



STUDY PROTOCOL

REVISED **ACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network) II: protocol for case based antimicrobial resistance surveillance [version 2; peer review: 2 approved]**

Yin Mo ¹⁻⁵, Ying Ding¹, Yang Cao⁶, Jill Hopkins ^{4,7}, Elizabeth A. Ashley ^{4,8}, Naomi Waithira ^{4,5}, Prapass Wannapinij⁵, Sue J. Lee ^{4,5}, Claire L. Ling^{4,7}, Raph L. Hamers ^{4,9}, Tamalee Roberts ^{4,8}, Yoel Lubell ^{4,5}, Abhilasha Karkey ^{4,9}, Samuel Akech ¹⁰, Samantha Lissauer^{11,12}, Japheth Opintan¹³, Iruka Okeke ¹⁴, Sergey Eremin¹⁵, Barbara Tornimbene¹⁵, Li Yang Hsu¹, Louise Thwaites ^{4,16}, Minh Yen Lam¹⁶, Ngoc Thach Pham¹⁷, Tieu Kieu Pham¹⁶, Jeanette Teo¹⁸, Andrea Lay-Hoon Kwa^{19,20}, Kalisvar Marimuthu^{21,22}, Oon Tek Ng^{21,22}, Shawn Vasoo^{21,22}, Suwatthiya Kitsaran²³, Siriluck Anunnatsiri²⁴, Pope Kosalaraksa²⁵, Darunee Chotiprasitsakul²⁶, Pitak Santanirand²⁶, Rongpong Plongla²⁷, Hock Hin Chua²⁸, Xun Ting Tiong²⁸, Ke Juin Wong²⁹, Sasheela Sri La Sri Ponnampalavanar³⁰, Helmi Bin Sulaiman³⁰, Mohd Zulfakar Mazlan³¹, Zeti Norfidiyati Salmuna³², Giri Shan Rajahram³³, Mohd Zaki Bin Mohd Zaili³⁴, Joshua R. Francis³⁵, Nevio Sarmiento^{35,36}, Helio Guterres³⁷, Tessa Oakley³⁵, Jennifer Yan³⁵, Ari Tilman³⁶, Muhammad Osama Rehman Khalid³⁸, Madiha Hashmi ³⁸, Syed Faisal Mahmood³⁹, Azizullah Khan Dhiloo⁴⁰, Ambreen Fatima⁴⁰, Inke Nadia D. Lubis⁴¹, Hendri Wijaya^{41,42}, Cybele L. Abad⁴³, Arthur Dessi Roman⁴⁴, Cecilia C. Maramba Lazarte^{44,45}, Gazi Md. Salahuddin Mamun⁴⁶, Rosmonaliza Asli⁴⁷, Muhd Haziq Fikry bin Haji Abdul Momin⁴⁷, Khurelbaatar Nyamdavaa⁴⁸, Ulziijargal Gurjav⁴⁸, Sotharith Bory⁴⁹, George M. Varghese⁵⁰, Lalit Gupta⁵¹, Pratik Tantia⁵², Robert Sinto⁵³, Yohei Doi⁵⁴, Basudha Khanal⁵⁵, Greco Malijan⁵⁶, Jezreel Lazaro⁵⁷, Samanmalee Gunasekara⁵⁸, Sumudu Withanage⁵⁸, Po Yu Liu⁵⁹, Yonghong Xiao⁶⁰, Minggu Wang⁶¹, David L. Paterson ^{1,3}, H. Rogier van Doorn ⁴, Paul Turner ^{4,7}

¹ADVANCE-ID, Saw Swee Hock School Of Public Health, National University of Singapore, Singapore, 117549, Singapore

²Division of Infectious Diseases, National University Hospital, Singapore, Singapore, 119074, Singapore

³Department of Medicine, National University of Singapore, Singapore, 119228, Singapore

⁴Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK

- ⁵Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Salaya, Nakhon Pathom, 10400, Thailand
- ⁶Singapore Clinical Research Institute, Singapore, 139234, Singapore
- ⁷Cambodia Oxford Medical Research Unit, Angkor Hospital for Children, Siem Reap, 171020, Cambodia
- ⁸Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic
- ⁹Oxford University Clinical Research Unit (OUCRU) Indonesia, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
- ¹⁰Kenya Medical Research Institute, Nairobi, Kenya
- ¹¹Liverpool School of Tropical Medicine (LSTM), University of Liverpool, Liverpool, England, UK
- ¹²Malawi-Liverpool-Wellcome Trust (MLW) Clinical Research Programme, Blantyre, Malawi
- ¹³University of Ghana, Accra, Ghana
- ¹⁴University of Ibadan, Ibadan, Nigeria
- ¹⁵World Health Organization, Geneva, Switzerland
- ¹⁶Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam
- ¹⁷National Hospital of Tropical Diseases, Ha Noi, Vietnam
- ¹⁸Department of laboratory Medicine, University Medicine Cluster, National University Hospital, Singapore, Singapore
- ¹⁹Pharmacy (Research), Singapore General Hospital, Singapore, Singapore
- ²⁰Emerging Infectious Diseases Programme, Duke-National University of Singapore Medical School, Singapore, Singapore
- ²¹National Centre for Infectious Diseases, Singapore, Singapore
- ²²Department of Infectious Disease, Tan Tock Seng Hospital, Singapore, Singapore
- ²³Sunpasitthiprasong Hospital, Ubon Ratchathani, Thailand
- ²⁴Department of Medicine, Faculty of Medicine, Khon Kaen University, Nai Mueang, Khon Kaen, Thailand
- ²⁵Department of Pediatrics, Faculty of Medicine, Khon Kaen University, Nai Mueang, Khon Kaen, Thailand
- ²⁶Ramathibodi Hospital, Bangkok, Thailand
- ²⁷King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand
- ²⁸Sarawak General Hospital, Sarawak, Malaysia
- ²⁹Sabah Women and Children's Hospital, Kota Kinabalu, Malaysia
- ³⁰University of Malaya Medical Centre, Kuala Lumpur, Malaysia
- ³¹Department of Anesthesiology and Intensive Care, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
- ³²Department of Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia
- ³³Queen Elizabeth II Hospital, Kota Kinabalu, Sabah, Malaysia
- ³⁴Hospital Queen Elizabeth, Kota Kinabalu, Sabah, Malaysia
- ³⁵Menzies school of health research, Charles Darwin University, Dili, Timor-Leste
- ³⁶Laboratorio Nacional da Saude, Ministerio da Saude, Dili, Timor-Leste
- ³⁷Guido Valadares National Hospital, Dili, Timor-Leste
- ³⁸Dr. Ziauddin Hospital Clifton Campus, Karachi, Pakistan
- ³⁹The Aga Khan University Hospital, Karachi, Pakistan
- ⁴⁰Dow University of Health Sciences, Karachi, Pakistan
- ⁴¹Faculty of Medicine, Universitas Sumatera Utara, Medan, North Sumatra, Indonesia
- ⁴²General Hospital H. Adam Malik, Medan, Indonesia
- ⁴³The Medical City, Pasig, Metro Manila, Philippines
- ⁴⁴Philippine General Hospital, Manila, Philippines
- ⁴⁵University of the Philippines Manila, Manila, Metro Manila, Philippines
- ⁴⁶International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh
- ⁴⁷Raja Isteri Pengiran Anak Saleha Hospital, Bandar Seri Begawan, Brunei-Muara District, Brunei
- ⁴⁸Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia
- ⁴⁹Calmette Hospital, Phnom Penh, Cambodia
- ⁵⁰Christian Medical College Vellore Association, Vellore, India
- ⁵¹Maulana Azad Medical College and Lok Nayak Hospital, New Delhi, India
- ⁵²Ananta Institute of Medical Sciences and Research Center, Siyol, India
- ⁵³Cipto Mangunkusumo National Hospital, Faculty of Medicine, Universitas Indonesia, Depok, West Java, Indonesia
- ⁵⁴Fujita Health University Hospital, Toyoake, Japan
- ⁵⁵B.P. Koirala Institute of Health Sciences, Dharan, Nepal
- ⁵⁶San Lazaro Hospital, Nagasaki University Collaborative Research Office, Manila, Philippines
- ⁵⁷Hospital Infection Control Unit, San Lazaro Hospital, Manila, Philippines
- ⁵⁸National Cancer Institute, Maharagama, Sri Lanka
- ⁵⁹

Taichung Veteran General Hospital, Taichung City, Vietnam

⁶⁰The First Affiliated Hospital Of Zhejiang University School Of Medicine, Hangzhou, China

⁶¹Huashan Hospital, Fudan University, Shanghai, China

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Abstract

Background: Antimicrobial resistance surveillance is essential for empiric antibiotic prescribing, infection prevention and control policies and to drive novel antibiotic discovery. However, most existing surveillance systems are isolate-based without supporting patient-based clinical data, and not widely implemented especially in low- and middle-income countries (LMICs).

Methods: A Clinically-Oriented Antimicrobial Resistance Surveillance Network (ACORN) II is a large-scale multicentre protocol which builds on the WHO Global Antimicrobial Resistance and Use Surveillance System to estimate syndromic and pathogen outcomes along with associated health economic costs. ACORN-healthcare associated infection (ACORN-HAI) is an extension study which focuses on healthcare-associated bloodstream infections and ventilator-associated pneumonia. Our main aim is to implement an efficient clinically-oriented antimicrobial resistance surveillance system, which can be incorporated as part of routine workflow in hospitals in LMICs. These surveillance systems include hospitalised patients of any age with clinically compatible acute community-acquired or healthcare-associated bacterial infection syndromes, and who were prescribed parenteral antibiotics. Diagnostic stewardship activities will be implemented to optimise microbiology culture specimen collection practices. Basic patient characteristics, clinician diagnosis, empiric treatment, infection severity and risk factors for HAI are recorded on enrolment and during 28-day follow-up. An R Shiny application can be used offline and online for merging clinical and microbiology data, and generating collated reports to inform local antibiotic stewardship and infection control policies.







Discussion: ACORN II is a comprehensive antimicrobial resistance surveillance activity which advocates pragmatic implementation and prioritises improving local diagnostic and antibiotic prescribing practices through patient-centred data collection. These data can be rapidly communicated to local physicians and infection prevention and control teams. Relative ease of data collection promotes sustainability and maximises participation and scalability. With ACORN-HAI as an example, ACORN II has the capacity to accommodate extensions to investigate further specific questions of interest.

Keywords


Antimicrobial resistance, surveillance, antibiotic stewardship

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1. **Dickson Aruhomukama**, Makerere University, Kampala, Uganda

2. **Bashar Haruna Gulumbe** , Federal University Birnin Kebbi, Birnin Kebbi, Nigeria

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Yin Mo (moyin@tropmedres.ac)

Author roles: **Mo Y:** Conceptualization, Funding Acquisition, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Ding Y:** Investigation, Project Administration, Writing – Review & Editing; **Cao Y:** Investigation, Project Administration, Writing – Review & Editing; **Hopkins J:** Investigation, Methodology, Project Administration, Writing – Review & Editing; **Ashley EA:** Methodology, Writing – Review & Editing; **Waithira N:** Methodology, Writing – Review & Editing; **Wannapinij P:** Methodology, Writing – Review & Editing; **Lee SJ:** Methodology, Writing – Review & Editing; **Ling CL:** Investigation; **Hamers RL:** Investigation; **Roberts T:** Investigation; **Lubell Y:** Investigation; **Karkey A:** Investigation; **Akech S:** Investigation; **Lissauer S:** Investigation; **Opintan J:** Investigation; **Okeke I:** Investigation; **Eremin S:** Investigation; **Tornimbene B:** Investigation; **Hsu LY:** Funding Acquisition; **Thwaites L:** Investigation; **Lam MY:** Investigation; **Pham NT:** Investigation; **Pham TK:** Investigation; **Teo J:** Investigation; **Kwa ALH:** Investigation; **Marimuthu K:** Investigation; **Ng OT:** Investigation; **Vasoo S:** Investigation; **Kitsaran S:** Investigation; **Anunnatsiri S:** Investigation; **Kosalaraksa P:** Investigation; **Chotiprasitsakul D:** Investigation; **Santanirand P:** Investigation; **Plongla R:** Investigation; **Chua HH:** Investigation; **Tiong XT:** Investigation; **Wong KJ:** Investigation; **Ponnampalavanar SSL:** Investigation; **Sulaiman HB:** Investigation; **Mazlan MZ:** Investigation; **Salmuna ZN:** Investigation; **Rajahram GS:** Investigation; **Zaili MZBM:** Investigation; **Francis JR:** Investigation; **Sarmiento N:** Investigation; **Guterres H:** Investigation; **Oakley T:** Investigation; **Yan J:** Investigation; **Tilman A:** Investigation; **Khalid MOR:** Investigation; **Hashmi M:** Investigation; **Mahmood SF:** Investigation; **Dhiloo AK:** Investigation; **Fatima A:** Investigation; **Lubis IND:** Investigation; **Wijaya H:** Investigation; **Abad CL:** Investigation; **Roman AD:** Investigation; **Lazarte CCM:** Investigation; **Mamun GMS:** Investigation; **Asli R:** Investigation; **Momin MHFbHA:** Investigation; **Nyamdavaa K:** Investigation; **Gurjav U:** Investigation; **Bory S:** Investigation; **Varghese GM:** Investigation; **Gupta L:** Investigation; **Tantia P:** Investigation; **Sinto R:** Investigation; **Doi Y:** Investigation; **Khanal B:** Investigation; **Malijan G:** Investigation; **Lazaro J:** Investigation; **Gunasekara S:** Investigation; **Withanage S:** Investigation; **Liu PY:** Investigation; **Xiao Y:** Investigation; **Wang M:** Investigation; **Paterson DL:** Conceptualization, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Doorn HRv:** Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Turner P:** Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

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REVISED Amendments from Version 1

We thank the reviewers for their insightful comments. In this updated version, we clarified the progression of the ACORN study from ACORN I (pilot) to ACORN II and the extension study, ACORN-HAI. We also highlight the synergy between ACORN II and ACORN-HAI in terms of enrolling more patients with HAI, and capturing their clinical data in greater detail. In the discussion, we also include the key limitations for the study.

Any further responses from the reviewers can be found at the end of the article

Background

Antimicrobial resistance is declared as 1 of the top 10 global public health threats facing humanity¹. Surveillance for the emergence and spread of antimicrobial resistance is a cornerstone of our response strategies. It is essential both at patient-level for informing empiric antibiotic prescribing and treatment guidelines, and at system-level for designing and evaluating treatment, infection prevention and control policies². Antimicrobial resistance surveillance involves systematic data collection, analysis and communication. The aim is to describe disease burden and epidemiology in a timely and unbiased manner that is relevant to the community and various stakeholders, including patients, physicians, researchers and policy makers.

Despite a global emphasis on antimicrobial resistance in recent decades, effective surveillance networks and systems remain sparse³. This is mainly because assembling comprehensive surveillance data which incorporate both clinical and microbiological records is challenging. Infection episodes are defined using clinical criteria which involves sourcing individual-level data from medical notes, microbiological reports and antibiotic prescription charts. Existing population-level surveillance databases, such as the European Centre for Disease Prevention and Control Surveillance Atlas, The Center For Disease Dynamics, Economics & Policy Resistance Map, and the World Health Organisation (WHO) Global Antimicrobial Resistance and Use Surveillance System (GLASS), are isolate-based and rely mainly on microbiology data alone⁴⁻⁶.

These isolate-based data present geospatial and temporal trends of resistant organisms but are prone to biases introduced by local characteristics such as differential access to antibiotics in the community versus hospital settings, antibiotic prescription practices, availability of laboratory resources, and practices of microbiological culture collection and reporting. Particularly in low- and middle-income countries (LMICs), microbiology cultures may only be performed after multiple courses of empirical antibiotics have failed or in situations where diagnostics are affordable. Importantly, interpreting microbiology cultures without considering clinical syndromes makes it impossible to differentiate innocent 'bystander' colonising versus true pathogens, i.e. if a patient became ill or died *due to* or *with* a resistant bacteria. In addition, quantifying morbidity and mortality impacts of drug-resistant infections requires longitudinal follow-up and cannot be reliably determined from death certificates⁷. Such high quality surveillance data is especially

lacking in LMICs where antimicrobial resistance burden is the highest⁸⁻¹⁰.

A Clinically-Oriented Antimicrobial Resistance Surveillance Network (ACORN) is a large-scale multicentre study which captures essential data on patient clinical features, management, and outcomes. ACORN adds value to isolate-based antimicrobial resistance surveillance (e.g. WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS)), using patient rather than pathogen denominators, syndromic and pathogen outcomes, along with associated health economic costs¹¹. It aims to implement an efficient clinically-oriented antimicrobial resistance surveillance system, incorporated as part of routine workflow in hospitals in LMICs. In addition, ACORN II is designed to accommodate extension studies with specific focuses on infection syndrome, pathogens or patient population.

An initial pilot phase (ACORN I) was completed in 2020, focusing on patients with clinically suspected meningitis, pneumonia, or sepsis^{11,12}. Specific target pathogens included *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Salmonella spp.*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Acinetobacter baumannii*. The current ACORN II study protocol refines the methodology ACORN I, and expands the scope to include all infection syndromes and bacterial pathogens. To illustrate the ability of ACORN design to accommodate extension studies, we describe the ACORN-healthcare associated infection (ACORN-HAI) extension study which focuses on healthcare-associated bloodstream infections and ventilator-associated pneumonia. Study procedures including site set up, diagnostic stewardship, data collection and rationale behind their design features are detailed below.

Methods/design**Ethics approval and consent to participate**

An overarching approval for ACORN II and ACORN-HAI was given by the Oxford Tropical Research Ethics Committee (OxTREC, ref 524-21). Local ethics approvals are sought prior to enrolment. Written informed consent is required for participation in all study sites except the following, where anonymised data may be collected without individual consent: Angkor Hospital for Children in Siem Reap (Cambodia), Sarawak General Hospital (Malaysia), Queen Elizabeth II Hospital (Malaysia), Sabah Women and Children's Hospital (Malaysia), University Malaya Medical Centre (Malaysia), National Hospital of Tropical Diseases, Hanoi (Vietnam).

Aims and objectives

The aim of ACORN II is to provide actionable data to local institutions, national and international surveillance systems, researchers and policy makers via an efficient clinically orientated antimicrobial resistance surveillance system (extended data 2). It is designed to be implemented alongside routine clinical care in hospitals, especially in LMIC settings. The data collected are fully compatible with WHO GLASS and are further expanded to enable classification of infection syndromes and outcomes. These data will be used to estimate syndromic and pathogen outcomes along with associated costs.

The specific objectives are to i) implement and assess a hospital-based system for patient-centred surveillance of drug resistant infections; ii) characterise drug-resistant infections by clinical syndrome, place of acquisition, patient group, and location; iii) quantify burden of drug-resistant infections in terms of attributable mortality and excess length of hospital stay (including determining the attributable mortality for extended spectrum beta-lactamase producing *Escherichia coli* and methicillin resistant *Staphylococcus aureus* bloodstream infection using the WHO attributable mortality protocol¹³); iv) determine the major indications for prescribing parenteral antibiotics by patient group, timing of prescription, and location; and, v) to determine the major empiric antibiotics used by clinical syndrome, place of acquisition, patient group, and location (Section “Surveillance data analysis and communication”).

Study design

ACORN II is a prospective observational cohort study of hospitalised patients with community-acquired and healthcare-associated bacterial infections (Figure 1). In the ACORN II workflow, community-acquired infections (CI) are identified by daily review of new admissions to designated surveillance wards. Healthcare-associated infections (HAI), which refer to infections in patients who had significant healthcare exposure in the three months prior to admission (extended data 2), are initially enrolled as CI and will be re-classified as HAI on analysis. Hospital-acquired infections (HI) are identified during weekly point prevalence surveys on these wards. All patients who are receiving antibiotic treatment for these infections will be eligible for enrolment. Basic demographic characteristics, comorbidities, clinician diagnosis, empiric treatment, markers of clinical severity and risk factors for HAI are recorded on enrolment. Final clinician diagnosis, hospital discharge and day 28 outcome data (from the last infection episode of the admission) are collected prospectively. To contribute to the WHO GLASS attributable mortality study, additional clinical and treatment data are collected on patients with confirmed *E. coli* or *S. aureus* bloodstream infection.

Surveillance targets include, but are not limited to, pathogens that are usually associated with bloodstream infections included in WHO GLASS: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Salmonella* spp., *Pseudomonas aeruginosa*, *Neisseria meningitidis*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, and *Acinetobacter* spp.

Study sites

Participating sites will i) undergo basic research training such as “Good Clinical Practice (GCP)” (<https://globalhealthtraining-centre.tghn.org/ich-good-clinical-practice/>); ii) set up infrastructure such as computers, data collection software and laboratory capacity; iii) form communication channels between the research investigators, clinicians and laboratory teams for collaborations and data sharing; and iv) familiarise themselves with local ethics and regulatory bodies.

At least three acute admission wards will be selected for surveillance per site, which should ideally include a general adult medical ward, a general paediatric ward, and an intensive

care unit. Consideration should be given to harmonisation with other surveillance activities, where possible. Senior clinicians, nurses and microbiology laboratory staff should be engaged as part of the study team, and understand the purpose and scope of ACORN II.

Online tools are available to guide the sites for study preparation and implementation. These cover areas such as laboratory assessment, diagnostic stewardship, and clinician knowledge, attitudes and practices (KAP) surveys:

- *Laboratory assessment*

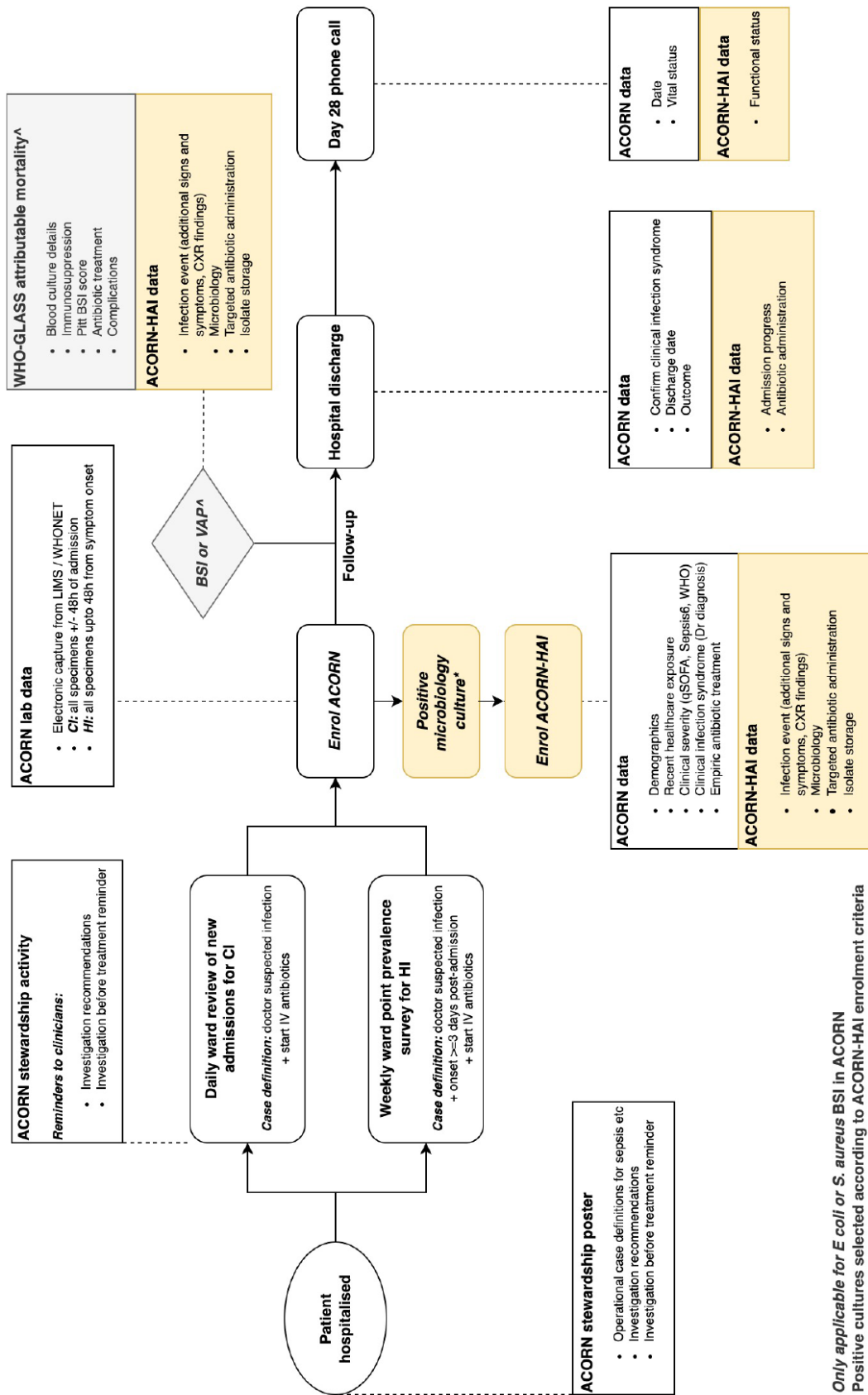
The purpose of laboratory assessment is to make a baseline evaluation of the laboratories that will be used for processing samples and submitting data for antimicrobial resistance (AMR) surveillance. Laboratory assessments will be performed using the Laboratory Pre-Assessment online survey (<https://tinyurl.com/ACORNlabsurvey>), the Site Laboratory Assessment tool (extended data 3), document review and virtual audits. The assessment tools allow the assessors to gather information on the current capacity of site laboratories including what routine specimen processing the laboratory already carries out, the current level of quality management and quality control in the laboratory, safety procedures and specimen reporting. Following completion of the laboratory assessment continual laboratory quality monitoring is performed using the Site Laboratory Quality Monitoring tool (extended data 3).

- *Assessment / implementation of diagnostic stewardship*

Diagnostic stewardship is designed to improve appropriate microbiologic testing of patients with suspected bacterial infection at ACORN II surveillance sites (extended data 3). The endpoint of diagnostic stewardship is to ensure that the right patients have the right tests at the right time and that results are used to ensure that they receive the right treatment. Systematic testing of patients with suspected infection will result in data that can be used to inform local treatment guidelines as well as be used for AMR surveillance activities. It is important that ACORN II stewardship is aligned with existing specimen collection, processing, and feedback procedures. A diagnostic stewardship checklist is available to determine the extent of existing diagnostic stewardship activities / materials at the site. Negative answers to any of the questions should prompt development of that particular item / activity in the form of recommendations for standardised investigations for suspected infection, at least covering when to collect a blood culture and / or sterile site fluid culture. Examples of appropriate guidelines are included in the ACORN diagnostic stewardship guideline and can be adapted to the local situation. Monitoring of culture rates, by patient group, clinical location, clinical syndrome, via the ACORN project app described will permit assessment of diagnostic stewardship activity success.

- *Clinician Knowledge, Attitudes and Practices survey*

The purpose of the clinician knowledge, attitudes and practices survey is to make a baseline assessment of the clinical staff working on ACORN II surveillance wards (extended data 3, <https://tinyurl.com/ACORNclinicianKAP>). The survey gathers information on current knowledge, attitudes and practices



[^] Only applicable for *E coli* or *S. aureus* BSI in ACORN
 * Positive cultures selected according to ACORN-HAI enrolment criteria

Figure 1. Flow diagram of key study processes for an enrolled patient. Boxes in white explain study processes in ACORN. Boxes in yellow represent additional activities and data collected for ACORN-HAI. Acronyms: CI – community acquired infection; HAI – healthcare-associated infection; HI – ventilator-associated pneumonia.

around diagnostic microbiology and AMR surveillance. The data will be used primarily to inform and iterate site-specific surveillance training and implementation.

Study participants

We adopt a pragmatic approach to identify potential patients for enrolment. Patients will be enrolled based on clinician diagnosis or, in the absence of clear clinician diagnosis, if they are assessed by the surveillance team as meeting the clinical case criteria for respective infections. For CI cases, newly admitted patients will need to be identified, e.g. from a ward admission logbook. The CI inclusion criteria are:

- Patient with clinically suspected infection on admission to a surveillance ward (including those transferred directly from another facility), in whom the decision to start intravenous antibiotic treatment has been made, and are willing to participate in the surveillance. This includes¹:
 - Patients transferred directly from another facility with an acute infection;
 - Patients admitted to a non-surveillance ward initially but transferred to a surveillance ward within 48 hours of admission;
 - Patients investigated and treated for suspected CI in the Emergency Department (Emergency Room / Accident and Emergency Department) with delayed transfer to the surveillance ward for any reasons, e.g. bed shortages, COVID-19 screening procedures, or other local operational challenges.

For HI cases, all admitted patients in the surveillance wards will be reviewed on a single day per week via a point prevalence survey (PPS). The HI inclusion criteria include:

- Clinical suspicion of bacterial infection and prescription / commencement of a new intravenous antibiotic (but not escalation of antibiotic treatment for an existing suspected or proven infection); and
- Onset of infection syndrome on or after day 3 of admission (day 1 refers to the 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 healthcare-associated infection point prevalence survey

An overarching approval for ACORN II to enrol without the need for individual consent was given by the Oxford Tropical Research Ethics Committee (OxTREC, ref 524-21). The requirement for informed consent will be catered to local ethics committees' advice. In participating sites where the need for explicit informed consent can be waived for minimal/negligible risk studies, potential participants in participating wards will be given a patient information sheet with details

about the study. At least one ACORN II information poster will be on display in each surveillance ward. Potential study participants will be asked to confirm verbally that they (or legally acceptable representatives) have read the surveillance information material and agree to participate. Any patient who requests not to be included in the study will be recorded accordingly in the screening logbook. In sites where informed consent cannot be waived, a typical consent taking process will be in place.

Further infection episodes may be identified during the weekly PPS. The final follow up is 28 days after the final infection episode. This can be done by telephone if the participant has been discharged. If the patient is readmitted before the 28 day follow up, the 28 day follow up should be completed as scheduled if no further infection episodes are diagnosed during the readmission.

Data collection and management

On enrolment, baseline clinical data will be extracted from the patient clinical records/electronic hospital information systems (Figure 2):

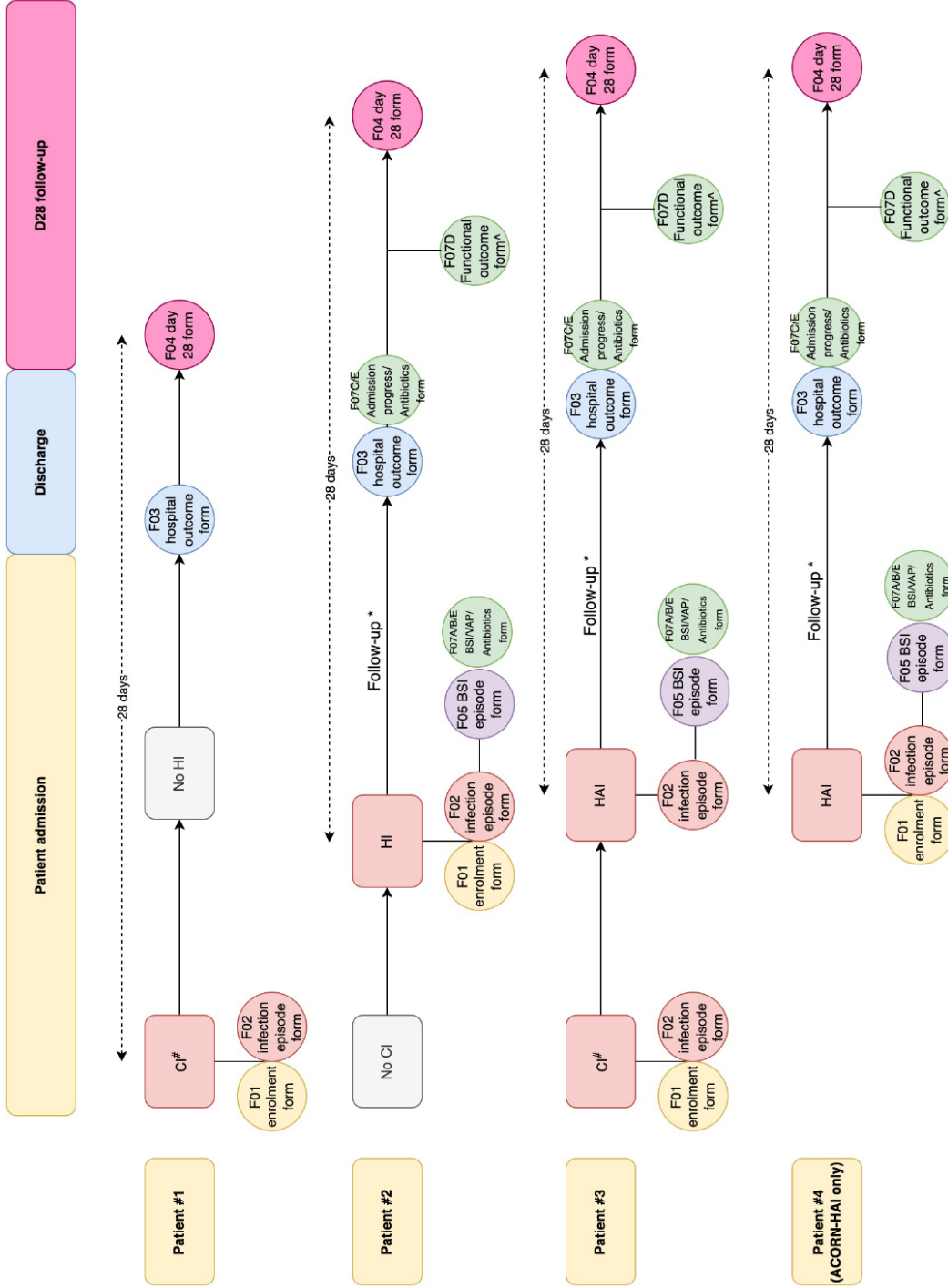
- Demographics
- Date of admission and ward location
- Primary reason for admission
- Co-morbidity status (modified Charlson comorbidity index)
- Healthcare exposure in the three months before current admission

The following data will be collected about the infection episode on enrolment and when a new infection episode is detected in the weekly ward PPS:

- Ward details
- Infection syndrome
- Clinical severity signs at symptom onset
 - qSOFA score for adults, ≥ 18 years¹⁴
 - Sepsis six recognition features for children, < 18 years¹⁵
 - General WHO severity signs for neonates, < 28 days
- Presence of medical devices / surgical procedures
- Microbiology and antibiotic susceptibility
- Empiric antibiotic treatment prescribed

For patients with laboratory proven *E. coli* or *S. aureus* BSI, additional clinical data are captured to fulfil the requirements of the WHO GLASS attributable mortality protocol¹³. The Pitt BSI score is calculated and details of immunosuppression are collected, along with complete details of antibiotic treatment for the infection and likely source of infection.

¹ CI patients may be reclassified as HAI if risk factors for HAI are present at enrolment.



● F07 only required if a participant is enrolled into ACORN-HAI
 # Patients initially enrolled into ACORN II with CI but had significant healthcare exposure in the 3 months prior to admission will be enrolled into ACORN-HAI in sites which conduct both ACORN II and ACORN-HAI
 * If new HA-BSI or VAP is detected during inpatient follow-up. F02, F05, F07A/B/E will be required.
 ^ F07D Functional outcome form should be filled in on day 28 from infection onset.

Figure 2. Data collection procedures during enrolment and follow-ups. Patient 1 represents a participant who enrolls into ACORN II with a community-acquired infection diagnosed on day 1 of hospitalisation. Patient 2 represents a participant who enrolls into both ACORN II and ACORN-HAI with a hospital-acquired infection which developed after 2 days of hospitalisation. Patient 3 represents a participant who enrolls into both ACORN II initially with a community-acquired infection, and then enrolls into ACORN-HAI after developing a hospital-acquired infection after 2 days of hospitalisation. Patient 4 represents a participant who enrolls into ACORN-HAI (from a study site which only implements ACORN-HAI) with a hospital-acquired infection after 2 days of admission.

Clinical data entry can be done either directly using the Open Data Kit (ODK) Collect app on an Android tablet or via paper case report forms (CRFs) with subsequent entry into the surveillance REDCap database using a laptop and web browser. All clinical data entered will be stored centrally in the ACORN REDCap database, where error checking and correction is performed regularly. All data stored in the central database are anonymised and securely stored.

Microbiology laboratory data, either extracted from an existing laboratory information management system (LIMS)/WHONET

file or entered into WHONET software specifically for surveillance, is linked to clinical data using the ACORN project RShiny application (<https://github.com/acornamr/acorn-dashboard>) (Figure 3). This data management application links clinical and laboratory data automatically based on patient identifier and key dates. To ensure data privacy and security, this application can be used offline to link laboratory data and pseudonymise the dataset. An identical online version is also available (<https://moru.shinyapps.io/acornamr/>). The application allows for real-time monitoring of surveillance and can be used for data visualisation and reporting. If it is not possible

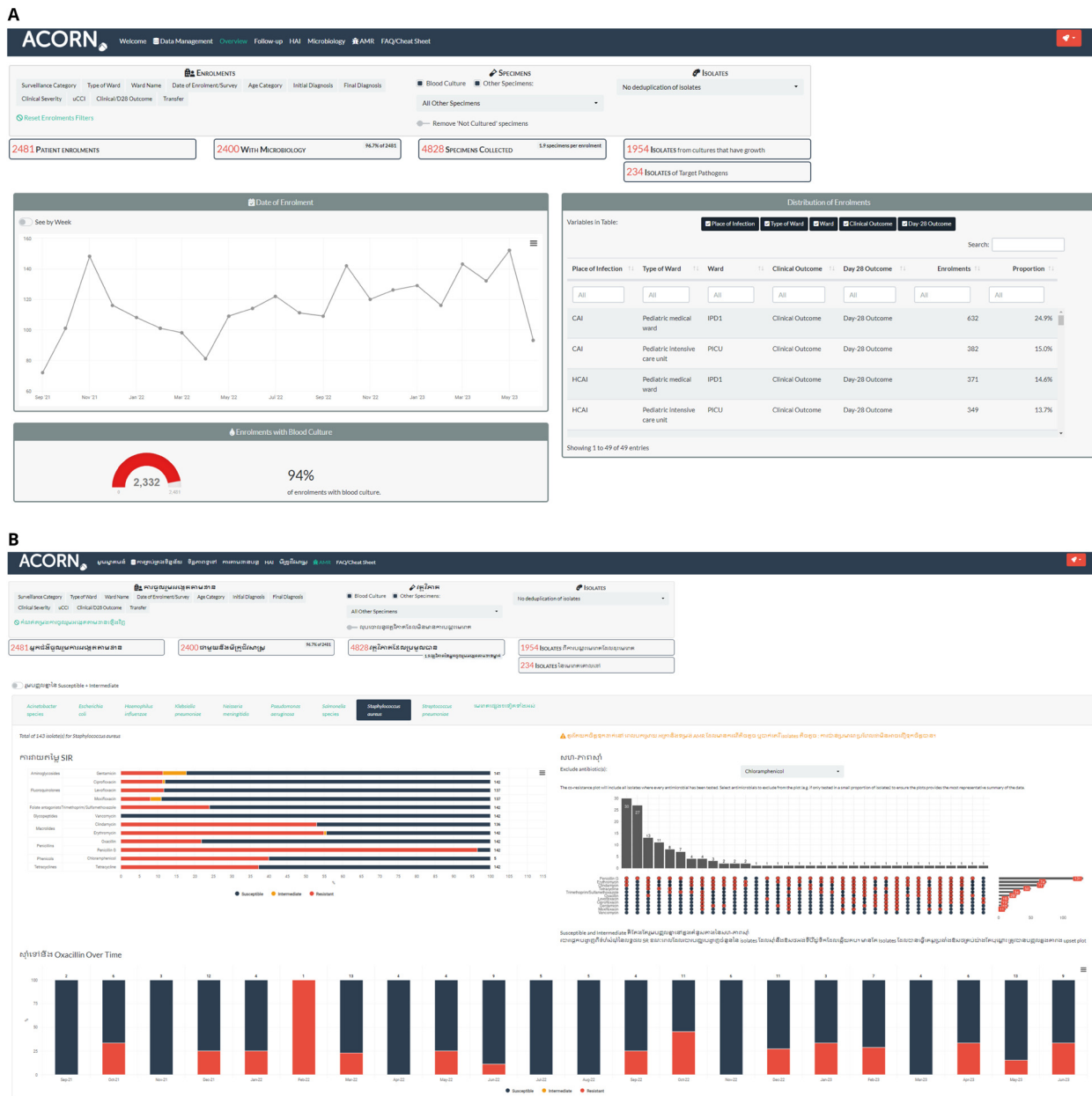


Figure 3. The ACORN project app/dashboard. Panel A shows part of the overview tab highlighting the data filters and high-level metrics. Panel B (Khmer language version) shows the AMR tab with data for *S. aureus*: standard SIR proportion plot (left side), an UpSet plot to summarise co-resistance patterns (right side), and temporal trends for key antimicrobials (methicillin, bottom).

to access existing laboratory LIMS or WHONET data extracts, microbiology data can be directly entered into a WHONET database specifically for the project.

ACORN-HAI extension study

ACORN-HAI follows the ACORN II main study methodologies and procedures closely, with a specific focus on healthcare-associated bloodstream infection and ventilator-associated pneumonia (extended data 4 and 5). These two infection syndromes are chosen due to their association with drug resistant organisms and high mortality. In ACORN-HAI, healthcare-associated bloodstream infections encompass hospital-acquired bloodstream infections, i.e. any bloodstream infections taking place either after two days of admission or within 3 months of significant healthcare exposures, can be enrolled into the study.

ACORN-HAI is complementary to ACORN II as it is designed to capture more cases of HAI and in more clinical detail for each enrolled case than ACORN II. ACORN II identifies HAI via weekly point prevalence surveys and daily ward screening (case-initiated), which will provide estimates for incidence and prevalence. However, the absolute number of HAI cases enrolled is likely to be lower than the actual incidence. ACORN-HAI aims to enrol all healthcare-associated bloodstream infection and ventilator-associated pneumonia in the participating wards through screening via positive blood or sputum cultures (isolate-initiated). Additional variables describing admission progression, antibiotic prescription and functional outcomes are collected with an addendum CRF (Figure 1 and Figure 2).

A participating site may participate in both or either ACORN II and ACORN-HAI study. In sites which implement both ACORN II and ACORN-HAI, only study participants who are enrolled into ACORN II will be enrolled into ACORN-HAI. In sites or wards which participate only in ACORN-HAI, similar clinical, microbiology and ward-level data as the ACORN II study will be collected such that the two datasets can be merged and analysed in a coherent manner (Table 1).

Enrolment criteria for ACORN-HAI are as follows:

- *Bloodstream infection*

Inclusion criteria:

- 1) Prescription/commencement of an intravenous antibiotic;
- 2) Growth of bacterial or *Candida* spp. pathogen(s) identified from blood specimen(s)² either taken on or after day 3 of admission (Day 1 refers to the day of admission), or within 3 months of significant healthcare exposures³; and

² Catheter tip cultures cannot be used in place of blood specimens for inclusion criteria.

³ Significant healthcare exposures refer to any of the following: admission to other healthcare facilities, regular contact with healthcare facilities (e.g. dialysis, outpatient antibiotic or chemotherapy), surgical procedures.

3) Pathogen(s) in the blood specimen(s) satisfies either of the following:

- i. 1 or more non-common commensal⁴ bacterial or *Candida* spp. pathogen(s) identified from 1 or more blood specimens obtained by a culture; or
- ii. the same common commensal bacterial pathogen identified from 2 or more blood specimens collected on separate occasions⁵; and

4) The same pathogen(s) in the blood specimen(s) was/were not present in the blood specimen(s) taken during the first 2 days of admission among those without significant healthcare exposures in the past 3 months.

Exclusion criteria:

Patient who has positive growth of organisms belonging to the following genera which are typically causes of community-associated infections and are rarely or are not known to be causes of healthcare-associated infections, or associated with severe immune suppression:

- a) *Burkholderia pseudomallei*,
- b) *Brucella* spp., including but not limited to, *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*,
- c) *Campylobacter*, *Salmonella*, *Shigella*, *Listeria*, *Vibrio* and *Yersinia*.

- Ventilator-associated pneumonia

- 1) Prescription/commencement of an intravenous antibiotic;
- 2) Clinical suspicion of ventilator-associated pneumonia⁶; and
- 3) Growth of bacterial pathogen(s) identified from respiratory specimen(s)⁷ taken on or after day 3 of ventilation.

⁴ Common commensal organisms include, but are not limited to, diphtheroids (*Corynebacterium* spp. not *C. diphtheriae*), *Bacillus* spp. (not *B. anthracis*), *Propionibacterium* spp., coagulase-negative staphylococci (including *S. epidermidis*), viridans group streptococci, *Aerococcus* spp., *Micrococcus* spp. and *Rhodococcus* spp.

⁵ 2 or more blood specimens collected on separate occasions are defined by samples collected on: the same calendar days from 2 separate sites (e.g. different venepunctures, different lumens of the same central catheter); or, different calendar days from the same or separate sites.

⁶ Mechanical ventilation refers to any device used to support, assist or control respiration (inclusive of the weaning period) through the application of positive pressure to the airway when delivered via an artificial airway, specifically an oral/nasal endotracheal or tracheostomy tube. Ventilation and lung expansion devices that deliver positive pressure to the airway (for example: CPAP, Bipap, bi-level, IPPB and PEEP) via non-invasive means (for example: nasal prongs, nasal mask, full face mask, total mask, etc.) are not considered ventilators unless positive pressure is delivered via an artificial airway (oral/nasal endotracheal or tracheostomy tube).

⁷ Respiratory tract specimens refer to endotracheal aspirate, bronchoalveolar lavage or protected specimen brushing. Other methods of specimen collection, e.g., cheek or mouth swabs and endotracheal tube cultures, are not acceptable.

Table 1. Comparison of main ACORN II and ACORN-HAI activities.

Activity	ACORN II	ACORN-HAI
Screening	<ul style="list-style-type: none"> ◦ Community-acquired infections via daily ward reviews (which can include healthcare-associated infections among patient with significant healthcare exposure in 3 months prior to admission) ◦ Hospital-acquired infections via weekly point prevalence surveys 	Healthcare-associated infections (which include hospital-acquired infections) via microbiology line lists
Data collection for specific infection syndromes	Various types of community- and hospital- acquired infection syndromes (detailed data collection for <i>E. coli</i> and <i>S. aureus</i> bloodstream infections)	Culture-positive healthcare-associated bloodstream infections and ventilator-associated pneumonia
Follow-up	During weekly point prevalence surveys (for hospital-acquired infections) and at discharge	Weekly during admission and at discharge
Pathogen isolate storage	No pathogen isolate storage required	Storage of pathogen isolates associated with infection episodes
Outcome assessment	Vital status	Vital and functional status

Exclusion criteria:

Patient who has positive growth of organisms belonging to the following genera which are typically causes of community-associated infections and / or are rarely or are not known to be causes of healthcare-associated infections:

- a) *Streptococcus pneumoniae*, *Streptococcus suis*, *Haemophilus influenzae*,
- b) *Burkholderia pseudomallei*,
- c) Coagulase-negative staphylococci,
- d) *Talaromyces marneffeii*,
- e) *Mycobacterium tuberculosis*,
- f) Rapidly growing Mycobacteria, including but not limited to, *M. mucogenicum*, *M. fortuitum*, *M. abscessus*, *M. chelonae*, *M. neoaurum*

Bacterial isolates including *Acinetobacter* spp., *Pseudomonas* spp., Enterobacterales, *Staphylococcus aureus*, *Enterococcus* spp. and *Candida* (only from positive blood cultures), grown from routine clinical cultures will be collected from the microbiology laboratory and stored. The isolates will undergo whole genome sequencing at accredited laboratories.

Sample size calculation

There is no formal sample size calculation. This surveillance will enrol all eligible and consenting patients admitted to the surveillance wards during the surveillance period.

Study monitoring and quality assurance

All participating sites will develop an internal data monitoring plan to ensure adherence to ethics requirements, completeness and accuracy of data entry, and if applicable, isolate collection and storage. The local and overall data manager will conduct regular audits of the data entered and raise queries when necessary. Collated reports for monitoring progress

and quality of data collected will be generated and presented to participating sites regularly.

Surveillance data analysis and communication

ACORN II site teams will interact with their local data in real time using the project app / dashboard. Via this dashboard, site investigators will have access to enrolment frequencies and patient demographics, follow-up on clinical outcome and day 28 status, weekly active HI point prevalence, microbiology summaries, and antimicrobial susceptibility and resistance patterns.

The secondary outcomes are to: i) characterise multidrug resistant infections by clinical syndrome, place of acquisition (CI, HAI/HI), patient age group (adult, paediatric, neonatal), sample type, and location (site, country, region), ii) quantify burden of multidrug-resistant infections in terms of attributable mortality and excess length of hospital stay, and iii) determine major parenteral antibiotic prescription indications by clinical syndrome, patient group (adult, paediatric, neonatal), timing of prescription (empirical versus definitive), and location (site, country, region). Analyses for these secondary outcomes will be performed after at least two years from study commencement (extended data 6).

In general, data will be summarised in tables and graphs using descriptive statistics. For each selected key pathogen, the proportions of cases will be calculated, using the total number of participants from whom any pathogen was isolated as the denominator. Summaries will include the proportions of isolates resistant to key antibiotics, as defined by WHO GLASS or categorised as multidrug resistant, using standard definitions. Univariable and multivariable logistic regression models will be fitted to explore whether any clinical or microbiological variables are associated with the outcomes of resistance, mortality and discharged moribund. The unit of analysis will be admissions, with patient and site fitted as random effects.

For attributable mortality analyses, the survival model approach outlined in the WHO GLASS protocol will be followed¹⁶. At each site, observed crude case fatality rates (survival data) will be compared between cohorts: patients with multidrug resistant infection for selected pathogen-antimicrobial combination (cohort 1), and patient with non-multidrug resistant infection for selected pathogen-antimicrobial combination (cohort 2). Patients from cohort 1 and 2 will be matched 1:1 retrospectively. Ideally, matching will be by age category, admission ward, month of infection, and clinical syndrome at enrolment, and by the time from admission to infection. The effect of antibiotic resistance on vital status will be estimated using cause-specific Cox proportional hazards models, assessing the competing events of mortality and discharge alive, from the time of infection. Admissions, rather than patients, will be used as the unit of analysis and only the first relevant infection episode will be considered. A composite all-cause end-of-stay endpoint (either death or discharge alive) will also be assessed which may be interpreted as an indication of the daily hazard of a patient's admission ending. All models will include adjustment for the time between admission and infection. Proportional hazards assumptions will be checked using Schoenfeld residuals and visual inspection of log-log plots. Non-proportional hazards will be corrected using stratification.

Excess length of stay in days will be calculated using multistate models. The difference in expected length of stay will be estimated between the multidrug resistant and susceptible states. For empiric antibiotic analyses, drugs prescribed on the day of admission or symptom onset will be classified according to the WHO AWaRe criteria⁹. Concordance (i.e. cultured isolate was susceptible) or discordance (i.e. cultured isolate was resistant) with microbiology test results will be determined. To assess the impact of initial treatment on mortality another set of Cox proportional hazards models will be run, but antibiotic resistance will be replaced by receipt of active initial therapy as the exposure of interest.

To examine trends in infection rates over time, we will first use plots to visually inspect the trends to determine the most appropriate model/approach for analysis, while anticipating that random effects modelling with hospital clusters will be likely. Monthly incidence will be modeled (i.e., cases per hospital-month) controlling for hospital characteristics including the country's income status, type of hospital (tertiary versus community), and proportion of patients in specific age ranges¹⁷.

In the ACORN-HAI study, all clinical isolates will be processed for genomic sequencing. These genomic data will inform geospatial distribution of pathogen species and phenotypic resistance patterns and trends over the study period.

Study status

Both ACORN II and ACORN-HAI are being implemented in study sites across Asia and Africa. ACORN II commenced in September 2021 in Asia and Africa and is actively enrolling in 19 hospitals. ACORN-HAI started enrolment in September 2022 and is fully implemented in 25 hospitals across Asia including Singapore, Malaysia, Vietnam, Thailand, Nepal, India, and Pakistan (Figure 4).

Discussion

ACORN II is a comprehensive antimicrobial resistance surveillance activity which advocates pragmatic implementation, and prioritises improving local diagnostic and antibiotic prescribing practices through patient-centred data collection and rapid feedback to physicians. It uses a systematic methodology to collect clinical, microbiology, and antibiotic use data. These data can be rapidly communicated to local physicians and infection prevention and control teams via an interactive web application to guide empiric antibiotic prescription and stewardship. Relative ease of data collection promotes sustainability and maximise participation and scalability.

A prospective cohort design has strengths with regards to less risk of bias and confounding when compared to cross-sectional and retrospective study designs, albeit at the expense of higher cost. Important confounders in evaluating burden of drug resistant infections, e.g. attributable mortality, include comorbidities, initial disease severity at symptom onset, prior antibiotic exposure and time from admission to infection¹⁸. In addition, prospectively collected data is less prone to information bias as relevant data are collected at baseline (without knowledge on outcomes) using standardised methods¹⁸. Selection bias is minimised by implementing this surveillance tool in multiple antimicrobial resistance 'hotspot' regions to achieve a representative cohort of patients with multidrug-resistant infections.

ACORN II has the potential to fill important gaps in our understanding of antimicrobial resistance epidemiology. Firstly, most existing antimicrobial resistance surveillance systems are passive, and based on routine antimicrobial susceptibility testing results generated by clinical microbiology laboratories alone. While such designs are useful to give broad pictures on the types of resistance and bacteria prevalent in a population, they cannot be used to relate the effect of resistance with patient outcomes. These proportions of resistance per pathogen antimicrobial combination lack relevant clinical metadata to be informative for local clinicians in their decision making or guideline development. Secondly, ACORN II focuses on LMICs where there is a mismatch in terms of antimicrobial resistance burden and surveillance capacity. ACORN II presents opportunities for participating sites to adopt and integrate a systematic surveillance programme into their routine workflows.

By focusing on severe healthcare-associated infections, ACORN-HAI builds on the main ACORN II protocol by collecting more detailed data on disease presentation, progression and treatment. The commonest pathogens causing healthcare-associated bloodstream infections and ventilator-associated pneumonia in LMICs are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales and extended-spectrum beta-lactamase-producing Gram-negative bacteria¹⁹⁻²¹. These antibiotic-resistant pathogens have been identified by the WHO as of the highest concern²². This is because treatment options for carbapenem-resistant organisms are severely limited, associated with high toxicity, and often ineffective. ACORN-HAI, led by the ADVANCE-ID (Advancing Clinical Evidence

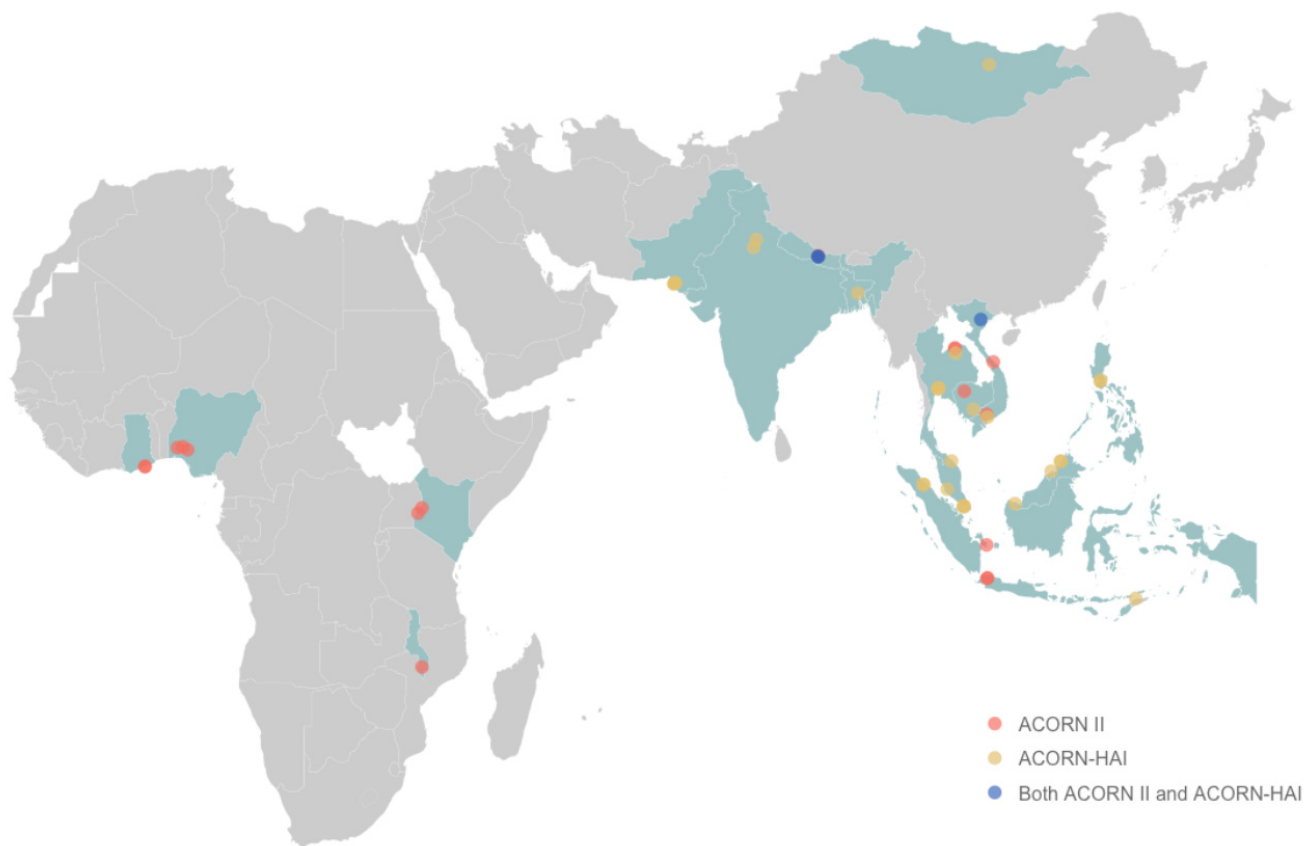


Figure 4. ACORN II and ACORN-HAI participating countries and study sites. Participating countries are highlighted in light teal. Study sites are represented by diamond points: ACORN II sites (coral), ACORN-HAI sites (yellow), ACORN II and ACORN-HAI sites (blue).

for Infectious Diseases) network, will form the groundwork for subsequent interventional clinical trials targeting drug resistant infections. This reflects ADVANCE-ID's main mission, which is to promote transnational research collaboration for a sustainable pipeline to conduct large-scale clinical trials in infectious diseases, particularly tackling antimicrobial resistance in LMICs where the need is the most urgent. With ACORN-HAI as an example, we foresee such extensions based on the ACORN II protocol in the future as hospital and research networks identify specific questions of interest.

We acknowledge several potential limitations. Firstly, though ACORN is designed to be as efficient as possible such that it can be incorporated as part of routine workflow, additional staff and resources are required to maintain the surveillance system. This is a barrier to sustainability beyond the research funding period, and will necessitate further development and adaptation of enrolment and data collection procedures for sustainable scale-up going forward. Secondly, surveillance for antimicrobial resistance serves to inform interventions, guide treatment decisions, and identify emerging threats. Hence, ACORN may be less beneficial for sites that have limited familiarity and resources in infection prevention and control, as well as

antibiotic stewardship. However, implementing an antimicrobial resistance surveillance system is an important first step to stimulate the initiation of such activities. Thirdly, differences in study implementation procedures across study sites, such as waiver of consent and choice of surveillance wards, may bias the demographics and disease severity of patients who enrol into the study. Lastly, identification of patients through clinical suspicion of infection syndromes, though pragmatic, may be sensitive to local physician practices and result in over- or under-estimation of certain infection syndromes such as ventilator-associated pneumonia.

Implementation of a robust surveillance network for drug resistant infections is the necessary first step towards improved empirical antibiotic prescription, designing infection prevention and control policies, guiding resource allocation, and motivating novel treatment therapy clinical trials. A focus on severe drug resistant infections with the highest health and economic consequences will align the interests and expectations from various stakeholders including patients, clinicians, health ministries and pharmaceutical industry. Such surveillance data will engage all parties to direct a concerted effort to tackle the urgent issues in antimicrobial resistance.

Data availability

Underlying data

No data are associated with this article.

Extended data

Extended data is available at doi: [10.5281/zenodo.7781160](https://doi.org/10.5281/zenodo.7781160).

Authors' contributions

RVD and PT conceptualised and designed ACORN II. MY and DLP conceptualised and designed ACORN-HAI. JH, EAA and SJL critically reviewed the study protocol as subject matter experts. All ACORN II and ACORN-HAI investigators offered feedback prior to local ethics approval submissions. All authors read and approved the final manuscript.

Yin Mo, Conceptualization, Funding Acquisition, Methodology, Project Administration, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Ding Ying, Project Administration, Writing – Review & Editing

Yang Cao, Project Administration, Writing – Review & Editing

Jill Hopkins, Investigation, Methodology, Project Administration, Writing – Review & Editing

Elizabeth A. Ashley, Methodology, Writing – Review & Editing

Naomi Waithira, Methodology, Writing – Review & Editing

Prapass Wannapinij, Methodology, Writing – Review & Editing

Sue J. Lee, Methodology, Writing – Review & Editing

David L. Paterson, Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing

H. Rogier van Doorn, Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Writing – Review & Editing

Paul Turner, Conceptualization, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

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Version 2

Reviewer Report 16 October 2023

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Bashar Haruna Gulumbe 

Federal University Birnin Kebbi, Birnin Kebbi, Kebbi, Nigeria

In response to my prior feedback, the authors have provided thoughtful revisions to the manuscript. I appreciate their clarification on the evolution of the ACORN study, detailing the transition from ACORN I (pilot) to ACORN II, and further to the extension study, ACORN-HAI. Their emphasis on the synergy between ACORN II and ACORN-HAI, especially in the context of enrolling an increased number of patients with HAI and capturing in-depth clinical data, is well-articulated. Furthermore, the inclusion of key study limitations in the discussion adds depth and transparency to the paper. The improvements notably address the initial concerns and enhance the manuscript's overall clarity and contribution.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Microbiology, AMR, infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 16 October 2023

<https://doi.org/10.21956/wellcomeopenres.21733.r65383>

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Dickson Aruhomukama

Makerere University, Kampala, Central Region, Uganda

I have thoroughly reviewed the current version provided by the authors, and I am pleased to note

that the majority of my concerns have been effectively addressed. I extend my appreciation to the authors for their diligent efforts and commendable work. I wish them all the best moving forward.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Microbiology, Computational Microbiology, Clinical Bioinformatics (Genomics)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 19 June 2023

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Bashar Haruna Gulumbe 

Federal University Birnin Kebbi, Birnin Kebbi, Kebbi, Nigeria

The article presents the protocol for ACORN II, a surveillance network aimed at monitoring antimicrobial resistance (AMR) in a clinically oriented manner. The study focuses on patients with severe bacterial infections in low- and middle-income countries (LMICs), where the burden of AMR is high and surveillance capacity is limited.

The ACORN II surveillance network aims to provide a comprehensive picture of AMR, focusing on both community-acquired and healthcare-associated infections. The study includes patients with clinically compatible acute bacterial infection syndromes and collects data on patient characteristics, infection syndromes, microbiology, and antibiotic use. The data is then rapidly communicated to local physicians and infection prevention and control teams via an interactive web application to guide empiric antibiotic prescription and stewardship.

The study also includes an extension, ACORN-HAI, which focuses on healthcare-associated bloodstream infection and ventilator-associated pneumonia due to their association with drug-resistant organisms and high mortality. The ACORN-HAI study follows similar methodologies and procedures as the main ACORN II study but collects more detailed data on disease presentation, progression, and treatment.

Constructive Feedback:

Clarify the Objectives/methods: The authors should provide a clearer link between the specific

objectives of the study and the methods used to achieve them. This would help readers understand how the study design and data collection methods will help achieve the stated objectives.

Clarify the Role of ACORN-HAI: The authors introduce ACORN-HAI as an extension of ACORN II, but it's not clear how these two studies are related. The authors should provide more information on the role of ACORN-HAI and how it fits into the overall ACORN II study.

Limitations: Every study has limitations, and it's important for the authors to acknowledge these. For instance, are there potential biases in the study design? How generalizable are the findings likely to be, given that the study is being conducted in LMICs?

Figures: The content of Figures 3A and 3B is not easily readable, which limits their usefulness in the context of the study.

Overall, the article presents a valuable protocol for monitoring antimicrobial resistance in LMICs. With some improvements in clarity and detail, it could serve as a useful guide for other researchers in this field.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Microbiology, AMR, infectious diseases

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 01 June 2023

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Dickson Aruhomukama

Makerere University, Kampala, Central Region, Uganda

I applaud the team for their brilliant work. The authors' aim to incorporate patient- or clinically-oriented AMR surveillance alongside isolate-based AMR surveillance is important because it acknowledges the multifaceted nature of AMR and can enable a comprehensive understanding of the problem. This approach can enhance the development of effective strategies to combat AMR and promote better patient outcomes through targeted interventions and improved antimicrobial stewardship. Upon evaluating this protocol, I have the following observations:

The authors describe ACORN-II and ACORN-HAI in this protocol. In the title, they present this as an ACORN-II protocol. They describe a surveillance system that includes hospitalized patients... with clinically compatible acute community-acquired or healthcare associated bacterial infection syndromes... They also mention diagnostic activities that will be implemented to optimize culture specimen collection practices and later state that patient characteristics are already being recorded on enrolment and after 28 days of follow up...

My concern with the authors' approach is that they mix various elements in this protocol, making it somewhat unclear. Moreover, the fact that the protocol is already being implemented adds complexity to evaluating its suitability.

I would have preferred the authors to follow a more systematic flow in their writing. They should have summarized ACORN-I since it presumably serves as the baseline for ACORN-II. Additionally, they should have described the advancements or updates in ACORN-II compared to ACORN-I, such as novel approaches, methodologies, or updated protocols etc. For instance, ACORN-I (the pilot study) focused on three infection syndromes, and it would be helpful to clarify which of these ACORN-II focuses on and why?

Currently, the authors seem to present ACORN-I as GLASS, which is somewhat perplexing. Since they state that ACORN-II builds on the WHO-GLASS, to measure... I think they need to base ACORN-II more on the pilot study (ACORN-I) and less on GLASS.

The authors briefly mention a surveillance system but fail to provide a comprehensive description of its components. Is it unclear whether this system encompasses ACORN in general, including both ACORN-I and ACORN-II, or if it specifically refers to ACORN-II and its extensions, such as ACORN-HAI? Although the authors introduce ACORN-HAI as an extension of ACORN-II, they should consider describing it fully in this protocol since it appears to be an independent study on its own. It would be helpful for the authors to clearly distinguish between ACORN-II and ACORN-HAI and explain the rationale behind the extension (ACORN-HAI).

The authors mention ongoing activities while also stating that some activities are not yet underway (based on their writing tenses). This makes it challenging to provide feedback on the protocol if certain study activities are already underway. I would appreciate clarification from the authors to better understand what has been done, what is in progress, and what remains to be done.

Regarding the study design versus the specific objectives, the authors state that ACORN-II is a prospective observational study (that is already in progress). This implementation phase makes it

difficult to provide comments on a protocol that is already being executed. However, I am concerned that the general design may not effectively achieve the specific objectives outlined by the authors (i to v). I recommend that the authors provide further clarification in this regard.

Lastly, I suggest that the authors clearly define the methods that they intend to use to achieve each specific objective in a systematic manner. This would facilitate a more thorough evaluation and allow for feedback on the proposed approaches.

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Microbiology, Computational Microbiology, Clinical Bioinformatics (Genomics)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
