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PREVALENCE, PATTERN, RISKS FACTORS AND CONSEQUENCES OF ANTIBIOTIC RESISTANCE IN COPD: A SYSTEMATIC REVIEW

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PREVALENCE, PATTERN, RISKS FACTORS AND CONSEQUENCES OF ANTIBIOTIC RESISTANCE IN COPD: A SYSTEMATIC REVIEW

A concern of antibiotic use in chronic obstructive pulmonary disease (COPD) is the emergence and propagation of antimicrobial resistance (AMR). A systematic review was conducted to determine prevalence, pattern, risk factors and consequences of AMR in COPD. Bibliographic databases were searched from inception to November 2020, with no language restrictions, including studies of any design that included patients with COPD and reported prevalence and pattern of AMR. 2748 unique titles and abstracts were identified, of which 63 articles, comprising 26387 patients, met inclusion criteria. Forty-four (69.8%) studies were performed during acute exacerbation. The median prevalence of AMR ranged from 0-100% for *P aeruginosa, M catarrhalis, K pneumoniae* and *A baumannii*. Median resistance rates of *H influenzae* and *S pneumoniae* were lower by comparison, with maximum rates ≤40% and ≤46%, respectively, and higher for *S aureus*. There was a trend towards higher rates of AMR in patients with poorer lung function and greater incidence of previous antibiotic exposure and hospitalisation. The impact of AMR on mortality was unclear. Data regarding antimicrobial susceptibility testing techniques and the impact of other risk factors or consequences of AMR were variable or not reported. This is the first review to systematically unify data regarding AMR in COPD. AMR is relatively common and strategies to optimise antibiotic use could be valuable to prevent the currently under-investigated potential adverse consequences of AMR.

Keywords: chronic obstructive pulmonary disease; drug resistance, bacterial; asymptomatic infection

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent and progressive airflow limitation. [1] COPD is estimated to affect 11.7% of the global population, although these figures may be an underestimate of the true current values due to rapidly increasing prevalence and underdiagnosis. [2-4] Patients with COPD experience acute exacerbations (AECOPD), defined as acute worsening of respiratory symptoms that results in additional therapy, [1] typically recognised clinically by deviation from usual sputum volume, sputum purulence and breathlessness. [5] The aetiology of AECOPD may be infective or non-infective; infective causes comprise bacterial, viral and bacterial-viral coinfection, which comprise 29%, 23% and 25% of infective hospitalised AECOPD, respectively. [6] The airways of patients with COPD are considered to be more susceptible to bacterial infection as a result of impaired barrier and innate immune cell function, which may be induced initially by cigarette smoke, other noxious particles or AATD. [7,8] In a cyclical manner, bacteria within the airway may influence bacterial acquisition or expansion by promoting inflammation and directly impairing host defences. [7] This interaction is well exemplified by non-typeable *H influenzae*, which is observed to adhere to mucous membranes, inducing epithelial cell damage, mucin production and ciliotoxicity. [9] Cumulatively, excessive mucus production and reduced mucous clearance in combination with impaired innate defences in COPD airways provide a fertile environment for bacterial infection. According, bacteria are detected in approximately 50% of AECOPD cases, prompting antibiotic use as a management strategy. approximately 50% of AECOPD treated with antibiotics in primary care and COPD patients receiving approximately 3 times more antibiotic prescriptions than the general public. [10,11]

A primary concern of antibiotic use in COPD, as in other conditions, is the emergence and propagation of AMR. AMR can be defined according to microbiological or clinical resistance, but is considered here to denote any reduction in susceptibility in a bacterial strain

compared to the susceptible wildtype. [12,13] AMR is recognised as a global threat and an NHS and UK government priority to reduce. [14-16] Besides frequent antibiotic provision, the COPD pulmonary environment may facilitate the development of AMR by being permissive towards the formation of biofilms, which limit antimicrobial infiltration and induce a phenotypically quiescent bacterial phenotype which persist and develop multidrug resistance. [17] Owing to the extent of antibiotic exposure, long-term prophylactic therapy could be perceived to put the greatest pressure on AMR development. This may be worsened by the relatively long half-life of azithromycin which may lead to prolonged suboptimal concentrations of the antibiotic, potentially below the minimum inhibitory concentration (MIC). [18] Evidence regarding resistance rates following macrolide therapy versus placebo are inconsistent across studies. [19-21] Furthermore, the use of chronic macrolide therapy for chronic respiratory diseases may link to population-level resistance. [22] Understanding AMR in COPD is therefore of importance for both public and individual health interventions.

In order to address the heterogeneous nature of the literature and guide future work, we aimed to systematically collate the evidence concerning the prevalence, pattern, risk factors and consequences of AMR in COPD.

Methods

The protocol for this review was registered with PROSPERO (2020:CRD42020218684) prior to commencing work. [23]

Inclusion/exclusion criteria

Study designs eligible were randomised controlled trials (RCTs), cohort studies, case control studies, case series ≥10 cases and systematic reviews. Duplicate publications or publications using the same dataset e.g. sub-group analyses, editorials and non-systematic reviews were

excluded. Studies published only in abstract form dated before 2017 were excluded. The population, intervention, comparator, outcome and study design (PICOS) framework was used to define the inclusion criteria. Included patients had a clinical diagnosis of COPD. Studies of chronic bronchitis (CB) or emphysema were also included. In the event of identifying studies with mixed populations, studies were included if data from COPD patients was presented separately. Patients with a primary clinical diagnosis of bronchiectasis were excluded. Included studies may have had intervention with an antibiotic, or could be observational in nature, in order to identify reports of the prevalence and pattern of AMR, irrespective of antibiotic use. In studies using antibiotics as the intervention or reporting on history of antibiotic use, the prevalence of antibiotic resistance in intervention versus control arms was considered, as was the association of previous antibiotic exposure on AMR rates. The comparator was placebo or usual care or none. This allowed inclusion of cohorts with relevant prevalence data.

Outcomes

The primary outcome was the prevalence and pattern of resistant isolates, as measured by rate of resistance of selected microorganisms to selected antibiotic. Microorganisms and antibiotics were selected on the basis of clinical relevance and pilot searches. Resistance rates of the following bacteria to the following antibiotics were recorded:

Bacteria: *H influenzae*; *P aeruginosa*; *S pneumoniae*; *S aureus*; *M catarrhalis*; *K pneumoniae*; *A baumannii.*

Antibiotics: Penicillin; Ampicillin; Amoxicillin; Co-Amoxiclav; Tetracycline; Doxycycline; Levofloxacin; Ciprofloxacin; Azithromycin; Erythromycin; Clarithromycin; Cefuroxime; Piperacillin/Tazobactam; Colistin.

Secondary outcomes and measures of these are presented in Supplementary Table 1.

Search strategy

Bibliographic databases were searched from inception to 02 November 2020 with no language restrictions. The Ovid interface was used to search MEDLINE and EMBASE. The Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were used to search for ongoing trials. The EBSCO interface was used to search CINAHL. Reference lists (e.g. from reviews) were searched manually to identify additional studies. The search strategy included terms relating to or describing COPD and AMR, including relevant synonyms and can be found in the supplementary material. Search limits were applied to include human studies only. Non-English texts were translated using a combination of online language translation services with input from native speakers when required.

Study selection, quality assessment and data extraction

Standard systematic review methodology aimed at minimising bias was employed, in accordance with guidance from the Cochrane Handbook of Systematic Reviews. [24] Following searches, duplicates were electronically identified and removed. Titles and/or abstracts were screened by two independent review authors with a similar process at full text (DS, AG and LH). Any disagreement over the eligibility of particular studies at both title/abstract and full text review stage was resolved by discussion with a third reviewer, AT. Any missing or additional required data was requested from the studies' corresponding authors.

During the full text review, DS, AG and LH independently assessed the risk of bias in the included studies. The risk of bias in included RCTs was assessed using the Cochrane Collaboration's Risk of Bias tool (RoB 2.0 tool). [25] The risk of bias in included prevalence studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for

Prevalence Studies. [26] This tool was also used for non-RCT studies where extraction of AMR prevalence was our primary interest.

A standardised form was created and used by DS to extract data from included studies for evidence synthesis and assessment of study quality. Full details of fields for data extraction are in the supplement.

Data synthesis

A narrative synthesis was produced together with summary statistics of resistance rates of selected bacteria to selected antibiotics in each major setting. Studies contributing antibiotic susceptibility testing in ≥10 samples per antibiotic per microorganism were used to calculate summary statistics (median and range of resistance rates (%)).

Results

Search results

A total of 3506 records were identified. After duplicate removal 2748 titles and abstracts were screened for inclusion. 231 articles were reviewed in full and 63 articles were judged to meet the inclusion criteria (Figure 1), including 26387 COPD patients. 58 studies were published primary research, 3 articles were published only in abstract or poster form and 2 articles were ongoing clinical trials. A summary of characteristics of studies is in Supplementary Table 2. Many studies failed to report data for lung function and other baseline demographic information. Types of sample used for testing and general methods for assessment of AMR varied and are shown in Figure 2. Five studies reported data on AMR genes only; this data is reported in the supplement since it is unclear whether it fully relates to resistance in clinical practice.

[Figure 1 near here]

[Figure 2 near here]

Prevalence of AMR

Forty-one (65.1%) studies included results of antibiotic susceptibility testing. Studies of hospitalised AECOPD comprised the majority of studies within the review (n=26, Supplementary Table 3), followed by non-hospitalised setting (n=17, Table 1), mixed/unclear settings (n=14, Supplementary Table 4) and ICU (n=6, Supplementary Table 5). Across all settings, resistance of *H influenzae* to amoxicillin was ≤40%, and lower to co-amoxiclav, as expected. Ten out of 19 (53%) of the median resistance rates calculated for *P aeruginosa* across all settings were >50%, of which 7 were 100%. Lower median rates of AMR were observed for *P aeruginosa* towards colistin and piperacillin/tazobactam, as expected. Variable patterns of resistance were seen for *S pneumoniae* ranging from 0% to 46%, greater

for macrolide and tetracycline antibiotics than other antibiotic classes, and higher in hospitalised compared to non-hospitalised patients. AMR rates were generally low for *M catarrhalis* (≤26%), with the exception of penicillin, amoxicillin and ampicillin, as expected. Antimicrobial susceptibility rates were available for *S aureus* isolates from hospitalised and ICU settings only, with AMR generally being higher in ICU cases. *A baumannii* was also studied in hospitalised and ICU settings, while *K pneumoniae* was only studied in the hospitalised setting.

Risk factors for AMR

Eight studies reported on the relationship between antibiotic exposure and AMR rates. Three studies identified higher rates of previous antimicrobial prescriptions in patients with multidrug resistant (MDR) microorganisms detected in sputum when compared to patients with susceptible isolates. [27-29] Higher rates of antibiotic prescriptions in the previous 3 months were seen in hospitalised patients with *P aeruginosa*-resistant compared to *P aeruginosa*-sensitive isolates (77% vs 33%, p = 0.01). [30] Brill et al analysed 243 isolates from 69 non-hospitalised COPD patients whom underwent antimicrobial susceptibility testing at baseline and following treatment with either moxifloxacin, azithromycin, doxycycline or placebo. [31] At 13 weeks, each antibiotic was associated with a ≥threefold increase in MIC compared to baseline with a parallel increase in clinical resistance in patients assigned to those antibiotics compared with placebo (p = 0.01 for all). Similarly, 54.4% of pneumococcal isolates from patients exposed to macrolides in the previous 3 months exhibited resistance to erythromycin versus 18.7% of isolates from non-exposed patients (p < 0.05). [32] Higher frequencies of β-lactamase-negative ampicillin-resistant strains have also been reported in cultures isolated from patients with a history of repeated antibiotic prescriptions. [33]

Six studies reported on the isolation of AMR microorganisms following long-term azithromycin therapy. Albert et al observed no difference in the overall prevalence of

macrolide resistance in patients receiving azithromycin v placebo (52% vs 57%; p = ns). [20] However, patients in the azithromycin group who were not colonised at baseline were more likely to become colonised during the trial with macrolide resistant microorganisms (81% vs 41%; p < 0.001). [20] Similarly a retrospective study of cyclical azithromycin was observed to increase the rate of detection of macrolide resistant organisms compared to baseline (9/18 vs 1/52). [34] Conversely, Uzun et al observed that the detection of macrolide resistant bacteria was significantly lower in patients receiving azithromycin compared to placebo (6% vs 25%, respectively, p = 0.036). [21] In another study, the number of patients receiving prophylactic macrolide therapy did not differ significantly between patients with sensitive versus resistant pseudomonas isolates. [30] Pettigrew et al observed a four-fold increase in macrolide MIC in 19% of H influenzae strains, which persisted following exposure to macrolides. [35] Brill et al noted increases in MIC and clinical resistance in patients treated for 13 weeks with azithromycin. [31]

Four studies reported a relationship between lung function and AMR; in general more severe COPD was associated with higher AMR rates. Three studies reported a relationship between frequent hospitalisation and higher rates of AMR, and studies of ICU care also supported a role for intubation and length of stay with worsening AMR rates. Smoking and demographic features exhibited inconsistent patterns of association with AMR. These results are shown in more detail in the supplement.

Impact of AMR

Five studies reported on the effect of AMR on mortality rate. [28] [36] [30] [29,37] There were no clear trends identified across the included studies. Three studies reported on the impact of AMR on duration of inpatient admission, two showing no difference [28] [38] and one suggesting stay was longer by 3 days. [39] There were no differences observed in the rate of ICU admission,

invasive or non-invasive mechanical ventilation between patients with microorganisms resistant to conventional antibiotic treatment compared to patients with susceptible and negative isolates. [28] AMR appeared to have no effect on future AECOPD frequency. [28] No data was available on the relationship between the incidence of AMR and chronic bacterial colonisation, quality of life or disease progression.

Study quality and bias

Variability in sample description and testing methods contributed to bias across studies in general (Figure 2). Most studies displayed moderate risks of bias. These are summarised in supplementary Tables 4 and 5.

Discussion

This review has demonstrated that AMR is relatively common in COPD, in particular during AECOPD. However, study of AMR has been driven by acute antibiotic studies, such that the impact of AMR at population level remains poorly described and may need to be a focus for future work.

It is well recognised that *H influenzae*, *S pneumoniae* and *M catarrhalis* are the most commonly isolated PPMs in both the stable and exacerbated COPD state. The higher levels of resistance of *H influenzae* and *M catarrhalis* to beta-lactam antibiotics in likely reflects the increasing global prevalence of beta-lactamase producing microorganisms, especially *M catarrhalis*, of which 95% of global clinical isolates were observed to be beta-lactamase produces. [40-42] In the UK, the recommended first line antibiotics for AECOPD are amoxicillin, doxycycline and clarithromycin. [43] However, we found that at least one of *H influenzae, S pneumoniae* and *M catarrhalis* to show high levels of resistance to at least one of these antibiotics, which likely contributes to treatment failure and facilitates emergence of

resistance. Accordingly, this represents a substantial barrier to the effectiveness of empirical antibiotic prescribing.

S aureus was observed to have very high median rates of resistance in this review, particularly in the ICU setting, with all median resistance rates ≥90%. While the lack of susceptibility testing results for *S aureus* in the non-hospitalised setting does not imply its absence in this setting, previous evidence has demonstrated low prevalence in the community. [44] Furthermore, *S aureus* is not typically considered to be a pathogen of major importance in COPD, unlike CF, in which *S aureus,* particularly resistant strains, have been shown to associate with disease progression. [45-49] Therefore, while the high rates of resistance of *S aureus* in this study should be viewed with caution, the clinical implication may be less than for other pathogens. Susceptibility rates of *K pneumoniae* and *A baumannii* were infrequently reported, making it hard to compare resistance rates between study settings. Of particular note, high median resistance rates were observed for *A baumannii* in the ICU setting. While previous evidence implicates colistin as the most effective antimicrobial for *A baumannii* eradication, we were only able to corroborate this finding in the hospitalised setting, owing to lack of susceptibility data in other settings. [50] In fact, across all bacteria, there was a tendency for greater rates of susceptibility to colistin and piperacillin/tazobactam, supporting the roles for these antibiotics in severe AECOPD cases, especially those with *P aeruginosa* infection. [43,51] Perhaps reflecting the severity of AECOPD encountered in non-hospitalised setting, we observed little evidence of colistin and piperacillin/tazobactam susceptibility testing in this setting, but surprisingly found no evidence of susceptibility testing in the ICU, where these antibiotics may be most required. Susceptibly to quinolones was generally high, with the exception of *S aureus* in the ICU setting, in agreement with previous studies. [52,53]

Our review has confirmed that use of antibiotics appears to drive AMR in COPD, at least when looking at data for *Pseudomonas* and for various species with regard to macrolides. Despite the lack of clear or high-quality evidence [54], antibiotics are used very frequently in COPD, with approximately 50% of AECOPD treated with antibiotics in primary care and COPD patients receiving approximately 3 times more antibiotic prescriptions than the general public. [10,11] This use of antibiotics is not without consequence. Aside from resistance, adverse effects include diarrhoea and *Clostridium difficile* infection and guidelines consequently emphasise the use of factors such as biomarkers or clinical signs to optimise antibiotic use in COPD. [55,56] [1,57]

We had hypothesised that AMR would be associated with poorer outcomes for patients, but were not able to prove this in the published works. Nevertheless hints that length of stay may be longer, and antibiotic choices more limited in primary care are a concern. Our review supports the fact that AMR is an increasing problem, such that stewardship is important if we are to reduce impact of this on clinical care – already where quinolone resistance rates are high, for example, treatment with intravenous agents may mandate admission for treatment in many healthcare systems.

The data was highly variable but use of median resistance rates assisted the interpretation of results. Variability of data may relate to a number of factors, not least the variations in definitions of COPD and AECOPD, disease severity, geographical location of the studies, year of publication, sample size and antimicrobial susceptibility testing (AST) technique. We noted substantial variation in AST technique, origin of sample and breakpoint guidelines used. The lack of reporting and standardisation between AST techniques and breakpoint guidelines hinders ability of researchers, including ourselves, to compare results across settings and disease state. Future studies should strive to employ standardised techniques and

methodology; the advent of application of metagenomic approaches to AMR may play a role in this regard, because of their ability to screen the full microbiome.

A key strength of our study is that by including a broad range of search terms, reviewing references of included works, and employing few restrictions other than human studies we are confident our searches should have retrieved all relevant data. We also included a comprehensive range of outcomes, thus aiding identification of future areas of priority for research. As with all systematic reviews we were limited by the quality and indexing of relevant studies, and it was primarily the variable quality and type of reporting in included works which limited the conclusions we could draw. Furthermore, by only reporting PPMs, we are unable to determine the extent of AMR in non-PPMs. It has recently been demonstrated than COPD microbiome acts as a reservoir for AMR genes, particularly macrolide resistant genes harboured by *Streptococcus* and *Actinomyces* gena, independent of antibiotic exposure. [58] Although clinical utility remains low at present, it is likely that metagenomic sequencing approaches may become the optimum method for investigating the airway microbiome, dispersion of AMR genes and inter-species interactions which may play a key role in AMR. Such methods may also overcome some measurement inconsistencies encountered by this review. [72] We suggest that the framework we used here to present data by organism and drug class may be a starting point for such a consensus to be drawn up on AMR reporting.

Conclusion

AMR is common in COPD, driven by antibiotic use, and may be associated with adverse clinical consequences for patients. Standardised reporting of AMR rates in all future antibiotic studies in COPD could help to quantify the problem fully. The framework we used here to present data by organism and drug class may be a starting point for such a consensus to be drawn up.

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Disclosure of interest

The authors report no conflict of interest.

Refences

1. Global Initiative for Chronic Obstructive Pulmonary Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 report). 2020.

2. British Lung Foundation. Chronic Obstructive Pulmonary Disease (COPD) statistics. https://statistics.blf.org.uk/copd. Accessed Nov 7, 2020.

3. Adeloye D, Chua S, Lee C, et al. Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health*. 2015;5(2):020415. doi: 10.7189/jogh.05-020415.

4. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402-407. doi: 10.1136/thx.2007.085456.

5. MacNee W. Pathogenesis of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2005;2(4):258-266. doi: 10.1513/pats.200504-045SR.

6. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645-2653. doi: 10.1056/NEJMoa032158.

7. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 201;106(2):196-204.

8. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*. 2006;173(10):1114-1121. doi: 10.1164/rccm.200506-859OC.

9. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: A state-of-the-art review. *Clin Microbiol Rev*. 2001;14(2):336-363. doi: 10.1128/CMR.14.2.336-363.2001.

10. Hoenderdos K, Condliffe A. The neutrophil in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol*. 2013;48(5):531-539. doi: 10.1165/rcmb.2012-0492TR.

11. Taylor AE, Finney-Hayward TK, Quint JK, et al. Defective macrophage phagocytosis of bacteria in COPD. *Eur Respir J*. 2010;35(5):1039-1047. doi: 10.1183/09031936.00036709.

12. Elomaa O, Sankala M, Pikkarainen T, et al. Structure of the human macrophage MARCO receptor and characterization of its bacteria-binding region. *J Biol Chem*. 1998;273(8):4530-4538. doi: 10.1074/jbc.273.8.4530.

13. Droemann D, Goldmann T, Tiedje T, Zabel P, Dalhoff K, Schaaf B. Toll-like receptor 2 expression is decreased on alveolar macrophages in cigarette smokers and COPD patients. *Respir Res*. 2005;6(1):68. doi: 10.1186/1465-9921-6-68.

14. Janciauskiene S, Wrenger S, Immenschuh S, et al. The multifaceted effects of Alpha1-antitrypsin on neutrophil functions. *Front Pharmacol*. 2018;9:341. doi: 10.3389/fphar.2018.00341.

15. Ostermann L, Maus R, Stolper J, et al. Alpha-1 antitrypsin deficiency impairs lung antibacterial immunity in mice. *JCI Insight*. 2021;6(3). doi: 10.1172/jci.insight.140816.

16. Smith DJ, Ellis PR, Turner AM. Exacerbations of Lung Disease in Alpha-1 Antitrypsin Deficiency. Chronic Obstr Pulm Dis. 2021 Jan;8(1):162–76. doi: 10.15326/jcopdf.2020.0173

17. Patel IS, Seemungal TA, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax*. 2002;57(9):759-764. doi: 10.1136/thorax.57.9.759 [doi].

18. Rosell A, Monso E, Soler N, et al. Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med*. 2005;165(8):891-897. doi: 10.1001/archinte.165.8.891.

19. Wood AM, Bassford C, Webster D, et al. Vitamin D-binding protein contributes to COPD by activation of alveolar macrophages. *Thorax*. 2011;66(3):205-210. doi: 10.1136/thx.2010.140921.

20. Hampson JA, Stockley RA, Turner AM. Free light chains: Potential biomarker and predictor of mortality in alpha-1-antitrypsin deficiency and usual COPD. *Respir Res*. 2016;17(1):34.

21. Foxwell AR, Kyd JM, Cripps AW. Nontypeable haemophilus influenzae: Pathogenesis and prevention. *Microbiol Mol Biol Rev*. 1998;62(2):294-308.

22. Davison HC, Low JC, Woolhouse ME. What is antibiotic resistance and how can we measure it? *Trends Microbiol*. 2000;8(12):554-559. doi: 10.1016/s0966-842x(00)01873-4.

23. Kraemer SA, Ramachandran A, Perron GG. Antibiotic pollution in the environment: From microbial ecology to public policy. *Microorganisms*. 2019;7(6). doi: 10.3390/microorganisms7060180.

24. World Health Organisation. Global action plan on antimicrobial resistance. https://www.who.int/publications/i/item/9789241509763. Updated 2016. Accessed 17 Mar, 2021.

25. NHS England. Fighting Antimicrobial Resistance. https://www.england.nhs.uk/patient-safety/fighting-antimicrobial-resistance/. Accessed 4 Mar, 2021.

26. HM Government. Department of Health and Social Care. Contained and controlled: The UK's 20-year vision for antimicrobial resistance. 2019. https://www.gov.uk/government/publications/uk-20-year-vision-for-antimicrobial-resistance Accessed 3 Mar, 2021

27. Kyd JM, McGrath J, Krishnamurthy A. Mechanisms of bacterial resistance to antibiotics in infections of COPD patients. *Curr Drug Targets*. 2011;12(4):521-530. doi: 10.2174/138945011794751519.

28. Nightingale CH. Pharmacokinetics and pharmacodynamics of newer macrolides. *Pediatr Infect Dis J*. 1997;16(4):438-443. doi: 10.1097/00006454-199704000-00027.

29. Seemungal TAR, Wilkinson TMA, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary

disease exacerbations. *Am J Respir Crit Care Med*. 2008;178(11):1139-1147. doi: 10.1164/rccm.200801-145OC.

30. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD [published correction appears in N Engl J Med. 2012 Apr 5;366(14):1356]. N Engl J Med. 2011;365(8):689-698. doi:10.1056/NEJMoa1104623

31. Uzun S, Djamin RS, Kluytmans JA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2014;2(5):361-368. doi: 10.1016/S2213-2600(14)70019-0.

32. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir Med*. 2013;1(3):262-274. doi: 10.1016/S2213-2600(13)70038-9.

33. PROSPERO. The prevalence, pattern and impact of antibiotic resistance in COPD: A systematic review (2020:CRD42020218684). https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020218684. Accessed Mar 10, 2021.

34. Higgins J, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021). 2021. www.training.cochrane.org/handbook. Accessed Mar 10, 2021.

35. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi: 10.1136/bmj.l4898.

36. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015;13(3):147-153. doi: 10.1097/XEB.0000000000000054.

37. Guo Z, Chang C, Chen Y, Zheng Y, Yao W. *Zhonghua Yi Xue Za Zhi* [Bacteriology in acute exacerbation in patients hospitalized frequently for acute exacerbation of chronic obstructive pulmonary disease [Chinese]] 2014;94(10):729-732.

38. Estirado C, Ceccato A, Guerrero M, et al. Microorganisms resistant to conventional antimicrobials in acute exacerbations of chronic obstructive pulmonary disease. *Respir Res*. 2018;19(1):119. doi:10.1186/s12931-018-0820-1.

39. Nseir S, Di Pompeo C, Cavestri B, et al. Multiple-drug-resistant bacteria in patients with severe acute exacerbation of chronic obstructive pulmonary disease: Prevalence, risk factors, and outcome. *Crit Care Med*. 2006;34(12):2959-2966. doi:10.1097/01.CCM.0000245666.28867.C6

40. Rodrigo-Troyano A, Suarez-Cuartin G, Peiró M, et al. Pseudomonas aeruginosa resistance patterns and clinical outcomes in hospitalized exacerbations of COPD. *Respirology*. 2016;21(7):1235-1242. doi:10.1111/resp.12825.

41. Brill SE, Law M, El-Emir E, et al. Effects of different antibiotic classes on airway bacteria in stable COPD using culture and molecular techniques: a randomised controlled trial. *Thorax*. 2015;70(10):930-938. doi:10.1136/thoraxjnl-2015-207194

42. Desai H, Richter S, Doern G, et al. Antibiotic resistance in sputum isolates of Streptococcus pneumoniae in chronic obstructive pulmonary disease is related to antibiotic exposure. *COPD*. 2010;7(5):337-344. doi:10.3109/15412555.2010.510162.

43. Inoue S, Watanuki Y, Miyazawa N, et al. High frequency of β-lactamase-negative, ampicillin-resistant strains of Haemophilus influenzae in patients with chronic bronchitis in Japan. *J Infect Chemother*. 2010;16(1):72-75. doi:10.1007/s10156-009-0020-5.

44. Pomares X, Montón C, Bullich M, et al. Clinical and Safety Outcomes of Long-Term Azithromycin Therapy in Severe COPD Beyond the First Year of Treatment. *Chest*. 2018;153(5):1125-1133. doi:10.1016/j.chest.2018.01.044

45. Pettigrew MM, Tsuji BT, Gent JF, et al. Effect of Fluoroquinolones and Macrolides on Eradication and Resistance of Haemophilus influenzae in Chronic Obstructive Pulmonary Disease. *Antimicrob Agents Chemother*. 2016;60(7):4151-4158. doi:10.1128/AAC.00301-16

46. Montero M, Domínguez M, Orozco-Levi M, Salvadó M, Knobel H. Mortality of COPD patients infected with multi-resistant pseudomonas aeruginosa: A case and control study. *Infection*. 2009;37(1):16-19. doi:10.1007/s15010-008-8125-9

47. Pan W, Yu J, Zhang L, Yang H, Yuan Y. Predictors of in-hospital mortality in patients with acute exacerbation of COPD requiring ventilation: A retrospective study. *Int J Clin Exp Med.* 2016;9(11):22093-22101

48. Vitacca M, Marino S, Comini L, Fezzardi L, Paneroni M. Bacterial Colonization in COPD Patients Admitted to a Rehabilitation Respiratory Unit and Impact on Length of Stay: A Real-Life Study. *COPD*. 2018;15(6):581-587. doi:10.1080/15412555.2019.1572731

49. Liu H, Zheng D, Lin Y, et al. Association of sputum microbiome with clinical outcome of initial antibiotic treatment in hospitalized patients with acute exacerbations of COPD. Pharmacol Res. 2020;160:105095. doi:10.1016/j.phrs.2020.105095

50. Bae S, Lee J, Lee J, et al. Antimicrobial resistance in haemophilus influenzae respiratory tract isolates in Korea: Results of a nationwide acute respiratory infections surveillance. *Antimicrob Agents Chemother*. 2010;54(1):65-71. doi: 10.1128/AAC.00966-09.

51. Hasegawa K, Chiba N, Kobayashi R, et al. Rapidly increasing prevalence of beta-lactamase-nonproducing, ampicillin-resistant haemophilus influenzae type b in patients with meningitis. *Antimicrob Agents Chemother*. 2004;48(5):1509-1514. doi: 10.1128/aac.48.5.1509-1514.2004.

52. Khan MA, Northwood JB, Levy F, et al. Bro {beta}-lactamase and antibiotic resistances in a global cross-sectional study of moraxella catarrhalis from children and adults. *J Antimicrob Chemother*. 2010;65(1):91-97. doi: 10.1093/jac/dkp401.

53. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease (acute exacerbation): Antimicrobial prescribing NICE guideline [NG114] [internet]. London: National Institute for Health and Care Excellence; 2018 [cited 2021 mar 19]. Available from: www.nice.org.uk/guidance/ng114

54. Shimizu K, Yoshii Y, Morozumi M, et al. Pathogens in COPD exacerbations identified by comprehensive real-time PCR plus older methods. *Int J Chron Obstruct Pulmon Dis*. 2015;10:2009-2016. doi: 10.2147/COPD.S82752.

55. Siddiqi A, Sethi S. Optimizing antibiotic selection in treating COPD exacerbations. *Int J Chron Obstruct Pulmon Dis*. 2008;3(1):31-44. doi:10.2147/copd.s1089

56. Sethi S. Bacteria in exacerbations of chronic obstructive pulmonary disease: Phenomenon or epiphenomenon? *Proc Am Thorac Soc*. 2004;1(2):109-114. doi: 10.1513/pats.2306029.

57. Sawicki GS, Rasouliyan L, Pasta DJ, et al. The impact of incident methicillin resistant staphylococcus aureus detection on pulmonary function in cystic fibrosis. *Pediatr Pulmonol*. 2008;43(11):1117-1123. doi: 10.1002/ppul.20914.

58. Goss CH, Muhlebach MS. Review: Staphylococcus aureus and MRSA in cystic fibrosis. *J Cyst Fibros*. 2011;10(5):298-306. doi: 10.1016/j.jcf.2011.06.002.

59. Cogen J, Emerson J, Sanders DB, et al. Risk factors for lung function decline in a large cohort of young cystic fibrosis patients. *Pediatr Pulmonol*. 2015;50(8):763-770. doi: 10.1002/ppul.23217.

60. Sieniawski K, Kaczka K, Rucińska M, Gagis L, Pomorski L. Acinetobacter baumannii nosocomial infections. *Pol Przegl Chir*. 2013;85(9):483-490. doi: 10.2478/pjs-2013-0075.

61. Montón C, Prina E, Pomares X, et al. Nebulized colistin and continuous cyclic azithromycin in severe COPD patients with chronic bronchial infection due to pseudomonas aeruginosa: A retrospective cohort study. *Int J Chron Obstruct Pulmon Dis*. 2019;14:2365-2373. doi: 10.2147/COPD.S209513.

62. Iffat W, Shoaib MH, Muhammad IN, Rehana n, Tasleem S, Gauhar S. Antimicrobial susceptibility testing of newer quinolones against gram positive and gram negative clinical isolates. *Pak J Pharm Sci*. 2010;23(3):245-249.

63. Kim ES, Hooper DC. Clinical importance and epidemiology of quinolone resistance. *Infect Chemother*. 2014;46(4):226-238. doi: 10.3947/ic.2014.46.4.226.

64. Vollenweider DJ, Frei A, Steurer-Stey C, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *The Cochrane database of systematic reviews*. 1029;10(10):CD010257. doi: 10.1002/14651858.CD010257.pub2.

65. Roede BM, Bindels PJ, Brouwer HJ, Bresser P, de Borgie CA, Prins JM. Antibiotics and steroids for exacerbations of COPD in primary care: Compliance with Dutch guidelines. *Br J Gen Pract*. 2006;56(530):662-665.

66. Shallcross L, Beckley N, Rait G, Hayward A, Petersen I. Antibiotic prescribing frequency amongst patients in primary care: A cohort study using electronic health records. *J Antimicrob Chemother*. 2017;72(6):1818-1824. doi: 10.1093/jac/dkx048.

67. Zhang H, Tan M, Qiu A, Tao Z, Wang C. Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: A network meta-analysis. *BMC Pulm Med*. 2017;17. doi: 10.1186/s12890-017-0541-0.

68. Cunha BA. Antibiotic side effects. *Med Clin North Am*. 2001;85(1):149-185. doi: 10.1016/s0025-7125(05)70309-6.

69. National Institute for Health and Care Excellence. chronic obstructive pulmonary disease in over 16s: Diagnosis and management. NICE guidelines NG115 [internet]. London: National Institute for Health and Care Excellence; 2018 [cited 2021 mar 16]. Available from: www.nice.org.uk/guidance/ng115.

70. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: A randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19. doi: 10.1378/chest.06-1500.

71. Butler CC, Gillespie D, White P, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *N Engl J Med*. 2019;381(2):111-120. doi: 10.1056/NEJMoa1803185.

72. Mac Aogáin M, Lau KJX, Cai Z, et al. Metagenomics Reveals a Core Macrolide Resistome Related to Microbiota in Chronic Respiratory Disease. *Am J Respir Crit Care Med*. 2020;202(3):433-447. doi:10.1164/rccm.201911-2202OC.

Tables

		Resistance rate (number of samples resistant/number of samples tested, (%))													
Microorganism	State*	Penicillin	Ampicillin [p]/		Co-amoxiclav		Tetracycline [t]/		Quinolones		Macrolides [x]		Cefuroxime		Piperacillin/		Colistin	
Author, year			Amoxicillin [x]				Doxycycline [d]		Ciprofloxacin [c] / Levofloxacin [l]		Azithromycin [a] / Erythromycin [e] / Clarithromycin [c]				Tazobactam			
H. influenzae																		
Median, range (%)			**39.7**	**20.4–73.3**	**1.85**	**0–40**	**0.5**	**0.2–6.7**	**0**	**0–0**	**4**	**0–46.7**	**0.2**	**0–0.5**				
Maddi et al, 2017	Stable		11/15 [p]	(73.3)	6/15	(40)	1/15 [t]	(6.7)	0/15 [c,l]	(0)	3/15 [a]	(20)						
			8/15 [x]	(53.3)							7/15 [e]	(46.7)						
											4/15 [c]	(26.7)						
Pettigrew et al, 2016	Mixed								0/100 [c,l]	(0)	1/100 [a]	(1)						
Pfaller et al, 2001	AE		-/- [p]	(26)	-/-	(0)	-/- [t]	(0.2)	-/- [c,l]	(0)	-/- [a]	(1)	-/-	(0.2)				
											-/- [c]	(7)						
Pfaller et al, 2002	AE		-/- [p]	(20.4)	-/-	(3.7)	-/- [d]	(0.5)	-/- [c,l]	(0)	-/- [a]	(0)	-/-	(0.5)				
											-/- [c]	(7.3)						
Querol-Ribelles et al, 2006	AE				-/-	(0)			-/- [c,l]	(0)	-/- [a]	(0)	-/-	(0)				
											-/- [c]	(0.6)						
P. aeruginosa																		
Median, range (%)									**51.3**	**50–52.6**					**19.2**	**19.2–19.2**	**2.6**	**2.6–2.6**
Gallego et al, 2014	Mixed								41/78 [c]	(52.6)					15/78	(19.2)	2/78	(2.6)
									39/78 [l]	(50)								
S. pneumoniae																		

Median, range (%)		**11.3**	**3–15**	**1.2**	**1.2–1.2**	**1.2**	**1.1–3**	**22.1**	**20.2–24**	**1**	**0–4.2**	**33.1**	**24–35**	**16.9**	**13.6–20.2**
Desai et al, 2010	Mixed	6/75	(8)									18/75 [e]	(24)		
Pfaller et al, 2001	AE	-/-	(15)			-/-	(3)	-/- [t]	(24)	-/- [l]	(1)	-/- [e]	(35)		
Pfaller et al, 2002	AE	13/89	(14.6)			1/89	(1.1)	18/89 [t]	(20.2)	0/89 [l]	(0)	29/89 [e]	(32.6)	18/89	(20.2)
Querol-Ribelles et al, 2006	AE	-/-	(3)	-/- [x]	(1.2)	-/-	(1.2)			-/- [l]	(4.2)	-/- [a,c]	(33.1)		(13.6)
												-/- [e]	(34.3)		
M. catarrhalis															
Median, range (%)		**93**	**93–93**	**90.4**	**90.4–90.4**	**0**	**0–0**	**0.5**	**0.3–0.7**	**0**	**0–0**	**2**	**0–3.7**	**0**	**0–0**
Pfaller et al, 2001	AE		(93)			0/323	(0)	1/323 [t]	(0.3)	0/323 [c,l]	(0)	-/- [e]	(2)	0/323	(0)
Pfaller et al, 2002	AE			-/- [p]	(90.4)	-/-	(0)	-/- [t]	(0.7)	-/- [c,l]	(0)	-/- [e]	(3.7)	-/-	(0)
Querol-Ribelles et al, 2006	AE					-/-	(0)			[c,l]	(0)	-/- [a,c]	(0)	-/-	(0)

Table 1: Antimicrobial resistances rates in non-hospitalised patients

Summary statistics for each bacterium are shown in bold type, with individual studies below. Studies which did not explicitly state the number of samples tested for antimicrobial susceptibility are listed above as percentages only and are denoted by "-/-". * 'State' refers to the status of the patients COPD during the study: stable, patients with stable (non-exacerbated COPD); AE, patients with acute exacerbations; mixed, a study cohort including patients with either exacerbated or stable COPD. Abbreviations: AE, acute exacerbation

Figures

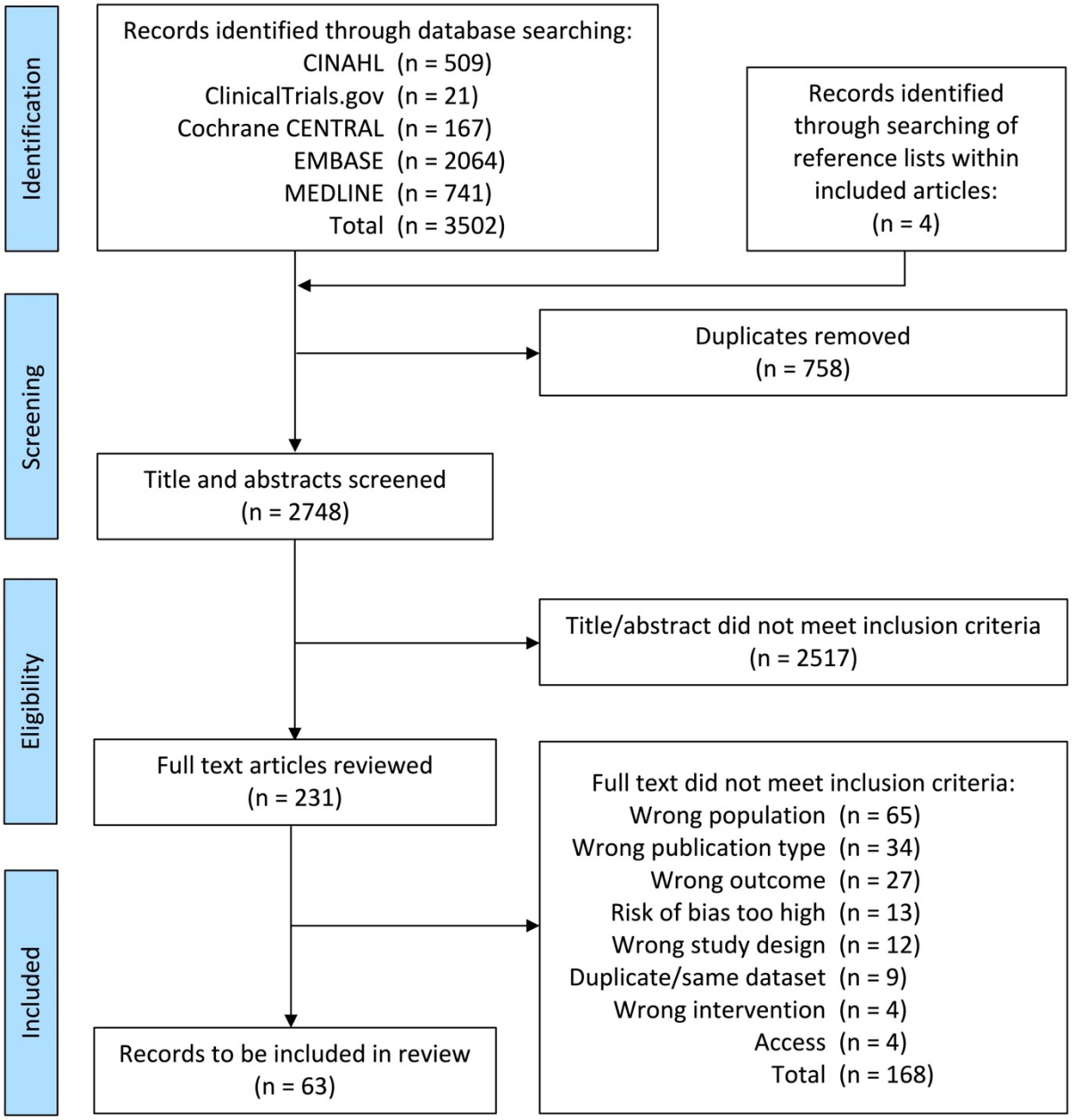

Figure 1

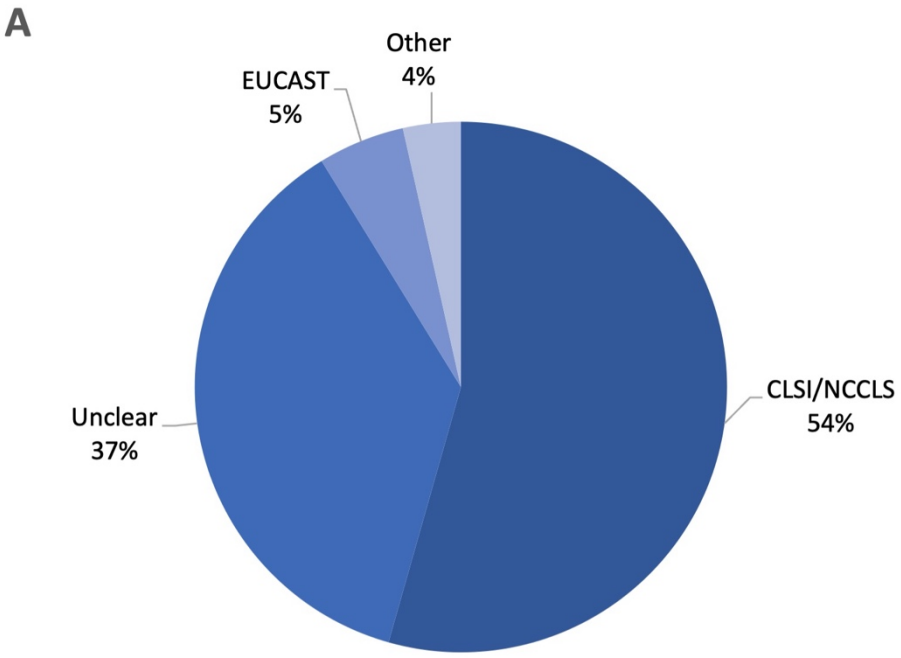

Figure 2A

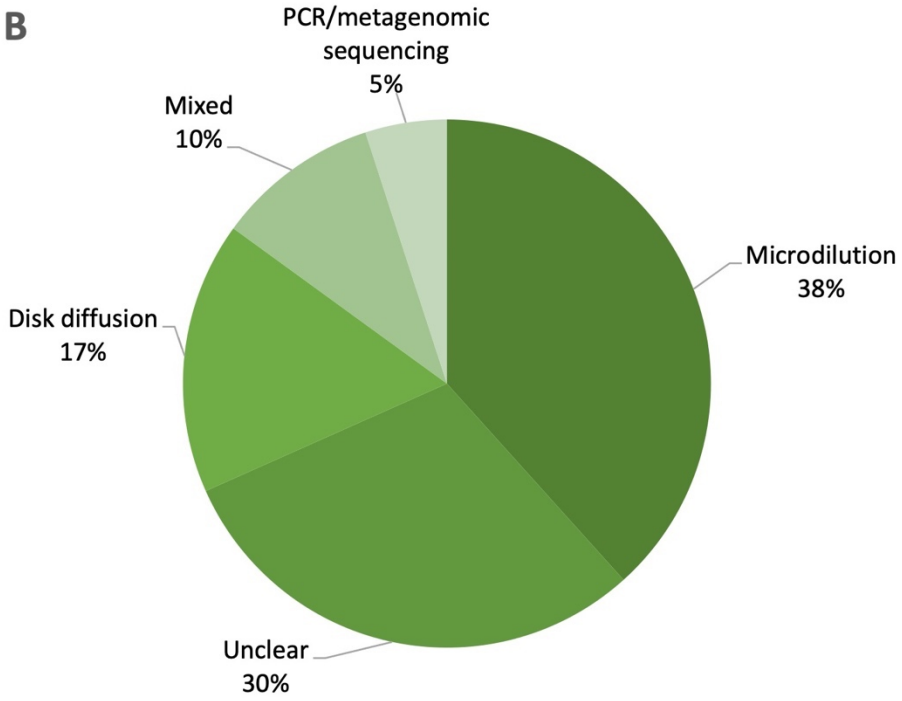
B
PCR/metagenomic sequencing 5%
Mixed 10%
Microdilution 38%
Disk diffusion 17%
Unclear 30%

Figure 2B

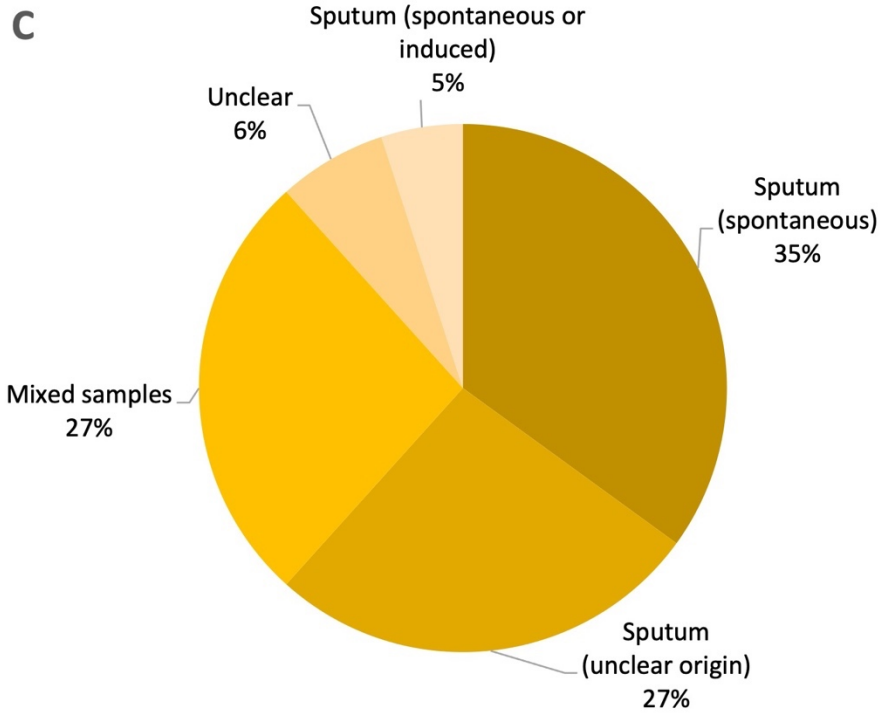
C
Sputum (spontaneous or induced)
5%
Unclear
6%
Sputum (spontaneous)
35%
Mixed samples
27%
Sputum (unclear origin)
27%

Figure 2C

Figure captions

Figure 1: PRISMA flow diagram

Figure 2: Visual representation of distribution of: (**A**) origin of sample for antimicrobial susceptibility testing, (**B**) antibiotic susceptibility testing technique and (**C**) breakpoint antimicrobial susceptibility guidelines used, within included studies. Abbreviations: CLSI, Clinical Laboratory Standards Institute; NCCLS, National Committee on Clinical Laboratory Standards; EUCAST, European Committee on Antimicrobial Susceptibility Testing.