

Title: A Simplified Clinically-Oriented Antimicrobial Resistance Surveillance Network – ACORN-lite

Short title: ACORN-lite Clinical AMR Surveillance

Acronym: ACORN-lite

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Conflict of Interest Statement

The investigators have no conflicts of interest to disclose

Confidentiality Statement

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1 SYNOPSIS

Title	A Simplified Clinically-Oriented Antimicrobial Resistance Surveillance Network – ACORN-lite	
Protocol No.	BAC25001	
Design	Clinical AMR surveillance	
Surveillance population	Hospitalised patients of any age with confirmed blood stream infection (BSI)	
Planned Surveillance Period	The planned surveillance period will depend on each site and will be influenced by the proposed sample size. Surveillance period will be specified in the site-specific protocol.	
Sample size	This surveillance will enrol all eligible and consenting patients admitted to the participating site during the surveillance period. Sites / countries will have several considerations when formulating sample size and/or duration of surveillance. For single site surveillance, then AST profiles for specific organism – drug combinations should contain at least 30 observations for development of local antibiograms (1). For multiple site surveillance with an intention to explore AMR attributable mortality, selecting an appropriate number of representative sites to generate sufficient isolates should follow WHO recommendations (2).	
Objectives		Outcomes
Primary	Characterise drug-resistant infections (DRI) by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, child, neonate), and location (ward, site)	<p>Antimicrobial susceptibility data for target pathogen BSI isolates, with specimen and admission-level denominators</p> <p>Incidence of target pathogen BSI (per 100,000 patient admissions) by clinical syndrome, place of acquisition, patient group, and location</p>
Secondary	Determine the health and economic impacts of AMR in target pathogen BSI	<p>Patient outcomes/ mortality for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p> <p>Duration of hospitalisation for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p> <p>Economic costs for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p>
Optional (see Appendix E)	Storage of bacterial isolates for molecular work/ whole genome sequencing (WGS)	Linkage of clinical and phenotypic laboratory data with molecular pathogen data

2 ABBREVIATIONS

ACORN	A Clinically-Oriented antimicrobial Resistance Network
AMR	Antimicrobial Resistance
AST	Antimicrobial Susceptibility Test
AWaRe	Access Watch Reserve (3)
BSI	Bloodstream Infection
CAI	Community Acquired Infection
CI	Chief Investigator
COMRU	Cambodia Oxford Medical Research Unit
CRF	Case Record Form
DALY	Disability Adjusted Life Year
DRI	Drug Resistant Infection
EC	Ethics Committee
ENT	Ear, Nose, and Throat
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLASS	Global Antimicrobial Resistance and Use Surveillance System
HAI	Hospital Acquired Infection
HCAI	Healthcare Associated Infection
ICU	Intensive Care Unit
ID	Identification
IPC	Infection Prevention and Control
LMICs	Low- and Middle-Income Countries
MORU	Mahidol-Oxford Tropical Medicine Research Unit
OUCRU	Oxford University Clinical Research Unit
OxTREC	Oxford Tropical Research Ethics Committee
PID	Pelvic Inflammatory Disease
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
(L)qSOFA	(Liverpool) quick Sepsis Related Organ Failure Assessment
REDCap	Research Electronic Data Capture
SOP	Standard Operating Procedure
sp/ spp	Species (single/ plural)
WGS	Whole Genome Sequence
WHO	World Health Organization

3 BACKGROUND AND RATIONALE

3.1 Background

Antimicrobial resistance (AMR) threatens to become one of the biggest health challenges facing humanity, with devastating consequences, if there is failure to take immediate action (4). Surveillance for the emergence and spread of AMR is one of five key response strategies (5). Surveillance data are essential

both at patient-level for informing empiric antibiotic treatment, and at systems-level for optimising treatment and infection prevention and control (IPC) policies (6).

Isolate- or sample-based data show trends in space and time but are prone to biases introduced by local characteristics such as community access to antibiotics and availability and use of laboratories. Critically, these data do not permit separation of community-acquired from healthcare-associated infections. Furthermore, mortality of drug-resistant infections cannot be reliably estimated from administrative data alone, such as death certificates (7). Assembling comprehensive surveillance data incorporating clinical, microbiological and outcome data thus involves sourcing individual-level data from medical records, microbiological reports and longitudinal follow-up, which is challenging, costly and especially lacking in low- and middle-income countries (LMICs) where the burden of AMR is highest (8-11).

Case-based surveillance, using standardised case definitions for identification of patients and associated specimens/ isolates, is essential for determination of clinical impacts of AMR (12, 13). A seminal publication on the global AMR burden in 2019 also concluded that scarcity of linked clinical and laboratory data was a major limitation of the dataset used to derive burden estimates (8, 14). It has been proposed recently that an appropriate global target should be a 10% reduction in mortality from AMR by 2030, effectively mandating collection of clinical outcome data in future human AMR surveillance activities (15).

A Clinically-Oriented Antimicrobial Resistance Surveillance Network (ACORN) is a case-based human AMR surveillance modality in which clinical and microbiology data are captured to generate representative data on AMR including, clinical variables and hospital outcome, in order to contribute to global understanding of AMR burden. This current ACORN-lite protocol incorporates lessons learned during the pilot (OxTREC ref: 536-19) and 2nd phase (ACORN2; OxTREC ref: 524-21), including expansion of patients of interest, refinements in case capture procedures (to be isolate-initiated rather than clinical infection-initiated), and optional storages of bacterial isolate for further molecular/ whole genome sequence (WGS) characterisation (16-18).

3.2 Aim

The aim of ACORN-lite is to expand routine care to include clinical AMR surveillance across networks of hospitals in LMICs, and to collect clinical data from patients with confirmed bloodstream infection (BSI), that will expand on the sample-based approach of WHO GLASS and enable classification of infection syndromes, origin of infection and outcome. Storage of bacterial isolates for separate molecular / WGS-based AMR surveillance activities will be encouraged as an optional laboratory activity (APPENDIX E: STORAGE OF ISOLATES FOR WHOLE GENOME SEQUENCING).

4 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures
Primary	
Characterise drug-resistant infections (DRI) by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, child, neonate), and location (ward, site)	<p>Antimicrobial susceptibility data for target pathogen BSI isolates, with specimen and admission-level denominators</p> <p>Incidence of target pathogen BSI (per 100,000 patient admissions) by clinical syndrome, place of acquisition, patient group, and location</p>
Secondary	
Determine the health and economic impacts of AMR in target pathogen BSI	<p>Patient outcomes/ mortality for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p> <p>Duration of hospitalisation for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p> <p>Economic costs for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location</p>
Optional (see Appendix E)	
Storage of bacterial isolates for molecular work/ WGS	Linkage of clinical and phenotypic laboratory data with molecular pathogen data

5 SURVEILLANCE DESIGN

Prospective surveillance of hospitalised patients with confirmed BSI by one of the target pathogens, summarised in APPENDIX A: SURVEILLANCE TARGET PATHOGENS. Informed by the results of ACORN 2, target pathogens include all current WHO GLASS surveillance pathogens plus additional global AMR priority pathogens (19, 20).

5.1 Definitions

- **Place of infection acquisition / origin**
 - **Community-acquired infection (CAI):** an infection with symptom onset <48 hours following admission to surveillance hospital
 - **Healthcare-associated infection (HCAI):** a subset of CAI, where the patient was known to have had exposure to healthcare facilities in the three months prior to admission
 - **Hospital-acquired infection (HAI):** an infection with symptom onset from Day 3 of admission onwards (Day 1 = day of admission)
- **Age category**
 - **Neonate:** patient aged <28 days at enrolment

- **Child:** patient aged 28 days to <18 years at enrolment
- **Adult:** patient aged ≥18 years at enrolment

5.2 Surveillance Sites

6 Locations included in this surveillance are summarised in 19APPENDIX B: LIST OF POTENTIAL SURVEILLANCE LOCATIONSAPPENDIX A: SURVEILLANCE TARGET PATHOGENS

Pathogen	Core AMR
WHO GLASS pathogen group	
<i>Acinetobacter</i> spp.	Carbapenems (doripenem, imipenem, meropenem)
<i>Escherichia coli</i>	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Haemophilus influenzae</i>	Ampicillin 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
<i>Klebsiella pneumoniae</i>	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Neisseria meningitidis</i>	Penicillin 3 rd generation cephalosporins
<i>Pseudomonas aeruginosa</i>	3 rd generation cephalosporins (ceftazidime) Carbapenems (doripenem, imipenem, meropenem)
<i>Salmonella</i> spp. (non-typhoidal)	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Salmonella</i> Paratyphi A	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Salmonella</i> Typhi	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Staphylococcus aureus</i>	Methicillin (tested by ceftazidime disk +/- oxacillin MIC)
<i>Streptococcus pneumoniae</i>	Penicillin (tested by oxacillin disk +/- penicillin MIC) 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
Additional surveillance pathogens	
<i>Burkholderia cepacia</i>	3 rd generation cephalosporins (ceftazidime) Carbapenems (meropenem) Trimethoprim-sulfamethoxazole
<i>Burkholderia pseudomallei</i>	Amoxicillin-clavulanate 3 rd generation cephalosporins (ceftazidime) Carbapenems (imipenem, meropenem) Trimethoprim-sulfamethoxazole
<i>Enterobacteriales</i> - <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Morganella</i> spp., <i>Pantoea</i> spp., <i>Proteus</i> spp., <i>Serratia</i> spp.	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Enterococcus</i> spp. - <i>E. faecalis</i> , <i>E. faecium</i>	Ampicillin Vancomycin
Beta-haemolytic streptococci	Penicillin

- Group A (<i>S. pyogenes</i>), Group B (<i>S. agalactiae</i>)	Macrolides (erythromycin, clindamycin)
<i>Stenotrophomonas maltophilia</i>	Trimethoprim-sulfamethoxazole
<i>Streptococcus suis</i>	Penicillin 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
Fungal species - <i>Candida</i> spp. - <i>Cryptococcus neoformans</i> / <i>gattii</i> - <i>Talaromyces marneffe</i>	N/A

APPENDIX B: LIST OF POTENTIAL SURVEILLANCE . Within a country, sites are recommended to be selected to include the full spectrum of patient groups, from neonates to elderly care, and to include primary- to tertiary-level government and non-governmental facilities with access to a quality-assured diagnostic microbiology laboratory (refer to section 12.2 for further details).

6.1.1 Site summary, diagnostic stewardship, and microbiology laboratory review

Prior to commencement of patient enrolment, data on the healthcare facility will be collected:

- Location
- Hospital type (general, adult, paediatric, specialist)
- Level of care and specialties provided
- Ownership (government, private, other)
- For the most recent complete year, the total number of:
 - Admissions
 - Patient days of care (or average length of stay if patient days of care is not available)
 - Acute and ICU beds
 - Medical and nursing staff

Where available, these data will be provided stratified by age category: neonate, child, adult.

Self-review of the site diagnostic stewardship materials and diagnostic microbiology laboratory will be undertaken using project-specific checklists, to verify that surveillance-relevant standard operating procedures are in place and that appropriate quality standards are met (i.e. those required for submission of data to WHO GLASS (19, 21, 22)).

6.1.2 Site denominator data

Admission, patient day / average length of stay, and the number of blood culture sets processed by the laboratory will be captured at monthly intervals during surveillance.

7 PARTICIPANT IDENTIFICATION

7.1 Surveillance Population

Hospitalised patients of any age with confirmed blood stream infection (BSI).

7.2 Inclusion Criteria

- Patients of all ages who are admitted at the study sites / facilities during the surveillance period.
- Blood-culture confirmed BSI by one of the target pathogens.
- Patients with target organism BSI identified from a blood culture collected during an emergency department or out-patient clinic visit within two calendar days of admission shall be eligible for inclusion.

7.3 Exclusion Criteria

None.

8 SURVEILLANCE PROCEDURES

8.1 Recruitment

As part of routine care, all patients with a suspected infection will have a clinical assessment, physical examination, laboratory tests, and other relevant investigations, provided by hospital staff in accordance with the local standard-of-care.

Potential surveillance participants will be identified during daily review of diagnostic microbiology laboratory data. Patients with a blood culture positive for one of the target organisms will be screened by surveillance personnel and those meeting the inclusion criteria will be enrolled.

For patients who are screened and excluded from surveillance, the reason for exclusion will be recorded. A surveillance screening and enrolment log will be maintained for this purpose.

8.2 Screening and Eligibility Assessment

A member of the surveillance team (clinician, nurse or research assistant) will review the clinical notes of each potential participant daily, Monday to Friday. The notes of patients with blood cultures becoming positive for a target pathogen over the weekend or on public holidays shall be reviewed on the following workday.

8.3 Informed Consent

Research ethics committees will be requested to waive the need for explicit written individual informed consent as this surveillance is a minimal / negligible risk activity, consisting of collection and use of limited clinical data that are expected to be collected as part of standard of care. No patient samples will be collected other than for clinical diagnostic purposes. Only indirectly identifying information will be collected (patient's hospital ID or other locally-used unique patient identifier and date of birth) in order to ensure that follow-up until hospital discharge is possible. Once this link is established the hospital ID and date of birth will be discarded rendering the data fully de-identified prior to analysis and / or sharing. The need for individual informed consent was waived during the ACORN pilot and phase 2 studies by the Oxford Tropical Research Ethics Committee (OXTREC 536-19 and 524-21), Cambodia National Ethics Committee for Health Research (215-NECHR and 119-NECHR), Laos Ministry of Health – University of Health Sciences Ethics Committee (211/19 and 0240/REC), and National Hospital for Tropical Disease Institutional Review Board, Hanoi, Vietnam (13/HDDD-NDTU and 01-2022/HDDD-NDTU). A suggested informed consent form is included in this protocol for use / adaptation in those sites where the need for such consent is not waived.

Surveillance participant information sheets (PIS) and posters will be available on hospital wards and admission areas. The PIS and poster will inform patients regarding the purpose and procedures of the surveillance, what it will involve for the participant, and any risks involved in taking part as well as how to obtain more information about the surveillance.

At the time of enrolment, the patient or legally acceptable representative (as per local legislation) will be approached by a surveillance team member, provided with a surveillance PIS, and asked to confirm agreement for participation in surveillance. For those unable to read the PIS, it will be read to them at this stage. The patient or legally acceptable representative will be given one hour to decide whether to participate in surveillance. Agreement to participate will be recorded in the recruitment logbook. In those sites where the need for individual consent is not waived, informed consent procedures will be followed according to local guidance.

It will be clearly stated that patients have the right to refuse participation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. It will also be stated how to withdraw from surveillance. Any patient who requests not to be included in surveillance will be recorded accordingly in the surveillance screening logbook and will be diagnosed and treated according to standard clinical care. Surveillance staff will be readily available to provide further information and answer any questions.

8.4 Baseline Assessments

On the day of enrolment, baseline clinical data will be extracted from the patient clinical records/ electronic hospital information systems and by brief interview of the patient:

- Patient hospital ID code (or other locally used unique patient identifier): not entered into the surveillance database
- Date of birth or age at hospital admission
- Sex
- Date of admission and date of original hospitalisation (if transferred directly from another healthcare facility)
- Admission type (emergency or elective)
- Primary reason for admission
- Co-morbidity status (updated Charlson Comorbidity Index)
- Healthcare exposure, hospitalisation, and surgery in the three months before admission

The following data will be collected about the BSI episode:

- Surveillance category (CAI or HAI; HCAI will be determined computationally during analysis by responses to recent healthcare exposure questions in those with CAI)
- Ward details
- Clinically suspected infection syndrome (adapted from (23))

Infection category	Examples
Central nervous system	Brain abscess, encephalitis, meningitis, myelitis, spinal abscess, ventriculitis
Cardiovascular system	Endocarditis, mediastinitis, myocarditis, pericarditis, vascular (arterial or venous) infection
Eye	Conjunctivitis, dacrocystitis, endophthalmitis, orbital cellulitis
ENT / Upper respiratory tract	Epiglottitis, mastoiditis, otitis media, retropharyngeal abscess, sinusitis, tonsillitis
Lower respiratory tract	Bronchitis, bronchiolitis, lung abscess, tracheitis, tracheobronchitis, without evidence of pneumonia
Pneumonia	Pneumonia
Gastrointestinal	Colitis, dysentery, gastroenteritis
Intra-abdominal	Appendicitis, cholangitis, cholecystitis, liver / spleen abscess, pancreatitis, peritonitis
Necrotising enterocolitis	Neonatal necrotising enterocolitis
Skin / Soft tissue	Abscess, bites, burn, cellulitis, infectious gangrene, lymphadenitis, lymphangitis, necrotising fasciitis, pyomyositis, ulcer
Bone / Joint	Disc space infection, osteomyelitis, septic arthritis / bursitis

Surgical site infection	Post-operative infection (<30 days / <90 days if implant in situ) involving the surgical incision or deeper tissues associated with the procedure
Urinary tract	Cystitis, pyelonephritis
Genital	Obstetric / gynaecologic infections (ovarian abscess, salpingitis / PID, endometritis, episiotomy infection), prostatitis, sexually transmitted infections
Febrile neutropenia	Febrile neutropenic episode (haematology-oncology patient)
Sepsis	Clinical sepsis (source unclear / WITHOUT obvious focus / not specified)
Other	Defined diagnosis but not included in the list
Unknown	Clinical diagnosis not documented

- Clinical severity signs on day of blood culture collection
 - qSOFA score for adults, ≥ 18 years (24)
 - LqSOFA for children, <18 years (25)
 - General WHO severity signs for neonates, <28 days (2)
- Presence of medical devices / surgical procedures (HAI only)
- Microbiology
 - Blood culture details (date of collection, organism cultured, antimicrobial susceptibility test results)
 - Received ≥ 1 dose of a systemic antibiotic in the 24 hours before the blood culture collected
- Empiric antibiotic treatment details (all antibiotics prescribed on the day of blood culture collection)

8.5 Subsequent Assessments

Only the first positive blood culture for a specific target organism will be captured. If a subsequent BSI is detected and is caused by one of the other target organisms, this will be captured on an additional infection episode CRF.

At or shortly hospital discharge, the following data will be retrieved from the patient clinical records / electronic hospital information systems:

- Hospitalisation outcome and date
- Number of days admitted to an intensive care unit

8.6 Withdrawal of Participants from Surveillance

There are no criteria for stopping or discontinuing, as this is not an interventional study. All participants will be informed about their right to withdraw consent for any further data capture or follow up at any time, without having to provide a reason for withdrawal nor having to fear negative consequences.

Withdrawal from surveillance will not result in exclusion of the data already collected for that participant from analysis, unless the participant does not permit this use.

The reason for withdrawal, if known, will be recorded in the surveillance screening logbook held at each site.

8.7 Definition of End of Surveillance

The end of surveillance is the date of the final hospital discharge outcome event.

9 INVESTIGATIONS

Specimens taken in the study are those required for routine clinical care only with no extra specimens for surveillance purposes. However, diagnostic stewardship materials, based on international guidelines (22), will be provided as part of the ACORN-lite implementation package to enhance collection of syndrome specific specimens. These materials will be implemented at the discretion of implementing sites / countries. Microbiology specimens will be processed by local laboratories, to identify pathogens and their antibiotic susceptibility profiles, following locally approved standard operating procedures (SOPs).

10 SAFETY CONSIDERATIONS

The surveillance is observational in nature with enhanced site-level diagnostic stewardship and collection of data only from participants. There are no invasive procedures, except for those routinely done as part of clinical care. For participating patients, risks are essentially no greater than they would be for routine health care at the hospital. For this reason, there will be no adverse event reporting.

11 SURVEILLANCE MONITORING AND EVALUATION

Investigators at each site will identify appropriate personnel to be included in surveillance training and implementation activities.

Site investigators will monitor enrolment characteristics and data in real-time using the project R-Shiny dashboard (see 13.2.1). Additionally, the project data manager will produce regular reports for each site to assess enrolment rates and to identify problems with data capture. Periodic (at least quarterly) teleconferences between site and central surveillance staff will be used to discuss and resolve problems.

12 STATISTICS AND ANALYSIS

12.1 Description of Statistical Methods

12.1.1 Site data

Site summary data will be summarised in tables and graphs. Simple descriptive statistics will be used where appropriate to compare data within and across sites, countries, and regions.

12.1.2 AMR surveillance data

Site-level data visualisation and analysis will be done onsite via a project specific R-Shiny web app, available at <https://acornamr.net> (26, 27).

Key outcome variables will be:

- Blood culture results
 - Target pathogen
 - Antimicrobial susceptibilities
- Duration of hospitalisation
- Hospital discharge vital status

Data will be summarised in tables and graphs. Categorical variables will be compared using Chi-squared or Fisher's exact test. Continuous variables will be compared using Student's t-test, one-way ANOVA, or their non-parametric equivalents. Appropriate corrections will be made for multiple comparisons. Results will be stratified by:

- Clinical infection syndrome
- Participant age category (neonatal, paediatric, adult)
- Place of acquisition (CAI, HCAI, or HAI)
- Location (ward type)

Univariable and multivariable logistic regression models will be fitted to explore whether any clinical or microbiological variables are associated with poor patient outcomes. Clinical comorbidity and severity score data will be included in these models. Impact of AMR on outcome and duration of hospitalisation will be assessed by time to event analysis.

For specimen- and isolate-based analyses, data will be deduplicated prior to calculation of infection and antimicrobial resistance rates, following WHO GLASS recommendations. For overall AST reporting, the first

BSI isolate of a given species per participant and place of acquisition (CAI, HCAI, HAI) will be analysed. Summaries will include:

- Incidence of target pathogen BSI per 100,000 patient admissions
- The percentage of isolates resistant to key antibiotics, as defined by WHO GLASS (19)
- The percentage of isolates categorised as multi-drug resistant, using standard definitions (28)

For empiric antibiotic analyses, drugs prescribed on the day of blood culture collection will be classified according to the WHO AWaRe criteria (3). Concordance (i.e. cultured isolate was susceptible) or discordance (i.e. cultured isolate was resistant) with microbiology test results will be determined.

For economic analyses, the impact of DRIs will be defined by compiling the mortality and morbidity data for patients admitted at the sites converted into disability adjusted life years (DALYs) using patient age, clinical diagnoses, and hospital outcome status (29). The costs of their care will be estimated using data on length of stay and for antibiotic treatment, with hospital- and country- specific unit costs attached, respectively. These will be reported for patients with susceptible versus resistant infections. Modelling approaches previously described will be applied to ascertain the incremental costs and DALYs lost that can be attributed to resistant infections as compared with susceptible infections (30).

12.2 The Number of Participants

This surveillance will enrol all eligible and consenting patients admitted to the participating site during the surveillance period. Sites / countries will have several considerations when formulating sample size and/or duration of surveillance. For single site surveillance, then AST profiles for specific organism – drug combinations should contain at least 30 observations for development of local antibiograms (1). For multiple site surveillance with an intention to explore AMR attributable mortality, selecting an appropriate number of representative sites to generate sufficient isolates should follow WHO recommendations (2). Based on ACORN2 data, approximately 5% (range 2 – 15%) of blood cultures collected from patients with suspected acute bacterial infection will be positive for a WHO GLASS surveillance pathogen.

13 DATA MANAGEMENT

13.1 Access to Data

Direct access will be granted to authorised representatives from appropriate international, national, and local Ethics Committees (EC) and any host institution for monitoring and/or audit of the surveillance to ensure compliance with regulations.

13.2 Data Handling and Record Keeping

13.2.1 AMR surveillance data

Clinical and microbiology laboratory data will be captured on paper-based CRFs with subsequent entry, or by direct entry, into a Research Electronic Data Capture (REDCap) database that can either hosted at the Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand or locally, as decided by implementing sites / countries. Exports from REDCap will be uploaded into the project R-Shiny web app for analysis and visualisation.

13.2.2 Personally identifiable data

Participant name, hospital ID, and specimen ID will be recorded in a subject identification log at each site, to facilitate hospital outcome data capture and linkage with additional laboratory results (e.g. WGS data). The paper subject identification logs will be stored at each site in a secure location (locked office / filing cabinet). These data will not be entered into the surveillance REDCap database.

13.3 Data Retention

13.3.1 AMR surveillance data

AMR surveillance data will be stored indefinitely in the REDCap database.

13.3.2 Personally Identifiable data

Paper-based records will be destroyed by cross-cutting shredder and / or incineration as soon as no longer needed (no later than one year following the end of the surveillance period).

13.3.3 Data sharing

Data sharing procedures will be defined by implementing sites / countries.

14 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The surveillance will be conducted in accordance with relevant regulations and standard operating procedures. Pre-surveillance site assessments will ensure that microbiology laboratory diagnostics meet baseline international standards. Surveillance staff will be trained in the protocol and relevant surveillance procedures prior to the start of the project. Surveillance staff will work closely with hospital staff to achieve the project goals while ensuring smooth continuation of care. International standard clinical case

definitions for surveillance syndromes will be used in all site-based training activities and diagnostic stewardship materials (22). Data quality will be assured by training, validation steps built into data capture and visualisation tools, and central monitoring. The local investigator shall be responsible for the conduct of the surveillance at their site, using a standard internal quality control procedure.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Declaration of Helsinki

The Chief Investigators will ensure that this surveillance is conducted in accordance with the principles of the Declaration of Helsinki.

15.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this surveillance is conducted in accordance with relevant regulations and with Good Clinical Practice (GCP). At a minimum, all staff involved in collecting participant data will be encouraged to complete GCP training.

15.3 Approvals

The protocol, participant information sheet and any proposed advertising material will be submitted to the local / national Research Ethics Committees (EC) and Oxford Tropical Research Ethics Committee (OXTREC) for written approval.

The Investigators will submit and, where necessary, obtain approval from the above parties for all amendments to the original approved documents.

15.4 Participant Confidentiality

Surveillance staff will ensure that the participants' anonymity is maintained. Personal information (i.e. name and hospital ID) necessary for follow-up will not be entered into the electronic surveillance database and will be recorded only in a paper subject identification log at the study site. This logbook will be destroyed as soon as it no longer required. Participants will be identified only by a participant ID number on other surveillance documents and electronic database. All documents will be stored securely and only accessible by surveillance staff and authorised personnel. The surveillance will comply with the General Data Protection Regulation (GDPR), which requires that personal data must not be kept as identifiable data for longer than necessary for the purposes concerned, and relevant local regulations.

15.5 Expenses and Benefits

Participants will not incur any surveillance-related expenses and will not be paid for their participation.

Hospital staff will receive additional training and support on diagnostic stewardship interventions, including enhanced use of cultures that are considered standard of care in many other settings. This may assist in the appropriate management of the illness, and improve the overall quality of care provided, which may or may not be beneficial to individual participants.

15.6 Risks

The only risk of taking part in this surveillance is loss of confidentiality, but the processes described in the data management section (section 13) above mitigate this risk.

15.7 Reporting

The Chief Investigators shall submit an Annual Progress Report to OxtREC on the anniversary of the date of approval of the surveillance. In addition, the Chief Investigators shall submit an End of Study Report to OxtREC within 12 months of completion of the study. Reports shall be submitted also to relevant Local / National ECs, as required.

15.8 Other Ethical Considerations

At each site, relevant local, sub-national and national standard operating procedures will be followed regarding conduct of surveillance during infectious diseases outbreaks (e.g. SARS-CoV-2 or Influenza viruses). Recruitment may need to be paused if significant local transmission is documented and / or at the request of relevant health authorities. Surveillance staff will be instructed to wear appropriate personal protective equipment (PPE) when working in clinical areas: the extent of PPE required shall be defined by local and/or national clinical guidelines.

16 FINANCE AND INSURANCE

16.1 Funding

This study is funded by The Fleming Fund.

16.2 Insurance

This study is covered by [INSERT INSURANCE DETAILS].

17 PUBLICATION POLICY

It is expected that a summary manuscript, reporting the overall results of the surveillance, will be prepared by each national investigator team. Authorships will be determined following guidelines developed by the International Committee of Medical Journal Editors(31). Publications will be reviewed and approved by all investigators and their institutions prior to release.

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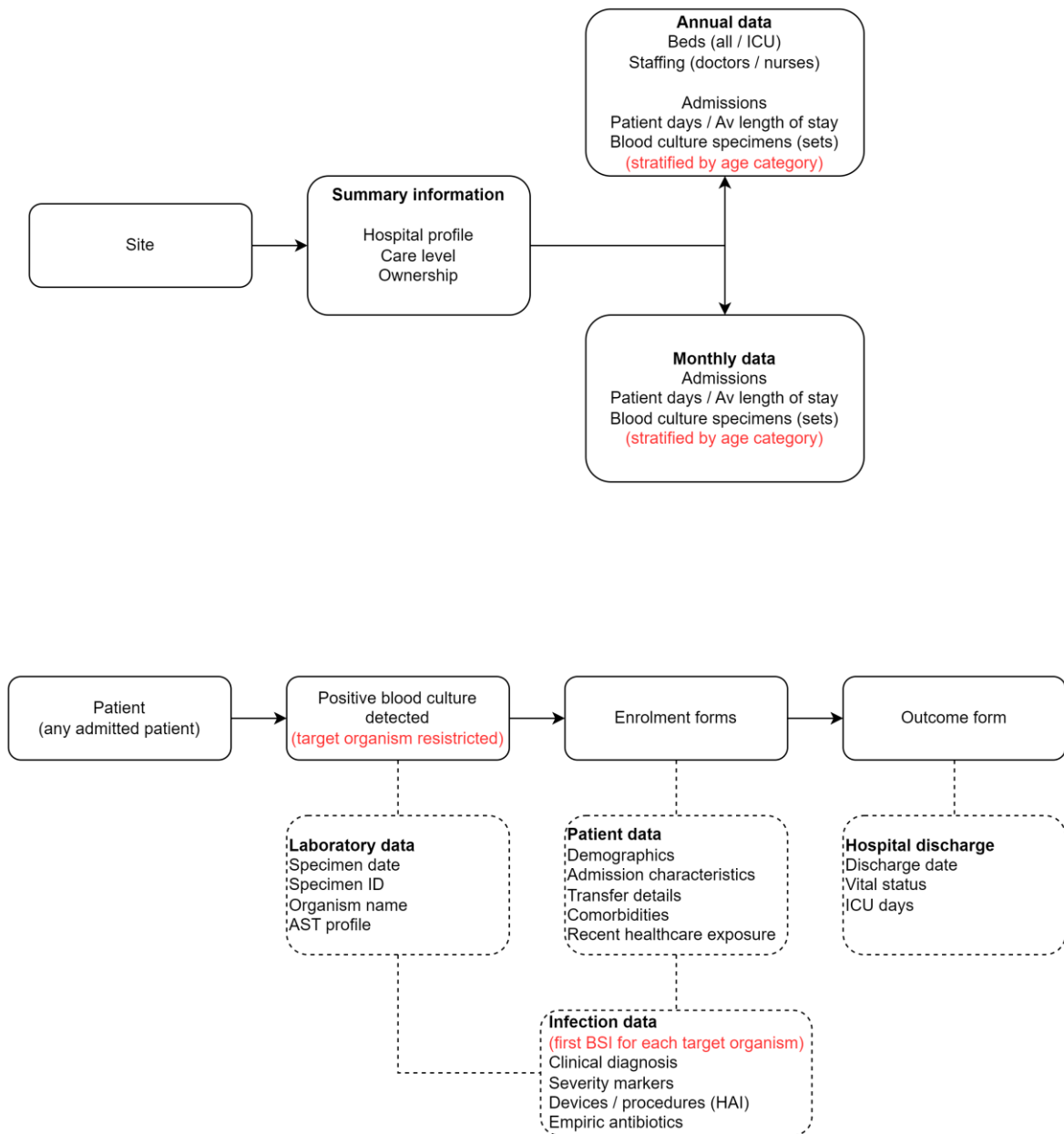
19 APPENDIX A: SURVEILLANCE TARGET PATHOGENS

Pathogen	Core AMR
WHO GLASS pathogen group	
<i>Acinetobacter</i> spp.	Carbapenems (doripenem, imipenem, meropenem)
<i>Escherichia coli</i>	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Haemophilus influenzae</i>	Ampicillin 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
<i>Klebsiella pneumoniae</i>	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Neisseria meningitidis</i>	Penicillin 3 rd generation cephalosporins
<i>Pseudomonas aeruginosa</i>	3 rd generation cephalosporins (ceftazidime) Carbapenems (doripenem, imipenem, meropenem)
<i>Salmonella</i> spp. (non-typhoidal)	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Salmonella</i> Paratyphi A	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Salmonella</i> Typhi	Fluoroquinolones (ciprofloxacin, levofloxacin) 3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone)
<i>Staphylococcus aureus</i>	Methicillin (tested by cefoxitin disk +/- oxacillin MIC)
<i>Streptococcus pneumoniae</i>	Penicillin (tested by oxacillin disk +/- penicillin MIC) 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
Additional surveillance pathogens	
<i>Burkholderia cepacia</i>	3 rd generation cephalosporins (ceftazidime) Carbapenems (meropenem) Trimethoprim-sulfamethoxazole
<i>Burkholderia pseudomallei</i>	Amoxicillin-clavulanate 3 rd generation cephalosporins (ceftazidime) Carbapenems (imipenem, meropenem) Trimethoprim-sulfamethoxazole
<i>Enterobacteriales</i> - <i>Citrobacter</i> spp., <i>Enterobacter</i> spp., <i>Morganella</i> spp., <i>Pantoea</i> spp., <i>Proteus</i> spp., <i>Serratia</i> spp.	3 rd generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) Carbapenems (doripenem, ertapenem, imipenem, meropenem)
<i>Enterococcus</i> spp. - <i>E. faecalis</i> , <i>E. faecium</i>	Ampicillin Vancomycin
Beta-haemolytic streptococci - Group A (<i>S. pyogenes</i>), Group B (<i>S. agalactiae</i>)	Penicillin Macrolides (erythromycin, clindamycin)
<i>Stenotrophomonas maltophilia</i>	Trimethoprim-sulfamethoxazole
<i>Streptococcus suis</i>	Penicillin 3 rd generation cephalosporins (cefotaxime, ceftriaxone)
Fungal species - <i>Candida</i> spp. - <i>Cryptococcus neoformans</i> / <i>gattii</i> - <i>Talaromyces marneffe</i>	N/A

20 APPENDIX B: LIST OF POTENTIAL SURVEILLANCE LOCATIONS

Country
Bhutan
Nepal

21 APPENDIX C: SURVEILLANCE FLOW CHART



Metrics

- Blood culture rate per 100,000 admissions / patient-days
- BSI rate per 100,000 admissions / patient-days
- AMR BSI rate per 100,000 admissions / patient-days
- Length of stay AMR versus non-AMR BSI (vs average for hospital)

(stratified by age category: neonate; child; adult)

22 APPENDIX D: SCHEDULE OF SURVEILLANCE PROCEDURES

Procedures	Site Level		Patient Visits	
	Prior to start of patient enrolment	End of surveillance period	Day 1	Hospital Discharge
			Baseline	Outcome
Site summary data collection	X			
Laboratory assessment	X			
Denominator data	Monthly			
Diagnostic stewardship	Continuous			
Eligibility assessment			X	
Demographic data collection			X	
Clinical syndrome data collection			X	
Investigation data collection			X	
Empiric treatment data collection			X	
Outcome data collection				X

23 APPENDIX E: STORAGE OF ISOLATES FOR WHOLE GENOME SEQUENCING

Sites are encouraged to store isolates from ACORN-lite for whole genome sequencing and obtain additional approvals for this work if required. Details of sample management, sample retention, and sample destruction must be specified in site-specific protocols.

Additional data collection forms and recommended ACORN protocols for storage and sequencing will be made available for sites on request.

24 APPENDIX F: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made