Title: A Clinically-Oriented Antimicrobial Resistance Surveillance Network – Phase 2

Short title: Infection surveillance to improve understanding of antibiotic resistance

Protocol No: BAC21002

OxTREC Ref: 524-21

Date and Version No: 26th April 2021; V1.0

Chief Investigator: **Prof Paul Turner**

Cambodia-Oxford Medical Research Unit (COMRU), Angkor Hospital for Children (AHC), Siem Reap, Cambodia

Telephone: +855 89287059

Email: pault@tropmedres.ac

Investigators: **Dr Sam Akech**; Kenya Medical Research Institute (KEMRI) / Wellcome Trust Programme, Nairobi, Kenya

Prof Elizabeth Ashley; Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit (LOMWRU), Vientiane, Laos

Prof H. Rogier van Doorn; Oxford University Clinical Research Unit (OUCRU), Hanoi, Vietnam

Prof Nick Feasey; Malawi-Liverpool-Wellcome Trust (MLW) Clinical Research Programme, Blantyre, Malawi

Prof Raph Hamers; Eijkman-Oxford Clinical Research Unit (EOCRU), Jakarta, Indonesia

Ms Jill Hopkins; Cambodia-Oxford Medical Research Unit (COMRU), Siem Reap, Cambodia

Dr Abhilasha Karkey; Oxford University Clinical Research Unit (OUCRU), Patan Hospital, Kathmandu, Nepal

Dr Sue Lee; Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand

Dr Clare Ling; Cambodia-Oxford Medical Research Unit (COMRU), Siem Reap, Cambodia

Dr Nantasit Luangasanatip; Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand

Prof Yoel Lubell; Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand

Prof Iruka Okeke; University of Ibadan, Ibadan, Nigeria

Dr Japheth Opintan; University of Ghana, Accra, Ghana

Dr Tamalee Roberts; Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit (LOMWRU), Vientiane, Laos

Dr Barbara Tornimbene; World Health Organization (WHO), Geneva, Switzerland

Ms Naomi Waithira; Mahidol-Oxford Tropical Medicine Research Unit (MORU), Bangkok, Thailand

Sponsor: University of Oxford

Funder: Wellcome Trust

Chief Investigator Signature:

Date: 26th April 2021

Conflict of Interest Statement

The investigators have no conflicts of interest to disclose

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team, and members of the Oxford Tropical Research Ethics Committee (OxTREC) and relevant Local / National Ethics Committees, unless authorised to do so.

TABLE OF CONTENTS

1 SYNOPSIS

Title	A Clinically-Oriented Antimicrobial Resistance Surveillance Network – Phase 2	
Protocol No.	BAC21002	
Design	Phase 2 implementation study of clinical AMR surveillance	
Surveillance population	Hospitalised patients of any age with suspected infection	
Planned Surveillance Period	24 months	
Sample size	2,500 patient infection episodes per site (estimated 37,500 infection episodes in total)	
	Objectives	**Outcomes**
Primary	Implement clinical antimicrobial resistance (AMR) surveillance of hospitalised patients with suspected acute bacterial infections at up to 15 sites in nine countries	Pre-implementation site assessments Site implementation status Numbers of patients enrolled by clinical syndrome, place of acquisition (community-acquired infection [CAI], hospital-acquired infection [HAI], healthcare associated infection [HCAI]), patient group (adult, paediatric, neonatal), and location (site, country, region) Proportion of timely (within 48 hours) and correctly (i.e. syndrome-relevant specimens collected) sampled patients per clinical syndrome, place of acquisition, and patient group by site, country, and region Clinician and surveillance staff acceptability and ease of use survey results by site, country, and region Surveillance staff time assessments and data collection app time measurements by site, country, and region
Secondary	Characterise drug-resistant infections (DRI) by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, paediatric, neonatal), and location (site, country, region)	Antimicrobial susceptibility data for WHO GLASS target pathogens with isolate, specimen, and case level denominators by location Incidence of WHO GLASS target pathogen bloodstream infection (per 1,000 patient episodes) by clinical syndrome, place of acquisition, patient group, and location Weekly HAI point prevalence data by clinical syndrome, patient group, and

		location (with denominator being the number of patients resident on the ward at 8am on day of survey) Duration of hospitalisation for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location Patient outcomes / mortality for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location Economic costs for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location
	Determine the attributable mortality for extended spectrum beta-lactamase producing *Escherichia coli* and methicillin resistant *Staphylococcus aureus* bloodstream infection	Incidence of bloodstream infection by *E. coli* and *S. aureus* (per 1,000 patient episodes) by clinical syndrome, place of acquisition, patient group, and location Antimicrobial susceptibility data of *E. coli* and *S. aureus* bloodstream infections by clinical syndrome, place of acquisition, patient group, and location Patient outcomes / mortality for susceptible vs. resistant *E. coli* and *S. aureus* bloodstream infections by clinical syndrome, place of acquisition, patient group, and location
	Determine the major indications for prescribing parenteral antibiotics by patient group (adult, paediatric, neonatal), timing of prescription (day of admission versus >2 days after admission), and location (site, country, region)	Empiric antibiotic treatment data by clinical syndrome, timing of prescription, patient group, and location
	Determine the major empiric antibiotics used by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, paediatric, neonatal), and location (site, country, region)	Empiric antibiotic prescription data, classified by WHO AWaRe group, by clinical syndrome, place of acquisition, patient group, and location

2 ABBREVIATIONS

AHC	Angkor Hospital for Children
AMR	Antimicrobial Resistance
ANOVA	Analysis Of Variance
AST	Antimicrobial Susceptibility Test
BSI	Bloodstream Infection
AWaRe	Access Watch Reserve (1)
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
EOCRU	Eijkman-Oxford Clinical Research Unit
ESBL	Extended Spectrum Beta-Lactamase
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLASS	Global Antimicrobial Resistance Surveillance System
HAI	Hospital Acquired Infection
HCAI	Healthcare Associated Infection
IV	Intravenous
KAP	Knowledge, Attitudes, and Practices
KEMRI	Kenya Medical Research Institute
LIMS	Laboratory Information Management System
LMIC	Low- and Middle-Income Countries
LOMWRU	Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit
MLW	Malawi-Liverpool-Wellcome Trust Clinical Research Programme
MORU	Mahidol-Oxford Tropical Medicine Research Unit
MRSA	Methicillin Resistant *Staphylococcus aureus*
ODK	Open Data Kit
OUCRU	Oxford University Clinical Research Unit
OxTREC	Oxford Tropical Research Ethics Committee
PID	Pelvic Inflammatory Disease
PIS	Participant Information Sheet
PPE	Personal Protective Equipment
qSOFA	quick Sepsis Related Organ Failure Assessment
REDCap	Research Electronic Data Capture
SOP	Standard Operating Procedure
sp / spp	Species (single / plural)
WHO	World Health Organization

3 BACKGROUND AND RATIONALE

3.1 Background

Current antimicrobial resistance (AMR) surveillance systems are typically passive and pathogen-focused, based on routine antimicrobial susceptibility testing (AST) results alone, generated by clinical microbiology laboratories. These systems lack relevant patient-level metadata and clinical syndromic denominators to appropriately inform treatment guidelines and decision making (2), and, especially in low- and middle-income countries (LMIC), suffer from various biases, due to lack of diagnostic stewardship and underutilisation of diagnostic microbiology resources (3). Collection of samples for microbiologic testing is often not part of a standard diagnostic work-up for many clinical syndromes. This can be due to many factors, including lack of trust between clinicians and the microbiology laboratory and (national) insurance systems that do not reimburse microbiological diagnostics. Therefore, it is more likely for samples to be collected only in more severe cases or in case of treatment failure. This limits direct assessment and subsequent modelling of the clinically relevant impacts and burden of drug resistant infections (DRI). Microbiologists often do not receive any clinical information important for interpreting laboratory results and surveillance data, e.g. whether an infection is community- or hospital-acquired. In addition, patients have access to over-the-counter antibiotics in the community and are often already taking these when admitted to hospital. These biases favour an overrepresentation of results from DRI among surveillance data. Therefore, if one was to use the current surveillance network results and resistance proportions to inform clinical guidelines, there is a risk of contributing to the problem of AMR rather than the solution and advocating the use of broader spectrum antibiotic regimens than would be justified if data were more representative.

The utility of integrated patient and laboratory-based surveillance, i.e. case-based surveillance, has been highlighted recently (4, 5). In addition to the bias-related problems noted above, there are several key patient-level questions that may not be adequately answered by passive pathogen-focussed AMR surveillance:

- What is the impact and cost of DRI at the patient level?
- What are the patient-level risk factors for DRI in a particular setting?
- Which AMR-syndrome combinations are associated with the poorest outcomes in particular patient groups?

High-quality patient-level surveillance data from LMICs are necessary to inform models to determine the impact of AMR, using big datasets with key patient-level variables, and to identify opportunities for intervention (6). The concept of ACORN is operationally efficient case-based AMR surveillance that can be

deployed in low resource settings to add value to existing laboratory capacity building efforts. A proof of principle pilot of the ACORN protocol was recently completed, involving three locations in southeast Asia (7, 8). Hospitalised patients with clinician suspected community-acquired sepsis, pneumonia, or meningitis were enrolled prospectively during daily reviews of new admissions to selected surveillance wards. Hospital-acquired sepsis or pneumonia cases were captured during weekly point prevalence surveys on the same wards. Diagnostic stewardship advice was provided to clinical staff to improve collection of microbiology specimens from patients with suspected infection, but surveillance specific specimens were not collected. Demographic, clinical, and outcome data were captured electronically using the Open Data Kit (ODK) system and Android tablets. Microbiology laboratory data was exported from existing hospital laboratory information management systems and linked to clinical data onsite using an automated computer script. Organisms of interest were the blood culture relevant pathogens included in the WHO Global Antimicrobial Resistance Surveillance System (GLASS) Manual for Early Implementation: *Streptococcus pneumoniae, Staphylococcus aureus, Salmonella* spp*., Klebsiella pneumoniae, Escherichia coli,* and *Acinetobacter baumannii* (9). Key metrics from the pilot are summarised in the table below.

	Angkor Hospital for Children	**Mahosot Hospital**	**National Hospital for Tropical Diseases**
Location	Siem Reap, Cambodia	Vientiane, Laos	Hanoi, Vietnam
Profile	Paediatric	General	Specialist
Subordination	Non-governmental	Government	Government
Surveillance wards / beds	3 / 49	5 / 94	5 / 168
Surveillance duration	12 months	11 months	6 months*
Infection episodes / patients	1,385 / 1,223	740 / 733	363 / 345
Microbiology specimens	1,872	1,154	412
Target organism isolates	129	92	25
Hospital outcome data	1,384 (99.9%)	737 (99.6%)	344 (94.8%)
Day 28 outcome data	1,184 (85.5%)	675 (91.2%)	359 (8.9%)

*Interrupted significantly by a local COVID-19 outbreak

Excluding the Hanoi pilot site, where a local COVID-19 outbreak disrupted surveillance shortly after site initiation, a total of 2,125 patient infection episodes were captured yielding 221 isolates of target pathogens, before deduplication. Blood culture data were captured in over 80% (1,768/2,125) of infection episodes. Day 28 follow-up data was obtained in almost 90% of cases. During the pilot, it was noted that

clinical diagnoses were not easy to ascertain across sites and alternative enrolment criteria were explored. If patients were identified on the basis of prescription of an antibiotic for suspected acute infection, then enrolment would have increased by 18% overall (+73% in Laos, +81% in Vietnam, but -47% in Cambodia as a result of frequent clinical suspicion of infection in young children with observation prior to commencement of antibiotics).

During the ACORN pilot, WHO-GLASS published a study protocol to determine the attributable mortality for bloodstream infections (BSI), specifically those caused by extended spectrum beta-lactamase-producing (ESBL) *E. coli* and methicillin resistant *S. aureus* (MRSA) (10). Assuming blood cultures are collected in all patients with suspected BSI, i.e. there is good diagnostic stewardship, then ACORN surveillance would be expected to capture all patients eligible for inclusion in the WHO-GLASS protocol. The entry point for this protocol is identification of either *E. coli* or *S. aureus* from a blood culture in a hospitalised patient. Clinical and laboratory variables are well harmonised with ACORN, with only small changes to the ACORN pilot protocol required for full harmonisation. The WHO-protocol study design proposed is a prospective cohort study where crude case fatality rates are compared between groups of patients (cohorts): patients with DRI (cohort 1) to those with infections caused by drug susceptible organisms (cohort 2), with an optional third cohort of matched non-infected patients (i.e. those without *E. coli* or *S. aureus* BSI, cohort 3). Comparing patients with drug resistant and drug susceptible infections permits determination of attributable mortality assuming that resistant infections replace susceptible ones (i.e. if DRI were prevented, they would be replaced by drug susceptible infections). Comparison of drug resistant infections to a non-infected patient group permits determination of attributable mortality assuming that DRIs occur in different patients to susceptible infections (i.e. adding to the overall infection burden). There is no definitive evidence indicating which scenario is more likely, but by considering both, the upper and lower limit of the impact of AMR can be determined.

This current ACORN protocol incorporates lessons learned during the pilot phase, including expansion of patients of interest and refinements in case capture procedures. Additionally, data will be collected to enable calculation of attributable mortality for BSI caused by resistant *E. coli* and *S. aureus* in accordance with the WHO-GLASS attributable mortality protocol.

3.2 Aim

The aim of this project is to roll out clinical AMR surveillance as part of routine care in a network of hospitals in across Asia and Africa, and to collect microbiology and clinical data from 2,500 patients per site, that will expand on the sample-based approach of WHO GLASS and enable classification of infection syndromes, origin of infection and outcome.

4 OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures
Primary	
Implement clinical antimicrobial resistance (AMR) surveillance of hospitalised patients with suspected acute bacterial infections at up to 15 sites in nine countries	Pre-implementation site assessments Site implementation status Numbers of patients enrolled by clinical syndrome, place of acquisition (community-acquired infection [CAI], hospital-acquired infection [HAI], healthcare associated infection [HCAI]), patient group (adult, paediatric, neonatal), and location (site, country, region) Proportion of timely (within 48 hours) and correctly sampled (i.e. syndrome-relevant specimens collected) patients per clinical syndrome, place of acquisition, and patient group by site, country, and region Clinician and surveillance staff acceptability and ease of use survey results by site, country, and region Surveillance staff time assessments and data collection app time measurements by site, country, and region
Secondary	
Characterise drug-resistant infections (DRI) by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, paediatric, neonatal), and location (site, country, region)	Antimicrobial susceptibility data for WHO GLASS target pathogens with isolate, specimen, and case level denominators by location Incidence of WHO GLASS target pathogen bloodstream infection (per 1,000 patient episodes) by clinical syndrome, place of acquisition, patient group, and location Weekly HAI point prevalence data by clinical syndrome, patient group, and location (with denominator being the number of patients resident on the ward at 8am on day of survey) Duration of hospitalisation for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location Patient outcomes / mortality for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location Economic costs for DRI and non-DRI by clinical syndrome, place of acquisition, patient group, and location

Objectives	Outcome Measures
Determine the attributable mortality for extended spectrum beta-lactamase producing *Escherichia coli* and methicillin resistant *Staphylococcus aureus* bloodstream infection	Incidence of bloodstream infection by *E. coli* and *S. aureus* (per 1,000 patient episodes) by clinical syndrome, place of acquisition, patient group, and location Antimicrobial susceptibility data of *E. coli* and *S. aureus* bloodstream infections by clinical syndrome, place of acquisition, patient group, and location Patient outcomes / mortality for susceptible vs. resistant *E. coli* and *S. aureus* bloodstream infections by clinical syndrome, place of acquisition, patient group, and location
Determine the major indications for prescribing parenteral antibiotics by patient group (adult, paediatric, neonatal), timing of prescription (day of admission versus >2 days after admission), and location (site, country, region)	Empiric antibiotic treatment data by clinical syndrome, timing of prescription, patient group, and location
Determine the major empiric antibiotics used by clinical syndrome, place of acquisition (CAI, HAI, HCAI), patient group (adult, paediatric, neonatal), and location (site, country, region)	Empiric antibiotic prescription data, classified by WHO AWaRe group, by clinical syndrome, place of acquisition, patient group, and location

5 SURVEILLANCE DESIGN

Prospective surveillance of hospitalised patients with a clinical suspicion of bacterial infection.

Community-acquired infections (CAI). Clinical, laboratory, and outcome data will be collected on patients who are admitted to specified surveillance wards and are prescribed / commenced on intravenous (IV) antibiotic treatment for suspected bacterial infection.

Hospital-acquired infections (HAI). Weekly point prevalence surveys will be done on specified surveillance wards to identify patients with active hospital-acquired infections. Clinical, laboratory, and outcome data will be collected on those patients who have been prescribed / commenced on a new IV antibiotic treatment for suspected bacterial infection not present at the time of admission.

Specific target pathogens will be *Streptococcus pneumoniae, Staphylococcus aureus, Salmonella* spp*., Pseudomonas aeruginosa, Neisseria meningitidis, Klebsiella pneumoniae, Haemophilus influenzae, Escherichia coli,* and *Acinetobacter* spp. (i.e. the blood culture associated WHO GLASS 2020 target organisms).

5.1 Surveillance Sites

The sites included in this surveillance are summarised in APPENDIX A: LIST OF POTENTIAL SURVEILLANCE SITES. Sites are 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 diagnostic microbiology laboratory. Each site will select three or more acute admission wards for surveillance: the selection should ideally include a general adult medical ward, a general paediatric ward and an intensive care unit.

5.1.1 Site summary and microbiology laboratory review

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

- Location
- Hospital type (general, paediatric, specialist)
- Level of care and specialties provided
- Ownership (government, private, other)
- For the most recent complete year, the total number of:
    - Admissions
    - Patients and patient days
    - Acute and ICU beds
    - Medical and nursing staff
- Details of existing
    - Electronic billing / patient record systems
    - Microbiology services and other relevant diagnostic services
    - Diagnostic and antimicrobial stewardship activities and materials

A review of the diagnostic microbiology laboratory will be undertaken to verify that surveillance-relevant standard operating procedures are in place and that appropriate quality standards are met. If areas of concern are identified then corrective actions will be requested, and implementation confirmed, to ensure laboratory data meets expected international standards (i.e. those required for submission of data to WHO GLASS (9, 11)).

Admission, patient day, bed, and staffing totals will be captured annually during surveillance.

5.1.2 Clinician knowledge, attitudes, and practices surveys

Prior to commencement of surveillance, all clinicians working on the surveillance wards will be invited to complete an anonymous knowledge, attitudes, and practices (KAP) survey focussed on AMR, diagnostic

microbiology, and hospital-based surveillance. Survey data will be used primarily to inform and iterate site-specific surveillance training and implementation.

6 PARTICIPANT IDENTIFICATION

6.1 Surveillance Population

All hospitalised patients of any age (i.e. children and adults) on pre-selected surveillance wards.

6.2 Inclusion Criteria

CAI: Patient with clinically suspected infection on admission to a surveillance ward (including those transferred directly from another facility), in whom the decision to start IV antibiotic treatment has been made, and willing to participate in the surveillance.

HAI: Patient resident on a surveillance ward during a scheduled point prevalence survey, willing to participate in the surveillance, and meeting the following criteria (adapted from the European Centre for Disease Prevention and Control definition (12)):

- Clinical suspicion of bacterial infection and prescription / commencement of a new IV antibiotic (but not escalation of antibiotic treatment for an existing suspected or proven infection)
  AND
- Onset of infection syndrome at least Day 3 of admission (Day 1 = day of admission)
  AND
- Infection syndrome was not active during the previous weekly review: i.e. onset at least one day following the most recent previous HAI point prevalence survey

6.3 Exclusion Criteria

None.

7 SURVEILLANCE PROCEDURES

7.1 Recruitment

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

Surveillance participants will be identified, screened and those who meet the inclusion criteria will be consecutively enrolled by surveillance personnel during daily review of new hospital admissions to surveillance wards (CAI) and during scheduled weekly point-prevalence surveys on these wards (HAI).

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

7.2 Screening and Eligibility Assessment

For CAI, a member of the surveillance team (clinician, nurse or research assistant) will review the clinical notes of each new admission on the surveillance wards daily Monday to Friday. The notes of patients admitted over the weekend or on public holidays shall be reviewed on the following workday.

For HAI, patients will be identified during weekly surveys of all patients resident in a bed on the surveillance ward at 8am on the day of the survey, excluding day case patients (i.e. those expected to be admitted and discharged on the same day).

7.3 Informed Consent

Research ethics committees will be requested to waive the need for explicit individual informed consent as this surveillance is a minimal / negligible risk activity, consisting of implementation of accepted quality improvement tools (diagnostic stewardship) and collection and use of limited clinical data that is 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 link clinical data to microbiology data held in the site laboratory information management system (LIMS). 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 study by the Oxford Tropical Research Ethics Committee (OXTREC 536-19), Cambodia National Ethics Committee for Health Research (215-NECHR), Laos Ministry of Health – University of Health Sciences Ethics Committee (211/19), and National Hospital for Tropical Disease Institutional Review Board, Hanoi, Vietnam (13/HDDD-NDTU).

All patients admitted to participating wards will be given an information sheet with details about the surveillance on admission. There will also be information posters visible on these wards. 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 parent / guardian / caretaker / legal acceptable representative will be approached by a surveillance team member 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. Agreement to participate will be recorded in the recruitment logbook.

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.

7.4 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)
- Date of birth or age
- Gender
- Date of admission and original hospitalisation (if transferred directly from another healthcare facility)
- Admission type (emergency or elective)
- Primary reason for admission
- Co-morbidity status (modified Charlson comorbidity index)
- Healthcare exposure, hospitalisation, and surgery in the three months before admission

The following data will be collected about the infection episode:

- Surveillance category (CAI or HAI)
- Ward details
- Clinically suspected infection syndrome / reason for prescription of IV antibiotics (adapted from (13))

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	Reason for antibiotic not documented

- Clinical severity signs on date of admission (CAI) or symptom onset (HAI)
    - qSOFA score for adults, ≥18 years (14)
    - Sepsis six recognition features for children, <18 years (15)
    - General WHO severity signs for neonates, <28 days (10)
- Presence of medical devices / surgical procedures (HAI only)
- Microbiology
    - Blood culture collected within 24 hours of admission (CAI) or symptom onset (HAI)
    - 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 admission (CAI) or symptom onset (HAI))

Standardised diagnostic stewardship advice will be offered to treating clinicians according to clinical syndrome.

7.5 Subsequent Assessments

7.5.1 During hospitalisation

A surveillance clinician will review pathogen positive cases to provide further diagnostic / treatment advice to the responsible clinician.

In cases with confirmed *E. coli* or *S. aureus* BSI (i.e. the organism detected in ≥1 blood culture), additional data will be collected:

- Admission ward details
- Immunosuppression status in the 48 hours prior to the blood culture
- Pitt BSI score on date of blood culture collection
- Empiric and targeted antibiotic treatment details, plus date of delivery of AST results to treating clinicians
- Likely source of infection
- Features of complicated infection (*S. aureus* only)

For all cases, clinical notes and electronic hospital information systems will be reviewed regularly to capture:

- Final categorisation of infection syndrome (or infection diagnosis rejected)
- Hospitalisation outcome and date
- Disposition (home, transfer to another healthcare facility, unknown)
- Number of days admitted to an intensive care unit

7.5.2 Day 28 assessment

The participant, or parent / guardian / caretaker / legal acceptable representative, will be contacted by telephone on day 28 (or next working day if day 28 falls on a weekend or public holiday) post enrolment to determine post-discharge health status (alive [fully recovered], alive [not fully back to normal activities], or dead) and date of death, if appropriate. If enrolled for >1 infection episode during an admission, then this assessment will occur 28 days following the final enrolment date. If unable to contact on day 28, two further attempts will be made to establish contact within the subsequent 10 days.

7.6 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.

7.7 Definition of End of Surveillance

The end of surveillance is the date of the final (attempted) telephone follow up of the last participant (i.e. a maximum of 10 days following the final scheduled day 28 follow up call).

8 INVESTIGATIONS

Specimens taken in the study are those required for routine clinical care only with no extra specimens for surveillance purposes. However, treating clinicians will be reminded of good practices for investigation of patients with suspected infection. This diagnostic stewardship will include encouragement to request blood cultures on all patients meeting clinical criteria for receipt of IV antibiotics, and other specimens as indicated (e.g. cerebrospinal fluid on patients with suspected meningitis), as well as appropriate radiologic investigations on selected patients (e.g. abdominal ultrasound scan on patients with sepsis and clinically-suspected liver abscess). Microbiology specimens will be processed by onsite laboratories, to identify pathogens and their antibiotic susceptibility profiles, following locally approved standard operating procedures (SOPs).

9 SAFETY CONSIDERATIONS

The surveillance is observational in nature with enhanced site-level diagnostic stewardship activities 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.

10 SURVEILLANCE MONITORING AND EVALUATION

Investigators at each site will identify appropriate personnel to be included in surveillance training and implementation activities. Surveillance staff will be asked to complete anonymous feedback

questionnaires, post-training and at the end of the surveillance period, on the features and usability of the surveillance tools, reports, and data visualisations. Time taken to collect ACORN data will be assessed by periodic audit during the surveillance and by review of data collection app timestamps.

The project data manager will produce regular reports for each site to assess enrolment rates and to identify problems with data capture. These reports, along with locally generated data summaries, will form the basis of monthly site review teleconferences. These meetings will include key site personnel and the central data and network managers.

Investigator meetings will be held on a quarterly basis to provide a forum to review progress and to deal with challenges. Towards the end of the project, a formal reflections meeting will be held to capture and discuss the experiences of the ACORN project. Participants will be briefed in advance on the purpose of the meeting and asked to seek the views and experiences of additional project partners before attending the meeting.

11 STATISTICS AND ANALYSIS

11.1 Description of Statistical Methods

11.1.1 Implementation data

Site summary, clinician KAP, and surveillance staff assessment questionnaire 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.

11.1.2 AMR surveillance data

Site-level data visualisation and analysis will be done onsite using the project specific R-Shiny app (see 12.2.2) or online via the identical web app (https://acornamr.net). For the overall project, site surveillance datasets will be merged prior to analysis.

Key outcome variables will be:

- Blood culture and other microbiology results
    - Presence or absence of target pathogen
    - Antimicrobial susceptibilities
- Duration of hospitalisation
- Hospital discharge vital status

- Day-28 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, HAI)
- Location (site, country, region)

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 infection / AMR on duration of hospitalisation will be assessed by time to event analysis.

Healthcare associated infections (HCAI) will be defined as the subset of CAI, where the patient was known to have had exposure to healthcare facilities in the three months prior to admission.

For syndrome-based analyses, the clinical syndrome will be that which was recorded at discharge (i.e. accounting for clinical course and additional diagnostic procedures undertaken subsequent to enrolment).

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

- Incidence of target pathogen bloodstream infection
- The percentage of isolates resistant to key antibiotics, as defined by WHO GLASS (9)
- The percentage of isolates categorised as multi-drug resistant, using standard definitions (16)

For empiric antibiotic analyses, drugs prescribed on the day of admission (CAI, HCAI) or symptom onset (HAI) will be classified according to the WHO AWaRe criteria (1). 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,

discharge diagnoses, and day-28 status (17). 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 no infection, susceptible infections, and resistant infections. Modelling approaches previously described (18) will be applied to ascertain the incremental costs and DALYs lost that can be attributed to resistant infections as compared with susceptible or no (in the case of HAIs, assuming many of them are preventable) infections, therefore conservatively assuming that resistant infections replace, rather than add to the burden of susceptible ones.

For E. coli and S. aureus BSI attributable mortality analyses, the survival model approach outlined in the WHO-GLASS protocol will be followed (10). Given the likely small numbers of BSI at each site, data from across the network will be combined, with appropriate adjustment to these exploratory models. At each site, observed crude case fatality rates (survival data) will be compared between cohorts: patients with AMR BSI for selected pathogen-antimicrobial combination (cohort 1), patient with non-AMR BSI for selected pathogen-antimicrobial combination (cohort 2), or ACORN-enrolled patient from the same surveillance ward in whom *E. coli* and *S. aureus* were not isolated from blood cultures (cohort 3). Models will be used to define the difference in mortality risk (hazard ratio) between groups. Other variables that might have an impact on the event of interest. (e.g. age, gender, co-morbidities, pre-existing conditions, antibiotic treatment, ICU stay, surgery, etc.) will be included in the models.

Cases of AMR *E. coli* or *S. aureus* bacteraemia (cohort 1) will be matched 1:1 retrospectively with cases of non-AMR *E. coli* or *S. aureus* bacteraemia (cohort 2). Optionally, randomly selected exposure density sampling plus additional matching criteria (age group and reason for admission) will be used to match 1:1 cohort 3 patients with cohort 1 and cohort 2 patients. This will result in three groups of patients (infected – drug susceptible, infected – drug resistant, non-infected) to enable robust determination of attributable mortality under both “additive” and “replacement” scenarios.

11.2 The Number of Participants

This surveillance will enrol all eligible and consenting patients admitted to the participating wards during the surveillance period. Based on pilot data, and the revised enrolment criteria, the target number of enrolments per site will be 2,500 over the 24-month surveillance period.

Assuming that 80% of enrolled patient episodes include a blood culture (pilot: 88% for Cambodia and 75% for Laos) and that 5% of blood cultures will yield a target organism (pilot: 4.9% for Cambodia and 7.4% for Laos), then the surveillance will yield 37,500 patient episodes, 30,000 blood culture results, and 1,500 target pathogen blood culture isolates with AST data. Non-blood culture specimen data, especially urine and pus / swabs, will be expected to increase the organism yield significantly (19).

12 DATA MANAGEMENT

12.1 Access to Data

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

12.2 Data Handling and Record Keeping

12.2.1 Implementation data

Site summary, clinician KAP, and surveillance staff assessment questionnaire data will be captured via Microsoft Forms online surveys, using the MORU Microsoft 365 Plan. MORU Microsoft Forms cloud data are held on a secure server located in the USA and access to data is restricted by user account, with two-factor authentication enabled. On completion of surveys, data will be downloaded, stored on a secure server at MORU in Bangkok, Thailand, and cloud will be deleted at this stage. No personal identifiers will be captured.

12.2.2 AMR surveillance data

Clinical data will be captured using password protected Android smartphones / tablets via an ODK app. These data will be uploaded to a secure ODK server at MORU, automatically synced to a Research Electronic Data Capture (REDCap) database, and accessed periodically using password-protected computers at each site. Laboratory data will be captured using the site's existing LIMS, WHONET (20), or using a MORU-designed Microsoft Access LIMS system for sites with no existing LIMS. Data will be extracted from these systems as text files, for onsite linkage with clinical data. Data validation procedures will be built into the ODK app and are included in both the MS LIMS and WHONET workflows. Transfer of clinical data from ODK to REDCap is done to enable robust editing of data, which is not currently possible using ODK alone.

Automated script-based linkage of the clinical and lab datasets will be performed locally at each site using a project specific app, developed in R and R-Shiny (21, 22). Linkages will be made on participant hospital ID, date of birth and hospitalisation / specimen dates. For CAI, all specimens collected +/- 2 days of admission are linked to the infection episode. For HAI, all specimens collected between the day of symptom onset and +2 days are linked to the infection episode. Thus, these identifiers will be captured via the ODK app. However, participant name and any other explicitly identifying detail will not be included in any electronic data file. Hospital sites will be identified by a unique code rather than name to reduce the

possibility of linking a participant hospital ID to a specific hospital. During the generation of merged clinical-laboratory data, a unique surveillance ID will be generated for each participant and the participant hospital ID and date of birth will be deleted automatically, rendering a fully de-identified dataset for analysis. De-identified finalised datasets will be uploaded to password protected site-specific "buckets" (folders) on a secure Amazon Web Services (AWS) cloud server, with backup managed by the MORU IT department. The AWS file storage enables sites to manage and access their own finalised data files efficiently and securely.

12.2.3 Personally identifiable data

Participant name, hospital ID, and telephone number will be recorded in a subject identification log at each site, to facilitate post-discharge follow-up. 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 an electronic database.

12.3 Data Retention

12.3.1 Implementation data

Data will be downloaded and stored indefinitely on a secure server at MORU.

12.3.2 AMR surveillance data

Electronic clinical data will be securely deleted from the ODK server and REDCap database once final merges with lab data are completed at the end of the surveillance period (no later than one year following the end of the surveillance period). AMR surveillance data (merged and anonymised clinical and laboratory data) will be stored indefinitely on a secure server at MORU Bangkok.

12.3.3 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 six months following the end of the surveillance period).

12.3.4 Data sharing

It is expected that anonymised line-list clinical and microbiology surveillance data will be made open access as per the Wellcome data sharing policy within one year of project completion or at the time of acceptance of the major project publication, whichever comes soonest (23).

13 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 (11, 24). 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.

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Declaration of Helsinki

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

14.2 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). All staff involved in collecting participant data will have received GCP training.

14.3 Approvals

The protocol, participant information sheet and any proposed advertising material will be submitted to the Local / National Research Ethics Committees 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.

14.4 Participant Confidentiality

Surveillance staff will ensure that the participants' anonymity is maintained. Personal information (i.e. name and telephone number) necessary for post-discharge 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.

14.5 Expenses and Benefits

Participants will not occur 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.

14.6 Risks

The only risk of taking part in this surveillance is loss of confidentiality, but the processes described in the data management section (section 12) above mitigate this risk. In particular, the final sharable AMR surveillance data file is anonymised during creation.

14.7 Reporting

The Chief Investigator shall submit an Annual Progress Report to OxTREC on the anniversary of the date of approval of the surveillance. In addition, the Chief Investigator 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.

14.8 Other Ethical Considerations

At each site, relevant local, sub-national and national and standard operating procedures will be followed regarding conduct of surveillance during the COVID-19 pandemic. 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 / national clinical guidelines.

15 FINANCE AND INSURANCE

15.1 Funding

This study is funded in full by a Wellcome Trust grant to the CI, reference number 222156/Z/20/Z.

15.2 Insurance

This research will be appropriately covered through the University of Oxford's legal liability insurances.

16 PUBLICATION POLICY

A summary manuscript, reporting the overall results of the surveillance, will be prepared by the core investigator team. Authorships will be determined following guidelines developed by the International Committee of Medical Journal Editors (25). Authorships on further manuscripts describing specific site-specific results or technical aspects of surveillance will be determined in a similar manner. Publications will be reviewed and approved by all investigators and their institutions prior to release.

17 REFERENCES

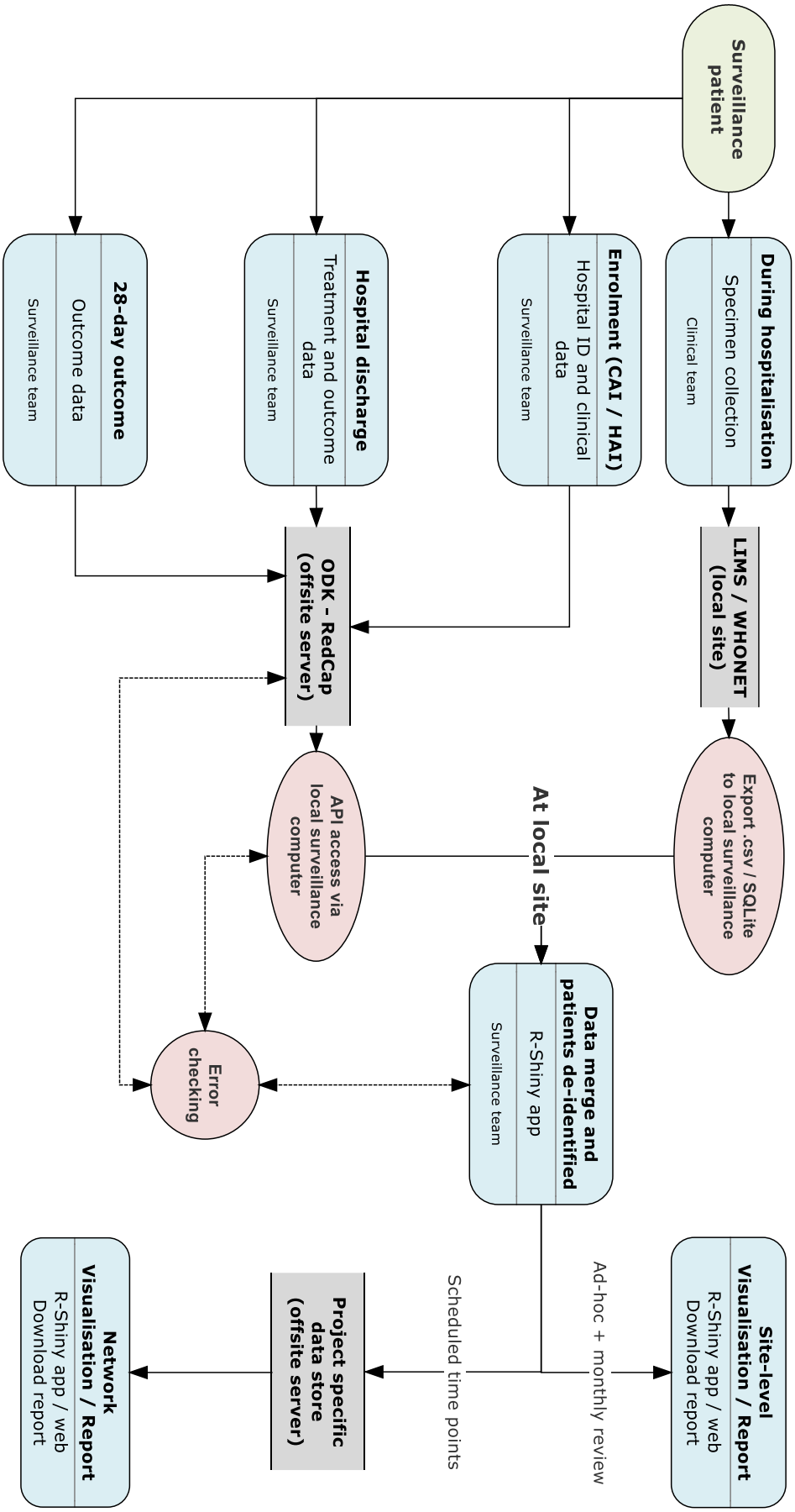
1. World Health Organization. Adopt AWaRe: Handle antibiotics with care. Available from: https://adoptaware.org/.
2. Ashley EA, Recht J, Chua A, Dance D, Dhorda M, Thomas NV, et al. An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000. J Antimicrob Chemother. 2018;73(7):1737-49.
3. Rempel OR, Laupland KB. Surveillance for antimicrobial resistant organisms: potential sources and magnitude of bias. Epidemiol Infect. 2009;137(12):1665-73.
4. Seale AC, Hutchison C, Fernandes S, Stoesser N, Kelly H, Lowe B, et al. Supporting surveillance capacity for antimicrobial resistance: Laboratory capacity strengthening for drug resistant infections in low and middle income countries. Wellcome Open Res. 2017;2(91):91.
5. Ryu S, Cowling BJ, Wu P, Olesen S, Fraser C, Sun DS, et al. Case-based surveillance of antimicrobial resistance with full susceptibility profiles. JAC-Antimicrobial Resistance. 2019;1(3).
6. Hay SI, Rao PC, Dolecek C, Day NPJ, Stergachis A, Lopez AD, et al. Measuring and mapping the global burden of antimicrobial resistance. BMC Med. 2018;16(1):78.
7. Turner P, Ashley EA, Celhay OJ, Douangnouvong A, Hamers RL, Ling CL, et al. ACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network): a pilot protocol for case based antimicrobial resistance surveillance. Wellcome Open Res. 2020;5:13.
8. van Doorn HR, Ashley EA, Turner P. Case-based surveillance of antimicrobial resistance in the ACORN (A Clinically Oriented Antimicrobial Resistance Surveillance Network) study. JAC Antimicrob Resist. 2020;2(1):dlaa018.
9. World Health Organization. Global Antimicrobial Resistance Surveillance System: Manual for Early Implementation. Geneva: World Health Organization; 2015.
10. Global Antimicrobial Resistance and Use Surveillance System. GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections Geneva: World Health Organization; 2020. Available from: https://www.who.int/publications/i/item/9789240000650.

11. AMR Surveillance in low- and middle-income settings: A roadmap for participation in the Global Antimicrobial Surveillance System (GLASS): London School of Hygiene & Tropical Medicine; 2016. Available from: https://amr.lshtm.ac.uk/wp-content/uploads/sites/12/2016/11/AMR-Surveillance-Protocol.pdf.
12. European Centre for Disease Prevention and Control. Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals – protocol version 5.3. Stockholm: ECDC; 2016.
13. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619-e29.
14. Rudd KE, Seymour CW, Aluisio AR, Augustin ME, Bagenda DS, Beane A, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries. JAMA. 2018;319(21):2202-11.
15. Tong J, Plunkett A, Daniels R. G218(P) The Paediatric Sepsis 6 Initiative. Archives of Disease in Childhood. 2014;99:A93-A.
16. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268-81.
17. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56-66.
18. Fox-Lewis A, Takata J, Miliya T, Lubell Y, Soeng S, Sar P, et al. Antimicrobial Resistance in Invasive Bacterial Infections in Hospitalized Children, Cambodia, 2007-2016. Emerg Infect Dis. 2018;24(5):841-51.
19. Vihta K-D, Gordon NC, Stoesser N, Quan TP, Tyrrell CSB, Vongsouvath M, et al. Antimicrobial resistance surveillance: can we estimate resistance in bloodstream infections from other types of specimen? medRxiv. 2020:2020.10.12.20211243.
20. WHO Collaborating Centre for Surveillance of Antimicrobial Resistance. WHONET: The microbiology laboratory database software. Available from: http://www.whonet.org/.
21. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.
22. Chang W, Cheng J, Allaire JJ, Xie Y, McPherson J. shiny: Web Application Framework for R. R package version 1.2.0. 2018.
23. Wellcome. Data, software and materials management and sharing policy. Available from: https://wellcome.org/grant-funding/guidance/data-software-materials-management-and-sharing-policy.
24. Dat VQ, Geskus RB, Wolbers M, Loan HT, Yen LM, Binh NT, et al. Continuous versus intermittent endotracheal cuff pressure control for the prevention of ventilator-associated respiratory infections in Vietnam: study protocol for a randomised controlled trial. Trials. 2018;19(1):217.
25. International Committee of Medical Journal Editors. Defining the Role of Authors and Contributors. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

18 APPENDIX A: LIST OF POTENTIAL SURVEILLANCE SITES

Country
Cambodia
Ghana
Indonesia
Kenya
Lao PDR
Malawi
Nepal
Nigeria
Vietnam

19 APPENDIX B: SURVEILLANCE FLOW CHART



20 APPENDIX C: SCHEDULE OF SURVEILLANCE PROCEDURES

Procedures	Site Level		Patient Visits			
	Prior to start of patient enrolment	End of surveillance period	Day 1	Day 2 - discharge	Hospital Discharge	Day 28
			Baseline	Follow-up	Outcome #1	Outcome #2
Site summary data collection	X					
Laboratory assessment	X					
Clinician KAP survey	X	X				
Staff feedback survey	X	X				
Eligibility assessment			X			
Demographic data collection			X			
Clinical syndrome data collection			X			
Investigation data collection			X			
Treatment data collection			X	X*		
Diagnostic stewardship			X	X		
Outcome data collection					X	X

** E. coli and S. aureus* BSI episodes only

21 APPENDIX D: AMENDMENT HISTORY

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