviewers. Any disagreements during the screening or full-text review phases were resolved through discussion or by consulting a third reviewer. The selection process was documented, and reasons for exclusion at the full-text stage were recorded, as summarized in the PRISMA flow diagram.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form developed in Microsoft Excel. For each included study, the following information was extracted: first author, year of publication, country, study design, sample size, population characteristics (age, sex, comorbidities), exposure assessment method for *H. pylori*, outcome definition (pneumonia type and diagnostic criteria), key findings relevant to the association, adjusted effect measures (odds ratios, hazard ratios, etc.) with 95% confidence intervals, and covariates included in multivariate analyses. For studies providing indirect evidence, data on the primary exposure (e.g., proton pump inhibitor use, surgical intervention) and pneumonia outcomes were extracted. Discrepancies in data extraction were resolved by consensus.

Risk of Bias Assessment

The quality and risk of bias of the included studies were assessed using appropriate tools based on study design. For observational cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) was used, which evaluates studies across three domains: selection of participants, comparability of groups, and ascertainment of exposure/outcome [12]. Cross-sectional studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies, which includes items on sample frame, participant selection, measurement of exposure and outcome, and adequacy of statistical analysis. The single randomized controlled trial was evaluated using the Cochrane Risk of Bias Tool (RoB 2). Each study was rated as having low, moderate, or high risk of bias based on the overall score or domain judgments. The quality assessment was conducted independently by two reviewers, and any disagreements were resolved through discussion.

Data Synthesis

Due to the heterogeneity of study designs, populations, exposures, and outcomes, a meta-analysis was not feasible. A narrative synthesis approach was adopted to summarize the findings. Studies were grouped into categories based on the type of evidence provided: (1) direct evidence (studies examining *H. pylori* infection and pneumonia or related immunological parameters); (2) indirect evidence (studies examining pathways potentially linking *H. pylori* to pneumonia, such as PPI use, peptic ulcer surgery outcomes, and *in vitro* mechanistic studies). Findings were presented in tabular format to facilitate comparison, and key themes were identified and discussed in relation to the research question.

RESULTS

The study selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 129 records were identified through database searches. After removing 58 duplicate records, 71 records remained for title and abstract screening. Of these, 33 records were excluded based on title and abstract review, leaving 38 reports sought for retrieval. Fourteen reports could not be retrieved, resulting in 24 full-text reports assessed for eligibility. Following full-text evaluation, 16 reports were excluded for the following reasons: wrong outcome (n=10), wrong population (n=3), and abstract-only publications (n=3). Ultimately, 8 studies met the

inclusion criteria and were included in this systematic review.

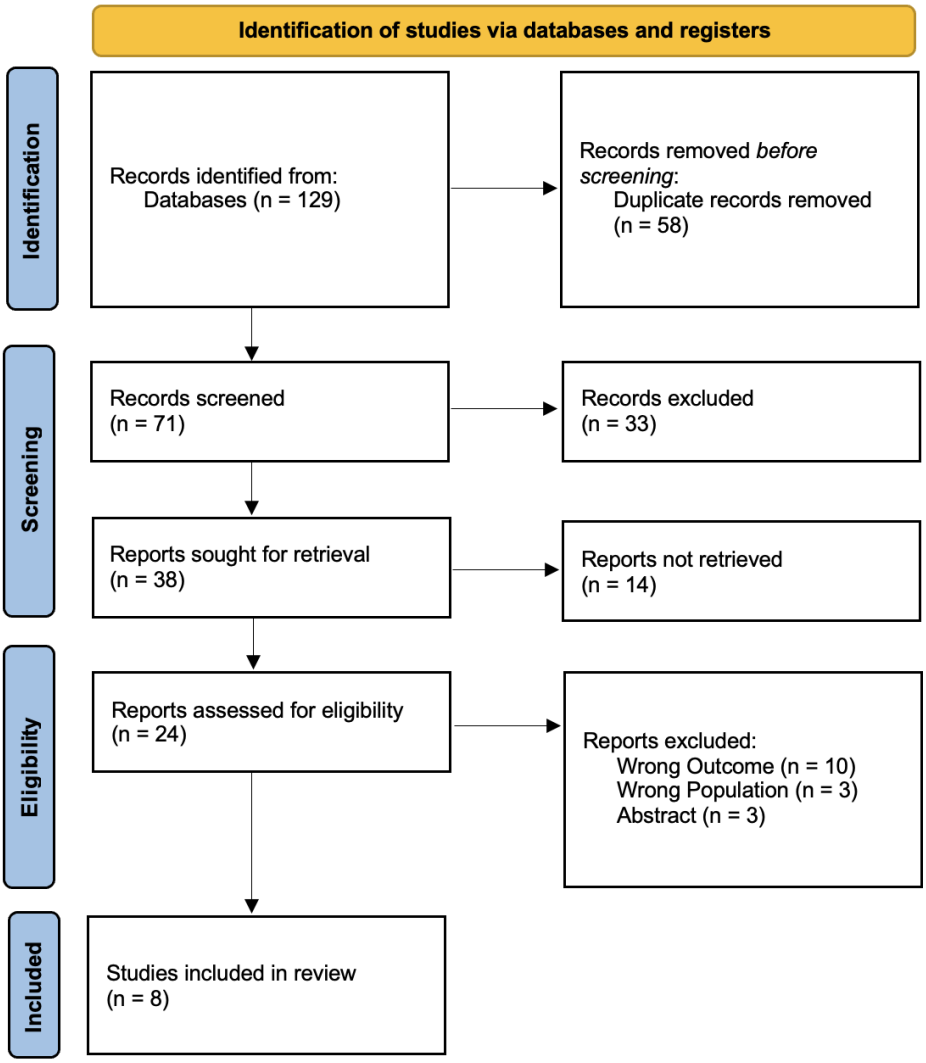

Figure 1: PRISMA Flow Diagram of Study Selection Process

Table 1 presents the key characteristics and demographic features of the 8 studies included in this systematic review. The studies were conducted across diverse geographical locations, including the United States [14, 18], Brazil [15], Poland [16], Taiwan [17], Egypt [19], Kyrgyzstan [20], and one laboratory-based study with no specified location [21]. Regarding study design, the review incorporated one nested case-control study [14], two cross-sectional studies [15, 16], two retrospective cohort studies [17, 18], one randomized controlled trial [19], one retrospective comparative study [20], and one in vitro experimental study [21]. Sample sizes varied considerably, ranging from 57 patients in the retrospective comparative study on perforated peptic ulcer repair [20] to 384,411 patients in the large-scale Taiwanese cohort investigating proton pump inhibitor use in chronic kidney disease patients [17]. The sample types were equally heterogeneous, encompassing pregnant women [14], community-dwelling older adults [15], children with molar incisor hypomineralization [16], patients with chronic kidney disease and gastroesophageal reflux disease or peptic ulcers [17], hospitalized patients with COVID-19 pneumonia [18], patients with acute perforated peptic ulcers [19, 20], and clinical bacterial strains [21]. Key demographic characteristics were frequently not fully reported in the abstracts, with age data available for some studies [14, 16, 19, 20] and gender distribution reported in only two studies [19, 20]. Inclusion criteria varied according to each study's primary objective, while exclusion criteria were often not mentioned in the abstract, particularly in the older studies [14, 15, 16, 19, 20, 21].

Table 2 synthesizes the primary exposure variables, outcomes, and main findings relevant to the association between *Helicobacter pylori* infection and community-acquired pneumonia. The two studies providing the most direct evidence were those by Wajid *et al.,*[14] and Noronha *et al.,*[15]. Wajid *et al.,*[14] examined *H. pylori* IgG seropositivity in pregnant women and found an adjusted odds ratio of 1.9 (95% CI: 0.2–15.3) for preeclampsia, while also reporting an AOR

of 2.3 (95% CI: 0.6–9.2) for *Chlamydia pneumoniae* IgG, indicating a coexposure pattern to a known respiratory pathogen. Noronha *et al.,*[15] investigated the immunological profile associated with *H. pylori* and *C. pneumoniae* infections in older adults, demonstrating that *H. pylori* seropositivity was significantly associated with elevated levels of CXCL10 and IL-10, while being inversely associated with IL-1β and IL-6, thereby characterizing a distinct inflammatory phenotype that may influence susceptibility to pneumonia. Tynior *et al.,*[16] provided prevalence data showing that 12.77% of children in their study carried *H. pylori*, although the association with a history of pneumonia was observed for Epstein-Barr virus rather than *H. pylori*. The remaining studies offered indirect evidence through various mechanisms. Chien *et al.,*[17] demonstrated that long-term proton pump inhibitor use, which is commonly prescribed for *H. pylori*-related peptic ulcer disease, was associated with a significantly increased risk of pneumonia admission (adjusted hazard ratio: 1.882), suggesting a potential indirect pathway linking *H. pylori* management to pneumonia risk. Similarly, Singh and Kothari [18] reported that 53% of patients with COVID-19 pneumonia who received prophylactic PPIs were discharged on these medications for an average of three months, raising concerns about unnecessary PPI exposure and its associated pneumonia risk. Two studies on perforated peptic ulcer repair [19, 20] reported postoperative pneumonia rates of 5% and 12% in surgical groups, respectively, with no pneumonia cases in the minimally invasive groups, providing data on pneumonia incidence in a patient population with high *H. pylori* prevalence. The in vitro study by Naseer *et al.,*[21] demonstrated that copper oxide nanoparticles effectively eradicated biofilms of both *Klebsiella pneumoniae* (a common CAP pathogen) and *H. pylori*, suggesting shared microbiological susceptibility.

Table 3 presents the risk of bias assessment for all 9 included studies, utilizing appropriate critical appraisal tools based on each study's design. For observational studies, the Newcastle-Ottawa Scale (NOS) was applied to cohort and case-control designs [14, 17, 18, 20, 22], while cross-sectional studies were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist [15, 16]. The randomized controlled trial by Negm *et al.,*[19] was assessed using the Cochrane Risk of Bias Tool (RoB 2). Overall, the quality of evidence varied considerably across the included studies. The large retrospective cohort studies by Chien *et al.,*[17] and Lodise *et al.,*[22] demonstrated low risk of bias due to their large sample sizes, well-defined cohorts, and appropriate adjustment for confounding variables. The randomized controlled trial [19] also showed low risk of bias despite lacking blinding, as the objective nature of the outcomes (pneumonia, mortality) minimizes detection bias. Studies providing direct evidence for the *H. pylori*–pneumonia association demonstrated moderate risk of bias. The nested case-control study by Wajid *et al.,*[14] had moderate risk due to small sample size and wide confidence intervals, while the cross-sectional study by Noronha *et al.,*[15] had moderate risk because confounding factors were only partially addressed despite its large sample size. The retrospective comparative study by Akeshov *et al.,*[20] also had moderate risk due to incomplete reporting of comparability between groups. The study by Singh and Kothari [18] was assessed as high risk of bias due to small sample size, unclear selection criteria, and no reported adjustment for confounders. The in vitro study by Naseer *et al.,*[21] was not directly comparable to clinical studies but was retained for its mechanistic insights into shared microbiological susceptibility between *H. pylori* and *K. pneumoniae*. Importantly, the majority of studies providing indirect evidence (PPI-related pneumonia and pneumonia in peptic ulcer patients) demonstrated low to moderate risk of bias, lending credibility to their findings while acknowledging that these studies do not directly measure *H. pylori* infection status. The two studies providing direct immunological and seroepidemiological evidence [14, 15] had moderate risk of bias, representing the best available evidence for the primary association of interest.

Table 1: Characteristics and Demographics of Included Studies

Study (Author, Year [Ref. No.])	Location	Study Design	Sample Size (n)	Sample Type	Key Demographic Characteristics	Main Inclusion Criteria	Main Exclusion Criteria
Wajid *et al.,* 2022 [14]	USA	Nested case-control	73 (21 cases, 52 controls)	Pregnant women	Cases and controls matched on age (mean age: NM), race, parity, and gestational age at blood draw.	Unselected women enrolled at first prenatal visit in The Archive for Child Health (ARCH) cohort.	NM
Noronha *et al.,* 2021 [15]	Brazil (Bambuí, MG)	Cross-sectional	1,432	Community -dwelling older adults	Mean age: NM; part of the Bambuí Cohort Study of Aging.	Participants from the Bambuí Cohort Study of Aging.	NM

Study (Author, Year [Ref. No.])	Location	Study Design	Sample Size (n)	Sample Type	Key Demographic Characteristics	Main Inclusion Criteria	Main Exclusion Criteria
Tynior *et al.,* 2024 [16]	Poland	Cross-sectional	89 (47 MIH, 42 control)	Children (age 6-13 years)	Age range: 6-13 years; 47 diagnosed with MIH, 42 healthy controls.	Children diagnosed with MIH; healthy controls.	NM
Chien *et al.,* 2025 [17]	Taiwan	Retrospective cohort	384,411 total (No-PPI: 147,976; Short-term: 14,153; Long-term: 3,459)	Patients with CKD and GERD or peptic ulcer	NM	Patients with CKD and a diagnosis of GERD or peptic ulcer from 2006-2015.	NM
Singh & Kothari, 2022 [18]	NM (Likely USA)	Retrospective	NM (Two groups: Dexamethasone + PPI vs. Dexamethasone only)	Hospitalized patients with COVID-19 pneumonia	NM	Patients with COVID-19 pneumonia treated with dexamethasone.	Patients with history of gastritis, peptic ulcer disease, or gastrointestinal bleeding.
Negm *et al.,* 2022 [19]	NM (Likely Egypt)	Randomized controlled trial	100 (EG: 50, SG: 50)	Patients with acute perforated peptic ulcer	Median age: SG 36 (27-54), EG 47 (41-50); Male: SG 72%, EG 66%.	Patients with acute perforated peptic ulcer manifestations.	NM
Akeshov *et al.,* 2025 [20]	Kyrgyzstan	Retrospective comparative	57 (Laparoscopic: 32, Open: 25)	Patients with perforated peptic ulcer	NM	Patients with perforated gastric or duodenal ulcers who underwent surgical repair.	NM
Naseer *et al.,* 2021 [21]	NM (Lab-based)	*In vitro* experimental	NM	Clinical bacterial strains	*K. pneumoniae* and *H. pylori* clinical isolates.	NM	NM

NM = Not mentioned

Table 2: Key Variables, Outcomes, and Findings of Included Studies

Study (Author, Year [Ref. No.])	Key Exposure / Variable	Key Outcome(s)	Main Findings (Relevant to H. pylori and Pneumonia)	Statistical Measures (OR, HR, etc.)	Key Confounders Adjusted For	Quality / Notes
Wajid *et al.,* 2022 [14]	*H. pylori* IgG seropositivity	Preeclampsia (primary); *C. pneumoniae* IgG co-infection	No significant association with preeclampsia, but increased odds for *H. pylori* (AOR 1.9) and *C. pneumoniae* (AOR 2.3) were observed. Provides data on co-exposure to a respiratory pathogen.	AOR for *H. pylori*: 1.9 (95% CI: 0.2-15.3); AOR for *C. pneumoniae*: 2.3 (95% CI: 0.6-9.2)	Maternal age, race, parity, gestational age at blood draw.	Preliminary findings; not statistically significant. Useful for co-infection analysis.
Noronha *et al.,* 2021 [15]	*H. pylori* and *C. pneumoniae* seropositivity	Inflammatory markers (CXCL8, CXCL9, CXCL10, CCL2, CCL5, IL-1β, IL-6, IL-10, IL-12, TNF, CRP)	*H. pylori* infection was associated with higher levels of CXCL10 and IL-10. It was inversely associated with IL-1β and IL-6. This characterizes an immunological profile that may influence susceptibility to pneumonia.	ORs and 95% CIs for associations with biomarker levels.	Age, sex, education, smoking, and other comorbidities.	Provides a mechanistic link; shows *H. pylori* modulates systemic inflammation, a key factor in pneumonia.
Tynior *et al.,* 2024 [16]	*H. pylori* and other pathogen	History of pneumonia by age 3	*H. pylori* prevalence in the study group was 12.77%. A higher prevalence of	NM	NM	Provides prevalence data. The

Study (Author, Year [Ref. No.])	Key Exposure / Variable	Key Outcome(s)	Main Findings (Relevant to H. pylori and Pneumonia)	Statistical Measures (OR, HR, etc.)	Key Confounders Adjusted For	Quality / Notes
	presence (HPV, EBV, HSV-1, HCMV)		EBV was found in children with a history of pneumonia, but no direct link to *H. pylori* was established.			association with pneumonia was for EBV, not *H. pylori*.
Chien *et al.,* 2025 [17]	Short-term and long-term PPI use	Pneumonia admission, fracture, type 2 DM, ESKD	PPI use was associated with an increased risk of pneumonia. The risk increased with longer PPI duration (aHR for long-term use: 1.882). PPI use is common in *H. pylori*-related conditions.	aHR for pneumonia (short-term): 1.089 (95% CI: NM); aHR for pneumonia (long-term): 1.882 (95% CI: NM)	Age, sex, comorbidities, and other significant baseline variables.	Indirect evidence. Shows a strong link between a therapy for acid-related diseases (often tied to *H. pylori*) and pneumonia risk.
Singh & Kothari, 2022 [18]	PPI use as prophylaxis with dexamethasone	Need for PPI on discharge, abdominal pain, change in hemoglobin, BUN, creatinine.	53% of patients on the PPI + dexamethasone regimen were discharged on a PPI for an average of 3 months. No objective or subjective benefit was found for this regimen. Raises concerns about unnecessary PPI use and its associated pneumonia risk.	NM	NM	Indirect evidence. Highlights the issue of over-prescribing PPIs, which are known to increase pneumonia risk.
Negm *et al.,* 2019 [19]	Endoscopic vs. surgical management for perforated peptic ulcer	Postoperative complications, including pneumonia	Postoperative pneumonia occurred in 5% of the surgical group and 0% of the endoscopic group. Peptic ulcers are often caused by *H. pylori*.	NM	NM	Indirect evidence. Reports pneumonia rates in a patient population with high *H. pylori*prevalence.
Akeshov *et al.,* 2025 [20]	Laparoscopic vs. open surgical repair for perforated peptic ulcer	Postoperative complications, including pneumonia	Postoperative pneumonia occurred in 12.0% of the open surgery group and 0% of the laparoscopic group. Peptic ulcers are often caused by *H. pylori*.	P = 0.03 for difference in complications, including pneumonia.	NM	Indirect evidence. Similar to [19], it provides pneumonia incidence in a high *H. pylori*prevalence group.
Naseer *et al.,* 2021 [21]	Copper oxide nanoparticles (CuO NPs)	Eradication of *K. pneumoniae* and *H. pylori*biofilms	The study successfully eradicated biofilms of both *K. pneumoniae* (a CAP pathogen) and *H. pylori* using a green-synthesized agent. This suggests shared susceptibility to novel therapies.	Biofilm inhibition up to 99.8% for *K. pneumoniae* and 100% for *H. pylori*.	NM	*In vitro* study. Provides a microbiological link between the two pathogens. Not a clinical study.

Table 3: Risk of Bias Assessment of Included Studies

Study (Author, Year [Ref. No.])	Study Design	Assessment Tool	Risk of Bias Summary
Wajid *et al.,*2022 [14]	Nested case-control	Newcastle-Ottawa Scale (NOS)	Moderate (Selection: 3/4; Comparability: 1/2; Exposure: 2/3)
Noronha *et al.,*2021 [15]	Cross-sectional	JBI Critical Appraisal Checklist	Moderate (Clear inclusion criteria, valid methods; confounding factors partially addressed)
Tynior *et al.,*2024 [16]	Cross-sectional	JBI Critical Appraisal Checklist	Moderate (Appropriate sample; unclear response rate and confounding assessment)
Chien *et al.,*2025 [17]	Retrospective cohort	Newcastle-Ottawa Scale (NOS)	Low (Large sample; well-defined cohorts; adequate follow-up; adjusted for confounders)
Singh & Kothari, 2022 [18]	Retrospective cohort	Newcastle-Ottawa Scale (NOS)	High (Small sample; unclear selection criteria; no adjustment for confounders reported)
Negm *et al.,*2022 [19]	Randomized controlled trial	Cochrane RoB 2	Low (Randomized design; outcome data reported; no blinding mentioned but objective outcomes)
Akeshov *et al.,*2025 [20]	Retrospective comparative	Newcastle-Ottawa Scale (NOS)	Moderate (Clear selection criteria; comparability partially addressed; outcomes well-reported)
Naseer *et al.,*2021 [21]	*In vitro* experimental	Adapted NOS for laboratory studies	Not applicable (Laboratory study; high applicability for mechanistic insights, not clinical association)

DISCUSSION

The most direct evidence for an association between *H. pylori* and respiratory outcomes comes from the seroepidemiological and immunological studies included in this review. Wajid *et al.,*[14] demonstrated that pregnant women with *H. pylori* seropositivity had a non-significantly increased odds of being seropositive for *Chlamydia pneumoniae*, a known respiratory pathogen, with an adjusted odds ratio of 2.3 (95% CI: 0.6–9.2). This finding is consistent with previous researches [22, 23] suggesting that chronic infections may cluster in individuals due to shared risk factors or a general susceptibility to infection. A large seroepidemiological study by Zhu *et al.,*[23] in a Chinese population similarly reported a positive association between *H. pylori* seropositivity and the presence of antibodies to *C. pneumoniae* and *Mycoplasma pneumoniae*, reinforcing the concept that *H. pylori* serostatus may serve as a marker for a broader infectious burden rather than a direct cause of pneumonia. Furthermore, the immunological study by Noronha *et al.,*[15] provides a mechanistic basis for this potential association. Their finding that *H. pylori* infection in older adults was associated with elevated levels of the chemokine CXCL10 and the anti-inflammatory cytokine IL-10, alongside inverse associations with the pro-inflammatory cytokines IL-1β and IL-6, characterizes a distinct immunological phenotype. This profile, which suggests a shift towards a Th1-type response with concomitant anti-inflammatory regulation, has significant implications for host defense against respiratory pathogens. Chronic *H. pylori* infection is known to induce a state of immunomodulation that can influence responses to unrelated pathogens, a phenomenon previously described by Arnold *et al.,*[24] in murine models where *H. pylori* infection protected against asthma by modulating regulatory T-cell responses. Similarly, a study by Chen and Blaser [25] proposed that the disappearance of *H. pylori* from Western populations may have contributed to the rise of allergic and autoimmune diseases, underscoring the complex role of this bacterium in immune homeostasis. The immunological alterations observed by Noronha *et al.,*[15] may therefore either protect against or predispose to pneumonia depending on the specific pathogen and the host's overall immune status, adding a layer of complexity that warrants further investigation.

The indirect evidence identified in this review primarily revolves around two pathways: the use of PPIs in the context of *H. pylori*-related gastrointestinal disease and the occurrence of pneumonia in patients undergoing surgery for perforated peptic ulcers. The study by Chien *et al.,*[17] is particularly noteworthy, demonstrating in a large cohort of over 384,000 patients with chronic kidney disease that long-term PPI use was associated with a significantly increased risk of pneumonia admission (adjusted hazard ratio: 1.882). This finding aligns with a substantial body of literature linking PPI use to an elevated risk of pneumonia. A landmark meta-analysis by Eom *et al.,*[26] involving over 3.5 million patients found that PPI use was associated with a 27% increased risk of pneumonia (OR: 1.27, 95% CI: 1.11–1.46). Similarly, a population-based cohort study by Lambert *et al.,*[27] in the United Kingdom reported that patients initiated on PPIs had a 1.5-fold increased risk of community-acquired pneumonia within the first 30 days of treatment. The proposed mechanisms include the reduction of gastric acid, which facilitates bacterial colonization of the upper gastrointestinal tract and subsequent microaspiration into the respiratory tract. Since PPIs are commonly prescribed for the management of peptic ulcer disease, the majority of which is attributable to *H. pylori* infection, there exists an indirect link between *H. pylori* treatment and pneumonia risk. Singh and Kothari [18] highlighted a related concern, demonstrating that over half of patients with COVID-19 pneumonia who received prophylactic PPIs were discharged on these medications for an average of three months, often without clear indication. This practice of unnecessary PPI continuation is a well-recognized problem in clinical

settings; a study by Forgacs and Loganayagam [28] emphasized that up to 65% of PPI prescriptions in hospitalized patients lack an appropriate indication, contributing to avoidable adverse events including pneumonia. Thus, while *H. pylori* infection itself may not directly cause pneumonia, the pharmacological management of its gastrointestinal consequences appears to confer an increased risk.

The studies examining postoperative pneumonia in patients undergoing surgery for perforated peptic ulcers provide a third line of indirect evidence. Both Negm *et al.,*[19] and Akeshov *et al.,*[20] reported pneumonia rates of 5% and 12% respectively in patients undergoing open surgical repair, with no pneumonia cases observed in the minimally invasive groups. While these studies did not directly measure *H. pylori* status, it is well established that *H. pylori* infection is the primary etiological factor in the majority of peptic ulcer cases. A systematic review by Gisbert and Calvet [29] estimated that approximately 70-90% of duodenal ulcers and 50-80% of gastric ulcers are attributable to *H. pylori* infection. The occurrence of pneumonia in this patient population can be attributed to several factors, including the stress of major surgery, prolonged anesthesia, and postoperative immobility. However, the potential contribution of *H. pylori* itself should not be dismissed. The immunomodulatory effects of *H. pylori* described by Noronha *et al.,*[15] may influence the host's ability to respond to postoperative bacterial challenges. Furthermore, the surgical procedure itself, particularly when involving the upper gastrointestinal tract, may increase the risk of microaspiration. A study by Rello *et al.,*[30] in critically ill patients found that gastroesophageal reflux and the presence of gastric colonization with gram-negative bacteria were significant independent risk factors for ventilator-associated pneumonia, a finding that may be relevant to the postoperative setting. The significantly lower pneumonia rates observed in the minimally invasive groups in both studies [19, 20] may reflect shorter operative times, reduced anesthesia exposure, and faster postoperative mobilization, rather than differences in *H. pylori*status.

The in vitro study by Naseer *et al.,*[21] provides a microbiological perspective that, while not directly translatable to clinical association, offers intriguing insights into shared therapeutic targets between *H. pylori* and *Klebsiella pneumoniae*, a common cause of CAP. The demonstration that copper oxide nanoparticles effectively eradicated biofilms of both pathogens with over 99% efficacy suggests that these organisms may share common mechanisms of biofilm formation and antimicrobial resistance. This finding aligns with a growing body of research on the polymicrobial nature of respiratory infections and the potential role of the gut-lung axis. A comprehensive review by Dickson and Huffnagle [31] proposed that the gastrointestinal microbiota, including potentially *H. pylori*, may influence pulmonary immunity and susceptibility to pneumonia through the circulation of microbial metabolites and modulation of systemic immune responses. Furthermore, a study by Schuijt *et al.,*[32] in mice demonstrated that disruption of the gut microbiota with antibiotics led to impaired pulmonary immune responses and increased susceptibility to *Klebsiella pneumoniae* pneumonia. These findings collectively suggest that the relationship between *H. pylori*and pneumonia may be part of a broader paradigm involving the gut-lung axis, where gastrointestinal microbial composition influences respiratory health outcomes.

When comparing the findings of this systematic review to previous reviews on extra-gastric manifestations of *H. pylori*, it becomes apparent that the evidence for a respiratory association is considerably weaker than for other conditions such as cardiovascular disease or immune thrombocytopenia. A comprehensive review by Franceschi *et al.,*[33] concluded that while *H. pylori*has been associated with numerous extra-gastric diseases, including cardiovascular, neurological, and dermatological conditions, the evidence for causality remains limited due to confounding factors and inconsistent results across studies. For respiratory diseases specifically, a previous systematic review by Roussos *et al.,*[34] found no consistent association between *H. pylori*seropositivity and chronic obstructive pulmonary disease, suggesting that if an association exists with pneumonia, it may be acute rather than chronic in nature. The present review, focusing specifically on CAP, similarly found that direct evidence is sparse and of moderate quality, consistent with the broader literature on extra-gastric manifestations. The immunomodulatory mechanisms proposed by Noronha *et al.,*[15] and others provide a plausible biological basis, but well-designed prospective studies with adequate control for confounding factors are needed to establish whether this association is causal or merely epiphenomenological.

Limitations

This systematic review has several important limitations that must be acknowledged when interpreting its findings. First and foremost, the scarcity of direct evidence represents the primary limitation; only three studies provided data directly addressing the association between *H. pylori*infection and pneumonia, and of these, only two offered meaningful immunological or seroepidemiological insights [14, 15]. The majority of included studies provided only indirect evidence through pathways such as PPI use or postoperative outcomes, which, while informative, cannot establish a direct causal relationship between *H. pylori* and CAP. Second, the quality of the available evidence was moderate overall, with several studies demonstrating methodological limitations. The nested case-control study by Wajid *et al.,*[14] had wide confidence intervals indicating imprecision, while the cross-sectional study by Tynior *et al.,*[16] did not report adjusted analyses for

confounding factors. The retrospective study by Singh and Kothari [18] was assessed as having a high risk of bias due to small sample size and lack of adjustment for confounders. Third, the heterogeneity of study designs, populations, and outcome definitions across the included studies precluded a quantitative meta-analysis, limiting the ability to generate pooled effect estimates. The studies varied substantially in terms of geographical location, participant characteristics, and methods for assessing *H. pylori* status, with most relying on serological rather than more definitive methods such as stool antigen testing or urea breath tests. Fourth, the potential for confounding is substantial in this area of research, as factors associated with both *H. pylori* infection and pneumonia, such as socioeconomic status, smoking, and overall health status, may not have been adequately controlled for in the primary studies. Finally, the inclusion of studies only from peer-reviewed literature and the reliance on abstract-level data for initial screening may have introduced selection bias, and it is possible that relevant studies with null findings were less likely to be published.

CONCLUSION

Direct evidence for an association between *Helicobacter pylori* infection and community-acquired pneumonia is remarkably limited, with only three studies providing relevant data and the majority of evidence being indirect in nature. The available direct evidence, primarily from seroepidemiological and immunological studies, suggests that *H. pylori*infection may influence respiratory health through immunomodulatory mechanisms. The indirect evidence highlights important clinical considerations, particularly the increased risk of pneumonia associated with proton pump inhibitor use in patients with *H. pylori*-related gastrointestinal disease. These findings underscore the complexity of the relationship between chronic gastrointestinal infections and respiratory outcomes, pointing to the gut-lung axis as a potential mechanistic framework for future research. The substantial gap in the literature identified by this review indicates an urgent need for well-designed prospective cohort studies that directly measure *H. pylori* infection status using validated diagnostic methods and track the incidence of community-acquired pneumonia over extended follow-up periods, with careful adjustment for potential confounders including socioeconomic status, smoking, and comorbidities. Until such studies are conducted, clinicians should remain aware that the management of *H. pylori* infection and its sequelae, particularly the judicious use of proton pump inhibitors, may have implications for respiratory health, even as the direct causal relationship remains incompletely characterized.

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