Statistical Analysis plan

Version 1: 21.07.2025

Title: A secondary analysis of the PEACH study data to investigate the impact of a penicillin allergy record on antibiotic use, AMR and patient health outcomes in patients admitted with COVID-19

1 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Coronavirus disease (COVID-19) is a viral respiratory tract infection caused by the SARS-CoV-2 virus. Antibiotics are often used in patients with COVID-19 because: a) there is clinical difficulty in distinguishing bacterial pneumonia from COVID-19 or b) there are concerns about co-infection either at the time of presentation or as a secondary infection related to COVID-19 or hospital admission. A large meta-analysis which included 30,623 patients, found that 74.6% (95% CI 68.3–80.0%) of inpatients with COVID-19 were prescribed antibiotics.[1] Despite the antibiotic usage in this cohort, systematic reviews have found the prevalence of bacterial infections to be only 7-9%, highlighting that antibiotic prescribing in this cohort is often inappropriate.[2-4]

The impacts of PenA on antibiotic prescribing and AMR in patients with COVID-19 is largely unknown. One United States based retrospective study investigating the impact of PenA on outcomes for patients with COVID-19 found that rates of hospitalisation, intensive care admission, acute respiratory failure, and mechanical ventilation were higher in patients with PenA compared to those without PenA.[5] This risk remained even in the absence of bacterial infection. Studies exploring this further are required. However, if we extrapolate from pre-pandemic data, we can hypothesise that patients hospitalised with COVID-19 with PenA and treated for bacterial infections, will be at risk of longer hospital stays, higher rates of treatment failure and have higher mortality when compared to patients without PenA.

This analysis will explore the impact of PenA on outcomes for patients COVID-19 in the UK, by conducting a secondary analysis of data from the PEACH (Procalcitonin: Evaluation of Antibiotic use in COVID-19 Hospitalised patients) study.

PEACH was a retrospective cohort study aimed at determining if the use of a biomarker for infection called procalcitonin (PCT) reduced antibiotic use among patients who were hospitalised with COVID-19 during the first wave of the pandemic. As such this data set will have data pertaining to antibiotic

use, allergy status, AMR and patient outcomes that will allow investigation of the impact PenA has on this patient group.

1.2 STUDY OBJECTIVES AND HYPOTHESIS

The study objective is to examine the relationship between PenA labels and AMR and patient health outcomes in patients admitted with COVID-19. Our hypothesis is that patients with penA will be higher rates of adverse health outcomes such as death and AMR infections.

2 STUDY METHODS

2.1 STUDY DESIGN AND DATA SOURCE

Secondary analysis of PEACH study data. The PEACH study was a multi-centre, retrospective, observational, cohort study using patient-level clinical data (IRAS: 290358) which investigated whether the use of procalcitonin testing, to guide antibiotic prescribing, safely reduced antibiotic use amongst hospitalised patients with COVID-19 during the first wave of the pandemic using routinely collected patient institutional clinical databases and patient medical records.[6] Data were collected in 11 NHS acute hospital Trusts and Health Boards in England and Wales, and data in a pseudo-anonymised format was received from the Cardiff Clinical Trials Unit who were the data controllers for the PEACH study. This study has been designed in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, which will also be followed in the reporting of results.[7]

2.2 SAMPLE SIZE CALCULATION

Mortality in COVID-19 patients in the first wave of the pandemic was approximately 30%.[8] Therefore using 5% significance level, a sample size of 7000 will provide 80% statistical power to detect a change of 4.5% or greater in mortality.

2.3 TIMING OF FINAL ANALYSIS

Analysis will be conducted once data has been received by the PEACH study team.

3 STATISTICAL PRINCIPLES

3.1 CONFIDENCE INTERVALS AND P-VALUES

All hypothesis tests and confidence intervals will be two-sided. A significance level of 0.05 will be used, and results will be presented with 95% confidence intervals.

3.2 ANALYSIS POPULATION

PEACH study participants which includes patients ≥16 years admitted to a participating NHS hospital and diagnosed with COVID-19 between 01/02/2020 and 30/06/2020. Only participants with their penicillin allergy status recorded will be included in the analysis population.

4 STUDY POPULATION

4.1 POPULATION

4.1.1 Inclusion criteria

Adult (>16 years) with confirmed COVID-19 (positive PCR test) and admitted to participating NHS Trusts/hospitals (for any reason) between 01/02/2020 to 30/06/2020.

4.1.2 Exclusion criteria

Patients with their allergy status missing from the database will be excluded.

4.2 BASELINE CHARACTERISTICS

Baseline data will include:

- Age
- Sex
- IMD
- Ethnicity
- Admission hospital
- Illness severity
- Co-morbidities

Baseline data were collected in the following sequence depending on availability: 1. Values on the day of COVID-19 test; 2. Values on day after COVID-19 test (if values on day of test are missing); and 3. Values on day before COVID-19 test (if values on day of test and values on day after the test are missing).

4.3 POTENTIAL CONFOUNDING COVARIATES

Directed Acyclic Graphs (DAG) display assumptions surrounding the exposure and outcome and serves as a tool to identify cofounder and mediators (which are responsible for part of the effect of the exposure).[9] A DAG (Figure 1) was created a-priori to identify potential confounding variables that might affect both the exposure and outcome relating to AMR, this was developed based on existing literature and expert consensus within the supervisory team. Co-morbidities include: Asthma, cancer, CHD, CKD, COPD, diabetes, PAD, smoking, stroke and TIA.

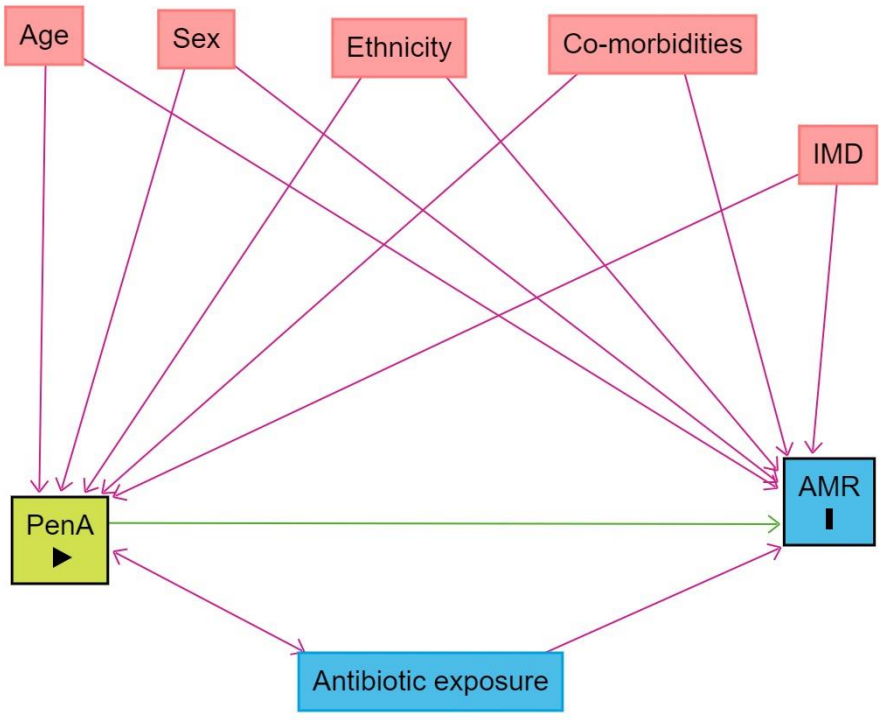

Figure 1. Directed acyclic graph of the proposed associated between penA and AMR mediated by antibiotic exposure

4.4 PECO SUMMARY

Population	Inpatients ≥16 years admitted with confirmed COVID-19 during hospital admission between 1 February 2020 and 30 June 2020.
Exposure	Presence of penicillin allergy record for the patient
Comparator	Patients without a penicillin allergy record
Outcomes	Primary: 60 day mortality
	Secondary outcomes: Presence antimicrobial resistant secondary bacterial infection Length of hospital stay Antibiotic usage in hospital *Clostridioides difficile* infection Treatment failure Day 30 mortality

5 ANALYSIS

5.1 OUTCOME DEFINITIONS

5.1.1 Primary outcome

The primary outcome is mortality within 60 days of COVID-19 diagnosis in patients with and without a penA. This will be measured from the date of positive COVID 19 test.

5.1.2 Secondary outcomes

5.1.2.1 Presence antimicrobial resistant secondary bacterial infection

This will be determined by blood cultures and deep respiratory culture positivity. Blood culture results will are considered to be defined as the detection of bacteria according to Appendix, table 1 in a blood culture. A bacteraemia caused by potential skin contaminants (e.g. coagulase-negative staphylococci

[CoNS], *Corynebacterium* species, Bacillus species, *Cutibacterium* species, and *Micrococcus* species) will be considered to be significant if isolated in two or more blood cultures within a 48 hour period.[10-12] Deep respiratory cultures are considered to be positive if they grow a recognised pathogen as per the PEACH study protocol.

For the purpose of this study, the Magiorakos et al [13] definition of resistance will be used and a infection will be considered to be a resistant infection if the isolated pathogen is resistant to ≥1 antibiotic agent in 3 or more antibiotic classes (Appendix, Table 2), antibiotic classes were derived from the WHO ATC/DDD Index 2024[14] and Mandel et al[15].

5.1.2.2 Length of hospital stay

Total hospital stay (day 0 = date of admission), calculated as days from admission date to the date of discharge or inpatient death (whichever occurred first).

5.1.2.3 Antibiotic usage

Inpatient antibiotic use including antibiotic agent, route of administration and duration following COVID-19 diagnosis in hospital from day 1 of COVID-19 diagnosis to date of discharge or death (inclusive of day 1 and last day).

5.1.2.4 Clostridioides difficile infection

As determined by a toxin positive result from day 1 of COVID-19 diagnosis

5.1.2.5 Treatment failure

This will be defined as re-prescription of an antibiotic within 30 days of index antibiotic prescription

5.1.2.6 Day 30 mortality

This will be measured from the date of positive COVID 19 test.

5.2 ANALYSIS METHODS

5.2.1 Descriptive statistics

Descriptive statistics will be used to summarise baseline characteristics (Table 2) and types of antibiotics used stratified by exposure (penA status). Categorical data will be reported as percentages and frequencies and continuous data reported as medians with interquartile ranges (IQR) or as means with standard deviations (SD) depending on the distribution and characteristics of the data.

The chi-square test of association or the Fisher exact test will be used to test for relationships between categorical variables and the exposure. For continuous data, the Mann-Whitney U Test will be used for data that is not normally distributed and the independent t-test will be used for normally distributed data.

Summary of baseline characteristics:

	Total	PenA	Non-PenA	p-value
Age in year, mean (SD) or median or IQR)				
Sex – female (n,%)				
IMD (n, %)				
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
Ethnicity (n,%)				
White				
Black, Black British, Caribbean or African				
Asian or Asian British				
Mixed or multiple ethnic groups				
Any other ethnic group				
Not known				
Total number of co-morbidities				
No comorbidities				
Only 1 comorbidity				
2 or more comorbidities				
AF, (n,%)				
COPD, (n,%)				
Asthma, (n,%)				

Cancer, (n,%)				
Coronary heart disease, (n,%)				
CKD, (n,%)				
CVS, (n,%)				
Dementia, (n,%)				
Depression, (n,%)				
Epilepsy, (n,%)				
Heart Failure, (n,%)				
HTN, (n,%)				
Learning disability (LD), (n,%)				
Mental Health, (n,%)				
Obesity (BMI), (n,%)				
Osteoporosis, (n,%)				
PVD, (n,%)				
Palliative care, (n,%)				
RA, (n,%)				
Stroke (not transient), (n,%)				
Stroke (transient), (n,%)				
Liver disease (mild to severe), (n,%)				
HIV, (n,%)				
CTD, (n,%)				
Chronic neurological condition, (n,%)				
Smoker, (n,%)				
Primary care frailty score¸ mean (SD) or median or IQR)				
Admission site (n, %)				
Leeds				
Royal Liverpool				
Aneurin Bevan UHB				
Sheffield				
Cornwall				
Mid Yorkshire				
Bristol				
Brighton				
Newcastle				
Salford				
Nottingham				
COVID severity at time of diagnosis				
Baseline temperature, mean (SD) or median or IQR)				
qSOFA, mean (SD) or median or IQR)				
4C mortality score, mean (SD) or median or IQR)				
Covid treatment Y or N				
Baseline CRP, mean (SD) or median or IQR)				

Baseline WCC, mean (SD) or median or IQR)				
ICU admission at diagnosis				

Descriptive statistics will also be used to summarise the antibiotic use (class of antibiotics, administration routes and duration of antibiotic use) within each exposure group.

5.2.2 Explanatory analysis

For the primary and binary secondary outcome analysis, associations between exposure, covariates and outcome will be tested using multivariable logistic regression for binary outcomes. Multivariable regression will be reported as odds ratios (ORs) with 95% confidence intervals (CIs) and p-values.

For the two time to event outcomes (length of hospital stay and total days on antibiotics) a competing risks survival analysis will be undertaken to account for the possibility that some patients may die before these outcomes can be fully observed. Inpatient death will be treated as a competing event, and a cause-specific Cox proportional hazards model will be used, with results reported as hazard ratios (HRs) along with 95% confidence intervals (CIs) and p-values.

Confounders included in the regression analyses will include those identified a-priori from the DAG.

	PenA (n/%)	Non PenA (n/%)	unadjusted OR/HR (95% CI)	adjusted OR/HR (95% CI)
Primary outcome				
60 day mortality				
Secondary outcomes				
Presence antimicrobial resistant secondary bacterial infection				
Length of hospital stay				
Total days antibiotic				
Clostridioides difficile infection				
Treatment failure				
Day 30 mortality				

A sensitivity analysis will be conducted using a competing risks model for the remaining secondary outcomes to assess the potential impact of inpatient death as a competing event.

5.2.3 Missing data

Data may or may not be missing at random, therefore patterns of missingness will be explored and summarised descriptively by penA status.

The frequency (percentage) of missing data will be reported for baseline characteristics and for the study outcomes. Characteristics of those with and without missing values will be to explore reasons for missingness and whether data may be missing at random.

Subsequent to initial analyses, and where deemed appropriate, sensitivity analyses will be undertaken. For variables exhibiting more than 10% missing data, multiple imputation methods will be considered. Additionally, a sensitivity analysis incorporating a 'missing' category will be performed and compared against complete case analyses to assess the robustness of the findings.

5.2.4 Additional analysis

n/a

5.2.5 Statistical software

Data will be analysed using R Studio, R version 4.3.3

6 APPENDIX

Appendix table 1. Categorisation of bacteria

Genus/Clinical Group	Subgroup Classification	Organism
Staphylococcus aureus	*Staphylococcus aureus*	*Staphylococcus aureus*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus capitis*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus caprae*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus cohnii*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus epidermidis*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus haemolyticus*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus hominis*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus saccharolyticus*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus saprophyticus*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus sciuri*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus* spp.
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus warneri*
Coagulase-negative Staphylococcus	Coagulase-negative Staphylococcus	*Staphylococcus xylosus*
Coagulase-negative Staphylococcus	*Staphylococcus lugdunensis*	*Staphylococcus lugdunensis*
Beta-haemolytic Streptococci	Group A Streptococcus	*Streptococcus pyogenes*
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, group B
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, group C
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, group D
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, group F
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, group G
Beta-haemolytic Streptococci	Other beta haemolytic Streptococcus	beta Haemolytic Strep, not groups ABCDFG
Streptococcus pneumoniae	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*
Other streptococcus spp.	S. anginosus group	*Streptococcus anginosus*
Other streptococcus spp.	S. anginosus group	*Streptococcus constellatus*
Other streptococcus spp.	S. anginosus group	*Streptococcus intermedius*
Other streptococcus spp.	Strep bovis group	*Streptococcus bovis group*
Other streptococcus spp.	Strep bovis group	*Streptococcus equinus*
Other streptococcus spp.	Strep bovis group	*Streptococcus gallolyticus*
Other streptococcus spp.	Strep bovis group	*Streptococcus infantarius*
Other streptococcus spp.	Strep bovis group	*Streptococcus lutetiensis*
Other streptococcus spp.	Nutritionally variant streptococci	*Abiotrophia* spp.
Other streptococcus spp.	Nutritionally variant streptococci	*Granulicatella* spp.
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus acidominimus*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus cristatus*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus gordonii*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus mitis*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus mutans*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus oralis*

Other streptococcus spp.	Other streptococcus spp.	*Streptococcus parasanguis*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus pasteurianus*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus salivarius*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus sanguinis*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus sanguinus*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus* spp.
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus uberis*
Other streptococcus spp.	Other streptococcus spp.	*Streptococcus vestibularis*
Other streptococcus spp.	Other streptococcus spp.	Viridans Streptococcus
Enterococcus spp.	*Enterococcus faecalis*	*Enterococcus faecalis*
Enterococcus spp.	*Enterococcus faecium*	*Enterococcus faecium*
Enterococcus spp.	Other Enterococcus spp.	*Enterococcus* spp.
Escherichia coli	*Escherichia coli*	*Escherichia coli*
Salmonella spp.	*Salmonella* spp.	*Salmonella* spp.
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella aerogenes*
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella oxytoca*
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella ozaenae*
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella pneumoniae*
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella rhinoscleromatis*
Klebsiella spp.	*Klebsiella* spp.	*Klebsiella* spp.
Other Enterobacterales	Other Enterobacterales	*Citrobacter braakii*
Other Enterobacterales	Other Enterobacterales	*Citrobacter diversus*
Other Enterobacterales	Other Enterobacterales	*Citrobacter freundii*
Other Enterobacterales	Other Enterobacterales	*Citrobacter koseri*
Other Enterobacterales	Other Enterobacterales	*Citrobacter spp.*
Other Enterobacterales	Other Enterobacterales	*Citrobacter youngae*
Other Enterobacterales	Other Enterobacterales	*Enterobacter aerogenes*
Other Enterobacterales	Other Enterobacterales	*Enterobacter agglomerans*
Other Enterobacterales	Other Enterobacterales	*Enterobacter amnigenus*
Other Enterobacterales	Other Enterobacterales	*Enterobacter asburiae*
Other Enterobacterales	Other Enterobacterales	*Enterobacter cloacae*
Other Enterobacterales	Other Enterobacterales	*Enterobacter gergoviae*
Other Enterobacterales	Other Enterobacterales	*Enterobacter intermedius*
Other Enterobacterales	Other Enterobacterales	*Enterobacter sakazakii*
Other Enterobacterales	Other Enterobacterales	*Enterobacter* spp.
Other Enterobacterales	Other Enterobacterales	*Escherichia* spp.
Other Enterobacterales	Other Enterobacterales	*Hafnia alvei*
Other Enterobacterales	Other Enterobacterales	*Hafnia* spp.
Other Enterobacterales	Other Enterobacterales	*Kluyvera* sp.
Other Enterobacterales	Other Enterobacterales	*Morganella morganii*
Other Enterobacterales	Other Enterobacterales	*Morganella* spp.
Other Enterobacterales	Other Enterobacterales	*Pantoea agglomerans*
Other Enterobacterales	Other Enterobacterales	*Pantoea* spp.
Other Enterobacterales	Other Enterobacterales	*Proteus mirabilis*
Other Enterobacterales	Other Enterobacterales	*Proteus* spp.
Other Enterobacterales	Other Enterobacterales	*Proteus vulgaris*

Other Enterobacterales	Other Enterobacterales	*Providencia alcalifaciens*
Other Enterobacterales	Other Enterobacterales	*Providencia rettgeri*
Other Enterobacterales	Other Enterobacterales	*Providencia* spp.
Other Enterobacterales	Other Enterobacterales	*Providencia stuartii*
Other Enterobacterales	Other Enterobacterales	*Raoultella (Klebsiella) ornithinolytica*
Other Enterobacterales	Other Enterobacterales	*Raoultella (Klebsiella) planticola*
Other Enterobacterales	Other Enterobacterales	*Raoultella (Klebsiella) terrigena*
Other Enterobacterales	Other Enterobacterales	*Serratia ficaria*
Other Enterobacterales	Other Enterobacterales	*Serratia liquefaciens*
Other Enterobacterales	Other Enterobacterales	*Serratia marcescens*
Other Enterobacterales	Other Enterobacterales	*Serratia odorifera*
Other Enterobacterales	Other Enterobacterales	*Serratia proteamaculans*
Other Enterobacterales	Other Enterobacterales	*Serratia rubidaea*
Other Enterobacterales	Other Enterobacterales	*Serratia* spp.
Pseudomonas spp.	*Pseudomonas aeruginosa*	*Pseudomonas aeruginosa*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas huttiensis*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas luteola*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas mallei*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas mendocina*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas oryzihabitans*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas pseudoalcaligenes*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas putida*
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas* spp.
Pseudomonas spp.	Other *pseudomonas* spp.	*Pseudomonas stutzeri*
Stenotrophomonas maltophilia	*Stenotrophomonas maltophilia*	*Stenotrophomonas maltophilia*
Acinetobacter spp.	Acinetobacter baumannii	*Acinetobacter baumannii*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter anitratus*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter haemolyticus*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter junii*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter lwoffii*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter radioresistens*
Acinetobacter spp.	Other Acinetobacter spp.	*Acinetobacter* spp.
Anaerobic organism	*Bacteroides* spp.	*Bacteroides* spp.
Anaerobic organism	*Clostridium* spp.	*Clostridium bifermentans*
Anaerobic organism	*Clostridium spp.*	*Clostridium botulinum*
Anaerobic organism	*Clostridium* spp.	*Clostridium butyricum*
Anaerobic organism	*Clostridium* spp.	*Clostridium cadaveris*
Anaerobic organism	*Clostridium* spp.	*Clostridium chauvei*
Anaerobic organism	*Clostridium* spp.	*Clostridium* spp.
Anaerobic organism	*Fusobacterium* spp.	*Fusobacterium necrophorum*
Anaerobic organism	*Fusobacterium* spp.	*Fusobacterium nucleatum*
Anaerobic organism	*Fusobacterium* spp.	*Fusobacterium* spp.
Anaerobic organism	*Porphyromonas* spp.	*Porphyromonas asacchrolytica*
Anaerobic organism	*Porphyromonas* spp.	*Porphyromonas gingivalis*
Anaerobic organism	*Porphyromonas* spp.	*Porphyromonas* spp.

Anaerobic organism	*Prevotella* spp.	*Prevotella* spp.
Anaerobic organism	*Anaerococcus* spp.	*Anaerococcus prevotii*
Other bacteria	*Actinomyces* spp.	*Actinomyces* spp.
Other bacteria	*Aerococcus* spp.	*Aerococcus* spp.
Other bacteria	*Aerococcus* spp.	*Aerococcus viridans*
Other bacteria	*Aeromonas* spp.	*Aeromonas caviae*
Other bacteria	*Aeromonas* spp.	*Aeromonas hydrophila*
Other bacteria	*Aeromonas* spp.	*Aeromonas sobria*
Other bacteria	*Aeromonas* spp.	*Aeromonas* spp.
Other bacteria	Aggregatibacter spp.	Aggregatibacter (Actinobacillus) actinomycetemcomitans
Other bacteria	Aggregatibacter spp.	Aggregatibacter (Haemophilus) aphrophilus
Other bacteria	Aggregatibacter spp.	Aggregatibacter aphrophilus (Haemophilus paraphrophilus)
Other bacteria	*Alcaligenes* spp.	*Alcaligenes dentrificans*
Other bacteria	*Alcaligenes* spp.	*Alcaligenes faecalis*
Other bacteria	*Alcaligenes* spp.	*Alcaligenes* spp.
Other bacteria	*Burkholderia* spp.	*Burkholderia cenocepacia*
Other bacteria	*Burkholderia* spp.	*Burkholderia cepacia*
Other bacteria	*Burkholderia* spp.	*Burkholderia cepacia complex*
Other bacteria	*Burkholderia* spp.	*Burkholderia gladioli*
Other bacteria	*Burkholderia* spp.	*Burkholderia multivorans*
Other bacteria	*Burkholderia* spp.	*Burkholderia* spp.
Other bacteria	*Burkholderia* spp.	*Burkholderia stabilis*
Other bacteria	*Burkholderia* spp.	*Burkholderia vietnamiensis*
Other bacteria	*Campylobacter* spp.	*Campylobacter fetus*
Other bacteria	*Campylobacter* spp.	*Campylobacter jejuni*
Other bacteria	*Campylobacter* spp.	*Campylobacter* spp.
Other bacteria	*Cardiobacterium* spp.	*Cardiobacterium hominis*
Other bacteria	*Cardiobacterium* spp.	*Cardiobacterium* spp.
Other bacteria	*Haemophilus* spp.	*Haemophilus influenzae*
Other bacteria	*Haemophilus* spp.	*Haemophilus* spp.
Other bacteria	*Listeria monocytogenes*	*Listeria monocytogenes*
Other bacteria	*Moraxella* spp.	*Moraxella catarrhalis*
Other bacteria	*Moraxella* spp.	*Moraxella lacunata*
Other bacteria	*Moraxella* spp.	*Moraxella osloensis*
Other bacteria	*Moraxella* spp.	*Moraxella spp.*
Other bacteria	*Neisseria gonorrhoeae*	*Neisseria gonorrhoeae*
Other bacteria	*Neisseria meningitidis*	*Neisseria meningitidis*
Other bacteria	*Pasteurella* spp.	*Pasteurella haemolytica*
Other bacteria	*Pasteurella* spp.	*Pasteurella multocida*
Other bacteria	*Pasteurella* spp.	*Pasteurella pneumotropica*
Other bacteria	*Pasteurella* spp.	*Pasteurella* spp.
Other bacteria	*Eikenella* spp.	*Eikenella corrodens*
Other bacteria	*Eikenella* spp.	*Eikenella* spp.
Other bacteria	Any other	*Rhodococcus* spp.

Other bacteria	Any other	*Actinobacillus* spp.
Other bacteria	Any other	*Arcanobacterium haemolyticum*
Other bacteria	Any other	*Aureobacterium* spp.
Other bacteria	Any other	*Capnocytophaga canimorsus*
Other bacteria	Any other	*Elizabethkingia meningoseptica*
Other bacteria	Any other	*Flavobacterium* spp.
Other bacteria	Any other	*Ralstonia mannitolilytica*
Other bacteria	Any other	*Ralstonia pickettii*
Other bacteria	Any other	*Ralstonia* spp.
Other bacteria	Any other	*Shewanella putrefaciens*
Skin commensals other than coagulase negative staph	*Bacillus spp.*	*Bacillus* spp.
Skin commensals other than coagulase negative staph	*Corynebacterium* spp.	*Corynebacterium* spp.
Skin commensals other than coagulase negative staph	*Cutibacterium* spp.	*Cutibacterium acnes*
Skin commensals other than coagulase negative staph	*Rhodococcus* spp.	*Rhodococcus equi*
Skin commensals other than coagulase negative staph	*Rhodococcus* spp.	*Rhodococcus* spp.
Skin commensals other than coagulase negative staph	*Dermabacter* spp.	*Dermbacter hominis*

Appendix table 2. Antibiotic classes

Antibiotic class	**Antibiotic sub-class**	**Antibiotics**
Penicillins	Natural penicillin	Phenoxymethylpenicillin
		Benzylpenicillin
	Penicillinase-resistant penicillin	Flucloxacillin
		Oxacillin
		Methicillin
	Aminopenicillins (+/- beta-lactam inhibitor)	Amoxicillin
		Ampicillin
		Co-amoxiclav
	Mecillinam	Picmecillinam
		Mecillinam
	Anti-pseudomonal penicillin	Piperacillin-tazobactam
		Ticarcillin +/-beta-lactam
	Temocillin	Temocillin
Tetracyclines	First generation	Tetracycline
		Oxytetracycline
	Second generation	Doxycycline
		Lymecycline
	Glycylcyclines	Tigecycline
	Third generation tetracyclines	Eravacycline
		Omadacycline

Cephalosporins	First generation	Cefalexin
		Cefradine
		Cefazolin
	Second generation	Cefuroxime
		Cefaclor
	Third generation (+/- beta-lactamase inhibitor)	
		Ceftriaxone
		Cefotaxime
		Ceftazidime
	Fourth generation (+/- beta-lactamase inhibitor)	Cefepime
	Fifth generation & siderophore	Ceftaroline
		Ceftobiprole
		Ceftolozane-tazobactam
		Cefiderocol
Monobactam		Aztreonam
Carbapenems (+/- beta lactam inhibitors)		Ertapenem
		Meropenem
		Imipenem
Sulfonamides and Trimethoprim		Trimethroprim
		Co-trimoxazole
Macrolide		Azithromycin
		Erythromycin
		Clarithromycin
Lincosamide		Clindamycin
Aminoglycoside		Gentamicin
		Tobramycin
		Amikacin
Quinolone/Fluroquinolone		Nalidixic acid
		Norfloxacin
		Levofloxacin
		Ciprofloxacin
		Moxifloxacin
Glycopeptide		Teicoplanin
		Vancomycin
		Dalbavancin
	Oxazolidinone	Linezolid
	Lipopeptide	Daptomycin
	Phosphonic acid	Fosfomycin
	Polymyxin	Colistin
	Imidazole	Metronidazole
	Nitrofuran	Nitrofurantoin
	Amphenicol	Chloramphenicol
	Rifamycin	Rifampicin

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