Domain-Specific Appendix:
ANTIBIOTIC DOMAIN

REMAP-CAP: Randomized, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia

Antibiotic Domain-Specific Appendix Version 4 dated 5th November, 2024

Summary

In this domain, participants meeting the platform entry criteria with severe community-acquired pneumonia will be randomized to receive one of up to four interventions depending on availability and acceptability:

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Amoxicillin-clavulanate + Macrolide

This domain includes patients aged 18 years and older.

This domain is available in the following States and Strata

Age Stratum	≥ 18 years old	
Illness Severity State	Moderate State	Severe State
Domain-specific strata	N/A	N/A
Interventions specified in this DSA	N/A	• Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Amoxicillin-clavulanate + Macrolide
Interventions submitted for approval in this jurisdiction	N/A	☐ Ceftriaxone + Macrolide ☐ Moxifloxacin or Levofloxacin ☐ Piperacillin-tazobactam + Macrolide ☐ Amoxicillin-clavulanate + Macrolide

Antibiotic Domain Summary	
Interventions	• Ceftriaxone + Macrolide • Moxifloxacin or Levofloxacin • Piperacillin-tazobactam + Macrolide • Amoxicillin-clavulanate + Macrolide
Timing of Reveal	Randomization with Immediate Reveal and Initiation, or Delayed Reveal and Initiation
Population	This domain will be offered to the following patient categories: • Adult Age Stratum • Severe Illness Severity State
Domain-Specific Inclusions	Patients will be eligible for this domain if: • Patient has community-acquired respiratory tract infection • Patient has pneumonia • Empiric antibiotic therapy for bacterial pneumonia is considered appropriate

Domain-Specific Exclusions	Patients will be excluded from this domain if they have any of the following:
	• Received more than 48 hours of intravenous antibiotic treatment for this index illness
	• More than 24 hours has elapsed since commencement of sustained organ failure support
	• A specific antibiotic choice is indicated, for example:
	  ○ Suspected or proven concomitant infection such as meningitis
	  ○ Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with Pseudomonas may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection.
	  ○ Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks).
	  ○ Suspected melioidosis
	  ○ There is specific microbiological information to guide specific antibacterial therapy
	• The treating clinician believes that participation in the domain would not be in the best interests of the patient

Intervention-Specific Exclusions	• Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin • Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone • Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, and ceftriaxone • Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention • Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, and ceftriaxone • Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.
Outcome measures	Primary endpoint: as specified in Core Protocol documents.

	Secondary endpoints refer to Core Protocol documents Secondary Domain-specific endpoints (during index hospitalization censored 90 days from the date of enrollment): • Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae, carbapenem resistant enterobacteriaceae (CRE). • *C. difficile* illness based on detection from feces using current standard of care diagnostics used at site • Serious Adverse Events (SAE) as defined in core protocol
Platform conclusions	The following Platform Conclusions are possible for this domain: • Superiority of any intervention compared with other interventions in this domain • Inferiority of any intervention compared with other interventions in this domain • Equivalence between a pair of interventions
Unit-of-Analysis and Strata	There is a single unit-of-analysis, corresponding to the patients who receive an allocation in this domain. Response Adaptive Randomization will be applied. No other strata contribute to the unit-of-analysis for this domain.
Evaluable treatment-by-treatment Interactions	No interactions will be evaluated with any other domain.
Nesting	There is one nest, comprising the following interventions: • Ceftriaxone + Macrolide • Piperacillin-tazobactam + Macrolide • Amoxicillin-clavulanate + Macrolide

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1. ABBREVIATIONS

ATS	American Thoracic Society
CAP	Community Acquired Pneumonia
C. difficile	*Clostridium difficile*
CVVHF	Continuous Veno-Venous Hemofiltration
COPD	Chronic Obstructive Pulmonary Disease
CRE	Carbapenem Resistant Enterobacteriacae
DSA	Domain-Specific Appendix
DSWG	Domain-Specific Working Group
DSMB	Data Safety and Monitoring Board
eGFR	estimated Glomerular Filtration Rate
ESBL	Extended Spectrum Beta-Lactamase
HIV	Human Immunodeficiency Virus
hMPV	Human Metapneumovirus
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
ITSC	International Trial Steering Committee
IV	Intravenous
MDR	Multi-Drug Resistance
MERS	Middle East Respiratory Syndrome
MRO	Multi-Resistant Organisms
MRSA	Methicillin-Resistant Staphylococcus Aureus
RCT	Randomized Controlled Trial
REMAP	Randomized, Embedded, Multifactorial Adaptive Platform trial
REMAP-CAP	Randomized, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia
RAR	Response Adaptive Randomization
RSA	Region-Specific Appendix
RSV	Respiratory Syncytial Virus
SAE	Serious Adverse Event
VRE	Vancomycin Resistant Enterococci

2. PROTOCOL APPENDIX STRUCTURE

The structure of this protocol is different to that used for conventional trials because this trial is highly adaptive and the description of these adaptations is better understood and specified using a 'modular' protocol design. While, all adaptations are pre-specified, the structure of the protocol is designed to allow the trial to evolve over time, for example by the introduction of new domains or interventions or both (see Glossary, Core Protocol for definitions of these terms) and commencement of the trial in new geographical regions.

The protocol has multiple modules, in brief, comprising a Core Protocol (overview and design features of the study); a Statistical Analysis Appendix (principles of the statistical analysis and models); a Patient, Pathogen and Disease Appendix to the Core Protocol (PANDA); multiple Domain-Specific Appendices (DSA) (detailing all interventions currently being studied in each domain), and multiple Regions-Specific Appendices (RSA) (detailing regional management and governance).

The Core Protocol contains all information that is generic to the trial, irrespective of the regional location in which the trial is conducted and the domains or interventions that are being tested. The Core Protocol may be amended but it is anticipated that such amendments will be infrequent.

The Core Protocol does not contain information about the intervention(s) within each domain, because one of the trial adaptations is that domains and interventions will change over time. Information about interventions within each domain is covered in the relevant DSA. These Appendices are anticipated to change over time, with removal and addition of options within an existing domain, at one level, and removal and addition of entire domains, at another level. Each modification to a DSA will be subject of a separate ethics application for approval.

The Core Protocol does not contain detailed information about the statistical analysis or simulations, because the analysis model will change over time in accordance with the domain and intervention trial adaptations but this information is contained in the Statistical Analysis and Simulations Appendices. These Appendices are anticipated to change over time, as trial adaptations occur. Each modification will be subject to approval from the International Trial Steering Committee (ITSC) in conjunction with advice from the Statistical Design Team and the Data Safety and Monitoring Board (DSMB).

The Core Protocol also does not contain information that is specific to a particular region in which the trial is conducted, as the locations that participate in the trial are also anticipated to increase over time. Information that is specific to each region that conducts the trial is contained within a

RSA. This includes information related to local management, governance, and ethical and regulatory aspects.

The current version of the Core Protocol, DSAs, RSAs and the Statistical Analysis Appendix is listed on the study website.

3. ANTIBIOTIC DOMAIN-SPECIFIC APPENDIX VERSION

The version of the Antibiotic Domain-Specific Appendix is in this document's header and on the cover page.

3.1. Version history

Version 1: Approved by the Antibiotic Domain-Specific Working Group (DSWG) on 18 November 2016

Version 1.1: Approved by the Antibiotic DSWG on 30 March 2017

Version 2: Approved by the Antibiotic DSWG on 12 December 2017

Version 3: Approved by the Antibiotic DSWG on 10 July 2019

Version 4: Approved by the Antibiotic DSWG on 05 November 2024

4. ANTIBIOTIC DOMAIN GOVERNANCE

4.1. Domain members

Chair:

Professor Allen Cheng

Members:

Professor Richard Beasley
Professor Marc Bonten
Dr. Nick Daneman
Dr. Lennie Derde
Dr. Robert Fowler
Associate Professor David Gattas

Professor Anthony Gordon

Mr. Cameron Green

Dr. Thomas Hills

Associate Professor Peter Kruger

Dr. Colin McArthur

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4.2. Contact details

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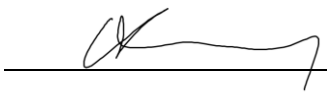
5. ANTIBIOTIC DOMAIN-SPECIFIC WORKING GROUP AUTHORIZATION

The Antibiotic Domain-Specific Working Group (DSWG) have read the appendix and authorize it as the official Antibiotic Domain-Specific Appendix. Signed on behalf of the committee,

Chair
Allen Cheng



Date 5th November, 2024

6. BACKGROUND AND RATIONALE

6.1. Domain definition

This is a domain to test the effectiveness of different empiric antibiotic treatments in hospitalized patients with severe community-acquired pneumonia (CAP) who are admitted to an Intensive Care Unit (ICU).

6.2. Domain-specific background

Antibiotics are an essential component of therapy for all patients with suspected or proven CAP. In patients with sepsis (including pneumonia) who have organ dysfunction, the International Surviving Sepsis Campaign Guidelines recommend initiation of antibiotics within 60 minutes of presentation. (Dellinger et al., 2013)

6.2.1. Microbiology of CAP

In the majority of cases of CAP, no microbiological diagnosis is made. (Charles et al., 2008) In patients in whom a microbiological diagnosis is made, the organism that is isolated most commonly is *Streptococcus pneumoniae.* Other bacteria that cause CAP include *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, and a range of gram-negative organisms. Although studies have demonstrated that clinical features are not specific to bacterial aetiology, the so-called "atypical" pathogens include Legionella species, *Mycoplasma pneumoniae*, and *Chlamydiphila pneumoniae*. Since the advent of sensitive nucleic acid tests, there is an increasing recognition of the role of viral pathogens, particularly influenza viruses and respiratory syncytial virus (RSV), either as the primary pathogen or associated with secondary bacterial pneumonia. (Musher and Thorner, 2014) Pathogens associated with outbreaks include *Legionella* spp, viral pathogens (particularly in closed environments such as cruise ships and institutions) and emerging infectious diseases such as Middle East Respiratory Syndrome (MERS) coronavirus.

Many studies have characterised the microbiological cause of infection in patients with severe CAP and a summary of these has been reported previously. (Mandell et al., 2007, Lim et al., 2009, Musher et al., 2013, Woodhead et al., 2011, Wiersinga et al., 2012) While there are clinically significant differences between studies in healthcare delivery (including criteria for hospital and ICU admission), the population under study and other epidemiological features, and study methodology, the distribution of identified pathogens is remarkably consistent in temperate developed countries.

The results of studies that have reported the microbiology findings in patients with CAP are outlined in Table 1.

Table 1: Distribution of identified pathogens in hospitalized patients with CAP in selected studies

Type of organisms	Australia (2004-2008) (Charles et al., 2008)	Europe (Woodhead, 2002)	United States (Musher et al., 2013)
Gram positive bacteria	*Streptococcus pneumoniae (13.9%)* *Staphylococcus aureus (1.2%)*	*Streptococcus pneumoniae (25.9%)* *Staphylococcus aureus (1.4%)*	*Streptococcus pneumoniae (24.7%)* *Staphylococcus aureus (3.5%)*
Gram negative bacteria	*Haemophilus influenzae (5.1%)* *Pseudomonas aeruginosa (1.6%)* *Enterobacteriaecae (1.5%)* *Moraxella catarrhalis (0.8%)*	*Haemophilus influenza (4.0%)* *Moraxella catarrhalis (2.5%)* *Gram-negative enteric bacteria (2.7%)*	*Haemophilus influenza (4.6%)* *Pseudomonas aeruginosa (2.3%)* *Klebsiella pneumoniae (0.8%)* *Escherichia coli (0.8%)* *Moraxella (0.4%)*
"Atypical"	*Mycoplasma pneumoniae (8.8%)* *Legionella (3.4%)* *Chlamydophila species (1.7%)*	*Legionella* spp*. (4.9%)* *Mycoplasma pneumoniae (7.5%)* *Chlamydia pneumoniae (7.0%)* *Chlamydia psittaci (1.9%)*	
Viral pathogens	*Influenza (7.7%)* *Picornaviruses (5.2%)* *RSV (1.9%)*	*Viruses (10.9%)*	*Rhinovirus (10%)* *Coronavirus (2.7%)* *Parainfluenza virus (1.5%)* *RSV (1.2%)* *hMPV (1.2%)* *Influenza (0.4%)*
Other	*Other pathogens (2.3%)* *Unknown (54.4%)*	*Coxiella burnetii (0.8%)* *Other pathogens (2.2%)* *Unknown (43.8%)*	*Other pathogens (6.9%)* *Unknown (45.9%)*

** More than one pathogen detected in 8.5% of patients, including both a viral and bacterial pathogen in 5.3%*

Drug resistant pathogens are an increasing concern globally. Macrolide resistant pneumococci are of little clinical relevance in patients treated with beta-lactams (Cheng and Jenney, 2016) and it appears that poor outcomes linked to penicillin resistant pneumococci (Tleyjeh et al., 2006) are likely to be attributed to age, underlying disease and severity of illness rather than treatment failure. (Moroney et al., 2001, Yu et al., 2003) Of greater concern is the advent of community-acquired

methicillin resistant *Staphylococcus aureus*, particularly those associated with the Panton Valentine leucocidin. (Rubinstein et al., 2008)

6.2.2.Guidelines recommend a number of different antibiotic treatment options

A "respiratory" quinolone (moxifloxacin or levofloxacin) or combination antimicrobial therapy with a beta-lactam and a macrolide, are both recommended empiric treatment for CAP in national and international guidelines. (Mandell et al., 2000, Mandell et al., 2007, Woodhead et al., 2011) Data, mostly from retrospective observational analyses, report that guideline-concordant therapy is associated with a mortality benefit in CAP (Baudel et al., 2009, Frei et al., 2010), but whether one of these options results in a lower mortality than the other remains an open question. It has been suggested that fluoroquinolone treatment may be optimal for pneumonia due to *Legionella* spp, but randomized clinical trial data are lacking. (Asadi et al., 2012) A summary of different recommendations in guidelines for the treatment of severe CAP is displayed in Table 2.

Table 2: Empiric antibiotic treatments recommendations for patients with severe pneumonia (without risk factors for pseudomonas) requiring intensive care

Guideline	First line	Second line
British Thoracic Society (Lim et al., 2009)	1. Co-amoxiclav AND macrolide (clarithromycin)	1. Cefuroxime or ceftriaxone AND clarithromycin
United States Infectious Diseases Society of America (IDSA)/ the American Thoracic Society (ATS) (Mandell et al., 2007)	1. Cefotaxime, ceftriaxone, or ampicillin-sulbactam AND either (a) azithromycin or (b) a respiratory fluoroquinolone	1. Respiratory fluoroquinolone AND aztreonam
Australia (Antibiotic Expert Groups, 2014)	1. Ceftriaxone AND azithromycin	1. Moxifloxacin
Canada (Mandell et al., 2000)	1. Moxifloxacin or levofloxacin	1. Cefuroxime, ceftriaxone or beta-lactam/beta-lactamase inhibitor AND intravenous (IV) macrolide
Swedish guidelines (Spindler et al., 2012)	1. Cephalosporin AND macrolide 2. Benzylpenicillin AND respiratory fluoroquinolone	
Europe European Society of Clinical Microbiology and Infectious Diseases / European Respiratory	1. Non-antipseudomonal 3rd generation cephalosporin AND macrolide 2. Non-antipseudomonal 3rd generation cephalosporin AND either	

Society (Woodhead et al., 2011)	(a) Moxifloxacin or (b) Levofloxacin	
Netherlands Dutch Working Party on Antibiotic Policy / Dutch Association of Chest Physicians (Wiersinga et al., 2012)	1. Moxifloxacin or levofloxacin 2. Penicillin (or amoxicillin) AND ciprofloxacin 3. 2nd or 3rd generation cephalosporin AND macrolide.	

The most studied interventions for pneumonia have involved antibiotic interventions. A 2008 systematic review that compared respiratory quinolones with beta-lactam and macrolide combinations identified 23 clinical trials that enrolled 7885 patients. (Vardakas et al., 2008) A higher proportion of patients treated with fluoroquinolones had treatment success (defined as clinical cure or improvement) compared with comparator-treated patients (primarily beta-lactam monotherapy and or macrolides), but there were no significant differences in mortality, and the majority of patients in these studies did not have severe pneumonia and were not treated an ICU.

Clinical trials that tested the addition of a macrolide to beta-lactams have not demonstrated clinical benefit. One trial found a shorter time to clinical stability in patients with severe pneumonia although the difference in this small trial was not statistically significant. (Garin et al., 2014) Additionally, there were no differences in other groups or outcomes including length of stay or mortality. A recent cluster randomized trial of beta-lactam monotherapy, beta-lactam and macrolide combination therapy, or fluoroquinolone monotherapy in patients with moderate severity CAP (who were not admitted to ICU at the time of randomization) did not find any differences in mortality or hospital length of stay associated with any strategy. (Postma et al., 2015) A systematic review of antibiotic treatments recommended in the IDSA/ATS guideline did not find any conclusive evidence that “atypical” coverage was associated with better outcomes in clinical trials, although an association with better outcome was found for treatments that included macrolides or quinolones in lower quality observational studies. (Lee et al., 2016)

Most of these studies were performed in hospitalized patients with CAP in whom mortality was relatively low and statistical power limited. Although the available evidence suggests that patients with moderate or severe pneumonia may benefit from atypical coverage, the choice of beta-lactam and whether atypical coverage should include a macrolide (in combination with beta-lactam) or a quinolone (as monotherapy) in severe CAP remains an open question.

6.2.3. There is a diversity of antibiotics used in clinical practice

Current guidelines recommend a number of different antibiotic treatment options and it is likely that others options are also being used at individual hospitals or by individual clinicians.

A survey of Australian and New Zealand ICU specialists indicates that more than 95% administer a beta-lactam antibiotic in combination with a macrolide (azithromycin) for empiric therapy but there is substantial variation in the choice of beta-lactam. The majority of patients receive ceftriaxone, as recommended in Australian guidelines, but one third of ICU specialists use piperacillin-tazobactam (unpublished data from the REMAP-CAP investigators). Although piperacillin-tazobactam has wider microbiological coverage, it penetrates less well into lung tissue, is less potent against pneumococci (the commonest cause of severe CAP), and is predicted to impose increased selection for resistant organisms. (Sime et al., 2012)

In New Zealand, IV amoxicillin-clavulanate and cefuroxime (both not available in Australia as IV formulations currently) are also used widely. A 2013 study found that both second/third generation cephalosporins (58%) and co-amoxiclav (36%) were used in patients with severe pneumonia defined by CURB-65 score. (Aikman et al., 2013)

Studies suggest a wide diversity of antibiotic regimens are used for pneumonia in Europe; the most common antibiotics used included penicillin/beta lactamase inhibitors, macrolides, quinolones and third generation cephalosporins, broad spectrum penicillins and second generation cephalosporins (Ansari et al., 2009, Torres et al., 2014)

6.2.4. Both the efficacy as well as adverse effects of antibiotics need to be considered

RCTs that compare antibiotics to treat infections in ICU patients have demonstrated unexpected differences in mortality. For example, doripenem was associated with a higher mortality than imipenem in patients with ventilator associated pneumonia (Kollef et al., 2012, Yahav et al., 2011) Moreover, the choice of agent may influence the risk of nosocomial super-infection including *Clostridium difficile (C. difficile)*. Despite the ubiquity of the agents used to treat severe CAP in clinical practice there have been no RCTs, conducted in critically ill patients, with sufficient statistical power to detect differences in clinically relevant endpoints. It is imperative that the comparative effectiveness of alternative beta-lactam agents and the role of respiratory quinolones is established, including any differences in acquisition of resistant organisms and *C. difficile.*

6.2.5. All antibiotics used in CAP have a well-established safety profile

Ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate, moxifloxacin and levofloxacin have a long history of use for pneumonia as well as for other indications and are regarded as having a good safety profile. The pharmacokinetics of all drugs may be altered in critically ill patients due to pathophysiological changes including altered volumes of distribution, augmented renal clearance, renal failure and hepatic failure. (Roberts and Lipman, 2009)

Both immediate and delayed hypersensitivity have been described with ceftriaxone, piperacillin-tazobactam, amoxicillin-clavulanate and moxifloxacin, and include rare cases of anaphylaxis, Stevens-Johnson syndrome and toxic epidermal necrolysis. Diarrhea, including that due to *C. difficile*, is a recognized complication of all antibiotic therapy.

Pipericillin-tazobactam and moxifloxacin have been associated with hematological abnormalities, including agranulocytosis, hemolytic anemia and pancytopenia. Amoxicillin-clavulanate has been associated with cholestasis and hepatitis. Moxifloxacin has been associated with a prolonged QT interval and arrhythmias. Pipericillin-tazobactam, ceftaroline and moxifloxacin have been associated with seizures but this is uncommon with doses within current clinical practice guidelines.

6.2.6. Bacterial co-infection or super-infection is more common with influenza than with COVID-19

Bacterial infection as a complication of influenza infection is well recognized, and was thought to be responsible for a significant proportion of the mortality associated with the 1918 pandemic (Morens et al., 2008). A 2016 systematic review of published studies since 1982 reported that overall, around 23% of patients admitted to hospital with influenza had bacterial infection (Morens et al., 2008). However, there was considerably heterogeneity between different studies. Bacterial infection was slightly more common in older people, in patients in ICU and in more recent studies, but these factors did not explain the variation between studies. The most common bacterial pathogens detected *included Streptococcus pneumonia* (35%), *Staphylococcus aureus* (28%), *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Hemophilus influenzae*, *Klebsiella pneumoniae* and *Mycoplasma pneumoniae* (all <10%).

In contrast, bacterial infection appears uncommon in patients with COVID-19. In an early systematic review, the authors estimated that overall, 7% of hospitalized COVID-19 patients had a bacterial co-infection (Lansbury et al., 2020). A higher proportion of ICU patients had bacterial co-infections than patients in mixed ward/ICU settings (14%, vs 4%). However, the rates were lower in studies limited to community-acquired infection, with around 3% of patients found to have bacterial infection on

admission (Langford et al., 2020, Garcia-Vidal et al., 2021). Although NIH treatment guidelines recommend against the [routine] use of empiric broad-spectrum antibiotics in patients with severe or critical COVID-19, they also note that "The use of antibiotics may be considered in specific situations…" and that "the use of antibiotics in patients with severe or critical COVID-19 should follow guidelines established for other hospitalized patients".

6.2.7.Transition from empiric to targeted antibiotic therapy

Microbiological tests identify a causative organism in less than 50% of patients with CAP (Jain et al., 2015). It is almost always the case that empiric antibiotic therapy is commenced before a microbiological diagnosis is available. Standard practice and international guidelines recommend that where a causative organism is identified and antibiotic susceptibilities are available that an antibiotic with a narrow spectrum of action that is active against the infecting organism is substituted for the initial empiric therapy. This domain tests only empiric therapy and the domain intervention is considered complete once microbiological test results are available that can guide appropriate targeted antibiotic therapy or, in the absence of identification of a causative organism for which its antimicrobial susceptibility is known, that sufficient time and clinical improvement have occurred to warrant cessation or de-escalation of initial empiric therapy.

7. DOMAIN OBJECTIVES

The objective of this domain is to determine the effectiveness of different antibiotic therapies for hospitalized patients with severe community-acquired pneumonia.

We hypothesize that the primary endpoint will differ based on the allocated empiric antibiotic treatment. The following interventions will be available:

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Amoxicillin-clavulanate + Macrolide

8. TRIAL DESIGN

8.1. Population

8.1.1. Age Strata

This domain is available to patients who are in the Adult Age Stratum, as defined in Core Protocol documents.

8.1.2. Illness Severity State

This domain is available to patients who are in the Severe Illness Severity State, as defined in Core Protocol documents.

8.1.3. Domain-specific strata

Domain-specific strata are not applied to patients at the time of assessment for this domain.

8.2. Eligibility criteria

Patients are eligible for this domain if they meet all of the platform-level inclusion and none of the platform-level exclusion criteria as specified in relevant core protocol documents. Patients eligible for the Platform may have conditions that exclude them from the Antibiotic Domain.

8.2.1. Domain inclusion criteria

Patients are eligible for this domain if:

- Patient has community-acquired respiratory tract infection
- Patient has pneumonia
- Empiric antibiotic therapy for bacterial pneumonia is considered appropriate

8.2.2. Domain exclusion criteria

Patients will be excluded from this domain if they have any of the following:

- Received more than 48 hours of intravenous antibiotic treatment for this index illness
- More than 24 hours has elapsed since commencement of sustained organ failure support
- A specific antibiotic choice is indicated, for example:
    - Suspected or proven concomitant infection such as meningitis

- Suspected or proven infection with resistant bacteria where agents being trialed would not be expected to be active. This includes cystic fibrosis, bronchiectasis or other chronic suppurative lung disease where infection with *Pseudomonas* may be suspected but does not include patients with suspected methicillin-resistant staphylococcus aureus (MRSA) infection*.
- Febrile neutropenia or significant immunosuppression (including organ or bone marrow transplantation, human immunodeficiency virus (HIV) Infection with CD4 cell count <200 cells/µL, systemic immunosuppressive, systemic corticosteroids comprising prednisolone, or equivalent, ≥20mg/day for > 4 preceding weeks).
- Suspected melioidosis ‡
- There is sufficient microbiological information to guide specific antibacterial therapy

- The treating clinician believes that participation in the domain would not be in the best interests of the patient

* MRSA: Suspected MRSA infection is not an exclusion criterion. If the treating clinician suspects MRSA pneumonia, these patients should be included (see Section 8.3.5).

‡ Melioidosis: Sites in areas where melioidosis is endemic (including Northern Australia and South-East Asia) where antibiotic treatment protocols specify antibiotics active against Burkholderia pseudomallei (e.g., ceftazidime or meropenem) will not participate in this domain. Where antibiotic protocols specify BPS active antibiotics for part of the year (e.g., during the monsoonal season), sites may participate in this domain where BPS specific antibiotics are not indicated.

8.2.3. Intervention exclusion criteria

Prior to the study commencement, sites will select which interventions that patients at their site will be allocated to, based on the current standards of acceptable care, local epidemiology and regulatory status of antibiotics as outlined below.

Patients may also be excluded from receiving one or more interventions within the domain for patient-specific reasons. In such cases, patients will be randomly allocated a remaining intervention from among those available at that site. An example would include patients with a history of a penicillin hypersensitivity, who may receive a cephalosporin or moxifloxacin. Patients may have multiple intervention exclusions (e.g. both a penicillin and a cephalosporin hypersensitivity).

Patients who are eligible for only a single intervention at a site (i.e. all other interventions are contraindicated) are not eligible for this domain. Patients in whom all interventions are contraindicated will be treated according to the current standard of care at the clinician's discretion.

Criteria that exclude a patient from a one or more interventions are:

- Known non-serious hypersensitivity to penicillins will result in exclusion from receiving interventions that include piperacillin and amoxicillin
- Known non-serious hypersensitivity to cephalosporins will result in exclusion from receiving interventions that include ceftriaxone
- Known serious hypersensitivity to beta-lactams, including penicillins or cephalosporins, will result in exclusion from interventions that include piperacillin, amoxicillin, and ceftriaxone
- Known hypersensitivity to moxifloxacin or levofloxacin will result in exclusion from moxifloxacin or levofloxacin intervention
- Known serious hypersensitivity to the macrolide will result in exclusion from interventions that include piperacillin, amoxicillin, and ceftriaxone
- Known or suspected pregnancy will result in exclusion from moxifloxacin or levofloxacin interventions. It is normal clinical practice that women admitted who are in an age group in which pregnancy is possible will have a pregnancy test conducted. The results of such tests will be used to determine interpretation of this exclusion criteria.

8.3. Interventions

8.3.1. Antibiotic interventions

Patients will be randomly assigned to receive one of the following open-label study interventions. The allocated intervention will be commenced immediately after allocation status is revealed.

- Ceftriaxone + Macrolide
- Moxifloxacin or Levofloxacin
- Piperacillin-tazobactam + Macrolide
- Amoxicillin-clavulanate + Macrolide

While it is expected that all sites will participate in the ceftriaxone intervention, each site has the option to opt-in to one or more of the remaining three interventions based on local practice and the availability of the antibiotic in the country. For sites that are including the moxifloxacin or levofloxacin intervention it is strongly encouraged that the sites participate in at least one intervention that includes a cephalosporin and one intervention that includes a penicillin so that

causal inference by random allocation is possible for patients who have known non-serious intolerance to either cephalosporins or penicillins but not both. All patients receiving ceftriaxone, piperacillin-tazobactam, or amoxicillin-clavulanate will also receive a macrolide. Patients allocated to the moxifloxacin or levofloxacin intervention will not receive a macrolide or any beta-lactam or monobactam agent.

8.3.2. Recommended antibiotic dosing

The doses specified below are recommended minimum doses and may be modified according to local guidelines or practice.

- Ceftriaxone ≥1 gram administered intravenously (IV) once daily
- Moxifloxacin 400mg administered IV once daily, or Levofloxacin 750mg IV q24h
- Piperacillin-tazobactam ≥4.5 grams administered IV every 8 hours
- Amoxicillin-clavulanate ≥1200mg administered IV every 8 hours

If no local guidelines exist, it is recommended that subsequent doses of antibiotics will be adjusted for estimated renal function (based on estimated Glomerular Filtration Rate (eGFR)) as follows:

Table 3: Minimum doses of antibiotics, by eGFR

Agent	eGFR >50 ml/min	eGFR 10-50 ml/min	eGFR <10	Receiving CVVHF
Ceftriaxone	1g-2g IV daily	1g-2g IV daily	1g IV daily	1g IV daily
Piperacillin-tazobactam	4.5g IV q6h	(eGFR 20-40) 4.5g IV q8h	(eGFR <20) 4.5g IV q12h	4.5g IV q8h
Amoxicillin-clavulanate	1200mg IV q8h	1200mg IV q8h	1200mg IV q12h	1200mg IV q8h
Moxifloxacin	400mg IV q24h	400mg IV q24h	400mg IV q24h	400mg IV q24h
Levofloxacin	750mg IV q24h	(eGFR 20-50) 750mg IV load, 750mg IV q48h	(eGFR<20) 750mg IV load, 500mg IV q48hr	750mg IV load, 500mg IV q48hr

It is permitted to provide these antibiotics via intermittent, prolonged, or continuous infusion. If administered by continuous infusion, the recommended daily dosing is the cumulative dose given in a 24-hour period in the intermittent IV dosing regimens outlined above.

8.3.3. Timing of initiation of antibiotics

In keeping with all international guidelines optimized empiric antibiotic treatment should commence as soon as possible. As such, most patients who receive an allocation within this domain will have already received empiric antibiotic therapy prior to enrollment. The allocated intervention should be commenced immediately after reveal of allocation.

8.3.4. Duration of administration of antibiotics

The duration of empiric antibiotics will be determined by the treating clinician based on daily reviews of the following criteria:

- Change to enteral antibiotics once patient is clinically stable
- Change to a targeted antibiotic therapy if a microbiological diagnosis has been made
- Cease antibiotics if an alternative diagnosis is made
- Cease antibiotics when there is evidence of sufficient clinical improvement, no microbiological diagnosis has been made and no clinical evidence of deep infection (e.g. empyema or lung abscess). The duration of antibiotic therapy will be decided by the treating clinician and local guidelines.
- Discontinuation if the patient experiences a serious adverse event (SAE) that is thought to be related to a study drug

8.3.5. Choice of macrolide

The choice of macrolide will depend on the availability and acceptability of the agents at each site in the following order of preference;

1. IV azithromycin, with switch to enteral azithromycin when appropriate
2. IV clarithromycin, with switch to enteral azithromycin when appropriate
3. Enteral azithromycin
4. Enteral clarithromycin or roxithromycin
5. IV or enteral erythromycin. Sites in which only erythromycin is available are not able to participate in the Macrolide Duration Domain.

Vancomycin, linezolid or other antimicrobials active against MRSA may be added if MRSA is suspected at the discretion of the treating clinician, irrespective of the intervention to which the participant is allocated.

8.3.6. Discontinuation of study intervention

Antibiotic therapy should be discontinued if there is development of a SAE which, in the opinion of the treating clinician, could be related to participation in this domain. The study interventions can be temporarily or permanently discontinued at any time by the treating clinician if doing so is regarded as being in the best interests of the patient.

8.4. Concomitant care

Additional non-beta-lactam antibacterial agents, such as vancomycin, gentamicin, clindamycin or cotrimoxazole, will be permitted at the discretion of the treating clinician. Other beta-lactams, carbapenems (meropenem, imipenem, doripenem, ertapenem), monobactams (aztreonam) and quinolones are not permitted at study enrollment, but a change to these agents is permitted if clinical cultures are positive for a resistant pathogen that necessitates commencement of one of these agents. Administration of an influenza antiviral agent (i.e. oseltamivir) will also be permitted in patients with suspected or confirmed influenza.

Any subsequent change of antibiotics, based on availability of microbiological data, will be permitted at the treating clinician's discretion. All other treatment that is not specified by assignment within the platform will be determined by the treating clinician.

8.5. Endpoints

8.5.1. Primary endpoint

The primary endpoint for this domain is the primary outcome specified in the Core Protocol.

8.5.2. Secondary endpoints

All secondary endpoints as specified in the Core Protocol.

The domain-specific secondary outcome measures (occurring during the index hospitalization, censored at 90 days after enrollment) will be:

- Multi-resistant organisms (MRO) colonization/infection: Isolation of multi-drug resistant (MDR) bacteria from clinical or screening specimens including vancomycin resistant enterococci (VRE), MRSA, extended spectrum beta-lactamase (ESBL)-producing enterobacteriaceae, carbapenem resistant enterobacteriaceae (CRE).

- *C. difficile* illness based on detection from feces using current standard of care diagnostics used at site
- Serious adverse event (SAE) as defined in Core Protocol

Table 4: Organisms of interest as baseline or outcome measures

Site	Organisms of interest
Blood, lower respiratory tract (endotracheal suction, bronchoalveolar lavage, sputum), Pleural fluid (e.g. pleural aspirate, chest drain)	*Staphylococcus aureus* *Streptococcus pyogenes*, or *S. pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis* Enterobacteriacae** *Acinetobacter* spp. *Pseudomonas* spp.
Multi resistant organisms from any clinical or screening* site	VRE, MRSA, ESBL- producing Escherichia coli or Klebsiella spp Carbapenem-resistant gram-negative

*screening specimens include fecal/rectal swabs, swabs of intact skin or nose

**Enterobacteriaceae includes *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp.

9. TRIAL CONDUCT

9.1. Microbiology

Isolates will be tested for susceptibility to study antibiotics using routine clinical testing. Specific isolates may be referred to a reference laboratory according to current clinical practice

9.2. Domain-specific data collection

Additional domain-specific data will be collected.

- Isolation or detection of MROs
- *C. difficile* isolation from feces

9.3. Criteria for discontinuation

Refer to Core Protocol documents for criteria for discontinuation of participation in this trial.

9.4. Blinding

All antibiotics will be administered on an open-label basis.

10.STATISTICAL CONSIDERATIONS

10.1. Domain-specific stopping rules

The following Platform Conclusions are possible in this domain:

- Superiority for any intervention within the domain
- Inferiority for any intervention within the domain
- Equivalence for any pair of interventions within the domain

All interventions within this domain are within the spectrum of accepted standard care. Consideration was given as to whether a harm trigger should be applied but this was not done as there was consensus within the Antibiotic DSWG that it was likely that a change in practice or guidelines would require demonstration of inferiority.

It is noted that an inferiority trigger is possible without an accompanying superiority trigger. If this was to occur a Platform Conclusion would be declared and the result reported, as rapidly as possible, with the option of reporting the treatment effect of the inferior intervention in comparison to either pooled results from other interventions (which preserve blinding among ongoing interventions) or in comparison to one or more identified interventions (with loss of blinding among ongoing interventions).

If a trigger occurs for inferiority when two or more additional interventions remain within the randomization schedule, the inferior intervention will be removed from the randomization schedule and will be subject of public disclosure. It is noted that public disclosure may also require identification of the active intervention against which the inferiority trigger occurred.

If a Platform Conclusion of equivalence in the primary endpoint is demonstrated the DSMB and the ITSC may consider continuation of randomization if clinically relevant differences in secondary endpoints have not been demonstrated and it is considered plausible that clinically relevant differences in one or more secondary endpoints may be capable of being demonstrated. In all other respects the stopping rules for this domain are those outlined in the Core Protocol documents.

10.2. Unit-of-analysis and strata

The unit-of-analysis for this domain is all patients who receive an allocation status in this domain. No strata are applied in the model, although this may be modified as an operational decision as specified in the Current State document.

10.3. Application of Response-Adaptive Randomization

Response-adaptive randomization will be applied to this domain.

10.4. Timing of revealing of randomization status

The timing of the revealing of allocation status and administration of interventions is specified to be Randomization with Immediate Reveal and Initiation, or Randomization with Deferred Reveal and Initiation if prospective agreement is required for participation in this domain.

10.5. Interactions with interventions in other domains

Interactions with all other domains are either not evaluable or are not considered possible and will not be incorporated into the statistical model or models in which the domain is evaluated.

If an interaction is specified with a future domain, it is sufficient for the interaction to be specified only in the DSA of a future domain.

10.6. Nesting of interventions

There is one nest within this domain, comprising ceftriaxone + macrolide, piperacillin-tazobactam + macrolide, and amoxicillin-clavulanate + macrolide interventions. The rationale for this is that each of these interventions comprises a beta-lactam antibiotic combined with a macrolide. The Macrolide component contributes to all interventions and the beta-lactam agents are all members of the same class of antibiotic.

10.7. Threshold probability for superiority and inferiority

The threshold probability for statistical triggers for superiority and inferiority are those specified in the Core Protocol documents.

10.8. Threshold odds ratio delta for equivalence

If two interventions within a domain, for a unit-of-analysis, have at least a 0.90 probability of being within a pre-specified delta for the primary endpoint then these interventions will be deemed as being equivalent. The size of the pre-specified odds ratio delta is 0.10.

10.9. Informative priors

This domain will launch with priors that are uninformative for main effects.

10.10. Post-trial sub-groups

Domain-specific post-hoc sub-groups will be used in analysis following the conclusion of one or more interventions within the domain. The *a priori* patient sub-groups of interest are:

- The microbiologic diagnosis
- Risk factors for aspiration pneumonia
- Age
- Chronic Obstructive Pulmonary Disease (COPD)
- Influenza strata
- All potentially evaluable treatment-by-treatment interactions with other domains

11. ETHICAL CONSIDERATIONS

11.1. Data Safety and Monitoring Board

The DSMB is convened under the guidance provided in the Core Protocol and DSMB Charter. The statistical triggers that apply to this domain are specified in this DSA. If requested by the DSMB, domain-specific safety secondary endpoints will be provided to the DSMB as part of the regular safety reports.

11.2. Potential domain-specific adverse events

The antibiotics used in this domain largely have a known toxicity profile. Additionally, it is expected that a high proportion of critically ill patients who will be enrolled in this trial will experience mortality or substantial morbidity. There are no specified domain-specific adverse events.

Other SAEs should be reported only where, in the opinion of the site-investigator, the event might reasonably have occurred as a consequence of a study intervention or study participation (see relevant Core Protocol documents).

11.3. Domain risk assessment

All the antibiotics to be tested in this domain are approved for this indication or are in common use in many countries for CAP or both. Sites will be able to opt out of interventions for all patients at that site if they believe that an intervention is not part of reasonable care of patients with pneumonia, or are not approved for use in the country, or conflict with local antimicrobial stewardship considerations. Additionally, clinicians may choose not to enroll individual patients if they feel that participation is not in the patient's best interests, and safety criteria are used to exclude patients from individual interventions for appropriate clinical reasons (e.g. hypersensitivity to one or more study drugs).

Where all interventions that are available at the participating site are regarded as being part of the acceptable spectrum of standard care and given the time imperative to commence antibiotics, entry to the study, for participants who are not competent to consent, is preferred to be via waiver-of-consent or some form of delayed consent.

Pregnant women are susceptible to pneumonia and a number of different antibiotics, including amoxicillin-clavulanate and ceftriaxone, are widely used and have a track record of safety in this population. Pregnant women will be excluded from the moxifloxacin and interventions.

11.4. Domain-specific consent issues

For patients who are not competent to consent, and where permitted in accordance with local jurisdictional requirements, entry into this domain is preferred to be via waiver-of-consent or some form of delayed consent. In any jurisdiction in which prospective agreement is necessary, reveal of assignment status will only occur after prospective agreement has been obtained.

During a pandemic visiting by relatives of affected patients may not be possible. In such situations, alternative methods for confirming consent including electronic and telephone communication, as permitted by an appropriate ethical review body, may be acceptable methods for confirming agreement to participate in this (and other) domains of the platform.

12.GOVERNANCE ISSUES

12.1. Funding of domain

Funding sources for the Platform are specified in the Core Protocol domain. This domain has not received any additional domain-specific funding but such funding, from any source, may be obtained during the life-time of the domain.

12.2. Funding of domain interventions and outcome measures

Domain interventions will be provided by participating hospitals. The interventions specified in this domain are part of the spectrum of standard care and are known to be inexpensive.

12.3. Domain-specific declarations of interest

A registry of interested for all members of the International Trial Steering Committee is maintained on the trial website. These are updated periodically and publicly accessible.

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