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Determinants of poor clinical outcome in patients with influenza pneumonia: A systematic review and meta-analysis

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ABSTRACT

Background: The clinical burden of influenza is increasing worldwide. Aging, immunosuppression, and underlying respiratory illness are determinants of poor clinical outcomes, including greater mortality. Bacterial infections seem to be the main reason. Updated information on the role of bacterial infection as the cause of complications would be of value in improving the prognosis of patients with influenza.
Methods: A systematic review and meta-analysis were performed by using the PubMed repository using keywords like: Influenza, H1N1, *Streptococcus pneumoniae*, bacterial coinfection, secondary coinfection, bacterial complications in pneumonia, and seasonal influenza. Only articles written in English were included in publications from 2010 to 2020. The analyses were conducted following the preferred reporting items for systematic review and meta-analyses guidelines. The results were independently validated using a TrinetX database cohort of roughly 4 million patients.
Results: We included 135 studies that contained data from 48,259 patients hospitalized with influenza of any age. Bacterial infections were diagnosed in 5391 (11.2%). *Streptococcus pneumoniae* (30.7%) and *Staphylococcus aureus* (30.4%) were the most frequent microorganisms, followed by *Haemophilus influenzae* (7.1%) and *Pseudomonas aeruginosa* (5.9%). The random-effects model of the meta-analysis indicated that bacterial infections posed a 3.4-fold increased risk of death compared with influenza infection alone. Unexpectedly, asthma was protective (odds ratio 0.8).
Conclusion: Bacterial infections diagnosed in 11.2% of patients with influenza increase 3.4-fold the mortality risk. *S. pneumoniae, S. aureus, H. influenzae*, and *P. aeruginosa* account for nearly 75% of the cases. Earlier diagnosis and use of antibiotics should improve outcomes in this population.

Introduction

Pneumonia associated with influenza virus infections was the ninth leading cause of death in 2019 in the United States [1]. Bacterial complications associated with influenza may cause either an acute or recurring respiratory illness [2]. Underlying pulmonary diseases and secondary bacterial respiratory tract infections are

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well-known determinants of poor prognosis in patients with influenza [3,4].

The etiology of respiratory bacterial infections remains elusive in many patients with influenza. However, the bacteria that commonly colonize the nasopharynx, including *Streptococcus pneumoniae, Staphylococcus aureus*, and *Haemophilus influenzae* tend to be responsible in most instances [4]. The studies examining lung tissue from patients who died during the 1918 influenza pandemic showed that 92.7% of deaths were likely due to bacterial superinfections [5]. More recent studies on autopsies equally support a high rate of bacterial infections as the driver of death in patients with influenza [5–8]. Therefore, earlier diagnosis and adequate treatment of bacterial infections could improve the prognosis of patients with influenza.

Influenza virus infections favor lung invasion by certain bacteria over others [9–12]. *S. pneumoniae*, followed by *S. aureus*, are considered the most common. Their presence has been associated with increased morbidity and mortality in patients with influenza with pneumonia [13–15]. Other pathogens have been reported to a lesser extent [16].

Most infections by influenza A virus (IAV) usually cause mild or moderate symptoms in healthy adults, but secondary bacterial infections frequently worsen their prognosis. Moreover, poorer clinical outcomes are more frequent in the elderly, during pregnancy, or in patients with comorbidities, including autoimmune diseases, cancer, immunosuppression, diabetes, or obesity [17–19]. Proper assessment of these risk factors that render mild influenza infections fatal has been key in defining the target groups for prevention and antiviral treatment for influenza, *i.e.*, tailoring vaccination policies. Herein, this report presents the results of a systematic review and meta-analysis of publications examining the clinical outcomes of patients diagnosed with influenza.

Methods

This study followed the preferred reporting items for systematic review and meta-analyses statement. The research protocol was registered at The International Prospective Register of Systematic Reviews (#CRD 42022370352).

A systematic review and meta-analysis were conducted in accordance with the preferred reporting items for systematic review and meta-analyses guidelines [20] to characterize the current burden of bacterial infections and outcomes in patients with a laboratory-confirmed diagnosis of influenza A over the last decade (2010-2020).

The inclusion of articles was limited to studies published between 2010 and 2020 that had a laboratory-confirmed diagnosis for influenza virus infection through viral cultures, serological tests, antigen detection tests, reverse transcription polymerase chain reaction, immunofluorescence tests, and rapid detection molecular tests and where the patients had also been studied to search for any other pathogens.

Any bacteria isolated from bronchoalveolar lavage samples, pharyngeal swabs, sputum culture, and blood samples, among others, where the pathology was diagnosed together with Influenza virus, were accepted as the presence of bacterial coinfection. The search criteria included patients of all ages, regardless of comorbidities, treated in all types of health care, gender, and with or without risk factors. The reasons for exclusion included animal studies; viral, fungi, or parasitic coinfections; duplicate studies; single-patient studies; and studies with partial or insufficient information.

Systematic scientific literature research

The literature used in the analysis was obtained through a systematic search of the international database PubMed, filtered by articles between 2010 and 2020. The keywords used to narrow the search range included influenza, H1N1, *Streptococcus pneumoniae*, bacterial coinfection, secondary coinfection, bacterial complications in pneumonia, and seasonal influenza. Only articles written in English were included.

Selection criteria

The articles obtained in the previous step were selected after reading the title and the abstract, evaluating them individually, and discarding duplicated articles by two independent readers. From the selected articles, reading of the full text and a final selection of the most suitable publications was made, as detailed in Figure 1a.

Extraction of the information

The relevant information of each publication was collected and added to an Excel document (Supplementary Excel file), including the author, the country where the study was performed, the year of the study, the total number of patients studied, the age of the patients, the number of patients with confirmed influenza, the number of patients with bacterial coinfection, the name of the pathogens present in those coinfections, the number of patients with obesity (body mass index $\geq$25.00), and the number of patients who died during the study.

Likewise, the primary risk factors present in the studied population were searched for and added in the same way as mentioned in the study to an Excel sheet for further analysis (Supplementary Excel file). These included autoimmune diseases, cancer, cardiovascular diseases, diabetes, obesity, hypertension, chronic obstructive pulmonary disease (COPD), asthma, or other chronic diseases.

R script/data treatment

The R 3.6.0 program was used to process the data, using meta4.11-0, metafor2.1-0, and dmeter0.0.9000 library packages to assist in the meta-analysis. The variation between the studies and the population was studied and corrected by using a random-effects approach (22).

The analysis included the study of a set of variables: general coinfection, coinfection divided by species, severity of the disease, and risk factors.

Model validation by TriNetX online tool

The results were validated using a TrinetX database (TrinetX's Research Network, https://trinetx.com/) that gathers information on patients hospitalized with influenza. This tool allows the screening of patients by real-time querying. It also allows to study the outcomes of different cohorts within an established period.

The validation data used in this study was collected in December 2021 from the TriNetX Global Collaborative Network, which provided access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 90 million patients from 73 healthcare organizations. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA), the US federal law which protects the privacy and security of health care data, and any additional data privacy regulations applicable to the contributing healthcare organization (HCO). TriNetX is certified to the International Organization for Standardization (ISO) 27001:2013 standard and maintains an information security management system to ensure the protection of the healthcare data to which it has access to, and to meet the requirements of the HIPAA security rule. Any data displayed on the TriNetX platform in aggregate form or any

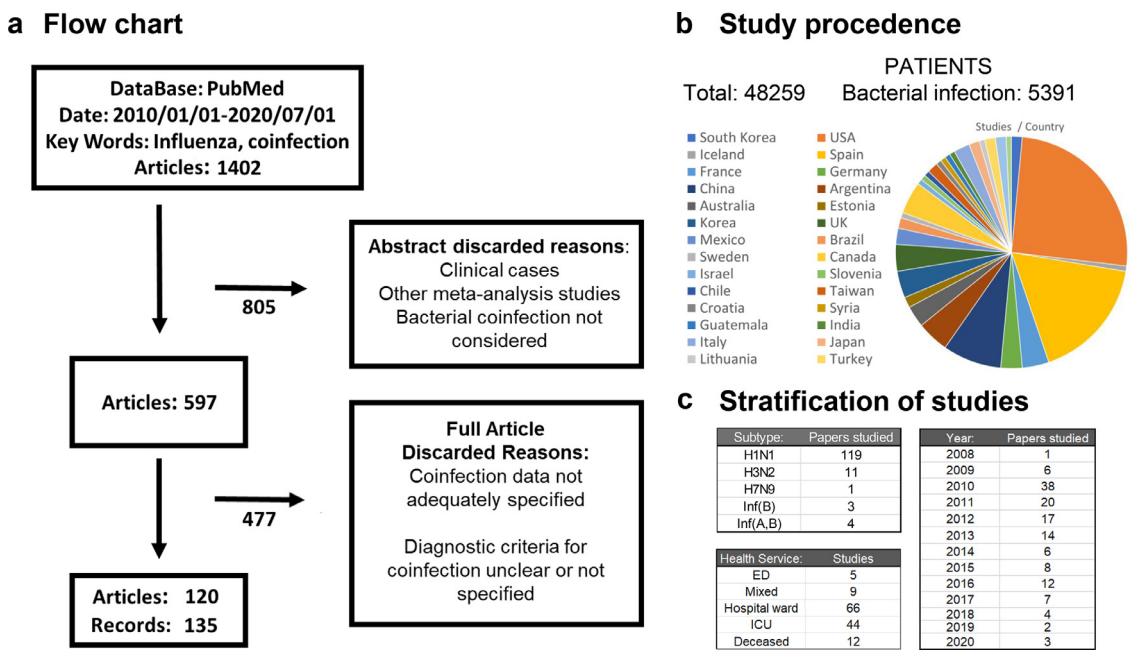

Figure 1. Selection process of the studies included in the meta-analysis and primary data analysis. (a) Schematic representation of the selection process, where 135 studies were finally analyzed. (b) Total number of patients included in this study (n = 48,259) and pie chart of the percentage of studies from each country. (c) Number of studies divided into virus subtypes, year, or health service department in which the patient was enrolled.
ED, emergency department; ICU, intensive care unit.

patient-level data provided in a data set generated by the TriNetX platform only contains deidentified data, as per the deidentification standard defined in Section §164.514(a) of the HIPAA privacy rule. The process by which the data is deidentified is certified through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA privacy rule. Because only deidentified patient records were used in this study and the study did not involve the collection, use, or transmittal of individually identifiable data, this study did not require institutional review board approval.

The overall cohort included all patients who were diagnosed with influenza and pneumonia (J09-J18). The comparative coinfected cohort not only included patients who were diagnosed with influenza and pneumonia (J09-18) but also with any bacterial coinfection (Supplementary Excel file) in the following month (TrinetX references: 85770-6, 61360-4, 92989-3, 225566-4, 22567-2, 31970-7, 1363918, 1364467, 50937, J14, J20.1, 92966-1, 1592901, J15.1, P23.5, J15.212, J15.21, J15.211, J13, J15.4, J15, J15.3, P23.3, 92951-3, 87541, 87278, 49616-6, 593-4, B44, B44.0, G00. B96.4, 1311228, B96.6, J15.8, G00.8, 43365-6, 55096-2, B95.2, 71718-1, B96.20, B96.29, 7288, 49671-1, 1363919, B95.4, 44798-7, 1491010, 92985-1). The overall cohort was subdivided into obesity and asthma cohorts by adding obesity status (E66.9) or asthma status (J45) in the moment of the influenza infection. The cohort for autoimmune patients was obtained by adding to the overall cohort the code for every autoimmune disease found in the database (TriNetX references: E06.3, K75.4, D59.10, E31.0, D89.82, 81490, M30-M36, H90.5, M35, T78.3XXA, L50.8, H93.8 × 9, E20, E28.39, E26.6, E27.1, D89.89, L50.6, E16.0, D59.10, D84.1, M35.5, D59.0, G04.81, D69.311, D59.19, D59.12, D59.11, 94697-0, 94708-5, D59.13, E11, 3E013GC, 86038, E10, H90.3, 86235, Z86.2, 86039, Z83.49, D69.59, L94.2, T88.8, E27.40, H90.42, H90.41, D89.8, J99, 3E013GC, E27.2, 86812, D69.0, 86148, E06.5, 86813, 86806, 86821, 86816). Critical care services (1013729), bacterial pneumonia (J15 and J15.9), and death were fixed as outcomes within 1, 3, or 6 months after initial diagnosis.

Statistical analysis

For statistical analysis, IBM SPSS statistics version 22 software was applied. The measurement data were expressed as mean ± SD and compared using an independent *t*-test, whereas the categorical data were expressed as numbers and percentages and compared by χ^2 or Fisher's exact test with continuity correction. Only *P*-values <0.05 were considered statistically significant. The RevMan software version 5.4.1 was used to assess the heterogeneity of the literature to draw forest plots.

Results

A total of 135 articles from 28 countries were chosen after an initial examination of 1402 studies that reported the outcomes of hospitalized patients with laboratory-confirmed IAV infection. The selection criteria discarded redundant studies, other meta-analyses, and studies with bacterial infections not considered separately or with unclear diagnostic criteria (Figure 1a). The articles chosen for further analysis included 48,259 patients of any age, of which 5391 (11.17%) had bacterial infections. Figure 1b and Excel file in the Supplementary material show the geographic origin of these studies.

The raw data were initially divided into different groups, according to influenza virus types or subtypes (H1N1, H3N2, H7N9, influenza B, or influenza A/B), year of the study, and hospital admission unit as a proxy of the severity of illness (emergency/admission, hospital ward, intensive care unit [ICU]) (Figure 1c).

S. pneumoniae *and* S. aureus *as the most frequent bacteria associated with influenza pneumonia*

The global distribution of bacterial microorganisms involved in respiratory infections in patients with influenza showed that *S. pneumoniae* (30.66%) and *S. aureus* (30.41%) were the most

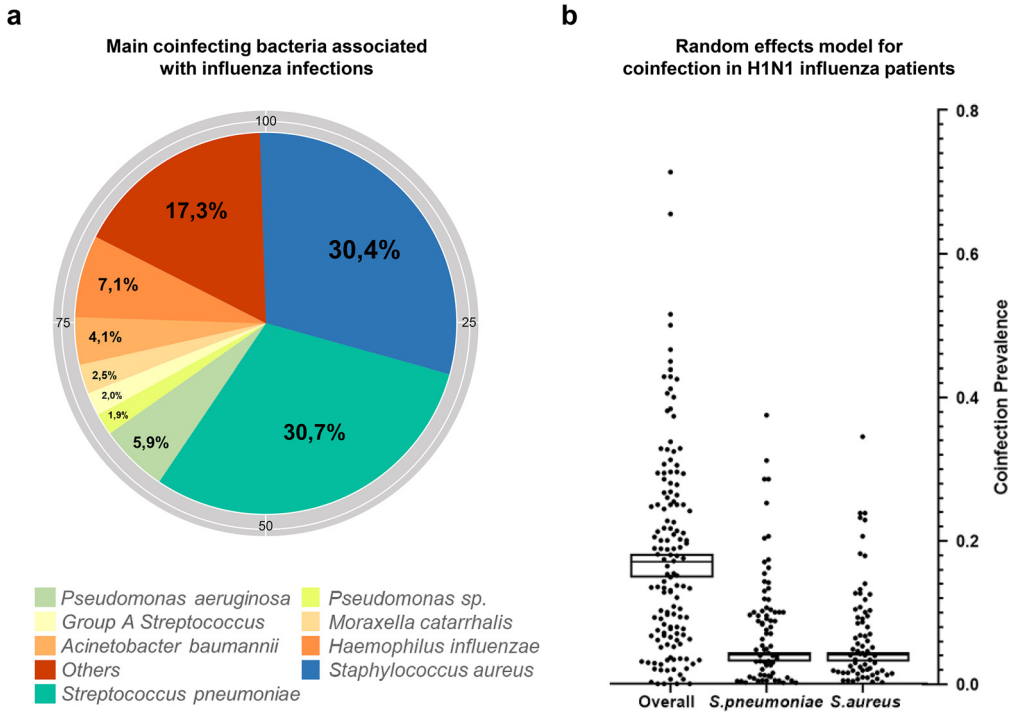

Figure 2. Prevalence of bacterial infections associated with influenza cases. (a) The percentage of reported bacterial infections in patients with influenza is shown as a pie chart. (b). Specific prevalence estimates with 95% confidence limits of patients with H1N1 influenza. The coinfection rates based on a random forest analysis model for the total bacteria coinfections, as well as *Streptococcus pneumoniae* or *Staphylococcus aureus* coinfections are represented as box plots.

prevalent. Other relevant pathogens included *H. influenzae* (7.11%), *Pseudomonas aeruginosa* (5.88%), *Acinetobacter baumannii* (4.11%), *Moraxella catarrhalis* (2.5%), Group A β-hemolytic streptococcal infections (2.0%), and nonspecified *Pseudomonas spp.* (1.9%) (Figure 2a).

Although the gross number of bacterial infections in patients with influenza from the total number of patients included in the studies was 11.17%, we meta-analyzed the estimated overall prevalence of any bacterial infection in patients infected with H1N1 (n = 116 studies). Data were corrected using a random-effects approach, and the weight of each study was included in the meta-analysis and represented as box plots (Figure 2b). The estimated prevalence of bacterial infections in the group infected with the IAV H1N1 subtype was 0.17 (95% confidence interval [CI], 0.15-0.18). A secondary analysis including all 135 records from 120 studies, regardless of the influenza variant, showed a similar prevalence of bacterial infections, 0.16 (95% CI, 0.15-0.17).

The prevalence of bacterial infections in H7N9 influenza cases was 0.20 (95% CI, 0.00-0.36) (one study), an infection prevalence of 0.13 (95% CI, 0.00-0.20) for studies that did not differentiate between influenza A or B (n = 4), an infection prevalence of 0.11 (95% CI, 0.00-1.00) for cases of H3N2 (n = 11), and an infection prevalence of 0.08 (95% CI, 0.01-0.15) for patients with influenza type B (n = 3). All models analyzed presented high values of heterogeneity (I^2 >90%), except for H3N2 (I^2 >85%) and non-typed influenza A/B (I^2 >75%) (data not shown).

Assessment of bias

Studies with a higher number of patients often increase the precision, highlighting the importance (weight) of sample size. Funnel plot analysis and chart symmetry (Supplementary Figure 1a) were examined to determine the presence of bias in our meta-analysis. Studies with a higher standard error in the lower part of the funnel (lower sample size) remained within the limits of the corrected model and maintained symmetry.

To discover which points might introduce bias into our analysis, a difference in fits analysis was performed (Supplementary Figure 1b). The plot showed that only 14 studies deviated from the model (red dots). To determine whether those points influenced our random model, we repeated the analysis after removing them. The results (data not shown) indicated that the prevalence changed from 0.1726 (95% CI, 0.1511-0.1941) to 0.1712 (95% CI, 0.1494-0.1929) and the heterogenicity from I^2 = 97.8% (95% CI, 97.7-98.0%) to I^2 = 97.2% (95% CI, 97.0-97.4%), indicating a small influence in our model.

Bacterial infections as the major determinant of mortality in patients with influenza pneumonia

The presence of comorbidities determines the risk of death in patients with infections in general and with influenza-associated pneumonia in particular. We examined the influence of distinct conditions on mortality in our patient population. Articles that did not report complete information on comorbidities or fatality rates were discarded. Age was analyzed separately because it is not a binary factor. The odds ratio (OR) values were obtained and added to random forest plots and funnel analysis for each condition (data not shown). The OR showing the risk of death in patients with different comorbidities is represented in a bar chart (Figure 3).

Bacterial infections posed the highest risk of mortality in patients hospitalized with influenza pneumonia (OR 3.36; $P = 2 \times 10^{-18}$). Other major determinants were hematologic diseases (OR 3.31; $P = 5.22 \times 10^{-3}$), neurologic disorders, renal insufficiency, immunosuppression, advanced liver disease, cardiovascular diseases, diabetes, lung disease in general, and COPD. Surprisingly, asthma appeared associated with lower odds of mortality (OR 0.8; $P = 6.13 \times 10^{-2}$). Advanced age was also identified as a risk factor for mortality in patients with influenza pneumonia. Bacterial infections exhibited a bimodal age peak, with a higher prevalence in infants and elderly patients (data not shown).

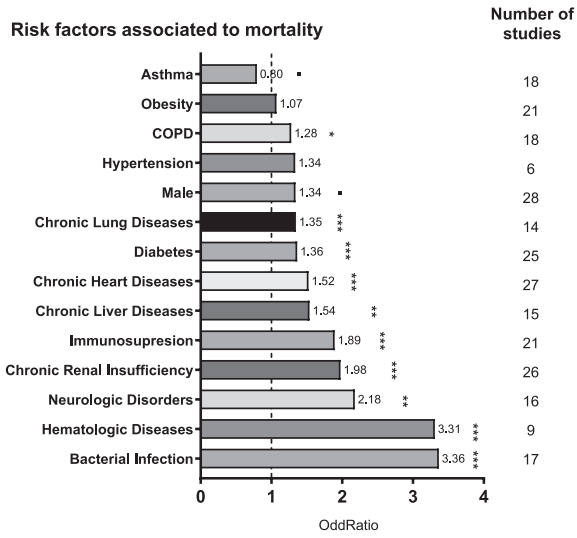

Figure 3. Odds ratio of mortality-associated risk factors of patients with influenza. Bar graph showing the odds of death in patients with influenza that previously had the indicated condition.
COPD, chronic obstructive pulmonary disease.
The number of studies indicates the number of articles in the metanalysis describing comorbidities listed in the chart. ***: $P < 0.001$; **: $P < 0.01$; *: $P < 0.05$,·: $0.06 > P > 0.05$.

Moderator effect value to score the main comorbidities in patients hospitalized with influenza and bacterial infections

Because bacterial infections appeared as the major determinant of influenza mortality, an evaluation of comorbidities associated with a bacterial infection in this context was made by calculating a moderator effect (ME) index. ME was computed by plotting the ratio of patients with influenza with bacterial infection versus the ratio of patients with a particular risk condition in the different studies. Each ME is the slope value of the linear regression for each condition. Supplementary Figure 2a represents the data distribution and lineal regression for autoimmune diseases, cancer, hypertension, diabetes, heart disease, and asthma. ME values for the main conditions associated with patients with influenza with bacterial infection are recorded in Supplementary Figure 2b. The probability of influenza and bacterial infection significantly increased in patients with autoimmune diseases, cancer, hypertension, or diabetes. In contrast, studies with a higher ratio of patients with asthma had a negative ME value, showing lower bacterial infection rates. Hematologic cancer depicted a protective effect; however, the low number of studies and the data variability did not show statistically significant differences (data not shown). Liver diseases, COPD, immunosuppression, male gender, neurologic diseases, renal diseases, and obesity exhibited positive trends, but no significant differences were detected.

Meta-analysis validation

TrinetX online platform database data were used as an independent data source to validate the results of the meta-analysis. The prevalence of patients with influenza and subsequent bacterial infection diagnosis was calculated by the ratio between the number of patients of two different TrinetX-generated cohorts: patients with pneumonia diagnosed with influenza plus bacterial infections and patients with pneumonia diagnosed with influenza (considered as total), following the calculation (virus + bacteria) ÷ virus. Coinfections were considered by querying patients with influenza and pneumonia plus the presence of any of the bacteria considered in the meta-analysis. TrinetX results indicate an overall prevalence of infection by both types of agents of 0.1476.

The differences in patient age were also analyzed. The incidence of patients with pneumonia diagnosed with influenza presents two waves: one between the age groups of 4-20 years and the other in patients above 50 years (Supplementary Figure 3a). When patients with influenza are further diagnosed with a bacterial infection (orange bars), a similar pattern is observed. However, the prevalence of co-diagnosis is higher in infants aged <2 years (despite the low influenza virus incidence) and in the older age group, reaching and maintaining the highest prevalence after the age of 70 years. The ICU outcome was also analyzed by comparing again both influenza and bacterial infection cohorts.

The results indicate that only 4.99% of patients with influenza needed critical care services compared with 13.05% of patients who were double-positive for influenza virus and bacteria, showing an OR value of 2.85 (2.83-2.88) (Supplementary Figure 3b). The outcome "deceased" was analyzed to determine the mortality risk in these two groups. In this case, the group of patients with influenza and pneumonia was compared with patients with influenza and pneumonia who had asthma, obesity, or bacterial infection (Supplementary Figure 3c). The mean mortality risk in these critical care patients with influenza was 6.04%. In comparison, patients diagnosed with influenza virus and bacteria present a mortality risk of 12.15%, whereas patients with asthma have a mortality risk of only 2.89%. Patients with influenza virus and bacteria presented a mortality OR of 2.15 (2.13-2.17), whereas the OR of patients with asthma was 0.46 (0.46-0.47). Obesity was taken as a control for a risk factor that had no relevant influence on death risk with an OR of 0.93 (0.92-0.94).

Asthma presents a clinical condition where patients may require a differential diagnosis or special care to discriminate between asthma and infections. For this reason, influenza infections, as well as bacterial infections, may be overrepresented in this group. To determine the possible bias of lower death risk in patients with asthma infected with Influenza virus compared with patients with influenza without asthma, the influenza, and bacterial infection risk was analyzed by comparing the outcomes "bacterial pneumonia, not elsewhere classified" OR "unspecified bacterial pneumonia" of those cohorts at different time points. This time, patients with influenza and pneumonia plus any autoimmune disease were also included because autoimmunity is a major risk factor in patients with influenza with bacterial infection (Supplementary Figure 3d). In this analysis, the overall co-diagnosis over a 6-month period (influenza and bacteria) was 2.74%. In the case of obesity, 2.64% (OR: 0.96) of patients with autoimmune disease presented 3.49% of bacterial infections (OR: 1.28). Patients with asthma presented a 2.37% risk of influenza and bacterial infection (OR: 0.86), indicating a modest but lower risk of influenza and bacterial infection than other risk groups. The results were repeated twice using a maximum time interval of 3 months and 1 month for death, influenza, and bacterial infection outcomes (data not shown), indicating that patients with influenza, and diagnosed with asthma are more protected from bacterial infection, as well as for ICU and death outcomes.

Discussion

In our meta-analysis, the percentage of bacterial infections in patients hospitalized with influenza was 11.17%. This figure could underestimate the real impact of bacterial infections in this population, as suggested by the results obtained after introducing random effects in the meta-analysis (16%) and subsequent validation using TrinetX (14.7%). Interestingly, *S. pneumoniae* and *S. aureus* accounted for 30.7% and 30.4%, respectively, of all bacterial compli-

cations associated with influenza, resulting in approximately 4% of all patients with influenza (95% CI: 3-4%) each. Our results are in line with those from a previous meta-analysis, which accounted *S. pneumoniae* and *S. aureus* for 35% (95% CI: 14-56%) and 28% (95% CI: 16-40%), respectively [21].

In our study, bacterial infections were the major determinant of mortality in patients hospitalized with influenza. Indeed, they increased death risk by 3.36-fold (95% CI: 2.56-4.41) compared with Influenza virus infection alone. In agreement with this, the TrinetX cohort analysis showed an increased risk of mortality due to bacterial infections of 2.88-fold (95% CI: 2.85-2.90). Given the lack of *postmortem* investigations, an underestimation is to be expected [5]. Further analysis of bacteria in the lungs of the bodies of those who died of influenza might provide more precise information on the rate of bacterial involvement in influenza deaths. In our study, patients with influenza admitted to the ICU had greater bacterial infection proportions and, not surprisingly, experienced the highest mortality.

Complications other than bacterial infections could contribute to influenza severity and mortality [22]. A German study [23] analyzed demographics, comorbidities, hospitalization length, and ventilator use during the pandemic and seasonal waves of influenza in Germany between 2005 and 2012. The authors concluded that immunosuppression, COPD, chronic heart failure, obesity, male sex, and older age were associated with higher mortality rates in hospitalized patients with influenza. In the United States, one study [13] highlighted an increased risk of mortality due to bacterial infections in patients with influenza with immunosuppression (Relative risk (RR): 1.57; 95% CI: 1.20-2.06). Interestingly, in this case, *S. aureus* seemed to be primarily responsible for the increased mortality rate (RR: 2.82; 95% CI: 1.76-4.51). In our meta-analysis, an increased mortality risk was also recognized for chronic heart disease (1.52, 95% CI: 1.25-1.86), diabetes (1.36, 95% CI: 1.16-1.60), chronic lung disease (1.35, 95% CI: 0.99-1.84), and COPD (1.28, 95% CI: 1.06-1.55). Immunosuppression had a relative mortality risk of 1.89 (95% CI: 1.25-2.86).

Age is a main factor associated with influenza-related mortality [24]. Children aged <2 and >65 years are recognized as the main population at risk with the highest hospitalization and death rates among infants aged <6 months (source Centers for Disease Control and Prevention https://www.cdc.gov/flu/highrisk/index.htm). The incidence of bacterial infections in hospitalized patients with influenza was lower in infants aged <2 years with influenza but similar in adults. Current vaccination strategies (Influenza virus, *H. pneumoniae* type B, and *S. pneumoniae*) in both children and adults might contribute to preventing bacterial infections in the elderly.

There was high variability in the ratio of bacterial infections among patients with influenza across studies (Supplementary table-bacteria tab). Indeed, wide CIs were seen in both our meta-analysis and in the TrinetX study. Multiple factors may explain this, including different clinical diagnostic practices (*e.g.*, use of standardized protocols following Murray-Washington criteria [25], polymerase chain reaction, antibody-based methods, bacterial cultures, *etc.*). In addition, diagnostic bias might have occurred in severely ill patients because they are generally tested more often than those with mild disease.

In cases where poor outcomes of influenza are expected, the empirical use of antibiotics is a common practice [22,26]. Antibiotic overuse is a growing problem that could be addressed by improving diagnostic procedures for both influenza and bacterial infections, allowing earlier detection of microorganisms complicating influenza-related pneumonia [27]. Although the presence of specific bacteria associated with influenza is increasingly been reported [28,29], their role as drivers of clinical severity and worse outcome remains poorly elucidated. The use of procalcitonin levels, for instance, could be a good sensitive and specific predictor of bacterial infections in this population [30]. Furthermore, a better characterization of viruses and bacteria complicating influenza infections using metagenomics could be helpful [28]. Finally, a better understanding of systemic inflammatory mediators that could potentially be used as biomarkers might help to improve outcomes in patients with influenza.

In our meta-analysis, asthma was protective against death in patients hospitalized with influenza (OR = 0.80, 95% CI: 0.63-1.01; $P = 6.13 \times 10^{-2}$). This finding has previously been observed by others, where patients with asthma were less likely to experience influenza-related complications [31]. Other studies have found that patients with allergic asthma were less likely to be hospitalized with COVID-19 than patients with nonallergic asthma [32]. In another study [23], patients with asthma with influenza experienced a lower mortality rate than patients with influenza without asthma. Surprisingly, this protective effect has never been highlighted in most studies. Our data also suggest that patients with asthma with influenza contracted bacterial infections significantly less frequently than patients without asthma (ME = −0.47, $P = 3.22 \times 10^{-7}$). Hypothetically, more frequent vaccinations (Influenza virus, *H. influenzae*, and *S. pneumoniae*) and earlier antibiotic use in this subset of patients [22,26] could account for this observation. Alternatively, patients with asthma could also be hospitalized with influenza more easily than those without pulmonary disease and present other complications, including obstruction rather than secondary bacterial pneumonia. Another possibility is that the inflammatory phenotype observed in patients with asthma [33] could contribute to a reduced probability of dying from influenza. In this regard, it would be interesting to investigate whether cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1β, and tumor necrosis factor-α (typically associated with asthmatic lung inflammation) [34], could play a protective role against influenza. In this respect, the activation of the innate immune system in patients with asthma could lead to increased protection against bacterial infections [35].

Our analysis consisted of an univariant estimation of the risk posed by bacterial infections in patients hospitalized with influenza during the last decade. This meta-analysis did not correct for interactions between distinct comorbid conditions that might lead to synergistic effects, increasing mortality ratios. Thus, patients with cancer would be more frequently immunosuppressed due to oncologic treatments or patients with obesity might experience heart disease more frequently. Despite these limitations, our results indicate that earlier clinical suspicion, diagnosis, and treatment of bacterial infections in patients hospitalized with influenza might improve the prognosis of this population.

Declaration of competing interest

The authors have no competing interests to declare.

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Ethical approval

Ethical approval is not required for this study.

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Author contributions

Javier Arranz-Herrero: data curation, formal analysis, investigation, methodology, validation, visualization, writing – original draft. Jesus Presa; conceptualization, formal analysis, investigation, methodology, software, validation, visualization, writing – original draft. Sergio Rius-Rocabert: formal analysis, supervision, writing – review & editing. Alberto Utrero-Rico: data curation, formal analysis, investigation, methodology, validation. José Ángel Arranz-Arija: formal analysis, methodology, writing – review & editing. Antonio Lalueza: formal analysis, supervision, writing – review & editing. María Marta Escribese: writing – review & editing. Jordi Ochando: formal analysis, supervision, funding acquisition, writing – review & editing. Vicente Soriano: interpretation, writing, and review. Estanislao Nistal-Villan: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, writing – original draft.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.04.003.

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