MBIRA study dataset – supporting documentation

December 2022

The name of the study MBIRA is an acronym for **M**ortality from **B**acterial **I**nfections **R**esistant to **A**ntibiotics. An mbira is also a “thumb piano”, played as a musical instrument across southern Africa.

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This document is intended as a high-level introduction the datasets from the MBIRA study, to facilitate understanding of the study for anyone wishing to make use of these data. These data are made public to allow independent re-use of the relevant data for other analyses through the LSHTM Data Compass site.

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December 2022.

1. Background to MBIRA study

Antimicrobial resistance is a major public health problem of the 21st Century. A key challenge for tackling this problem is that it is difficult for policy-makers in Low and Middle Income Countries (LMIC) to make a connection between high rates of antimicrobial resistance in bacteria and patient-level outcomes, such as risk of death (mortality) and prolonged or additional hospital admissions (morbidity). This disconnection is due, in part, to the lack of local research work in LMIC that makes a connection between microbiological measurement of antibiotic resistance in laboratories and patient-level clinical impacts in wards and clinics. For more extensive background information, see the literature review section in the study protocol document.

The MBIRA study aimed to make a first multi-national attempt to bridge this gap between laboratory information on antibiotic resistance and clinical outcomes in sub-Saharan African countries. The study included patients from hospitals across multiple different African countries in 2020-2022. The project was focussed on bloodstream infections (=bacteraemia) caused by Gram-negative enteric bacteria (Enterobacteria, such as *E. coli* and *Klebsiella pneumoniae*) and included patients of all age groups, from neonates to adults. The MBIRA study was **purely observational**, with the intention of only measuring what normally happens in routine clinical activity in the participating hospitals. The participating hospitals / academic institutions were:

Site, country	Level of facility	Anticipated main support for blood cultures
Tygerberg Hospital / Stellenbosch University, South Africa	Tertiary hospital	Government
Kilifi District Hospital / KEMRI-Wellcome Research Programme, Kilifi, Kenya	District Hospital	Research programme
Korle Bu Hospital / University of Accra, Accra, Ghana	Tertiary hospital	Government+ Fleming Fund
National Hospital, Abuja, Nigeria	Tertiary hospital	Government
Hiwot Fana Hospital, Harar, Ethiopia / Haramaya University	Tertiary hospital	Research programme
Kilimajaro Christian Medical Centre / Kilimanjaro Clinical Research Institute, Moshi, Tanzania	Tertiary hospital	Government+ Fleming Fund
University Teaching Hospital, Lusaka, Zambia / Centre for Infectious Diseases Research, Zambia	Tertiary Hospital	Government+ Fleming Fund
Queen Elizabeth Hospital, Blantyre, Malawi / Malawi-Liverpool-Wellcome Research Program	Tertiary hospital	Research programme

The MBIRA study was funded by the Bill+Melinda Gates Foundation and was led by researchers at the London School of Hygiene and Tropical Medicine in the UK. This current study was the second part of the MBIRA study work – an initial pilot study was conducted in 2017-18, using historical laboratory and clinical data from 6 African hospitals, 3 of which have continued to participate in this current MBIRA study (pilot study manuscripts published Jan 2021 see https://academic.oup.com/jacamr/article/3/1/dlaa130/6104122). A second pilot study manuscript describing prospective data collection in one hospital in South African only was published in Jan 2022 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9200643/pdf/main.pdf).

A cohort description study is planned for submission to the Gates Open Research journal – this paper describes the circumstances at the 8 participating hospitals that relate to treatment and control of Enterobacterales infections. A paper describing the impacts of 3rd generation cephalosporin resistance as a main exposure is planned.

2. MBIRA study structure

Preliminary work in the MBIRA study involved collection of information about hospitals and access to antibiotics. These data are captured at hospital level, either as one-off or repeated monthly data collections. The study site used as the identification in these data is replicated in later work.

The main work in the MBIRA study revolved around identification of patients with positive blood cultures and recording information on their antibiotic treatment and outcomes. Any patient with a blood culture (taken for routine clinical diagnostic purposes) that was **positive for any bacterial species within the Enterobacterales order** (other than Salmonella species) was eligible for inclusion. Each patient with a positive blood culture (a bacteraemia patient) was typically matched to 2 comparison patients without currently-known bacteraemia (matching patients) who were in hospital at a similar time, to form groups of 3 patients ("triads"). The non-infected patients are included in the study to allow us to adjust for other factors causing ill-health in the hospitalized population. All of these patients were followed up together for a period of up to 30 days or their eventual discharge from hospital, whichever was the later.

3. Main study reference number format

For individual patients in the MBIRA study, we used a unique study reference number for tracking the participating patients. The names of these patients is not recorded electronically for purposes of preserving confidentiality. The MBIRA study reference number (the Study ID) has the following format:

Study ID = ☐☐-☐☐☐☐-☐☐ (all in digits)

This first part of the study ID relates to the study site, and was always the same in that site for the duration of the study. The numbers are as follows

01	South Africa
04	Nigeria/Abuja
05	Kenya
06	Ghana
08	Ethiopia
09	Tanzania
10	Zambia
11	Malawi

This second part of the study ID relates to the "triad" of patients – one bacteraemia case and their corresponding matched uninfected patients. These numbers were assigned sequentially, starting from 0001 for the first "triad" in each site

This third part of the study ID relates to the "type" of patient.

00 = bacteraemia patient
01 = match #1
02 = match #2
03 = match #3 (if needed)
04 = match #4 (if needed)
…

The bacteraemia patient in each triad is number 00. Normally, we aimed to match each bacteraemia case to 2 non-infected patients – the first two matches approached were assigned as 01 and 02. Occasionally, a 3rd or a 4th matched patient was included in the study.

4. Inclusion + exclusion criteria for bacteraemic patients in MBIRA

Inclusion criteria

All consecutive patients identified to have proven bacteraemia caused by species of Enteric bacteria (technically, bacteria in the Enterobacterales order – typically E. coli and K. pneumoniae, but many other minor species) were eligible to participate in this study were included, if possible. Patients with bacteraemia caused by Salmonella species (either Salmonella typhoid or non-typhoidal Salmonella species) were **not** eligible for inclusion.

All age-groups were eligible, from neonates through to adults.

Note that blood cultures typically take 2-3 days between collection from a patient and identification of the bacteria – this is because the culture are based on bacterial growth, which typically takes at least 24hrs. Patients who had died in the interval between blood culture collection and a positive identification of a suitable pathogenic bacteria **were still eligible for inclusion in the study** and were retrospectively included where-ever possible.

Exclusion criteria

Repeat isolation of same organism in same patient. A repeat positive blood culture of the same species within 30 days of a previous positive blood culture was not eligible for inclusion as a new study patient – we considered this to represent a recurrence of incompletely treated infection rather than a new disease episode.

Outpatients. The MBIRA study requires that patients with bacteraemia are hospital inpatients. A positive blood culture for an individual who was not a hospital inpatient at the time the blood culture was collected was therefore not eligible to be included in the study.

Mixed pathogens. Where there are 2 or more recognized different pathogens identified in the same blood culture sample (including 1 enterobacteria and 1 or more other non-enterobacteria pathogen), these bacteraemic individuals were not eligible for inclusion in the MBIRA study. These patients were excluded because it would be too difficult to interpret impacts arising from these mixed infections. We did include bacteraemia patients where there is a mixture of 2 or more different enterobacteria (eg *E.coli* and *K.pneumoniae* in same blood culture) – we called this polymicrobial bacteraemia - or an enterobacteria and a recognized contaminant species (eg. coagulase-negative Staphylococci).

5. Matching non-infected inpatients in MBIRA study

A key feature of the MBIRA study was the matching of infected patients with bacteraemia to otherwise similar hospital inpatients who did not (as far as we know) have bacteraemia. This matching process allowed us to establish a "baseline" risk of mortality and duration of hospital admission in what should be otherwise similar hospital inpatients.

The principle for matching was that the non-infected patients were picked such that they were matched to the patient with bacteraemia, in terms of

- **Time-period of admission** – i.e. they were admitted to hospital on an approximately similar date as the bacteraemia case (within 2 weeks before or after by calendar date is ideal, though longer periods than this are acceptable). This criterion was flexible if the bacteraemia patient has a long admission prior to a positive blood culture – the matching patients were "as close as possible" in terms of date of admission.
- **Hospital location at recruitment**. For example, if the bacteraemia case patient was currently in the Paediatrics ward at time of enrolment into the study, the matching patients was recruited from the same ward.
- **Age category** (grouped as neonate (0-28 days) / infant (29-364 days) / child (1 – 14 yrs)/ adult (>14yrs)). For example, if the bacteraemia case was an infant, only infants are eligible to be matches. It was acceptable in some circumstances for a patient in an "adjacent" age category to be included (eg. for an "infant" bacteraemia case to be matched to a "neonate" or "child" who is close in age).
- **Time-in-hospital**. This was the most difficult part of the matching process. This means that at time of recruitment, a potential matching patient must have been in hospital for at least as long as the time from admission to development of bacteraemia (defined as the day the blood culture was collected) in the corresponding bacteraemia case.

Sex of patient was not a matching criteria, so in a mixed sex ward, a bacteraemia patient could be matched to a patient of a different sex.

Patients had to be alive **at time of selection** for being potential matches in the MBIRA study – we did not attempt to include patients who were already deceased when selecting potential matches.

Exclusion criteria for potential matching patients – patients known to have bacteraemia (any form of disease-causing bacteria) at any point in their hospital admission were not eligible for inclusion, but patients with any other form of infection (eg. pneumonia, UTI, suspected "sepsis", chronic infections such as TB or HIV) were eligible to be in the study. Patients that have already died are not eligible for matching (as above), but patients that are severely unwell can be approached for matching if eligible based on above criteria.

If there were >2 potential matches available, the matching patients were **selected at random** from the available patients. We suggested use of the "Random: All Things Generator" app to choose between patients.

7. Overview of dataset

In the MBIRA study, we collected data about hospitals, patients, bacterial isolates and antibiotic use. The main CRF that was used for the study is attached as Appendix 3 at the end of this document, two other forms are given as Appendix 1 and 2. The individual variables that correspond to the main CRF are described in the accompanying data dictionary file.

In brief, the dataset is divided into four parts, as five separate data tables. The study ID (as described above) is the linking variable for the parts of the study relating to human participants – one human individual always has the same study ID.

The four parts are as follows

1. The hospital-level data – this is in the form of two small data tables. One relates to the "hospital form" (a one-off data collection, see Appendix 1) and the second relates to the "antibiotic form" (repeated monthly collection of data about antibiotic availability in pharmacies, see Appendix 2). These are two small data tables (mbira_hospital.xls and mbira_pharmacy.xls) that are in the form of excel spreadsheets.

2. The "combined" data table (mbira_combined.dta) – this is the main summary table for clinical individual-specific information, including relevant key dates (admission, discharge, blood culture), clinical descriptors and outcome data. These are types of data where there is only one occurrence of the information for this patient. This table does include some summary information that is generated by use of data from the other tables, principally the concordancy of antibiotic use in the first two days of BSI treatment. Both BSI and matched patients both have rows of data in this table. BSI patients and matching patients are grouped together by their study numbers and other variables. All BSI patients have at least one matched patient; there are no solitary BSI patients without matches nor uninfected patients that are not matched to a BSI patient.

3. The "species" data table (mbira_species.dta). This is the information for the microbiology laboratory work from the study. Most individuals with BSI in the study have one row in this table, but a minority (about 5%) have polymicrobial (ie 2 different enterobacterales bacteria) infection, so have two rows. This table combines data from the local study laboratory (in each site) with the study reference laboratory (in South Africa) – the variables are appended with _local and _ref respectively. There is information for antibiotic susceptibility testing, both in terms of raw results (eg zone size diameters, MIC values) and also for interpretations based on CLSI criteria. Matched patients without infection do not have rows in this table.

4. The "antibiotic" data table (mbira_antibiotic.dta). This is the information for the use of antibiotic drugs in the study. Each row of this table represents the use of one antibiotic drug for one day for one BSI patient, so most BSI patients have multiple rows. We limited the range of data collection to antibiotic drugs (excluding anti-TB, anti-HIV and anti-fungal agents) and for just between day -1 to day 30 where date of blood culture collection = day 0. This table includes dose of drug and a judgement on whether the antibiotic use was "appropriate" (or concordant) for this individual patient (ie corresponds to in vitro laboratory testing sensitivities). Matched patients do not have data in this table.

8. Introduction to appropriate-ness of antibiotic use in MBIRA

One of the main research questions of the MBIRA study was to examine how the appropriate-ness (or concordancy) of use of antibiotics, in terms of antibiotic drug being used, related laboratory testing results.

There are many different aspects of whether antibiotic use is appropriate, including

1. Suitable antibiotic drug for empirical treatment of an infection "syndrome" in a certain age group
2. Suitable antibiotic drug for an identified bacterial pathogen, based on antibiotic resistance tests
3. Suitable dosing of antibiotic drug for this patient, based on their weight, renal function, other factors
4. Suitable route of administration of antibiotic drug – intra-venous versus oral versus other
5. Suitable timing of the first (and subsequent) doses of antibiotics from onset of illness
6. Suitable duration of antibiotic use, in terms of overall number of days of (effective) therapy
7. Suitable choice of agent, based on local availability, costs, antibiotic usage guidelines/policies

And there are other aspects of appropriate use of antibiotics in addition to these.

We were not able to assess all of these in this study, but rather focussed on aspect "2", with some attention also to aspects "3", "6" and "7". Individual staff members at each site examined the individual antibiotic use for each patient and compared it to local antibiotic susceptibility testing results. Later, once the reference laboratory testing had been performed, these scorings were checked and updated as needed by another investigator.

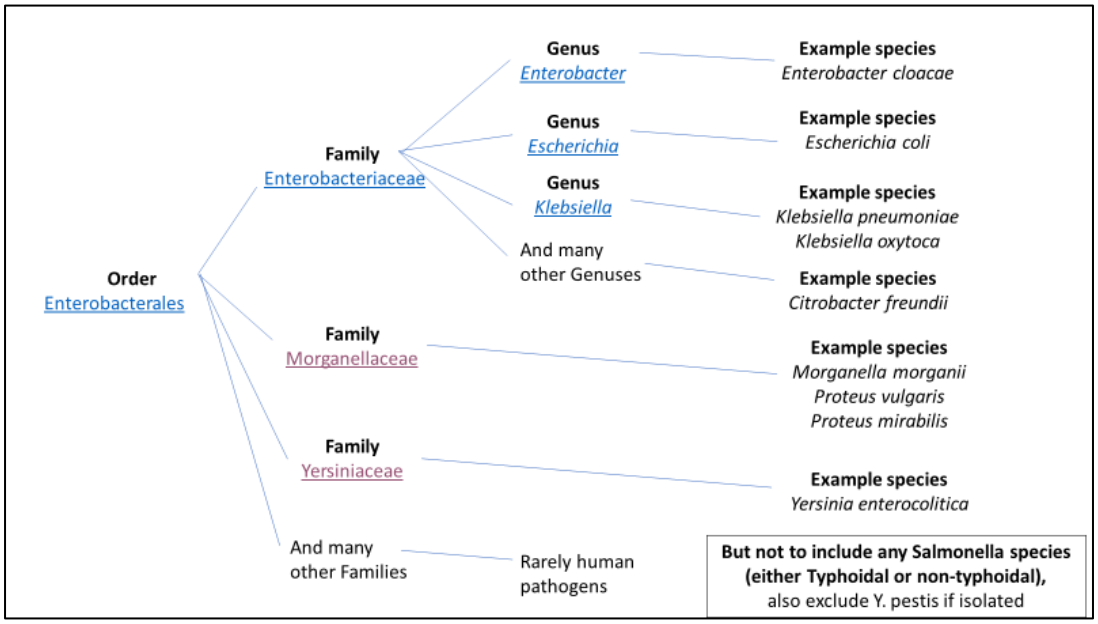
For more extensive discussion and description of how this "antibiotic appropriate-ness" part of the MBIRA study was conducted, please see the longer document "MBIRA study: Guide to scoring appropriate-ness of antibiotic use, v1.1", which is now included as Appendix 4 of this document.

9. Microbiology work in MBIRA

In the MBIRA study, we recognize the challenges faced in many African hospital microbiology laboratories.

The study reference laboratory in Stellenbosch University in South Africa used VITEK2 machines for performing identification and AST. This included generating MIC results for susceptibility tests, interpreted according to CLSI criteria.

The bacterial species of interest in this study were all bacteria identified from clinical blood cultures within the order Enterobacterales. Typically, the most common bacterial species in this order are *E.coli* and *K.pneumoniae* (in the Enterobacteriaceae family), but other bacteria that are in this category are other species of Klebsiella, Proteus species, Enterobacter species, Citrobacter species, Morganella species and various other less common organisms. The classification hierarchy is shown below



We excluded polymicrobial infections from the study when one Enterobacterales infection was found in conjunction with another pathogenic organism in the same blood culture. If an Enterobacterales infection was found with a contaminating organism, that BSI was eligible for inclusion. Individual sites made local decision about what represented pathogens versus contaminants. We recommended the following table as a starting point for determining whether organism isolated is a pathogen or contaminant (from Ombelet et al, "Best Practices of Blood Cultures in Low and Middle Income Countries", 2019).

TABLE 1 | Examples of common bacterial species grown in blood cultures.

	Gram-positive		Gram-negative		Yeast
	Pathogen	**Contaminant**	**Pathogen**	**Contaminant**	**Pathogen**
Aerobic		*Bacillus* species	*Pseudomonas aeruginosa* *Burkholderia pseudomallei* *Acinetobacter* species	*Stenotrophomonas maltophilia** *Pseudomonas* species (non-aeruginosa)*	*Cryptococcus neoformans*
Anaerobic	*Clostridium* species	*Cutibacterium acnes*	*Bacteroides* species		
Facultative /aero-tolerant	*Streptococcus pneumoniae* *Staphylococcus aureus*	Coagulase-negative *Staphylococcus* spp. *Micrococcus* species	*Escherichia coli* *Klebsiella pneumoniae* Non-typhoidal *Salmonella* *Salmonella* Typhi		*Candida albicans* *Candida glabrata*

*Uncertainty of interpretation according to current literature.

Appendix 1. Hospital form from MBIRA study

Appendix 2. Pharmacy form from MBIRA study

Appendix 3. Case Record Form (CRF) template from MBIRA study

Appendix 4 “MBIRA study: Guide to scoring appropriate-ness of antibiotic use, v1.1”

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Hospital Survey

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Hospital profile survey

Date of hospital survey started ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy

Date of hospital survey completed ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy

Staff contributing to completion of this survey:		
Name:		Research Nurse ☐ Laboratory Scientist ☐ Clinician ☐ Other ☐ _____
Name:		Research Nurse ☐ Laboratory Scientist ☐ Clinician ☐ Other ☐ _____
Name:		Research Nurse ☐ Laboratory Scientist ☐ Clinician ☐ Other ☐ _____
Name:		Research Nurse ☐ Laboratory Scientist ☐ Clinician ☐ Other ☐ _____

Hospital characteristics

Full physical address

Urban or rural ? **Urban** ☐ **Rural** ☐ **Mixed urban and rural** ☐

Hospital type ? **Public (Government funded)** ☐ **Private, not-for-profit (inc mission)** ☐
Private, for-profit, ☐ **Other** ☐ **describe** _____

Hospital level
District Hospital ☐
Tertiary/Referral/Regional Hospital ☐
Quaternary/ National Hospital ☐

Hospital total beds + cots total _____ **as of date of survey, include both acute and non-acute beds**

Total ICU beds _____ **Level of ICU care: level 1** ☐ **Level 2** ☐ **Level 3** ☐ **unable to determine** ☐
Paediatric ICU beds/cots _____ **Level of ICU care: level 1** ☐ **Level 2** ☐ **Level 3** ☐ **unable to determine** ☐
NICU cots _____ **Level of ICU care: level 1** ☐ **Level 2** ☐ **Level 3** ☐ **unable to determine** ☐

For description of ICU levels of care, see excerpt table from Marshall JC, J Crit Care Med 2017 next page

Total hospital admissions in 2019 (round 1) or 2020 (round 2) _____ **from 1st Jan to 31st Dec for relevant year**

Total hospital inpatient-days in 2019 (round 1) or 2020 (round 2) _____ **from 1st Jan to 31st Dec for relevant year**

For determining level of ICU care, please refer to Table 2 below, from the publication "What is an intensive care unit? A report of the task force of the World Federation of Societies of Intensive and Critical Care Medicine" Marshal JC et al, J Crit Care Med, 2017.

Table 2
A proposed classification of ICUs.

	Level 1	Level 2	Level 3
Therapeutic capacity	Physiologic stabilization and short-term support of mild organ dysfunction	Basic support of failing organ function	Complex, comprehensive support and management of organ dysfunction
Personnel	Physicians with some experience in critical care available at least during the day	Physicians with ICU training or comparable experience present during day and available at night	Physicians with formal ICU training on call 24/7; immediate in-hospital availability of medical staff with ICU experience
	Experienced nurses provide 24/7 care	Nurses have extra training or comparable experience in critical care and provide 24/7 care	Nursing staff with specialist ICU training provide 24/7 care
	Other personnel available	Variable inclusion of allied health personnel—respiratory therapists, physiotherapists, dieticians, pharmacists, etc—as part of ICU care team	Allied health personnel—respiratory therapists, physiotherapists, pharmacists, dieticians, etc—as regular members of ICU team
	Nurse-patient ratio higher than on ward; preferably 1:4 or 1:3 (1 nurse for 4 patients)	Nurse-patient ratio appropriate to patient needs but usually no less than 1:3	Nurse-patient ratio appropriate to patient needs and no less than 1:2
	Daily rounds; ad hoc structure	Formal daily ICU rounds with physicians and nurses	Formal multidisciplinary ICU rounds daily and as needed based on patient complexity and acuity
	Variable engagement in critical care continuing professional education	Engagement in continuing professional education	Regular engagement in continuing medical/nursing education
	Variable access to other medical specialties in hospital	Ready access to respirologists, nephrologists, cardiologists, infectious disease specialists, general surgeons	Rapid access to and variable engagement of full complement of medical and surgical consultant specialists
Monitoring capacity	Noninvasive or minimally invasive monitoring—transcutaneous oxygen saturation, cardiac monitoring, urine output	Invasive monitoring of blood pressure and central venous pressures as dictated by patient status	Advanced hemodynamic monitoring (cardiac catheterization, ultrasonography, etc); advanced monitoring of pulmonary, cerebral, and other physiology as directed by clinical needs
		Blood gas analyzer immediately available	Blood gas analyzer and stat lab associated with ICU
Unit design and organ support	Dedicated geographic area	Dedicated geographic area with central monitoring station	Dedicated geographic area with individual patient care areas and central monitoring station
	Capacity for oxygen therapy and noninvasive respiratory support	Basic mechanical ventilatory support, pharmacologic support of cardiovascular function, intermittent renal replacement therapy, parenteral nutrition	Advanced ventilator and hemodynamic support, continuous renal replacement therapy, capacity for tracheostomy and other basic surgical procedures
			Capacity for isolation of patients needing contact or airborne precautions
Integration within the hospital	Defined geographic area only	Ad hoc interactions with other acute care areas such as emergency department	Outreach team(s), integration with step-down or high-dependency unit; close collaboration with emergency department
Research and education	Ad hoc activity	Organized educational activities for staff	Formal educational programs for staff
	Basic quality improvement program	Formal quality improvement program	Formal quality improvement program
		Ad hoc engagement in clinical research	Active involvement in clinical research
			Training of residents and fellows as available
Responsiveness to regional and societal needs	Ad hoc only, but available and responsive in event of disaster	Serves as resource for critically ill patients within hospital	Referral resource for community and district hospitals and for other ICUs
	Formal policy outlining criteria for patient transfer to higher level ICU		Disaster preparedness plan and capacity

The criteria within each stratum should be regarded as guidelines: specific criteria will vary with regional resources and capabilities as well as with different clinical needs; and for an ICU to be classified at a certain level, it must meet most, but not all, of the suggested criteria.

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Hospital Survey

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Infection control characteristics and Antibiotic stewardship characteristics	
See WHO Infection Prevention and Control (IPC) Self-Assessment Framework at Facility Level – separate document	
Core component 1 total score: IPC programme	**/100**
Core component 2 total score: IPC guidelines	**/100**
Core component 3 total score: IPC education and training	**/100**
Core component 4 total score: Health-care Associated Infection surveillance	**/100**
Core component 5 total score: Multimodal strategies for implementation of IPC interventions	**/100**
Core component 6 total score: Monitoring / audit of IPC practices and feedback	**/100**
Core component 7 total score: Workload, staffing and bed occupancy	**/100**
Core component 8 total score: built environment, materials and equipment for IPC at the facility level	**/100**
Total score (= sum of all core Components above)	**/800**

Note: The completed full version of the IPC Self-assessment framework sheets will need to be scanned and loaded to the REDCap database.

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Hospital Survey

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Antibiotic stewardship	
See Table 4 from WHO Antimicrobial Stewardship Programmes in Healthcare Facilities in LMIC – separate document	
Section 1. Leadership Commitment (Q1-3)	**Total "yes" / 3**
Section 2. Accountability and Responsibilities (Q4-9b)	**Total "yes" / 7**
Section 3. AMS Actions (Q10-17b)P;; L	**Total "yes" / 10**
Section 4. Education and Training (Q18-20)	**Total "yes" / 3**
Section 5. Monitoring and Surveillance (Q21-24)	**Total "yes" / 4**
Section 6. Reporting and Feedback (q25-28)	**Total "yes" / 4**
Total of all sections (sum of above scores)	**Total "yes" / 31**

Note: The completed full version of the Antimicrobial Stewardship assessment will need to be scanned and loaded to the REDCap database.

Hospital and laboratory survey CHECKING after DATA COLLECTION		
All fields completed hospital characteristics section	Yes ☐	No ☐
All fields completed laboratory characteristics section	Yes ☐	No ☐
All fields completed IPC assessment section	Yes ☐	No ☐
All fields completed Antibiotic stewardship section	Yes ☐	No ☐
This form was completed by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**
Hospital and laboratory survey CHECKING after DATA ENTRY		
All data entered and forms scanned	Yes ☐	No ☐
This data was entered by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Antibiotic Survey

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Hospital pharmacy: antibiotic availability survey

Date of pharmacy survey ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy

Perform this Antibiotic Availability Survey on 1st Tuesday of each month, as far as possible. This survey should always be performed via direct inspection of hospital pharmacy stores, in conjunction with a local Registered Hospital Pharmacist. Always check expiry date of ≥1 box of each antibiotic. This survey is NOT for external / private pharmacies where patients pay on a "per drug" basis in advance of treatment.

Staff performing survey:		
Name:		Research Nurse ☐ Registered Pharmacist ☐ Clinician ☐ Other ☐ _____
Name:		Research Nurse ☐ Registered Pharmacist ☐ Clinician ☐ Other ☐ _____

Section 1. Core drug availability

Antibiotic availability – for each of the following antibiotic agents, please estimate the number of Defined Daily Doses (DDD, i.e. sufficient drug for administration to a "normal" 70kg adult at typical dosing regime) that are currently (ie at the time of survey) available AND within expiry date in the hospital pharmacy.

See overleaf for summary of DDD (IV or PO) for each drug. Source of information on DDD according to WHO is http://www.whocc.no/atcddd/ .

Include both IV and PO formulations in total drug availability, where relevant.

It is NOT necessary to quantify the availability of the following drugs (which are only suitable to treat Gram-positive and/or anaerobic infections)

Penicillin, Flucloxacillin, Doxycycline, Erythromycin, Clindamycin, Clarithromycin, Vancomycin, Teicoplanin, Linezolid, Rifampicin, Metronidazole

Amoxicillin	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Co-amoxiclav (=a BLBI)	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Gentamicin	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Ciprofloxacin	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Ceftriaxone	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Cefotaxime	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Ceftazidime	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Amikacin	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Meropenem	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Imipenem	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Chloramphenicol	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name					
Piperacillin-tazobactam	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name eg. tazocin					
Co-trimoxazole	**Out of stock** ☐	**Not normally available** ☐	**1-100 doses** ☐	**100-1000 doses** ☐	**1000+ doses** ☐
Local typical brand name eg septrin, bactrim					

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Antibiotic Survey

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Section 2. Additional drug availability – additional specialist agents

For each of the following groups of antibiotic agents, please describe if there is <u>currently</u> any of the following drugs held in the Hospital Pharmacy.

Group 1 : Other cephalosporins **no** ☐ **yes** ☐

Including cefazolin, cefipime, cefuroxime, any others

if yes, list drug names _____

Group 2 : Other β-lactam, β-lactamase inhibitors (BLBI) **no** ☐ **yes** ☐

Including ampicillin-sulbactam, ceftazidime-avibactam, ceftolozane-tazobactam, any others

if yes, list drug names _____

Group 3 : Other carbapenem antibiotics **no** ☐ **yes** ☐

Including ertapenem, doripenem, any others

if yes, list drug names _____

Group 4 : Tigecycline **no** ☐ **yes** ☐

Group 5: Any other agents for resistant Gram-negative infections

no ☐ **yes** ☐

Including aztreonam, IV Fosfomycin, colistin, any others **if yes, list drug names** _____

Drug name	DDD IV	DDD PO
amoxicillin	3g	1.5g
co-amoxiclav	3g of amoxcillin component	1.5g of amoxicillin component
gentamicin	0.24g	N/A
ciprofloxacin	0.8g	1g
ceftriaxone	2g	N/A
cefotaxime	4g	N/A
ceftazidime	4g	N/A
amikacin	1g	N/A
meropenem	3g	N/A
Imipenem	2g	N/A
chloramphenicol	3g	N/A
piperacillin-tazobactam	14g of piperacillin component	N/A
co-trimoxazole	8 x unit dose (UD) of sulfamethoxazole 0.2 g/ trimethoprim 40 mg	4 x unit dose (UD) of sulfamethoxazole 0.4 g/ trimethoprim 80 mg

Antibiotic survey CHECKING after DATA COLLECTION		
All fields completed?	Yes ☐	No ☐
Date planned for Pharmacy survey next month	☐☐/☐☐/☐☐☐☐ dd/mm/yyyy	
This survey form was completed by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**
Antibiotic survey CHECKING after DATA ENTRY		
All fields entered ?	Yes ☐	No ☐
This data was entered by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Case Report Form

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Key identifiers and contacts page

Study code =	☐☐ - ☐☐☐☐ - ☐☐		
	Site - matching triad - patient type **00 = bacteraemia pt** **01 = match #1** **02 = match #2** **03 = match #3 (if needed)**	**Date of visit =**	☐☐/☐☐/☐☐☐☐ dd/mm/yyyy
Ward name =		**Note: Date of visit = first contact with patient, this is not the same as date that patient is enrolled to study from.**	

IDENTIFIERS - COMPLETE THIS SECTION FOR ALL PATIENTS					
Name (1)		**Name (2)**		**Name (3)**	
Note that patient name is not recorded in the study Redcap database, use local identifier records					
Gender	**Male** ☐	**Female** ☐	**Hospital internal number (MRN)**		
Date of Birth	☐☐/☐☐/☐☐☐☐ dd/mm/yyyy			Unknown ☐	
If DOB not known, best estimate of age in		**Years** ___	**Months** _____	**Days** _____	
Patient age group:	**Neonate (0-28 days)** ☐	**Infant (29-364 days)** ☐	**Child (1-14yrs)** ☐	**Adult (>14yrs)** ☐	
Informed consent information					
Did patient give informed consent to participate in the study	Yes ☐ No ☐	Date of consent			
Date of consent	☐☐/☐☐/☐☐☐☐ dd/mm/yyyy				
if No, describe why if possible _____					
If did not give informed consent, then thank patient / relative for their time and do not collect any further data					

Telephone contact information		**For contacting patient / relatives for 30-day outcome**	
Patient	**Primary personal phone for patient**	**N/A**	**Phone number** ☐☐☐☐☐☐☐☐ ☐☐☐☐
Patient	**Alternative personal phone number**	**N/A**	**Phone number** ☐☐☐☐☐☐☐☐ ☐☐☐☐
Relative 1	**Name:**	**Relationship:** _____	**Phone number** ☐☐☐☐☐☐☐☐ ☐☐☐☐
Relative 2	**Name:**	**Relationship:** _____	**Phone number** ☐☐☐☐☐☐☐☐ ☐☐☐☐

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Case Report Form

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Laboratory information page

COMPLETE THIS SECTION FOR BACTERAEMIC (BSI) PATIENTS ONLY
Date of Blood Culture: ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy **Laboratory (internal) blood culture number:** _____
Number of days from admission to Blood culture collection (for matching) = _____days
For example, if patient admitted to hospital on 10/04/2020 (dd/mm/yyyy), and blood culture (which became positive) was collected on 15/04/2020, then "days" = 5 If blood culture taken on same day as admission to hospital, then "days" = 0
Bacterial species identified: E.coli ☐ K.pneumoniae ☐ Other Klebsiella species ☐ Enterobacter species ☐ Proteus species ☐
Morganella species ☐ Citrobacter species ☐ Oher enterobacteria species ☐
Name of bacterial species _____
Polymicrobial infection – were other bacteria identified in same blood culture set? : No ☐ Yes ☐ if yes, specify which _____
Antibiotic susceptibility testing results for Enterobacterales isolate
Amoxicillin Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Co-amoxiclav Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Gentamicin Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Amikacin Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Ciprofloxacin Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Ceftriaxone Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Cefotaxime Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Cefpodoxime Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Ceftazidime Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Imipenem Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Meropenem Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Chloramphenicol Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Piperacillin-tazobactam Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Co-trimoxazole Susceptible ☐ Intermediate / ATU ☐ Resistant ☐ Unknown / not tested ☐ zone size or MIC recorded (mm) ___
Further resistance status of isolate If isolate is intermediate or resistant to 1 or more cephalosporin antibiotics (eg ceftriaxone, ceftazidime, cefotaxime), this could be an Extended Spectrum β-lactamase (ESBL) producing organism. Has further testing been done to investigate ESBL status ? yes ☐ no ☐ Final outcome of ESBL status: Not ESBL-producer ☐ Possible ESBL-producer ☐ Presumed ESBL-producer ☐ Confirmed ESBL -producer ☐
Date of storage of isolate in freezer : ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy
Freezer location: _____
**** We recommend always storing MBIRA isolates in duplicate, where possible ****

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Case Report Form

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Clinical information page

CLINICAL INFORMATION - COMPLETE THIS SECTION FOR ALL PATIENTS ON DAY OF ENROLLMENT

Date of hospital admission: ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy = first day when patient stayed overnight in hospital

= date of blood culture collection for bacteraemia patients

Date of study enrolment: ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy = date of admission + days_to_bacteraemia_in_matched_bacteraemia_case for non-infected control patients

Weight and Height

Weight (kg) _____ **kg** Unknown / Missing ☐

Height (cm), to nearest 10cm if estimated _____ **cm** Unknown / Missing ☐

Prior healthcare exposure

Admitted to hospital from: Community ☐ Other hospital ☐ Birth episode ☐ Unk ☐

Patient previously admitted to any hospital in last 30 days? No ☐ Yes ☐ Unk ☐

Patient previously admitted to any hospital in last 12 months? No ☐ Yes ☐ if yes, how many times? _____ Unk ☐

Any surgical operation in the last 30 days? No ☐ Yes ☐ Unk ☐

Type of admission to hospital Elective ☐ Emergency ☐ Unk ☐

Current hospital admission diagnosis group (circle single most relevant)

Cardiovascular	Connective tissue	Dermatological	Endocrine/metabolic	Gastrointestinal
Genitourinary	Gynaecological	Haematological	Infectious disease	Neurological
Oncological	Orthopaedic	Pulmonary	Trauma	Undetermined

Comorbid illnesses

Underlying medical conditions (for calculation of Charlson Co-morbidity Index), circle all that apply NONE ☐

1 = Myocardial infarct	Cardiac failure	Peripheral Vascular disease	Dementia	Cerebrovascular disease
COPD	Connective tissue disease	Diabetes – no complications	Peptic ulcer disease	Mild chronic liver disease
2 = hemiplegia/stroke	Chronic kidney disease	Diabetes with complications	Any cancer (without metastases)	
3 = severe liver disease/cirrhosis				
6 = malignant tumour with metastases		AIDS/HIV stage 3 and 4	TB (circle: pulmonary vs extrapulm; circle: DS v MDR-TB)	

DS = drug-susceptible MDR = multi drug-resistant

Other relevant diseases: Asplenia inc. sickle cell disease ☐ Burns ☐ Other notable illness _____

For children under the age of 1 year only: Prematurity ☐ Gestational age at birth = weeks (to nearest week)

RVD status **unknown** ☐ **Negative** ☐ **Positive on ART** ☐ **Positive not on ART** ☐ **RVD exposed, uninfected child** ☐

Current severity of illness (for qSOFA score) – circle if feature is present.
Use WORST readings / values obtained on the day of the first positive blood culture was obtained OR day before (if nosocomial bacteraemia).
Use column with cut-offs appropriate for age of the patient , see relevant training materials

qSOFA variable	0-28 days	29 days – 1 yr	1-14 years	Adult
Conscious level	**Comatose** Data not available ☐	**Responsive to Pain only or unresponsive** Data not available ☐	**Responsive to Pain only or unresponsive** Data not available ☐	**GCS ≤ 14** Data not available ☐
Respiratory Rate (breaths / min)	**> 40** Data not available ☐	**> 34** Data not available ☐	**> 22** Data not available ☐	**> 22** Data not available ☐
Systolic BP (mmHg)	**< 70** Data not available ☐	**< 100** Data not available ☐	**< 100** Data not available ☐	**< 100** Data not available ☐

Clinical information page – continued

Presumed source of bacteraemia infection (bacteraemia patients only)

Circle most likely source according to medical notes

Bone / joint	CNS focus	intervention	ear – nose -throat	Intra-abdominal
Intravascular	Lower Respiratory Tract	Skin / soft-tissue	Urinary – genital	Maternal infection (neonates only)
		Unknown source of infection		

Indwelling devices present <u>at time of enrolment</u> (all patients)

Circle all medical devices present

Tracheal tube	Central Venous Catheter	Arterial venous Catheter	peripheral venous catheter	Urinary catheter
Trachostomy	Nasogastric tube	Wound drainage tube	Other _____	

Antibiotic use information

ANTIBIOTIC USE HISTORY – COMPLETE THIS FOR BACTERAEMIC PATIENTS ONLY

Date of Blood Culture: ☐☐/☐☐/☐☐☐☐ dd/mm/yyyy = DAY 0

Start recording antibiotic use from day PRIOR to blood culture collection = DAY -1

Disregard antibiotic treatment prior to this time regardless of whether in hospital or community.

Use separate lines of this table for each antibiotic, each day - thus 10 days of the same antibiotic will use 10 lines of the table.

Use separate lines for different antibiotics – thus use of 3 different antibiotics on the same day will use 3 lines of the table.

Exclude all other anti-infective therapy (inc. ARV, TB therapy, antifungal), but <u>include</u> co-trimoxazole/septrin

Continue recording antibiotic use day-by-day until earliest of

a) No antibiotic use for 3 consecutive days (= consider as completed treatment episode)
b) Patient death or discharge (or other departure) from hospital
c) 30 days from blood culture collection (ie DAY+30)

Date (dd/mm/yy)	Day of episode (date of blood culture = DAY 0)	Name of antibiotic agent	Dose	Route (IV / IM / PO / PR)	Number of doses given this day
☐☐ / ☐☐ / ☐☐					
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Continue on next page as needed

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Case Report Form

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

Date (dd/mm/yy)	Day of episode (date of blood culture = DAY 0)	Name of antibiotic agent	Dose	Route (IV / IM / PO)	Number of doses given this day
☐☐ / ☐☐ / ☐☐					
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Outcome and data completion page

MBIRA study (Mortality from Bacterial Infections Resistant to Antibiotics): Case Report Form

Site: (insert here) Local PI: (insert name here) Telephone: (insert here)

OUTCOME INFORMATION - COMPLETE THIS SECTION FOR ALL PATIENTS		
Date of hospital outcome: ☐☐/☐☐/☐☐☐☐ **dd/mm/yyyy**	**Hospital outcome:** **Discharged** ☐ **Died** ☐ **Transferred** ☐ **Other, inc absconded** ☐	
DATE FOR 30 day outcome CHECK/PHONE CALL = 30 days from blood culture collection (bacteraemia patients) or 30 days from date of enrolment (uninfected patients)	☐☐/☐☐/☐☐☐☐ dd/mm/yyyy	
30d OUTCOME telephone interview?	Completed verbally ☐ No response after 3 attempts ☐ Unable to complete for other reason _____	
30-day outcome status	**Alive** ☐ **Died** ☐ **Unknown** ☐	

Attempt	Date	Free text notes – not necessary for data entry
1		
2		
3		

CRF CHECKING after DATA COLLECTION		
All fields completed	Yes ☐	No ☐
Hospital outcome completed	Yes ☐	No ☐
30-day telephone outcome completed	Yes ☐	No ☐
This CRF was completed by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**
CRF CHECKING after DATA ENTRY		
All fields completed	Yes ☐	No ☐
Hospital outcome completed	Yes ☐	No ☐
30-day telephone outcome completed	Yes ☐	No ☐
This CRF data was entered by:		**Name**
Date: ☐☐/☐☐/☐☐☐☐		**Signature:**

Now store this CRF in project information folder for reference to end of study

Training Manual Appendix 2
MBIRA study: Guide to scoring appropriate-ness of antibiotic use by pathogen, including imputation of missing antibiotic susceptibilities

Contents

Excerpt from MBIRA Training Manual – Section 12

Section 12. Introduction to appropriate-ness of antibiotic use in MBIRA

One of the main research questions of the MBIRA study is to examine how the appropriate-ness of use of antibiotics, in terms of antibiotic drug being used, relates to outcomes for the patient.

There are many different aspects of whether antibiotic use is appropriate, including

1. *Suitable antibiotic drug for empirical treatment of an infection "syndrome" in a certain age group*
2. *Suitable antibiotic drug for an identified bacterial pathogen, based on antibiotic resistance tests*
3. *Suitable dosing of antibiotic drug for this patient, based on their weight, renal function, other factors*
4. *Suitable route of administration of antibiotic drug – intra-venous versus oral versus other*
5. *Suitable timing of the first (and subsequent) doses of antibiotics from onset of illness*
6. *Suitable duration of antibiotic use, in terms of overall number of days of (effective) therapy*
7. *Suitable choice of agent, based on local availability, costs, antibiotic usage guidelines/policies*

And probably there are several other factors too! We are not able to assess all of these in this study, but we are going to focus on aspects "2", with some attention also to aspects "3", "6" and "7". We are therefore particularly looking at just the question of whether the antibiotic agent being used would be expected to be active against the specific bacteria identified from the positive blood culture.

In order to do this, one or two experienced people (→ see below) in each site need to assess each antibiotic used for each patient with bacteraemia to say whether or not, in terms of the local antibiotic susceptibility testing results, this antibiotic would be expected to be active against this particular bacteria.*

This is obviously a very narrow interpretation of the "appropriate-ness" of antibiotic use – patients might receive an "appropriate" choice of drug agent, but at an inadequate (or excessive) dose or via an inappropriate route or at an excessive cost to the hospital or patient. Drugs might have passed their expiry date or not be administered appropriately. The patient might miss some doses of an appropriate antibiotic due to limited availability or oversight by treating staff. Also, there may be some antibiotic drugs used where there is no local testing information available to determine whether or not the agent is likely to be effective. Furthermore, for some types of antibiotic resistance (eg resistance mediated by ESBL enzymes), there are differences of opinion amongst microbiologists over whether or not particular antibiotic agents are "appropriate" to use, though current versions of major antibiotic susceptibility testing guidelines (EUCAST and CLSI) now make broad recommendations on interpretation of test results in most situations.

For the purposes of this study, we are just going to focus on this narrow question relating to aspect number "2" above – ***does this particular drug potentially have therapeutic activity against this particular bacteria?*** *This will mean each drug will typically need a "yes" or "no" answer each day to say whether the relevant person/people considers this to be an appropriate drug to use. We will also allow options for "unable to determine" and "Yes, but at inadequate dosing" to be used. All of these choices will be based on the professional opinion of the relevant person. The next section describes how to enter this information.*

** In each site, an appropriate person with extensive clinical and microbiological experience should be making this assessment for "appropriate-ness" of antibiotic drug choice all the patients in the study – this assessment should not be performed by a study research nurse in isolation. Typically, this person will be the site lead or another clinical microbiologist and will participate in further relevant study trainings. The choice of who will perform this part of the study should be agreed in advance with the study co-ordinators.*

Purpose of this guide

This guide is intended to support a standardized approach to recording the "appropriate-ness" of antibiotic use in the MBIRA study, as a supplementary training material to the MBIRA study Training Manual. This guide includes some general information, a flow-chart for step-by-step performance of this scoring, 5 training cases, some Frequency Asked Questions and an Appendix of Rules of Imputing (=inferring) antibiotic resistance results for additional antibiotics.

One (or at most two) individual(s) in each site of the MBIRA study should be responsible for reading this guide, including doing the training cases, and scoring the "appropriate-ness" of antibiotic use.

General principles and Terminology

We have used the term "appropriate-ness" for this document, but it may be more helpful to think of this work in terms of "**effectiveness**" or "**activity**" of antibiotics. What we are attempting to record is whether or not the particular antibiotic agent was, in retrospect, actually "effective" or "active" against the specific infecting bacteria, based on the full laboratory results. The clinicians treating the patient at start of the patient's illness would not have had access to this information, so they may have inadvertently used ineffective antibiotic agents, or not have given any antibiotics at all. We are not trying to make any judgement about whether those clinicians made a right or wrong decision, just to determine if, in retrospect, the drugs should have been effective.

When considering whether the antibiotics used for patients in the MBIRA study were, in retrospect, active against the isolated bacteraemia pathogen, we will assess each individual pathogen-antibiotic combination separately using the locally-reported antibiotic susceptibilities, as available. **As a general principle, we will normally directly follow the results of the in-vitro susceptibility testing,** so long as these appear consistent with the bacterial species identified.

Individual institutions differ on which drugs are used for susceptibility testing, though the majority of sites are following the CLSI guidelines for interpretation. This guide uses the following abbreviations

R = Resistant
S = Susceptible (also sometime used to abbreviate for "sensitive")
I = Intermediate

For simplicity, we will always consider "Intermediate" (or alternatively "Area of Therapeutic Uncertainty") susceptibility results as being "resistant".

All susceptibility testing will be repeated at the MBIRA study Reference Laboratory in South Africa at the end of the study. Therefore, bacterial isolates from bacteraemia cases where the patients were enrolled into the MBIRA study must be saved in a suitable freezer until the end of the study (end of 2021 / early 2022) and then will be sent to the reference laboratory.

Dosing

As far as the dose of antibiotics used is concerned, our general principle will be to follow dosing recommendations for antibiotics as described in the British National Formulary (BNF) for adults and the British National Formulary-Children (BNF-C) as appropriate for age of patient. Ideally, we will use the most recent information available, but the BNF website does not normally allow access if you are outside of the UK. We have pdf versions for 2018-19 editions (in Dropbox folder) – it seems unlikely there are substantial changes in dosing for these drugs in the past year. For patients with known renal impairment, we will also refer to the Renal Drug Handbook (3rd Edition) for specialist dosing recommendations. So long as the dose of antibiotic recorded to be administered in a 24 hour period falls within the recommended range of dosing for the antibiotic described for the particular patient circumstances, we will consider this as "appropriate" antibiotic treatment. The patient does not have to be on the "maximum" allowable dose of a particular agent, just within the recommended dose range for the relevant route of administration.

Where there are known to be special circumstances for the particular patient (eg. under-weight or overweight, acute or chronic renal impairment) that affect the dosing, we will consider the dosing as "appropriate" if the relevant circumstances are described in the BNF, BNF-C or Renal Drug Handbook.

British National Formulary	https://bnf.nice.org.uk/ OR 2018-19 pdf version in Dropbox folder
British National Formulary – Children	https://bnfc.nice.org.uk/ OR 2018-19 pdf version in Dropbox folder
Renal Drug Handbook (3rd Edition)	pdf version available in MBIRA study Dropbox folder

Imputation rules

In some cases, the susceptibilities to specific antibiotics that were actually used may not be listed in local susceptibility reports – in several MBIRA study sites, a wider range of antibiotics is used than is routinely tested in the laboratory. We do not expect any additional susceptibility testing to be performed in the participating laboratories, so sometimes, it may not be possible to determine if the antibiotic used would or would not have been effective against the infecting bacteria. However, sometimes the response of particular bacteria to certain antibiotics can be predicted ("**imputed**") based on general microbiological principles or known susceptibility results of other antibiotics.

We therefore have created a set of rules to impute some further antibiotic susceptibilities using microbiologic principles and knowledge of the spectrum of likely activity for each antibiotic-pathogen combination – this is given in Appendix 1. A "key" to the abbreviations used in these imputations is shown at the start if the Appendix, followed by the general and species-specific rules. Not all antibiotic sensitivities can be imputed – in some cases it will be impossible to determine "appropriate-ness" without a relevant test being performed.

There are some circumstances relating to the interpretation of 3rd generation cephalosporin (3GC) antibiotic susceptibility (based on particular mechanisms of resistance) where there is some degree of uncertainty about interpretation. In Appendix 2, we describe some additional sub-group analyses that we will perform at the end of the study to allow for different inferences from particular mechanisms of resistance.

Practical work

For entering this information into the Redcap database, this recording of information needs to be done for each drug on a day-by-day basis – this is a bit repetitive, but it allows for changes of drug doses each day. We suggest that these information are completed at each site on a monthly basis – we estimate it make take an individual 1-2 hours to complete all the information for all the MBIRA patients in a month.

We recommend that this work is done by 1 or 2 individuals at each MBIRA site. Ideally this work should be staff with a professional training as a clinical microbiologist or as an experienced clinician. In some situations, there may be an element of judgement to make about these interpretations – if there is uncertainty these can be discussed with the MBIRA lead investigators (Alexander Aiken alexander.aiken@lshtm.ac.uk and Andrew Whitelaw awhitelaw@sun.ac.za) if needed.

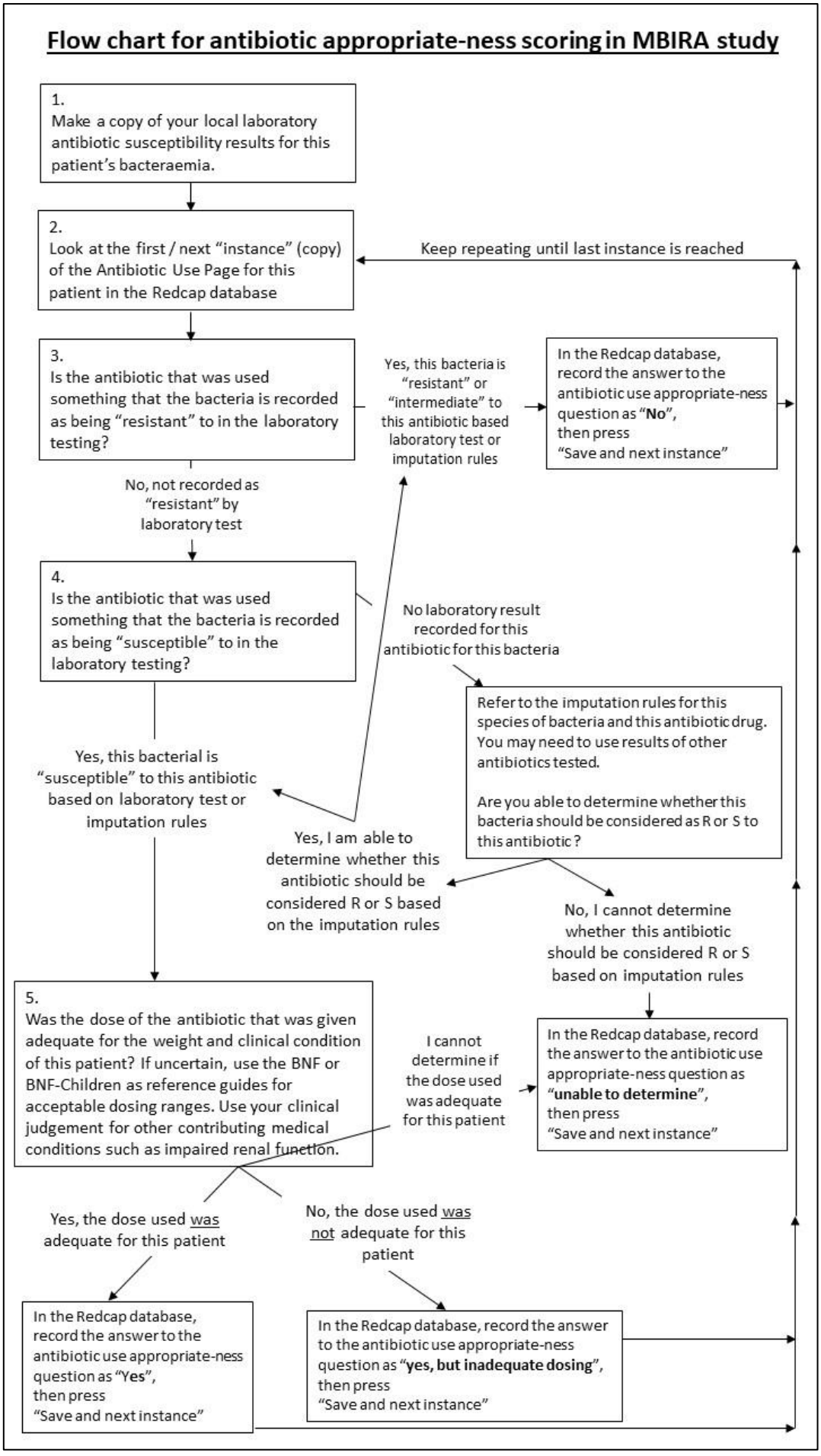
** Now read text in Section 12 of MBIRA Training Manual on "Training exercise 4 – coding appropriate-ness of antibiotic use in MBIRA" – this illustrates how the RedCap interface is used **

As further materials to try to make this process easier, please see the following

- Flow chart for antibiotic appropriate-ness scoring process
- 5 example cases for practicing this scoring
- Frequently Asked Questions

The full imputation rules for the MBIRA study are provided in Appendix 1.

The further planned analyses are detailed in Appendix 2.


Flow chart for antibiotic appropriate-ness scoring in MBIRA study
1.
Make a copy of your local laboratory antibiotic susceptibility results for this patient's bacteraemia.
2.
Look at the first / next "instance" (copy) of the Antibiotic Use Page for this patient in the Redcap database
Keep repeating until last instance is reached
3.
Is the antibiotic that was used something that the bacteria is recorded as being "resistant" to in the laboratory testing?
Yes, this bacteria is "resistant" or "intermediate" to this antibiotic based laboratory test or imputation rules
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "No", then press "Save and next instance"
No, not recorded as "resistant" by laboratory test
4.
Is the antibiotic that was used something that the bacteria is recorded as being "susceptible" to in the laboratory testing?
No laboratory result recorded for this antibiotic for this bacteria
Refer to the imputation rules for this species of bacteria and this antibiotic drug. You may need to use results of other antibiotics tested.
Are you able to determine whether this bacteria should be considered as R or S to this antibiotic ?
Yes, this bacterial is "susceptible" to this antibiotic based on laboratory test or imputation rules
Yes, I am able to determine whether this antibiotic should be considered R or S based on the imputation rules
No, I cannot determine whether this antibiotic should be considered R or S based on imputation rules
5.
Was the dose of the antibiotic that was given adequate for the weight and clinical condition of this patient? If uncertain, use the BNF or BNF-Children as reference guides for acceptable dosing ranges. Use your clinical judgement for other contributing medical conditions such as impaired renal function.
I cannot determine if the dose used was adequate for this patient
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "unable to determine", then press "Save and next instance"
Yes, the dose used was adequate for this patient
No, the dose used was not adequate for this patient
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "Yes", then press "Save and next instance"
In the Redcap database, record the answer to the antibiotic use appropriate-ness question as "yes, but inadequate dosing", then press "Save and next instance"

Training cases for recording antibiotic appropriateness

These are 5 fictitious cases created to illustrate some of the difficulties of recording this antibiotic appropriate-ness information. The MBIRA study site lead for this aspect of the study should work through these to check they are familiar with the recommended approach, even if they are an experienced clinical microbiologist. Fill in the column titled "Was this antibiotic appropriate" using the options from the box at the bottom of the page.

Training Case 1

Bacteraemia details	
Bacteria identified	E. coli
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	S
Ciprofloxacin	R
Ceftriaxone	S
Amikacin	S
Co-trimoxazole	S

Patient details	
Age	5 yrs
Weight	16.0 kg
Other medical conditions	Nil known
Outcome	Patient discharged on day 4 of treatment, to go home with an oral antibiotic for 7 days

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	400 mg	iv	4	
0	Gentamicin	40 mg	iv	2	
1	Ampicillin	400 mg	iv	6	
1	Gentamicin	40 mg	iv	3	
2	Ampicillin	400 mg	iv	6	
2	Gentamicin	40 mg	iv	1	
3	Ceftriaxone	1200 mg	iv	1	
3	Gentamicin	40 mg	iv	3	
4	Ceftriaxone	1200 mg	iv	1	
4	Gentamicin	40 mg	iv	1	
4	Co-trimoxazole	240 mg	po	2	
5	Co-trimoxazole	240 mg	po	2	
6	Co-trimoxazole	240 mg	po	2	
7	Co-trimoxazole	240 mg	po	2	
8	Co-trimoxazole	240 mg	po	2	
9	Co-trimoxazole	240 mg	po	2	
10	Co-trimoxazole	240 mg	po	2	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 1.

1. For this child, you may need to check what the recommended doses are for these drugs based on the child's weight – you can look these up, if you need, in the BNF-Children.
2. Day 0 = the day that the blood culture was taken. In most cases, this will also be the day that antibiotic treatment is started, though sometimes a patient will already be on antibiotics before this day. For example, the patient may have been admitted to hospital in the afternoon, so it may only have been possible to give 1-2 doses of some of the multi-dose medications that day. Therefore, on Day 0, the patient may often not receive the full number of doses in a 24 hour period that would be recommended. Do not score this day as "inadequate dosing" as there may not have been sufficient time for full number of doses to be given.
3. Similar to note 1 above, on a day that a patient leaves hospital (or dies), there may not be time in that 24 hour period to receive all the recommended doses of antibiotic treatment. Again, do not score this an "inadequate dosing of antibiotic" as the patient may not have been available to receive the full number of doses, or there may have been a change of prescription.
4. Similar to notes 1 and 2, the same situation may apply on any day when a patient changed antibiotic treatments. Again, for any other day where the antibiotics are stopped or started, do not consider these days as inadequate dosing.
5. Apart from Day 0 and the day the patient left hospital, for one day of one of the antibiotics treatments in the example above, this patient did not receive an "adequate" dosing of the drug, according to the British National Formulary for Children. Did you identify which drug on which day this was ? Hint: look at the number of doses of Gentamicin given on Day 4.
6. When patients are discharged home with an oral antibiotic treatment, it is very difficult to determine their compliance to this treatment. Therefore, only assess whether the antibiotic would have been appropriate for treating this bacteria – we cannot assess whether this drug was actually taken.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	400 mg	iv	4	No
0	Gentamicin	40 mg	iv	2	Yes
1	Ampicillin	400 mg	iv	6	No
1	Gentamicin	40 mg	iv	3	Yes
2	Ampicillin	400 mg	iv	6	No
2	Gentamicin	40 mg	iv	1	Yes, but inadequate dosing
3	Ceftriaxone	1200 mg	iv	1	Yes
3	Gentamicin	40 mg	iv	3	Yes
4	Ceftriaxone	1200 mg	iv	1	Yes
4	Gentamicin	40 mg	iv	1	Yes, but inadequate dosing
4	Co-trimoxazole	240 mg	po	2	Yes
5	Co-trimoxazole	240 mg	po	2	Yes
6	Co-trimoxazole	240 mg	po	2	Yes
7	Co-trimoxazole	240 mg	po	2	Yes
8	Co-trimoxazole	240 mg	po	2	Yes
9	Co-trimoxazole	240 mg	po	2	Yes
10	Co-trimoxazole	240 mg	po	2	Yes

Training Case 2

Bacteraemia details	
Bacteria identified	K .pneumoniae
Drugs reported	Laboratory result
Gentamicin	R
Ciprofloxacin	R
Ceftriaxone	R
Amikacin	S
Meropenem	S

Patient details	
Age	56 yrs
Weight	73.5 kg
Other medical conditions	Nil known
Outcome	Patient died on day 4

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Ciprofloxacin	500 mg	po	2	
0	Ciprofloxacin	500 mg	Po	1	
0	Ampicillin	1000 mg	iv	2	
0	Gentamicin	250 mg	iv	1	
1	Ceftriaxone	1000 mg	iv	1	
1	Gentamicin	250 mg	iv	3	
2	Ceftriaxone	1000 mg	iv	1	
2	Gentamicin	250 mg	iv	3	
3	Ceftriaxone	1000 mg	iv	1	
3	Amikacin	540 mg	iv	3	
4	Imipenem	1000 mg	iv	3	
4	Amikacin	540 mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 2

1. For this adult, you may need to check what the recommended doses are for these drugs based on the patient's weight – you can look these up, if you need, in the BNF.
2. This is a more extensively antibiotic-resistant bacteria, so much more of the antibiotic treatment is not appropriate or "not effective". Only the amikacin and meropenem drugs are effective here.
3. This patient was already on antibiotic treatment at the time the blood culture was taken. There is a drug treatment recorded for "Day -1" – this means this drug was being given the day before the blood culture was taken.
4. For the ampicillin (which is effectively the same drug as amoxicillin) and the imipenem antibiotics, you need to look these antibiotics up in the "imputation rules" later in Appendix 1 of this Guide. Some bacteria are inherently resistant to certain antibiotics, so the laboratory may not bother to test these drugs.
5. Note that gentamicin and amikacin (both are aminoglycoside drugs) can be dosed as once daily, twice daily or three times daily regimens, but with different drug amounts for each different regime. In many African countries, multiple daily doses (typically 3 times daily) is preferred – this can achieve suitable treatment levels.
6. Note that the patient died on Day 4 – so do not score the antibiotic treatment on this day as "inadequate dosing", as there was not necessarily time available to receive this drug.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Ciprofloxacin	500 mg	po	2	No
0	Ciprofloxacin	500 mg	Po	1	No
0	Ampicillin	1000 mg	iv	2	No
0	Gentamicin	250 mg	iv	1	No
1	Ceftriaxone	1000 mg	iv	1	No
1	Gentamicin	250 mg	iv	3	No
2	Ceftriaxone	1000 mg	iv	1	No
2	Gentamicin	250 mg	iv	3	No
3	Ceftriaxone	1000 mg	iv	1	No
3	Amikacin	540 mg	iv	3	Yes
4	Imipenem	1000 mg	iv	3	Yes
4	Amikacin	540 mg	iv	1	Yes

Training Case 3

Bacteraemia details	
Bacteria identified	Proteus vulgaris
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	R
Ciprofloxacin	S
Cefotaxime	R
Amikacin	S
Co-amoxiclav	R

Patient details	
Age	1 year and 4 months
Weight	10.2 kg
Other medical conditions	Nil known
Outcome	Discharged on Day 8

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	250 mg	iv	4	
0	Gentamicin	25 mg	iv	3	
0	Vancomycin	100 mg	iv	3	
1	Ceftriaxone	500 mg	iv	1	
1	Amikacin	75 mg	iv	2	
1	Vancomycin	100 mg	Iv	4	
2	Ceftriaxone	500 mg	iv	1	
2	Amikacin	75 mg	iv	2	
3	Meropenem	100 mg	iv	1	
3	Amikacin	75 mg	iv	2	
4	Amikacin	75 mg	iv	2	
5	Amikacin	75 mg	iv	1	
6	Amikacin	75 mg	iv	2	
7	Amikacin	75 mg	iv	2	
8	Amikacin	75 mg	iv	2	
9	Amikacin	75 mg	iv	2	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 3

1. Note that the laboratory testing here is performed with the antibiotic Cefotaxime, but the patient is treated with Ceftriaxone. You may need to look up in the "imputation rules" in Appendix 1 to check how to interpret the susceptibility status for Ceftriaxone.

2. The Research nurse has recorded the use of the Drug "Vancomycin" for this patient. Look up in the "imputation rules" to see which antibiotic drugs have no effective activity against the Gram-negative bacteria that we are studying in MBIRA. You could give feedback to the study nurse that it is not necessary to record the use of drugs that have no activity against Gram-negative bacteria

3. This patient received a single dose of treatment with drug "meropenem" on Day 3. Are you able to use the imputation rules for this species to determine if this drug would have been effective ? What do you think of the dosing received here, bearing in mind that this drug is started (and stopped) on this day ?

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	250 mg	iv	4	No
0	Gentamicin	25 mg	iv	3	No
0	Vancomycin	100 mg	iv	3	No
1	Ceftriaxone	500 mg	iv	1	No
1	Amikacin	75 mg	iv	2	Yes
1	Vancomycin	100 mg	Iv	4	No
2	Ceftriaxone	500 mg	iv	1	No
2	Amikacin	75 mg	iv	2	Yes
3	Meropenem	100 mg	iv	1	Yes, but inadequate dosing*
3	Amikacin	75 mg	iv	2	Yes
4	Amikacin	75 mg	iv	2	Yes
5	Amikacin	75 mg	iv	1	Yes, but inadequate dosing
6	Amikacin	75 mg	iv	2	Yes
7	Amikacin	75 mg	iv	2	Yes
8	Amikacin	75 mg	iv	2	Yes
9	Amikacin	75 mg	iv	2	Yes

* In practice, if a drug was just given for a single dose in this way, it would be difficult to say whether or not the agent was dosed adequately – the drug may and been started and stopped on the same day. We are trying to gain consistency across the study sites, but this will be difficult in some situations.

Please make your best judgements and seek advice as needed.

Training Case 4

Bacteraemia details	
Bacteria identified	E.coli
Drugs reported	Laboratory result
Amoxicillin	R
Gentamicin	S
Ciprofloxacin	R
Cefotaxime	R
Amikacin	S
Ceftazidime	R
Co-amoxiclav	R
Co-trimoxazole	R
Imipenem	S
Chloramphenicol	S

Patient details	
Age	9 days
Weight	1.9kg
Other medical conditions	Prematurity (born 34/40)
Outcome	Completed treatment, discharged from hospital 6 weeks after completing antibiotic treatment

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	60 mg	iv	3	
0	Flucloxacillin	50mg	iv	3	
0	Gentamicin	10 mg	iv	1	
1	Co-amoxiclav	60 mg	iv	2	
1	Gentamicin	10 mg	Iv	1	
2	Co-amoxiclav	60 mg	iv	2	
2	Gentamicin	10 mg	iv	1	
3	Gentamicin	10 mg	iv	1	
4	Meropenem	40 mg	iv	3	
5	Meropenem	40 mg	iv	3	
6	Meropenem	40 mg	iv	3	
7	Meropenem	40 mg	iv	3	
8	Meropenem	40 mg	iv	3	
9	Meropenem	40 mg	iv	3	
10	Meropenem	40 mg	iv	3	
11	Meropenem	40 mg	iv	3	
12	Meropenem	40 mg	iv	3	
13	Meropenem	40 mg	iv	3	
14	Meropenem	40 mg	iv	3	
15	Meropenem	40 mg	iv	3	
16	Meropenem	40 mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 4

1. For the antibiotics Flucloxacillin and Meropenem, you may need to look at the "imputation rules" in Appendix 1.

2. Not that amoxicillin and ampicillin are, in microbiological terms, equivalent drugs, so the susceptibility testing results for these two are interchangeable. The only different in pharmacological terms is that amoxicillin is water soluble, so the drug can be taken orally.

3. What do you think about the duration of treatment with the antibiotic Meropenem ? Typically, Gram-negative bloodstream infections need only 7-10 days antibiotic treatment, so long as there has been adequate "source control" of any focus of infection (such as an abscess or gastro-intestinal perforation). So, the duration of the treatment for this patient may be excessively long. However, making a judgment on the duration of treatment is not the purpose of our evaluation here – you just need to decide if the antibiotic is "effective" against the bacterial causing the bloodstream infection.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
0	Ampicillin	60 mg	iv	3	No
0	Flucloxacillin	50mg	iv	3	No
0	Gentamicin	10 mg	iv	1	Yes
1	Co-amoxiclav	60 mg	iv	2	No
1	Gentamicin	10 mg	Iv	1	Yes
2	Co-amoxiclav	60 mg	iv	2	No
2	Gentamicin	10 mg	iv	1	Yes
3	Gentamicin	10 mg	iv	1	Yes
4	Meropenem	40 mg	iv	3	Yes
5	Meropenem	40 mg	iv	3	Yes
6	Meropenem	40 mg	iv	3	Yes
7	Meropenem	40 mg	iv	3	Yes
8	Meropenem	40 mg	iv	3	Yes
9	Meropenem	40 mg	iv	3	Yes
10	Meropenem	40 mg	iv	3	Yes
11	Meropenem	40 mg	iv	3	Yes
12	Meropenem	40 mg	iv	3	Yes
13	Meropenem	40 mg	iv	3	Yes
14	Meropenem	40 mg	iv	3	Yes
15	Meropenem	40 mg	iv	3	Yes
16	Meropenem	40 mg	iv	1	Yes

Training Case 5

Bacteraemia details	
Bacteria identified	K .pneumoniae
Drugs reported	Laboratory result
Ampicillin	R
Gentamicin	S
Ciprofloxacin	R
Amikacin	S
Cefotaxime	S
Imipenem	S
Co-trimoxazole	R

Patient details	
Age	72 yrs
Weight	82.9 kg
Other medical conditions	HIV+, advanced disease Renal failure, on haemodialysis x 3 weekly
Outcome	Patient died on day 3

Recorded antibiotic use for this patient

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Co-trimoxazole	480mg	po	1	
0	Ceftriaxone	500 mg	iv	1	
0	Co-trimoxazole	480mg	po	1	
1	Ceftriaxone	500 mg	iv	1	
1	Gentamicin	80 mg	iv	1	
2	Ceftriaxone	1000 mg	iv	2	
2	Meropenem	500 mg	iv	1	
3	Meropenem	1000mg	iv	1	

Options available
Yes
Yes, but inadequate dosing
No
Unable to determine

Notes for Training Case 5.

1. Note that this is a patient with known chronic renal impairment and on 3 x weekly haemodialysis, so you may need to check the dosing details in the Renal Drug Handbook, available in the MBIRA study Dropbox folder. Some of the recommended dosing changes are surprising, so always worth checking for patients with renal disease.

2. You many need to check the imputation rules for the drugs “meropenem” and “ceftriaxone” – these are not the same drugs that the laboratory report describes.

3. This is an HIV+ patient who is receiving oral co-trimoxazole on Day -1 and Day 0, mostly likely as long term prophylaxis. If a research nurse records other specialist medications in the MBIRA database (eg anti-retroviral or anti-TB drugs) that have no activity against enterobacteria, you should make sure that you let them know that this is not needed for this study. Co-trimoxazole (and some quinolone drugs used for treating TB) can have activity against Gram-negative bacteria, so should be recorded.

Model answer

Day	Drug	Dose (mg)	Route	Number of doses given	Was this antibiotic appropriate ? (see options below)
-1	Co-trimoxazole	480mg	po	1	No
0	Ceftriaxone	500 mg	iv	1	Yes, but inadequate dosing
0	Co-trimoxazole	480mg	po	1	No
1	Ceftriaxone	500 mg	iv	1	Yes, but inadequate dosing
1	Gentamicin	80 mg	iv	1	Yes, but inadequate dosing
2	Ceftriaxone	1000 mg	iv	2	Yes
2	Meropenem	500 mg	iv	1	Yes
3	Meropenem	1000mg	iv	1	Yes

Frequently Asked Questions

1. **What should I do if there are more than one bacteria recorded in the blood culture – for example 1 x E.coli (with very few drug resistances) and 1 x K. pneumoniae (with more extensive drug resistance) ? What about if one of the bacteria in the blood culture is thought to be a skin contaminant ?**

Response: When there are multiple different bacteria in the blood culture, you should only give responses to the "appropriate-ness" questions for the Enterobacteria isolated. So, if there are other non-enterobacteria pathogens (eg. S. aureus, Strep. penumoniae or Pseudomonas aeruginosa) or likely contaminating bacteria (eg. Coagulase-negative staphylococci, bacillus spp. , micrococcus spp.), you should ignore these.

If there are two (or more) separate Enterobacteria in the same blood culture, this is more difficult. The best approach is to consider what is the "worst case" scenario of treatment across the different identified organisms – so if one bacteria is Resistant and the other is Susceptible for a particular antibiotic, then to use the "resistant" result when considering the appropriate-ness of the particular antibiotic.

2. **What should I do if the dose of the antibiotic given seems <u>excessively high</u> for the patient, either based on their weight or other medical conditions ?**

Response: excessively high dosing is a different aspect of "appropriate-ness" that we are not assessing in this study, so no need to record this – you should just indicate whether or not this drug was effective against the particular bacteria in this patient. However, if you notice that this is a frequent occurrence and you think that patients may be at risk, this information/concern should certainly be fed back to ward-based clinicians and/or pharmacists.

3. **If the dosing of the medication for the patient seems to be consistently too low, but there is no medical explanation for this, what should I do ?**

Response: it is possible that there are some clinical details for this patient that have not been captured by the MBIRA study form or the research nurse has recorded incorrectly (eg wrong weight). If you have concerns about the dosing for medications, it would be prudent to speak to the research nurse about the case or to review the medical records for this patient directly.

Appendix 1 : Full imputation rules

Key for abbreviations

Imputation abbreviation	Explanation
R	This means that the organism will always be considered to be resistant to the antibiotic. (R = Resistant). *Example: vancomycin for Klebsiella spp. will always be considered as a non-active antibiotic.*
S	This means the organism will always be considered as susceptible to the antibiotic. (S= Susceptible). There are no examples of this situation for the Enterobacterales bacteria.
E	This means Equals, meaning that the susceptibility for this antibiotic is considered equivalent to the result for a different antibiotic. *Example: For E.coli, "E meropenem" for doripenem means that if doripenem susceptibility is missing, but meropenem is reported as susceptible, then doripenem can be considered to be susceptible too.*
If missing then "rule(s) for alternate antibiotic"	This means that if the susceptibility for the antibiotic of interest is missing, then the algorithm looks at the next part of the rule and applies that. These further follow a hierarchial order; *For example, for ceftriaxone: "if missing then E cefotaxime; if missing then E cefpodoxime; else ." This means the algorithm first looks to see if there is susceptibility reported for cefotaxime; if missing, then the algorithm looks for susceptibility for cefpodoxime, if that is also missing, then the result is considered as missing.*
If missing then .	This means that if the susceptibility to the antibiotic is missing (note that missing is typically recorded in a database as "."), then the algorithm will list that particular antibiotic-organism combination as missing (because an imputation could not be reliably performed). In this case, if an antibiotic was used and the susceptibility status is "missing", then the "appropriateness" of that antibiotic use should be recorded as "unable to determine"
If missing then R	This means that the algorithm will report the organism to be resistant to the antibiotic if the susceptibility is missing. This is used when the organism is typically, but not always, resistant to this agent.

Agents always considered as inactive against all Enterobacterales

Antibiotic	**Susceptibility imputation**
Clindamycin	R
Flucloxacillin / Oxacillin / Cloxacillin / Nafcillin	R
Linezolid	R
Metronidazole	R
Oxacillin	R
Penicillin G / Penicillin V	R
Rifampicin	R
Vancomycin	R

Agents always considered inappropriate for treating gram-negative bacteraemia due to lack of appropriate concentration in the vascular compartment

Antibiotic	**Susceptibility imputation**
Oral nitrofurantoin	R
Oral fosfomycin	R
Oral trimethoprim	R
Oral pivmecillinam	R

In the following sections, the algorithms for each antibiotic-pathogen imputation are shown.

Citrobacter freundii (but not other Citrobacter species), Enterobacter spp., Serratia spp., Providencia spp., Morganella morganii, Hafnia alvei (these bacteria are typically constitutive AmpC producers)

Antibiotic	**Susceptibility Imputation**
Amikacin	If missing then .
Amoxicillin-clavulanate	R
Amoxicillin	R
Ampicillin	R
Ampicillin-Sulbactam	R
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S of cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	R
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then .
Cefuroxime	If missing then .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then . (though some species intrinsically R)
Doripenem	E meropenem
Ertapenem	If missing then.
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E impenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Notes

Nalidixic acid an acceptable alternative testing agent for ciprofloxacin but not other quinolones (this applies to all subsequent tables also)

E. coli, other Escherichia species, Shigella, Citrobacter species (apart from C. freundii), P. mirabilis

Antibiotic	**Susceptibility Imputation**
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then S if ampicillin-S; else .
Amoxicillin	E to ampicillin
Ampicillin	E to amoxicillin
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; if missing then S if ampicillin-S; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then .
Doripenem	E meropenem
Ertapenem	If missing then .
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E imipenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Notes:

Eschericia hermanii – this species is intrinsically R to pip-taz

Proteus mirabilis – this species is intrinsically R to tigecycline

Klebsiella species

Antibiotic	Susceptibility Imputation
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then .
Amoxicillin	R
Ampicillin / Amoxicillin	R
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	If missing then .
Doripenem	E meropenem
Ertapenem	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Gentamicin	If missing then .
Imipenem	E meropenem
Levofloxacin	If missing then .
Meropenem	E imipenem
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; else .
Tigecycline	If missing then .
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else .

Proteus vulgaris and Proteus penneri

Antibiotic	Susceptibility Imputation
Amikacin	If missing then .
Amoxicillin-clavulanate	If missing then .
Amoxicillin	R
Ampicillin	R
Ampicillin-Sulbactam	If missing then E amoxicillin-clavulanate; else .
Azithromycin	If missing then .
Aztreonam	If missing then .
Cefepime	If missing then S if ceftriaxone-S or cefotaxime-S or cefuroxime-S; else .
Ceftazidime	If missing then .
Ceftriaxone	If missing then E cefotaxime; if missing then E cefpodoxime; if missing then S if cefuroxime-S; else .
Cefazolin	R
Cefotaxime	If missing then E ceftriaxone; if missing then E cefpodoxime; else .
Cefoxitin	If missing then S if cefazolin-S; else .
Cefuroxime	R
Chloramphenicol	If missing then .
Ciprofloxacin	If missing then .
Colistin	R
Doripenem	E meropenem
Ertapenem	If missing then S if ceftriaxone-S or cefotaxime-S; else .
Gentamicin	If missing then .
Imipenem	If missing then .
Levofloxacin	If missing then .
Meropenem	If missing then S if imipenem-S; if missing then S if ceftriaxone-S or cefotaxime-S; else .
Moxifloxacin	If missing then .
Piperacillin-Tazobactam	If missing then S if co-amoxiclav-S; if missing then S if amoxicillin-S or ampicillin-S; else .
Tigecycline	R
Co-trimoxazole (TMP-SMX)	If missing then S if trimethoprim-S; else R

Appendix 2 : Planned additional sub-group analyses

1. **ampC – 3rd generation cephalosporins.** For the ampC producing organisms, some professionals interpret these to be inherently resistant to all 3rd generation cephalosporins (3GC), regardless of in-vitro testing result. Our planned primary analysis is to interpret according to the in-vitro testing results. However, we will do an additional analysis of this sub-group of bacteria to see if defaulting all 3GC (ceftriaxone, cefotaxime, ceftazidime) to a resistant state changes the interpretation of the impact. We expect the number of these organisms treated with this type of antibiotic alone to be relatively small.

2. **ESBL – 3rd generation cephalosporins.** For organisms that are achieving 3GC resistance through expression of an Extended Spectrum β-lactamase (ESBL) enzyme, some professionals regard these bacteria as inherently resistant to all 3rd generation cephalosporins, regardless of in-vitro testing results. However, both EUCAST and CLSI both currently recommend reporting for ESBL-producing isolates based on the in-vitro test result for individual antibiotics. Therefore, according to current guidelines, it would be possible to have an ESBL-producing isolate that is ceftazidime-S and cefotaxime-R; or ceftazidime-R and cefotaxime-S. Our imputation rules therefore follow these guidelines, but we will make a planned additional analysis (once ESBL status is confirmed) to see a default interpretation of ESBL-producing organisms as being resistant to all 3GC changes the interpretation of impact. We expect the number of ESBL-producing organisms that have discrepant in vitro sensitivities between different 3GC antibiotics (eg ceftazidime-S and cefotaxime-R) to be relatively small.

3. **BLBI v carbapenem mortality impact.** Depending on numbers of suitable 3GC-resistant isolates available, we will make an additional analysis to investigate whether there is evidence of different mortality impacts of treating these with beta-lactam/beta-lactamase inhibitor combinations (eg piperacillin-tazobactam) versus carbapenem antibiotics (eg meropenem). This would represent a similar investigation to the MERINO trial, though using an observational format and the MBIRA study is not powered for this comparison.

4. **Inadequate dose**. If dose is considered to be “yes but inadequate” then primary analysis is to analyse this category of exposure separately. Secondary analysis is to consider this “yes but inadequate” as “inappropriate” antibiotic treatment (ie to merge this category with inappropriate antibiotic treatment). We expect there to be a relatively small number of antibiotic treatments in this “inadequate dosing” category.

Supporting references / further reading

1. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Magiorakos A et al, Clinical Microbiology and Infection, 2011
2. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. Kadri SS et al, Lancet Infectious Diseases, 2020
3. supplementary materials available from Prevalence of Antibiotic-Resistant Pathogens in Culture-Proven Sepsis and Outcomes Associated With Inadequate and Broad-Spectrum Empiric Antibiotic Use. Rhee C et al, JAMA Open 2020
4. Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With E coli or Klebsiella pneumoniae Bloodstream Infection and Ceftriaxone Resistance: A Randomized Clinical Trial. Harris PNA et al, JAMA 2018 (=MERINO trial).
5. Impact of antibiotic timing on mortality from Gram-negative bacteraemia in an English district general hospital: the importance of getting it right every time. Baltas I et al, Journal of Antimicrobial Chemotherapy, 2020.