FULL/LONG TITLE OF THE STUDY

INTerrupting prolifERation of Carbapenem resistance in Indonesia: clinical and genomic Evaluation of Pathways of Transmission

SHORT STUDY TITLE / ACRONYM

INTERCEPT

PROTOCOL VERSION NUMBER AND DATE

V1.3 DEC-2025

This protocol has regard for the HRA guidance and order of content

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VERSION CONTROL

Version and date	Major changes
v1.0 07-JUN-2025	First version
v1.1 18-JUN-2025	Minor edits (remove sponsor ID, trial registry ID as not yet available)
V1.2 15-SEP-2025	Correct typos; add reference to Nagoya protocol compliance
V1.3 04-DEC-2025	Add nasopharyngeal, hand, and clothing swabs from healthcare workers to the sampling framework of the transmission study. Clarify that bacteraemia participants can be recruited throughout the study (not just during 6 week sampling periods).

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles, outlined in the Declaration of Helsinki, GCP guidelines, the Sponsor's SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:
...../...../.....

.....

Name (please print):

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Position:
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Chief Investigator:

Signature: Date:
..../...../.....

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FUNDER(S)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
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iii. ROLE OF STUDY SPONSOR AND FUNDER

The Sponsor and Funders have no influence over the design, analysis and interpretation of the study

iv. LAY SUMMARY

Bacteria that are resistant to last-line antibiotics of the carbapenem class are a global public health threat, and classified as critical priority pathogens by the World Health Organisation. In Indonesia, they are a serious problem with common disease-causing bacteria which are frequently resistant to carbapenems. The routes by which people acquire these bacteria are unknown, but scarce data from Indonesia and experience in other settings suggests that transmission in hospitals is likely to be common, therefore strategies to block transmission are needed.

Infection prevention and control (IPC) and antimicrobial stewardship provide tools to do just that; the principles of these disciplines have been established in high-income settings since the 1950s, yet despite sporadic attempts to deploy them in Indonesia, carbapenem resistance has emerged and proliferated. This mirrors the earlier rapid spread of extended-spectrum beta-lactamase (ESBL) producing bacteria: these bacteria – problematic to treat in their own right - confer resistance to older antibiotics of the beta-lactam class. Carbapenems are commonly used to treat infections with ESBL producing bacteria, which in turn has driven carbapenem resistance. To break this vicious cycle, new interventions to block transmission of resistant bacteria that are adapted to and sustainable in the local context are required.

But understanding transmission is complex. Bacteria can resist antibiotics by acquiring genes that confer resistance, but these acquired genes can be transported by many vehicles, often nested, like a *Matryoshka* Russian doll: “jumping genes” (transposons) can jump to and from bacterial chromosomes and replicating genetic fragments (mobile genetic elements like plasmids), which can themselves move between bacteria, even between different bacterial species. Bacteria can move between animals, the environment, and humans, living harmlessly in the human gut , a phenomenon called colonisation) prior to causing invasive disease when they escape into (for example) the bloodstream. At the health system level, humans carry resistance genes with them as they move between health facilities and the community; travel disseminates them globally.

INTERCEPT brings together UK and Indonesian researchers to tackle this problem, using cutting-edge techniques to identify key transmission routes across a complex healthcare system, then co-designing and piloting interventions to block them. At different levels of the Indonesian health care system, we will test hospital inpatients and the hospital environment for colonisation with carbapenem-resistant bacteria, as well as community members and hospital wastewater, defining flow of resistance genes into and out of health facilities. We will test humans by collecting stool or rectal swab samples and testing these samples for resistant bacteria. We will recruit a cohort of patients with bloodstream infection (a serious type of infection where bacteria have spread into the blood) to properly define current treatments and outcomes of people with carbapenem-resistant infection, and identify and interview government and healthcare staff to understand what they perceive as barriers to the implementation of effective antimicrobial stewardship and IPC interventions.

Whole-genome sequencing - a technique to record (“sequence”) the full genetic code (“genome”) of an organism will fully describe bacteria, resistance genes and mobile genetic elements, tracking them through this system; mathematical models will identify key transmission routes. We will take isolated bacteria into the laboratory where molecular biology techniques developed at the Liverpool School of Tropical Medicine will allow us to understand mechanisms of resistance and the capability of carbapenemase genes to transfer within and between bacteria.

Ultimately, insights from these analyses will inform design of locally-adapted interventions. We will convene workshops of key health care and government stakeholders to co-design interventions, and pilot them whilst ongoing sampling assesses the impact on transmission. INTERCEPT will provide practical data to guide interventions aligned with national and international AMR-control priorities, suitable for scale-up and larger scale assessment, but also insights into transmission of carbapenem resistance that will benefit hospitalised patients in Indonesia.

v. KEY WORDS:

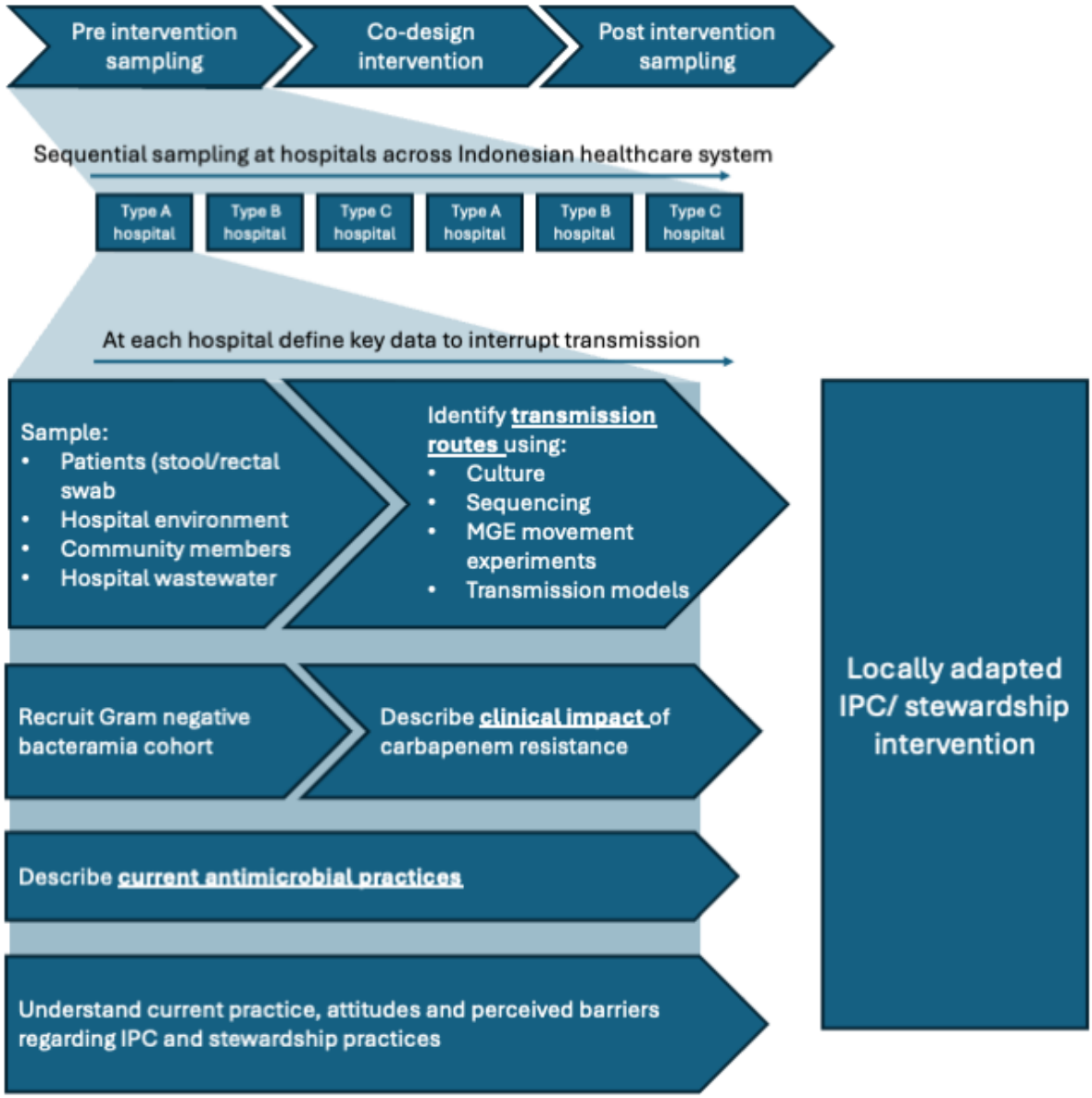
Antimicrobial resistance; carbapenemase; Enterobacterales; bloodstream infection

vi. STUDY SUMMARY

Study Title	INTerrupting prolifERation of Carbapenem resistance in Indonesia: clinical and genomic Evaluation of Pathways of Transmission
Short title	INTERCEPT
Study Design	Three linked substudies **INTERCEPT-transmission:** Observational cohort study of colonisation with carbapenem-resistant bacteria **INTERCEPT-bacteraemia:** Observational cohort study of clinical outcomes of Gram-negative bacteraemia using routinely collected anonymised data **INTERCEPT-intervention:** Qualitative study to understand attitudes towards and perceived barriers to stewardship and IPC interventions and co-design locally adapted interventions
Study Participants	**INTERCEPT-transmission:** Arm 1: Hospitalised adults Arm 2: Community dwelling adults Arm 3: Healthcare workers **INTERCEPT-bacteraemia:** Adults and children with Gram-negative bacteraemia **INTERCEPT-intervention:** Healthcare workers and other stakeholders
Planned Sample Size	**INTERCEPT-transmission:** Arm 1: 1000 Arm 2: 300 Arm 3: 120 **INTERCEPT-bacteraemia:** 200 **INTERCEPT-intervention:**50
Follow up duration	**INTERCEPT-transmission:** Arm 1: Until hospital discharge Arm 2: Cross sectional only Arm 3: 6 weeks **INTERCEPT-bacteraemia:** Until hospital discharge **INTERCEPT-intervention:** Cross sectional
Planned Study Period	September 2025 - April 2027
Aims AIM 1: Define routes of transmission of carbapenem resistance	**Primary outcome** Parameter values from transmission models Qualitative analysis of perception of and barriers to IPC/stewardship interventions

AIM 2: Describe current antimicrobial stewardship /IPC practices and barriers to intervention	
AIM 3: Co-develop and pilot locally adapted interventions to interrupt transmission of resistant bacteria	Perceived acceptability and feasibility of interventions
AIM 4: Describe the impact of carbapenem-resistant bloodstream infection	Description of microbiologic and clinical features and outcomes of Gram-negative bacteraemia
AIM 5: Strengthen research capacity in Indonesia and UK, and UK-Indonesia collaborative research network	Establishment of clinical research network

vi. STUDY FLOW CHART


Pre intervention sampling
Co-design intervention
Post intervention sampling
Sequential sampling at hospitals across Indonesian healthcare system
Type A hospital
Type B hospital
Type C hospital
Type A hospital
Type B hospital
Type C hospital
At each hospital define key data to interrupt transmission
Sample:
• Patients (stool/rectal swab
• Hospital environment
• Community members
• Hospital wastewater
Identify transmission routes using:
• Culture
• Sequencing
• MGE movement experiments
• Transmission models
Recruit Gram negative bacteramia cohort
Describe clinical impact of carbapenem resistance
Describe current antimicrobial practices
Understand current practice, attitudes and perceived barriers regarding IPC and stewardship practices
Locally adapted IPC/ stewardship intervention

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LIST OF ABBREVIATIONS

AMR	Antimicrobial resistance
BSI	Bloodstream infection
ESBL	Extended-spectrum beta-lactamase
GCP	Good clinical practice
IPC	Infection prevention and control
LMIC	Low and middle income countries
LSTM	Liverpool School of Tropical Medicine
MCA	Mental capacity act
MGE	Mobile genetic element
ONT	Oxford nanopore technologies
PIS	Patient information sheet
REC	Research ethics committee

1 BACKGROUND AND RATIONALE

Antimicrobial resistance (AMR), associated with 5 million deaths worldwide per year[1], is a pressing global public health concern, and bacteria that produce enzymes that inactivate the last line antimicrobial class carbapenems have been identified by WHO as critical priority pathogens[2]. Worldwide, carbapenem resistant infections confer a high mortality but the clinical impact of AMR is most severe in low- and middle-income countries (LMIC)[3].

The situation in Indonesia, a middle-income country, is dire. WHO data shows that 66% of *Acinetobacter baumannii* and 24% of *Klebsiella pneumoniae* bloodstream infection (BSI) isolates were resistant to meropenem in 2021[4], but data describing almost all aspects of this epidemic in Indonesia are lacking. Newer drugs active against carbapenem-resistant strains are largely unavailable. Key transmission routes of bacteria are unknown as are drivers of colonisation, generally considered a prerequisite for infection. Clinical descriptions of carbapenem resistant infection and outcomes are largely absent. It seems likely that nosocomial acquisition is important: what data are available suggest that at least 37% of ICU patients in Jakarta acquire colonisation with carbapenem resistant bacteria during admission[5] but data from anywhere other than tertiary-hospital critical care units are absent. These available surveillance data suggest that containment efforts – including infection prevention and control, and stewardship - are failing, and new, locally-adapted approaches to curb nosocomial transmission of carbapenem-resistant bacteria are needed.

In this respect, history is repeating itself; widespread ceftriaxone use has provided selection pressure for bacteria to produce ceftriaxone-inactivating extended-spectrum beta-lactamase (ESBL) enzymes and 76% of *K. pneumoniae* BSI isolates are now resistant to ceftriaxone[4]. This proliferation of ESBL resistance, itself a key driver of carbapenem use, has occurred despite implementing apparently successful sporadic local antimicrobial stewardship/IPC protocols as far back as 2003[6]. To break these cycles of increasing AMR-proliferation, IPC and stewardship interventions at scale can likely have a significant impact on the AMR epidemic in LMIC[3], and in Indonesia in particular; the challenge is to locally design sustainable interventions that will succeed in the Indonesian setting.

The INTERCEPT study proposes a three-step approach: first, gather data to inform design of an intervention: sample humans and the environment across a spectrum of Indonesian healthcare facilities; use whole genome sequencing, transmission modelling and laboratory experiments investigating the intra- and intercellular mobility of resistance to define routes of transmission of carbapenem resistance; and determine the disease burden in a cohort of patients with bacteraemia. Second, collect data on antimicrobial use and perceived stakeholder barriers to IPC/stewardship; then engage key stakeholders to co-design locally adapted interventions to block transmission, based on IPC/stewardship principles, but targeted to local transmission routes. Third, conduct a pilot intervention with ongoing assessment on the impact of transmission using methods used in stage one.

This project brings together expertise from the UK and Indonesia to address this critical national public health crisis. Transmission of antimicrobial resistance in bacteria occurs at many levels: at the level of the health system, the human (or animal, or environmental niche) affected; at the level of the bacteria; or at the level of the mobile genetic element (Figure 1). We will use limited-diversity metagenomic sequencing techniques to provide strain resolution at scale to define within sample diversity in humans and the environment, which can be incorporated into transmission models to infer the key transmission routes. Experimental laboratory work will use local expertise in entrapment vectors to understand intra cellular transmission of carbapenem resistance and conjugation assays will determine inter-cellular transmission of resistance-harbouring plasmids. We will examine determinants of plasmid-lineage association, providing insights into AMR transmission.

The Indonesian INTERCEPT team bring a profound clinical understanding of the setting and more than twenty years' experience of research into and AMR and implementing antimicrobial stewardship and IPC interventions in Indonesian hospitals[6]. The study has been co-designed between Indonesian and UK researchers to tackle a problem that is a priority for Indonesian clinicians and policymakers: key objectives in the Indonesian AMR action plan, for example, include development of comprehensive antimicrobial stewardship programmes and national strategic plans for IPC with an aim to improve IPC in government hospital wards[7]. INTERCEPT will provide data for policymakers and clinicians to refine these programmes, and pilot data to inform larger interventional trials.

A further key pillar of INTERCEPT is Indonesian research capacity strengthening; key areas identified during the study co-design process are in genomics and bioinformatics, and in qualitative research methods. Sustainable interventions to block transmission of carbapenem resistant bacteria will require ongoing monitoring and assessment as new strains and determinants of resistance arise. INTERCEPT will provide not only data and tools to guide the interventions to achieve this aim and deliver benefit for patients in Indonesia but facilitate the development of a research environment that will ensure sustainability of the local capacity to respond to novel AMR agents as they arise.

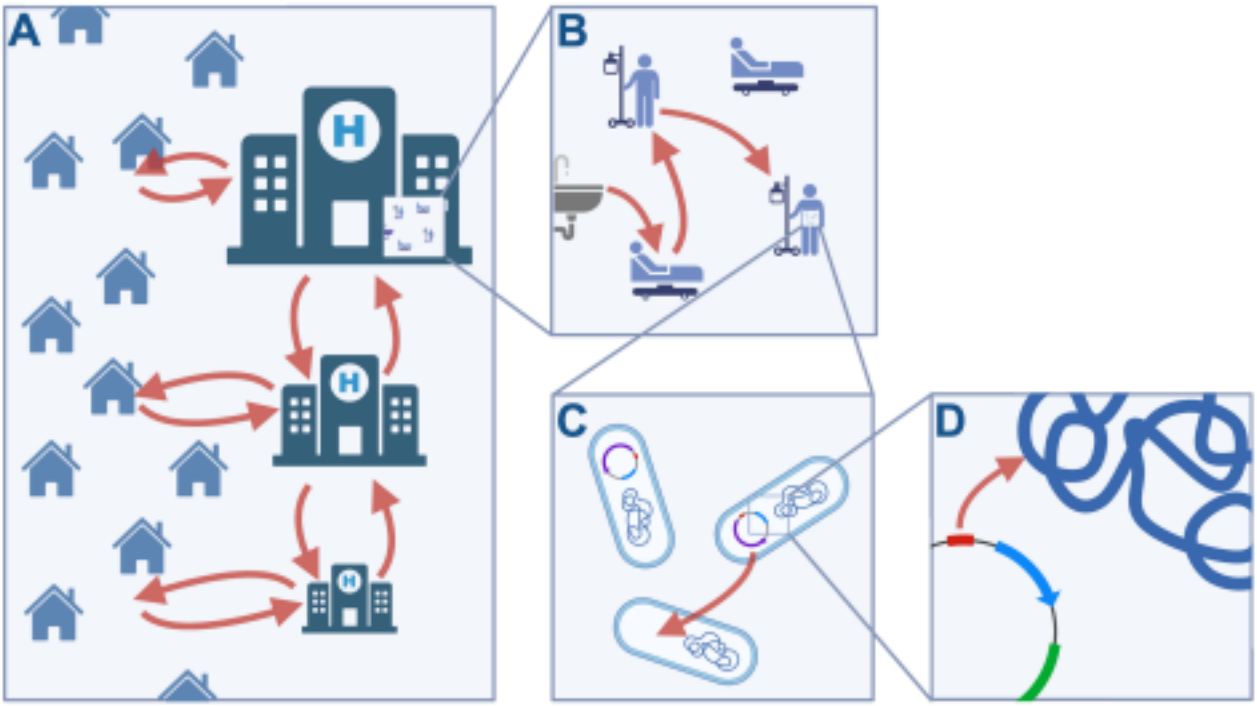


Figure 1: Transmission of antimicrobial resistance (arrows) occurs the level of (A) the health system with flow between healthcare facilities and the community; (B) the individual, between patients, environment and staff on a hospital ward; (C) the bacterium (in the human microbiota, or in the environment) with intercellular transmission of mobile genetic elements; or (D) the cell with intracellular transfer of mobile genetic elements conferring carbapenem resistance – shown here a transposon jumping from plasmid to bacterial chromosome. The INTERCEPT study spans this spectrum.

2 OBJECTIVES

AIM 1: Define likely routes of transmission leading to carbapenem resistance in hospitals in Indonesia, considering hospitals, people and environment.

OBJECTIVE 1.1 Describe clinical features, risk factors, bacterial strains, resistance mechanisms and mobile genetic elements responsible for carbapenem resistance in three Indonesian hospitals (patients, environment, hospital wastewater) covering the spectrum of hospitals in the Indonesian healthcare system (type C [district]; type B [referral], type A [tertiary]).

OBJECTIVE 1.2 Describe prevalence of bacterial strains and mechanisms of carbapenem resistance in populations served by these hospitals.

OBJECTIVE 1.3 Experimentally determine with entrapment vectors and plasmid conjugation experiments the mechanisms by which successful carbapenem resistance genes are spread on mobile genetic elements.

OBJECTIVE 1.4 Using data from 1.1-1.3 build agent-based transmission models to identify likely routes of transmission of carbapenem resistance in the Indonesian healthcare system and quantify flow of carbapenem resistance between healthcare facilities and the communities served by these facilities.

AIM 2: Describe current antimicrobial/IPC practices across the spectrum of healthcare facilities in Indonesia to inform interventions.

OBJECTIVE 2.1 Describe and compare antimicrobial use, antimicrobial stewardship and IPC protocols at type A, B and C hospitals.

OBJECTIVE 2.2 Determine knowledge, attitudes and perception of healthcare workers, managers, local and national policymakers to antimicrobial stewardship and IPC

AIM 3: Develop and pilot locally adapted interventions to interrupt transmission of carbapenem resistance in Indonesian hospitals

OBJECTIVE 3.1 Using data from aim 1-2, co-design with key local and national stakeholders stewardship/ IPC interventions appropriate to the Indonesian healthcare system.

OBJECTIVE 3.2 Pilot the interventions in type A, B and C hospitals, assessing feasibility and acceptability and the effect on transmission routes identified in aim 1.

AIM 4: Describe the impact of carbapenem-resistant bloodstream infection across the spectrum of Indonesian hospitals, and identify opportunities for carbapenem-sparing regimens in suspected bloodstream infection

OBJECTIVE 4.1 Describe clinical and microbiologic features of bloodstream infection with Gram-negative bacilli in Indonesia.

OBJECTIVE 4.2 Describe the effect of carbapenem resistance on outcomes in bloodstream infection.

OBJECTIVE 4.3 Propose carbapenem-sparing regimens to treat suspected bloodstream infections in Indonesia.

AIM 5: Strengthen research capacity across the UK-Indonesia collaborative research network

OBJECTIVE 5.1 Develop a cross-discipline and cross practice-research network in Semerang, Indonesia across all tiers of the health system.

OBJECTIVE 5.2 Strengthen Indonesian research capacity in whole-genome sequencing, bioinformatics, and qualitative research methods.

OBJECTIVE 5.3 Synthesise South-North learning outcomes for local stewardship / IPC interventions in the UK and elsewhere.

3 STUDY DESIGN

Overall, the study objectives will be achieved by three linked sub-studies recruiting human participants (see Figure 2 for overview):

- **INTERCEPT-transmission:** an observational cohort study of colonisation with carbapenem-resistant bacteria in hospital inpatients and community members, sampling humans and the environment to define transmission routes of carbapenem resistance. Weekly antimicrobial point prevalence audits will ecologically define antimicrobial use.
- **INTERCEPT-bacteremia**: an observational cohort study of patients with Gram-negative bacteraemia to establish clinical impact of carbapenem resistance, using anonymised routinely collected data.
- **INTERCEPT-intervention:** a qualitative study recruiting key stakeholders aiming to understand current practices and attitudes towards and perceived barriers to stewardship and IPC practices. These insights will be used to inform the co-design and implementation of pilot interventions to interrupt transmission of carbapenem resistant bacteria.

The way that these linked studies will achieve the study objectives is shown in Table 1. INTERCEPT-transmission and INTERCEPT-bacteraemia will rotate between three different study sites (type A, B and C hospitals in the tiered Indonesian healthcare system - see below), with a 6 week recruitment window at each site. To account for seasonality the six week period will be repeated at each site, giving a total 36-week recruitment period. During the three-year study this 36-week recruitment period will be repeated twice: pre- and post- pilot interventions.

Details of each of these sub-studies is given in turn below.

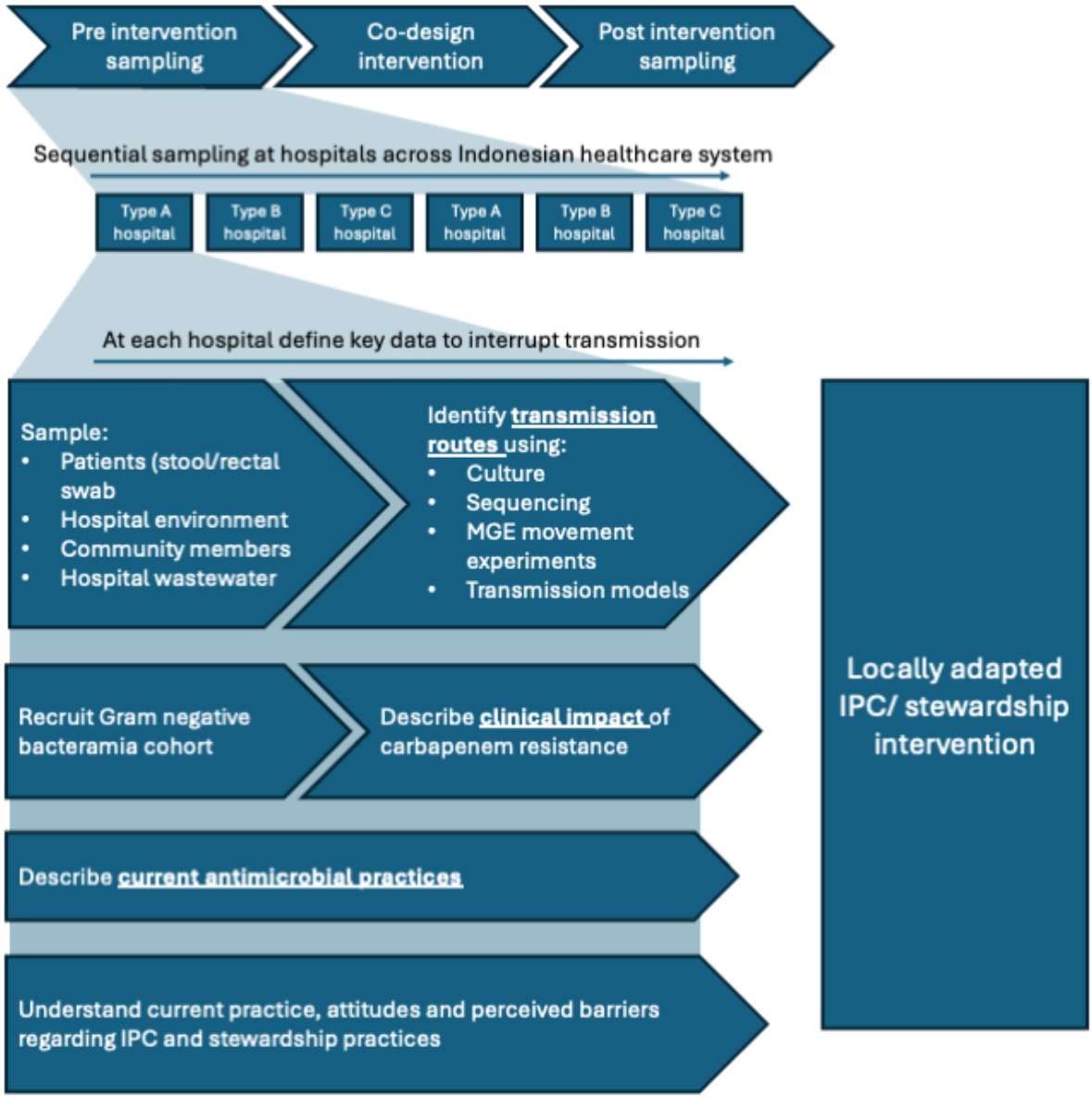


Figure 2: Overview of INTERCEPT study. Study activities occur for 6 weeks rotating around each of three hospitals (Type A, B, C - see below for details) twice to give a 9-month total sampling period.

TABLE 1: Matrix of studies and overall aims

Aim	INTERCEPT-transmission	INTERCEPT-bacteraemia	INTERCEPT-intervention
1: Define transmission routes	Yes		
2: Describe antimicrobial/IPC practices, attitudes and perceptions	Yes		Yes
3: Co-develop, pilot interventions			Yes
4: Describe impact of resistant BSI		Yes	
5: Strengthen research capacity	Yes	Yes	Yes

3.1 INTERCEPT-transmission: overview

This study samples humans and the environment to describe colonisation, using genome sequencing to track pathogens and mathematical modelling to identify routes of transmission of carbapenem resistant bacteria. Antimicrobial point prevalence audits will define antimicrobial use at study sites. Study activities will be carried out pre- and post- pilot interventions to assess impact.

3.1.1 Recruitment and sample collection

The Indonesian healthcare system has a tiered structure with different hospital types: type A, or tertiary, hospitals, type B, or referral hospitals, and type C, or district hospitals, with flow of patients between hospitals up and down the hierarchy and between hospitals and the community at each level. To define sources of acquisition of carbapenem resistance in humans within healthcare facilities, intensive sampling of humans and the hospital environment will be carried out; to define aggregate flow of carbapenem resistance from healthcare facilities to the community, less intensive sampling of community members served by the hospital and hospital wastewater will be sampled.

Hence all patients admitted to one critical care and one general ward at three hospitals (one each of type A, B and C) will be eligible to be recruited and asked to provide stool or rectal swab samples at recruitment, day 3, 7, and weekly thereafter and on discharge. Clinical data on patient demographics and treatments will be collected. Swabs will be collected weekly from the hospital environment (e.g. sinks, showers, toilets, high-touch surfaces, air-conditioner outlets, medical equipment) and from healthcare workers (nasopharyngeal, hand, and clothing samples).twice during each six-week sampling period. Hospital wastewater samples will also be collected weekly during the sampling period for microbiological and metagenomic analysis. To capture seasonality across the wet and dry seasons, two 6-week sampling periods will be carried out at each hospital, one in each season, giving a 9-month (36 week) rolling programme of sampling across the three facilities. During each 6-week sampling period and in parallel with hospital sampling, a random cross-sectional sample of community members will be recruited and asked to provide a single stool sample. First, community sensitisation activities will be carried out in the areas around the hospital in conjunction with community leaders. Then, participants will be recruited by approaching random households (identified by random walk from the hospital) and offering recruitment to one member per household.

Stool/rectal swab and environmental samples will be selectively cultured for carbapenem-resistant organisms and DNA extracted for i) single colony short read whole-genome sequencing which will give high resolution of the sequence strain ii) plate sweep limited diversity metagenomics will inform about diversity within our sample and iii) long-read nanopore sequencing will yield completely assembled

genomes and plasmids will allow us to accurately identify whether the carbapenem resistance is chromosomal or on a plasmid. Corresponding metagenomic DNA samples will be obtained from hospital wastewater. Whole genome sequencing and metagenomic sequencing of this range of samples will provide a comprehensive picture of circulating carbapenem resistant bacteria and genes which will inform the transmission model.

For the 6-week sampling period at each hospital, a weekly antimicrobial point prevalence audit will be carried out: the agent, dose, route of administration, planned duration (if known) and appropriateness as compared to local antimicrobial prescription guidelines.

3.1.2 Analysis

Whole genome sequencing to understand molecular mechanism of carbapenem resistance acquisition

The mechanism by which people acquire carbapenem resistance in Indonesian hospitals is unknown and is likely to be due to acquisition of bacteria and/or horizontal gene transfer in mobile genetic elements (MGEs) such as plasmids. We will use a combination of high-throughput short-read sequencing (feasible to perform at scale but unable to resolve many MGEs) and long-read Oxford Nanopore Technology (ONT) sequencing (able to resolve MGEs) of cultured isolates and to resolve the molecular mechanism of nosocomial acquisition and the genomic landscape of carbapenem resistance. A further critical necessity to understand sources of transmission is to robustly describe within-host diversity of carbapenem resistant bacteria, which would be missed by a single colony pick strategy. We will use the MSWEEP/MGEMS pipeline following selective culture for carbapenem resistant bacteria to achieve this. This tool uses limited-diversity metagenomic sequencing of microbiologic plate sweeps following selective culture to reconstruct strain-level diversity[13]. This will allow us to describe, at scale, within-host and environmental diversity of carbapenem resistant bacteria. Short read limited-diversity metagenomics cannot reliably associate plasmids with bacteria so a combination of single colony Illumina and ONT sequencing alongside limited diversity metagenomics will robustly describe within-host diversity of strains and plasmids to infer transmission pathways.

The genomic data will be used to infer transmission routes in two ways. Where sampling is intensive, to infer routes of nosocomial transmission using transmission models. Where sampling is sparser (community and hospital wastewater), describing bacterial species, lineages, strains and mobile genetic elements responsible for carbapenem resistance in hospital, community and environmental compartments will enable a description of the extent to which transmission between compartments is occurring.

Transmission modelling to understand routes of nosocomial acquisition of carbapenem resistance

The clinical and phenotypic bacterial resistance data collected will be used to build progressively complex stochastic multistate transmission models of nosocomial transmission of carbapenem resistant bacteria. Initially, these will consider phenotypic data with participants considered to be colonised / non colonised, with instantaneous transition rates between the two states governed by dynamic external pressure of infection (i.e. colonised humans and environment) and other patient and facility factors. These will be fit in a Bayesian framework.

The optimal way to incorporate genomic data into transmission models is an open research question. Fundamentally, inferring transmission from genomic data usually consists of considering two isolates to be consistent with recent transmission if they are below some arbitrary similarity threshold. In INTERCEPT we will leverage the description of within-host diversity provided by limited diversity metagenomics to dispense with an arbitrary threshold and probabilistically model the likelihood of transmission given the diversity of strains in two samples. First, all-against-all pairwise comparisons of

isolate similarity will produce empirically-derived within- and between-host diversity distributions for the isolates. This will allow calculation of a probability that any two isolates arise from the same distribution, and will allow joint modelling of a likely transmission tree and parameter values governing transmission. The primary outputs of these models will be values of parameters that quantify force of infection from different sources in Indonesian hospitals; this will allow identification of the most likely sources of carbapenem resistant bacteria to guide prevention efforts.

Experimental exploration of mechanisms of AMR dissemination

Plasmids are the major drivers accelerating transmission of AMR genes between different bacterial lineages and species[38]. Using long-read sequence data will enable us to fully resolve genomes from carbapenem resistant bacterial isolates including plasmids. This will allow us to differentiate between clonal lineages that are carbapenem resistant and clonal plasmids which would be found in different lineages or species. There is currently a gap in understanding why certain plasmids are associated with specific lineages or why certain plasmids are very successful spreading widely while others are restricted.

We will investigate genomes from our isolates with complete plasmid assemblies for common replicon types of plasmids harbouring carbapenem resistance genes found in different lineages and species to identify dominant and successful plasmids. We will analyse the evolutionary relatedness of these plasmids using pling (https://github.com/iqbal-lab-org/ pling (https://github.com/iqbal-lab-org/pling)) and their association with different lineages will be investigated. We will then select a subset of these plasmids, prioritising the most common, and experimentally test their ability to conjugate (or to be mobilised) using conjugation assays in the laboratory. For plasmids with higher than mean conjugation efficiencies, the genomic context will be investigated including genes known to be involved in regulation of conjugation or transfer to potentially link increased conjugation to repressor mutations.

We can assess the frequency of conjugation using methods optimised in our laboratories[32] and then take these investigations beyond the state of the art using novel MGE capture vectors we have designed, constructed and validated. Lastly, we will use comparative plasmid genomics to compare carbapenem plasmids found in Indonesia in the global context.

3.1.3 Prior work and justification

No study has systematically sampled hospital inpatients to describe acquisition of colonisation with carbapenem resistant bacteria in Indonesian hospitals, nor are any data available to define community prevalence. The only available data on nosocomial acquisition come from the ICUs of the national referral hospital in Jakarta where up to 37% of ICU patients acquired colonisation with carbapenem-resistant bacteria in 2013/14[5] There are no data describing acquisition of carbapenem-resistant bacteria in other Indonesian healthcare settings. Scanty data from cross sectional studies in different patient groups show that carbapenem resistance is common in routinely collected specimens[8] (e.g. 11-19% in collections of UTI isolates[9,10] and 50% in isolates from burn patients[4]) and in national surveillance data[12].

Similarly, community population prevalence of colonisation with carbapenem resistance is unknown, but is likely to be significant, extrapolating from what data are available to describe proliferation of ESBL-producing bacteria. ESBL colonisation prevalence was only 1% on admission for hospitalised patients in Java in 2001/02[13] but by 2017 56% of a sample of medical students in Surabaya[14] and 40% of pregnant women in Jakarta in 2018/19 were colonised with ESBL producing bacteria[15].

Hospital wastewater in other settings has been found to act as a reservoir for carbapenem resistance[16]; in Indonesia data are sparse: a single study of 12 hospital wastewater samples in a referral hospital in Malang detected carbapenemase genes in all samples by PCR, but no genomic characterisation of genes, strains of samples was carried out[17]. INTERCEPT will, therefore,

dramatically expand our understanding of the genomic epidemiology of carbapenem resistance in Indonesia, a necessary first step in identifying transmission routes and designing interventions to block transmission.

In determining the sampling frame, it is necessary to sample with sufficient spatiotemporal intensity to successfully fit transmission models. Sparse sampling results in a large number of potential sources of transmission whose colonisation status is unknown resulting in a high-dimensional parameter space to explore in the modelling process and models that are infeasible to fit in a tractable time frame. Here we build on our experience of similar studies (TRACS-Liverpool https://www.isrctn.com/ISRCTN17060051 (https://www.isrctn.com/ISRCTN17060051)) and others[18,19] to inform our sampling strategy. We have previously demonstrated a rapid apparent acquisition of resistant bacteria by day 7 following hospital admission, driven by antimicrobial exposure in Blantyre, Malawi [18]. We expect colonisation dynamics to be similar here, and so there is a need for temporally intensive sampling to capture acquisition with sufficient granularity to inform transmission models. We will restrict the study to a subset of hospital wards in order to achieve as high as possible coverage of patients and the environment. The additional hospital wastewater sampling will provide important information on the numbers and types of carbapenem resistant bacteria, and carbapenem resistance genes, leaving the hospital environment, crossing that One Health interface from the human health to the environment. Our intensive hospital wastewater sampling within the ongoing STRESST project (https://www.lstmed.ac.uk/stresst (https:// www.lstmed.ac.uk/stresst)) has enabled us to optimise bacterial recovery techniques and demonstrate high levels of carbapenem resistance leaving our study hospital in Blantyre, Malawi.

We leverage expertise and previous modelling work and in Malawi[18,21,22] and Liverpool (TRACS-Liverpool and others[19]) to INTERCEPT. We will use new sequencing techniques that make describing within-host diversity at scale feasible, to develop novel approaches to incorporating genomic data in transmission models. Genomic epidemiology studies generally infer transmission of bacteria by considering a threshold in single-nucleotide polymorphism (SNP) differences between two isolates though the value which these thresholds should take is a matter of debate[23] and is likely setting dependent. Such studies may identify putative transmission events – which can provide some insight - but without a principled way to include genomic data in transmission models it is difficult to use these data to quantify the importance of different transmission routes. Previous attempts have included joint modelling strategies to infer bacterial phylogenies and transmission networks simultaneously[24] which is computationally intensive and in which it is difficult to include unsampled sources; or to consider directly distributions of pairwise genomic distances between isolates[25] which requires strong assumptions about the distributions of diversity of isolates within-hosts. By directly measuring this in INTERCEPT, we will be able to both develop novel modelling strategies and to provide insight into transmission of carbapenem resistance in Indonesian hospitals.

Defining within-host (or within-source) diversity of carbapenem-resistant bacteria colonisation at scale with a reasonable resource requirement has only recently become possible with advances in limited-diversity metagenomics. Shotgun metagenomics (sequencing all the genomic material in a sample) is prohibitively expensive because of the sequencing depth required and, even at high depth, low-variant bacteria or resistance genes may be missed[26]. Bacterial culture can select for bacteria of interest but whole-genome sequencing of single colonies may miss diversity. Limited diversity metagenomics – selective culture followed by metagenomic sequencing of all variants in a sample, then bioinformatic reconstruction of strain diversity, provides a solution. The MSWEEP/MGEMS pipeline which we will use in INTERCEPT[20] has been used to describe strain level diversity of the pneumococcus and infer transmission[27] and to describe diversity in *E. coli* within-host diversity in Punjab, Pakistan[28].

The novel MGE capture vector is called pBACpAK[40]. This is based on a positive selection cassette encoding a repressed tetracycline resistance gene. Upon transposition of a mobile genetic element into a *cI* repressor which controls the expression of the tetracycline resistance gene, tetracycline

resistance can be selected for. Intracellular transfer experiments will be carried out on the transconjugants of the most commonly circulating carbapenem resistance genes to determine their between-replicon transfer potential compared to some of the rarer ones we find. This will enable us to delineate the exact mobile genetic element responsible for intracellular transmission of relevant resistance genes between different replicons in the same cell and link this to plasmid transfer between different bacteria providing another level of transmission modelling. Our work within the STRESST project has allowed us to optimise these experimental protocols enabling previous capture of carbapenem and colistin resistance gene containing MGEs[41,42]

3.2 INTERCEPT-bacteraemia: overview

INTERCEPT-transmission describes routes of transmission of carbapenem-resistant bacteria, resulting in colonisation. This is considered a prerequisite for infection, but describing invasive disease is necessary to understand the burden of the problem. In addition, severe febrile illness is a major driver of carbapenem prescription and so to develop stewardship / carbapenem sparing strategies, describing severe febrile illness is key. This work package describes a cohort of patients with bloodstream infection with Gram-negative bacilli to address these aims, using routinely collected anonymised data.

3.2.1 Data and sample collection and analysis

During each 6-week sampling period patients with bloodstream infection with Gram-negative bacilli will be identified via the microbiology laboratory at each institution. Data will be collected on patient demographics, physiology, treatments received; this will be requested in anonymised form from medical records departments. The primary outcome will be in-hospital mortality, and secondary outcome will be length of stay. No extra samples will be collected from participants.

Causative isolates of bloodstream infection will be subjected to short- and long-read whole-genome sequencing. Analysis will describe the microbiologic and clinical features of Gram-negative bloodstream infection, and will use mixed-effect regression techniques to compare outcomes of carbapenem-resistant infection to non-resistant.

Antimicrobial sensitivity testing and whole-genome sequencing will provide an antibiogram for the isolates and inform stewardship strategies and consideration of carbapenem-sparing regimens. Genome sequences of invasive isolates will also inform inference on transmission by identifying clinically relevant invasive strains versus colonising strains that are not causing disease.

3.2.2 Previous work and justification

Though it is clear from isolate-level data that carbapenem resistance in Indonesia is a serious problem, data on patient level outcomes are largely absent. Retrospective chart reviews of carbapenem-resistant infection describe in-hospital mortality of 50-57%[29,30]. High-quality prospective data on clinical features and outcomes are crucial to define the burden of disease and the patient population in which it occurs to target prevention efforts – but also to engage policymakers to drive forward such efforts and to inform stewardship programmes that could incorporate carbapenem sparing strategies.

3.3 INTERCEPT-intervention: overview

Here, we will use a qualitative approach to understand attitudes towards and perceived barriers to current stewardship and IPC interventions amongst stakeholders; then use these findings alongside data from INTERCEPT-transmission and -bacteraemia to co-design and pilot locally adapted interventions. This study will facilitate the formation of a clinical research network across type A, B and C hospitals incorporating academics, non-academic clinicians and hospital managers, providing a

platform for not only developing and piloting an intervention but also to build on for future interventional trials.

3.3.1 Methods

Attitudes, perceptions and barriers to stewardship and IPC interventions

We propose that facility-based AMR acquisition is influenced by the behaviour of health staff as they perform their roles as antibiotic prescribers, carers, and as managers who make decisions on facility priorities and policy guidelines. Thus, their experiences, practices and initial reflections will be critical to understanding the key issues and design setting appropriate interventions We will use a qualitative methodological approach to understand attitudes, perceptions and perceived barriers to current stewardship and IPC practices using the theoretical domains framework[31].

The research team will conduct semi-structured key informant interviews with managers, policymakers and non-clinical staff involved in stewardship and IPC at and across the hospital sites. This will include hospital managers, stewardship leads, IT staff, and local and national policymakers and relevant professional societies (e.g. pharmacy). We will also conduct focus group discussions with front line hospital staff to understand their attitudes, perceptions and perceived barriers to current stewardship and IPC practices. This will include clinicians (including microbiologists, paediatricians, general physicians, intensivists), pharmacists and nursing staff.

Participants for key informant interviews will be selected purposely based on their role in IPC and/or stewardship within the hospital or at local or national policy level. Focus groups will consist of consenting individuals working on each study site ward to represent the ward teams that implement stewardship and IPC practice. Participants will be contacted by a member of the research team and, following informed consent, will undergo an interview or participate in a focus group. Snowball sampling will be used to identify additional participants for key informant interviews.

Interviews will take place in a private space at a time suitable for the participant and transcripts will be anonymised after transcription. Focus group participants will be given a number to be able to recognise specific contributions during the discussions but retain anonymity. Interview and focus group transcripts will be managed using NVivo software and thematic analysis will be used, to identify emergent themes. These interviews and focus groups will also identify, based on their role and interest, key stakeholders who will be critical for the design and implementation of stewardship/IPC interventions. These stakeholders will be invited to contribute to the co-design of stewardship/IPC interventions through a series of workshops.

To describe and understand current IPC and stewardship practices at the ward level we will also conduct ethnographic participant observation at each site over the course of the study. One IPC team member from each study site will be requested to perform ethnographic observation of IPC practice and will be trained in ethnographic research by members of the study team. Staff on each study ward will be informed of the purpose of the observation and consent will be sought. Staff who decline to participate will not be included in the observation. Participant observers will keep a daily reflexive diary of their observations. These observations will be triangulated with the data gathered from interviews and focus groups to gain a deeper understanding of how IPC and stewardship guidelines are practiced at ward level.

Co-design and pilot intervention

We will synthesise evidence on antimicrobial use and qualitative data from this and other INTERCEPT sub-studies to inform the design of a locally-adapted stewardship/IPC intervention. Stakeholder workshops will be convened at each site to present the research findings. These data will be used by

the workshop participants to set intervention priorities and then design interventions. The nature of the intervention will be guided by data and the research team but may include stewardship aspects (e.g. antimicrobial guidelines, carbapenem sparing antimicrobial regimens, regular antimicrobial audits, teaching programmes) and IPC aspects (e.g. handwashing, screening for carbapenem resistance and patient cohorting or isolation, vascular device care, environmental decontamination). Workshop participants will be selected based on the findings from the qualitative research and will include policymakers, practitioners and members of the community being sampled. Research team members involved in the workshops will keep reflexive diaries to help understand the decision making process in the development of the interventions.

Interventions will then be piloted in the wards from which patients have been sampled at the three hospitals. Post intervention, semi-structured interviews and ethnography will assess staff and patient perceptions of feasibility and acceptability; ongoing antimicrobial point prevalence audit (INTERCEPT-transmission) will describe post-intervention prescribing behaviour; ongoing rolling sampling with sequencing and transmission modelling (INTERCEPT-transmission) will describe routes of transmission and ongoing recruitment of the bacteraemia cohort (INTERCEPT-bacteraemia) will describe management of severe febrile illness.

Analysis of this pilot intervention will focus on perceived acceptability and feasibility of implementation and wider scale roll out, but secondary outcomes that will be assessed will be pre- to post-intervention differences in antimicrobial prescribing, acquisition of carbapenem-resistant bacteria and antimicrobial management of severe febrile illness using the methods described in INTERCEPT-transmission and -bacteraemia

3.3.2 Previous work and justification

WHO global[32] and Indonesian[7] AMR action plans key objectives both include reducing incidence of infection and optimising use of antimicrobial medicines. Antimicrobial stewardship and IPC interventions have been shown in other settings to be effective tools to achieve these aims (including LMIC[33]) and the Indonesian AMR action plan includes aims to develop comprehensive antimicrobial stewardship programmes and to develop national strategic plans for IPC with an aim to improve IPC in government hospital wards. However, the optimal stewardship and IPC interventions for this setting are unknown.

Survey data suggests that IPC guidelines are in place in many Indonesian hospitals[34] but high rates of nosocomial acquisition of carbapenem resistant bacteria in tertiary facilities[8] suggests that they may be ineffective. A single centre ITU study in Jakarta found that a multimodal intervention was effective at reducing nosocomial acquisition of resistant Gram-negative bacteria[35] but otherwise there is no evidence base to inform locally-adapted IPC guidelines. To effectively interrupt transmission, interventions must cover the spectrum of healthcare facilities, but many facilities lack healthcare-associated infection surveillance; hence the scale of the effectiveness (or otherwise) of IPC protocols across type A, B and C hospitals is unknown in Indonesia.

Similarly, optimal stewardship interventions for Indonesia are unknown. What antimicrobial prescribing data that are available suggest a high rate of 3GC and carbapenem use which is commonly inappropriate[36]. Barriers to stewardship programmes include unreliable infrastructure with high antibiotic use to cover healthcare system structural vulnerabilities and ineffective resourcing / institutional buy-in of stewardship interventions[37]. INTERCEPT will tackle these difficulties by generating a clear evidence base to inform stewardship protocols where evidence is lacking and involving stakeholders from the ground up to facilitate engagement across the levels of the government health system and to generate co-developed, locally-adapted, and hence sustainable interventions.

4 STUDY SETTING

All three linked sub-studies are based in and around three hospitals (Table 2), one each of type A, B and C hospitals.

Table 2: Characteristics of participating hospitals

Name of Hospital	Dr. Kariadi	KRMT Wongsonegoro	M. Ashari
Class	A	B	C
Accreditation	Paripurna	Paripurna	Paripurna
Location	Semarang City - urban	Semarang – sub urban	Pemalang – sub urban
Number of total bed	1108	538	323
ICU/ CCU bed	38	28	10
Infection prevention control nurses	9	3	1
Antimicrobial resistant control team	+	+	+ (A resistance control team is in place; however, its functions have not been fully optimized)

5 PARTICIPANT ELIGIBILITY CRITERIA

5.1 Inclusion and exclusion criteria

The inclusion and exclusion criteria for the three linked sub-studies are shown below (Tables 3-5)

5.1.1 INTERCEPT-transmission

Table 3: Inclusion and exclusion criteria for INTERCEPT-transmission

Inclusion criteria	Exclusion criteria
Arm 1: Adults (18+) admitted to participating wards	Arm 1 Undergoing management with palliative intent and/or likely to die within 24hrs Does not speak English or Indonesian Lack capacity to consent to enrolment AND no representative can be identified

Arm 2: Community-dwelling adults (18+) in the community served by the hospital	Arm 2: Hospital admission within previous 6 months Lack capacity to consent to enrolment Does not speak English or Indonesian
Arm 3 Staff members (adults 18+) working on participating wards	Not willing or available to participate in the study Does not speak English or Indonesian

5.1.2 INTERCEPT-bacteraemia

Table 4: Inclusion and exclusion criteria for INTERCEPT-bacteraemia

Inclusion criteria	Exclusion criteria
Adults or children with Gram-negative bacilli bacteria identified in blood culture	None

5.1.3 INTERCEPT-intervention

Table 5: Inclusion and exclusion criteria for INTERCEPT-intervention

Inclusion criteria	**Exclusion criteria**
Adult (18+) working in collaborating hospitals with a role that impacts on IPC and/or stewardship	Not willing or available to participate in the study Does not speak English or Indonesian

6 STUDY PROCEDURES

6.1 Recruitment

6.1.1 Identifying eligible participants

INTERCEPT-transmission

INTERCEPT-transmission will use a rolling recruitment strategy, moving between the type A, B, and C hospitals and spending 6 weeks at each site. To capture seasonality each site will be visited twice, resulting in a 36-week sampling period. This 36-week sampling period will be repeated twice; pre- and post- pilot intervention. Sampling will recruit three groups of participants: hospitalised inpatients (arm 1) who will be longitudinally sampled (see below) and community members (arm 2) who will have a single sample collected. Environmental sampling will also be carried out (see below), and staff members working on the participating wards (arm 3) will be recruited and samples collected.

For arm 1 (hospital inpatients), all patients who are currently admitted to participating wards during the sampling window will be eligible for recruitment, and will be identified by discussion with ward nursing and clinical team. They will be approached for recruitment. See section 6.2 for informed consent procedure.

For arm 2 (community members), random households will be identified by walking from the hospital in a random direction, determined by spinning a bottle. A single eligible adult will be offered recruitment at each random household (see consent procedures in section 6.2).

For arm 3 (staff members) all staff working on the ward at the time of sampling will be eligible for recruitment, and will be approached by the study team.

INTERCEPT-bacteraemia

INTERCEPT-bacteraemia willrecruit throughout the study period i.e. will not be restricted to the 6-week sampling periods. .

Adults or children with Gram-negative bacteremia will be identified in the routine clinical microbiology laboratory at each of the hospital sites; Gram-negative bacteraemia is here defined as an organism identified on blood culture (using whatever blood culture system is in routine use at the hospital sites) with Gram-negative bacilli identified on microscopy. Following identification of eligible participants anonymised data will be requested from the medical records teams at the participating hospitals.

INTERCEPT-intervention

Participants for interview will be selected purposely based on their role in IPC and/or stewardship management, policy or support services (e..g IT or estates) supplemented by snowball sampling approach. Recruitment will aim to select both male and female participants and those in both senior and junior roles within the hospital. The research team includes some researchers who currently work in participating hospitals as infection doctors. We will leverage their knowledge of the health system and local networks to identify potential participants for the study. We will also liaise with the hospital leadership and infection control and stewardship teams to identify potential participants . This will include individuals from the operations, estates, and data departments to explore topics relating to patient flow and discharge, safety, hygiene, and facility layout.

Identified participants will be contacted by a member of the research team, either by email, phone or in person. The study will be discussed with this prospective participant, and they will be provided with the participant information sheet (PIS). An interview time and format (virtual or face-to-face) will be

agreed. During the interviews, respondents will be asked to recommend other participants that may enhance our understanding of key aspects of the study. Where a prospective participant is identified informally through a snowball approach, the known contact of the participant will be requested to seek permission from the participant for their contact details to be shared with the research team.

Focus groups will consist of consenting individuals working on each study site ward to represent the ward teams that implement stewardship and IPC practice. Participants will be contacted by a member of the research team and, following informed consent, will undergo an interview or participate in a focus group.

For the observation ethnographic study of current IPC and stewardship practices staff on each study ward will be contacted to get permission to conduct the observations. Those who do not consent to participate will not be included in the observation. Observations will be carried out for the duration of the study and captured using a reflexive diary. Observations will be carried out by a member of the ward staff involved in IPC who will be trained in observational ethnography by members of the study team. Patients who will be interviewed as part of the intervention assessment will be informed of the purpose of the interview and consented. Observational ethnography will also be undertaken by members of the research team during the intervention development workshops using reflexive diaries. This ethnography will aim to understand the decision making process that led to the development of the interventions.

6.2 Consent

6.2.1 Capacity to consent to enrolment and assessing capacity

Across the three linked studies, arm 1 of INTERCEPT-transmission will recruit participants who lack capacity to consent to enrolment because they have a temporary or permanent impairment that means they lack capacity to make a decision about participation in the study (see Table 6). Other arms of the study will recruit only participants who have capacity to consent to enrolment.

The test for capacity will follow UK mental capacity act guidelines. Capacity to make a decision to consent to participation will be assumed to be present unless it is demonstrated to be absent. All researchers who are trained to consent will be trained in capacity assessment; in the case of any uncertainty then assessment of capacity to consent to participation will be made by a medical doctor study team member in conjunction with their usual medical team.

Assessment of capacity will follow the two-stage test as laid out in the UK MCA:

- Is there an impairment of, or disturbance to, the functioning of the mind or brain?
- Is the impairment or disturbance sufficient that the person is unable to make that particular decision?

The MCA says that a person is unable to make a decision if unable to:

- understand the information relevant to the decision
- retain the information
- use or weigh the information
- communicate his or her decision (by any means)

Table 6: Categories of participants recruited to the studies of INTERCEPT

Study	Adults or children recruited	Consent sought for inclusion	Participants without the capacity to consent recruited?
INTERCEPT-transmission arm 1 (hospitalised inpatients)	Adults	Yes	Yes
INTERCEPT-transmission arm 2 (community members)	Adults	Yes	No
INTERCEPT-transmission arm 2 (staff members)	Adults	Yes	No
INTERCEPT-bacteraemia	Adults and children	No - anonymised use of routinely collected data	N/A
INTERCEPT-intervention	Adults	Yes	No

6.2.2 Recruitment procedure - adults with capacity to consent

- Eligible participants will be identified as described above.
- Putative study participants will then be approached individually by study team members and the study explained to them, with the opportunity to ask questions. They will be given as much time as they need to decide (up to 24 hours) and encouraged to discuss with friends and family members if needed. A patient information sheet (PIS) will be provided. If they wish to participate, they will be asked to sign a consent form.
- If participants are unable to read the PIS/consent form then the forms will be read to them in the presence of a witness unrelated to the study team and, if they wish to participate, then they will sign the consent form along with the witness who will confirm that the conversation was a true representation of the PIS/consent.
- If prospective participants cannot sign a consent form (e.g. due to lack of ability to write, visual acuity, limb weakness, or other cause of inability to write) then an independent witness can sign the consent to indicate that the participant has agreed to participate.
- In all cases above “independent witness” means a person who is not linked to the study in any way; this could be a family member or staff member.

6.2.3 Recruitment procedure - adults without capacity to consent

- Eligible participants who lack capacity to consent to participation will be identified as described above.
- As per Indonesian law and ethical guidelines, the patient’s legal guardian or closest family member will be identified by discussing with the ward team - this person is henceforth referred to here as the potential participant’s representative.

- If the potential participant has no representative (or no representative can be identified) then they will not be recruited to the study.
- The representative will be given information about the project, provided with a PIS, the study explained to them, with the opportunity to ask questions. They will be given as much time as they need to decide (up to 24 hours) and encouraged to discuss with friends and family members if needed. They will be asked to advise on what the participant's wishes and feelings would be about taking part.
- If the personal consultee advises that the participant would be in favour of participating, then they will be asked to sign a consent form.

If participants lacked capacity to consent to enrolment at baseline and were enrolled following the advice of a representative, they may regain capacity during the sampling period or subsequent sampling periods. If this occurs, then they will be reconsented for participation in the study following the procedures above for individual consent. Representatives are advised to discuss the study with the participant if they regain capacity, and requested to inform the study team of the change in circumstances.

If participants have consented to enrolment but then lose capacity to consent to participation during the course of the study then we will assume that their initial agreement to participate persists and they will continue to be enrolled in the study.

6.2.5 Anonymised antimicrobial point prevalence audit

This data will be true anonymised data extracted from routinely collected medical records hence no individual signed consent will be sought from participants.

6.2.6 Participant Reimbursement

In accordance with the Indonesian ethical practices, participants in INTERCEPT-will be offered appropriate reimbursement for time and inconvenience (IDR 50,000-100,000). The amount and method of reimbursement will be approved by the local REC and detailed in the participant information sheet

6.3 Data collection

Data will be collected using tablet devices and the REDCap platform (see section below) for INTERCEPT-transmission, INTERCEPT-bacteraemia and for observational ethnography in INTERCEPT - intervention. An outline of the data collected for the three linked studies is given below.

6.3.1 INTERCEPT-transmission

Personal data

Personal data regarding participants will be collected from two sources: directly from participants/their representative (family member or friend or consultee) by study staff and from health records for those admitted to hospital.

Data collected will include

- Demographics (name, age, ethnicity, address , employment)
- Foreign travel within last 6 months

- Animal or pet exposure
- Hospital admissions within the last 6 months
- Antimicrobials received within last 6 months
- Comorbidity and chronic medication prescriptions
- Microbiology results including blood culture results

For hospital inpatients

- Reason for admission
- Dates and times of admission
- Ward/hospital areas admitted to
- Treatments received
- Procedures carried out
- Outcome of admission (discharged/died)
- Discharge diagnosis

For staff members

- Demographics (name, age, ethnicity, address , staff grade)
- Foreign travel within last 6 months
- Animal or pet exposure
- Hospital admissions within the last 6 months
- Antimicrobials received within last 6 months

Anonymised antimicrobial point prevalence data

An antimicrobial point prevalence audit will be conducted weekly on the participating wards during the 6-week sampling window. Antimicrobial prescription data (drug, dose, route, intended duration, indication) will be collected for all patients present on the ward before 8am on the day of the audit. This data will be extracted from the medical records of all eligible patients. This data will not be linked to any personal identifiable data i.e. will be true anonymised data.

6.3.2 INTERCEPT-bacteraemia

Data collected will include

- Demographics (name, age, ethnicity, address , employment)
- Foreign travel within last 6 months
- Animal or pet exposure
- Hospital admissions within the last 6 months
- Antimicrobials received within last 6 months
- Comorbidity and chronic medication prescriptions
- Microbiology results including blood culture results
- Reason for admission
- Dates and times of admission
- Ward/hospital areas admitted to
- Treatments received
- Procedures carried out
- Outcome of admission (discharged/died)

6.3.3 INTERCEPT-intervention

Key informant interviews

Primary data collection involving semi-structured interviews with relevant key informants will be carried out to obtain their perspectives on IPC/stewardship practices and to assess the interventions developed based on the findings of the INTERCEPT studies. Individual interviews will provide participants sufficient privacy to discuss their experiences and views freely. Interviews will be conducted by experienced qualitative researchers. Each interview shall last for approximately 30-45 minutes, will be audio-recorded using a separate audio recording device and complemented by written notes. Topic guides will be developed with broad open-ended and probing questions to guide the interviews, and will explore a wide range of relevant topics including risk factors for infection/colonisation, barriers to IPC/stewardship etc.

Focus group discussions

Focus group discussion will be carried out with staff from the study wards in a sufficiently large and private space to allow for discussion. Focus group participants will be given a number to be able to recognise specific contributions during the discussions but retain anonymity. Each focus group will last approximately one hour and will be audio-recorded using a separate audio recording device and complemented by written notes. Focus group discussion guides will be developed with broad open-ended and probing questions to guide the group discussions, and will explore a wide range of relevant topics including risk factors for infection/colonisation, barriers to IPC/stewardship etc.

Observational ethnography

For the ethnographic observation data will be collected using the reflexive diary of the participant observer over the course of the study. This reflexive diary will be kept on a password protected tablet device and uploaded to the study server on a weekly basis.

Intervention co-design workshops

For the ethnographic observation data will be collected using the reflexive diary from the researchers involved in the workshops. This reflexive diary will be kept on a password protected tablet devices or computers and uploaded to the study server after each workshop.

6.4 Sample collection, storage and processing

6.4.1 INTERCEPT-transmission

Stool (or rectal swab samples if participants are unable to provide stool) will be collected from arm 1 participants (hospitalised inpatients) at day 0 (day of recruitment), day 3 (+/- 1 day), day 7 (+/- 1 day) then weekly (+/- 3 days) whilst they remain an inpatient and until the end of the 6-week sampling period, whichever is sooner.

A single stool (or rectal swab samples if participants are unable to provide stool) will be collected from arm 2 participants (community dwelling adults) on the day of recruitment.

A nasophrangeal swab, hand swab, and clothing swab (taken from the front of the chest area of the clothing) will be collected from all arm 3 participants (staff members) twice during each six-week sampling period; on recruitment (week 1-2 of sampling period) and during the final week of the sampling period.

Environmental samples will be collected weekly from the participating wards during the sampling window - these will aim to purposely sample likely sinks and sources of carbapenem-resistant bacteria (toilets, sinks, showers, air-conditioner outlets), medical equipment and high touch surfaces.

These samples will be identified in the laboratory by a pseudonymised unique study ID, rather than using any identifiable participant data, which will link back to participant data via the secure study database (see section 8.1). Samples will undergo selective culture for carbapenem resistant bacteria, and bacterial identification using standard microbiology techniques. DNA will be extracted from individual isolates and plate sweeps and sent for sequencing at sequencing facilities which may be outside Indonesia, including the UK. Bacterial isolates will be stored in Indonesia and shipped to the UK for further plasmid/MGE conjugation experiments.

A single hospital wastewater sample will be collected weekly during each 6-week sampling period at the A, B, or C hospital. DNA will be extracted and sent to sequencing facilities which may be outside Indonesia, including the UK.

Samples, isolates and DNA will be stored securely for the duration of the study and at least 5 years afterwards. Samples (stool) will be stored in indonesia. Bacterial isolates and/or DNA will be stored in Indonesia and UK; formal approval for a material transfer agreement (MTA) will be sought from the Indonesian Ministry of Health as per standard Indonesian protocols (following the procedures laid out in https://www.badankebijakan.kemkes.go.id/layanan-mta-material-transfer-agreement/). Because non-human genetic material (i.e. microbes and microbial DNA) will be collected from human (stool/rectal swab) and environmental samples, this MTA will hence come under the scope of the Nagoya protocol. Indonesia ratified Nagoya in 2014 but has not implemented any specific access and benefit sharing (ABS) legislation or procedures. ABS principles are therefore applied via existing legislation and via existing government institutions (see https://absch.cbd.int/en/countries/ID?status=All at access and benefit sharing house). In our case we as we plan to ship microbes / microbial DNA necessary permissions and MTA via the Ministry of Health will fulfil the requirements of Nagoya.

Colonisation with carbapenem-resistant organisms has no clinical relevance for study participants so colonisation status will not be fed back to study participants. Aggregated results of presence of carbapenem-resistant bacteria in environmental samples will be fed back to hospital IPC teams. Colonisation with carbapenem-resistant bacteria has no relevance for staff so colonisation status will not be fed back to them; there will be no negative consequences for staff found to be colonised as there is no Indonesian guidance which mandates any IPC precautions for staff or any decolonisation protocols. Aggregate staff colonisation results will be fed back to IPC teams.

6.4.2 INTERCEPT-bacteraemia

No samples will be collected from participants for INTERCEPT-bacteraemia. Isolates from blood cultures will be subcultured and transferred from the clinical laboratories to study laboratories where DNA will be extracted and DNA and isolates will be stored securely in the Indonesian study laboratory. DNA will be sent for sequencing at sequencing facilities which may be outside Indonesia, including the UK. Isolates will be sent to the UK for further plasmid/MGE conjugation experiments, following approval of an MTA as described above.

6.4.3 INTERCEPT-intervention

No samples will be collected in INTERCEPT-intervention.

6.5 Withdrawal criteria and management of withdrawal from the study

Participants may withdraw from any study at any time without giving a reason. If they wish their data and/or samples collected up to that point to be destroyed then this will be done, except for

anonymised data from INTERCEPT - intervention, once this is doen the data cannot be linked to a specific participant.

6.6 End of study

The study will be complete when all rounds of sampling at the sample locations are complete plus six months to allow for sample processing time.

7 STATISTICS AND DATA ANALYSIS

7.1 Statistical analysis plan and sample size calculation

7.1.1 INTERCEPT-transmission

To identify routes of transmission, we will build stochastic Markov multistate models of inpatients where participants can be either colonised or uncolonised, and move between the two with a rate determined by a linear combination of covariates, building on our previous work[18,19,22]. Other colonised patients and environmental sources will act to increase the rate of colonisation or decolonisation via a force of infection term. Initially these will use only phenotypic data but genomic data will be incorporated by constructing a pairwise genomic distance matrix and models where (similar to[25]), but building on this method by directly measuring within-participant diversity (see below). Using a simulation-based approach we estimate that 500 patients per sampling round (i.e. over 9 months, 1000 patients total) is likely to identify a clinically relevant effect on driving increase in colonisation (Figure 3). The primary outcome is the value of the parameter governing acquisition of carbapenem-resistant bacteria.

Staff members will be incorporated in the models providing a force of infection term to the patients, where staff are colonised. No formal sample size calculation for staff has been carried out but we aim to sample as many staff as possible for a given ward – we estimate that 20 staff per ward is feasible, resulting in 120 people in total.

100 community members recruited from the communities served by each hospital will (assuming community prevalence of colonisation 5%) result in 300 participants in total, and allow an estimation of the community prevalence of colonisation with carbapenem-resistant bacteria of +/-3%.\

We will use a variety of sequencing techniques to understand transmission of carbapenem resistant bacteria: individual isolates from human and environmental samples will be short-read whole-genome sequenced and genomes assembled and antimicrobial resistance genes identified using standard techniques. Plate sweeps (following selective culture) will be used to define within-sample diversity by short-read sequencing the whole plate sweep and identifying all strains within the sample using the MSWEEP/MGEMS pipeline[13]. Hospital wastewater samples will undergo short-read shotgun metagenomic sequencing and taxonomy and resistome defined using standard techniques. Long read sequencing using Oxford Nanopore Technology (ONT) sequencing on representative samples will recover MGEs such as plasmids

7.1.2 INTERCEPT-bacteraemia

The analysis of this study will be a description of the clinical and bacteriologic features of Gram-negative bacteraemia. Anonymised patient metadata (age, gender, clinical outcome, length of stay) will be used to describe clinical features of bacteraemia. No sample size calculation is carried out for this descriptive cohort; 100 patients over 9 months (3 per week) is feasible.

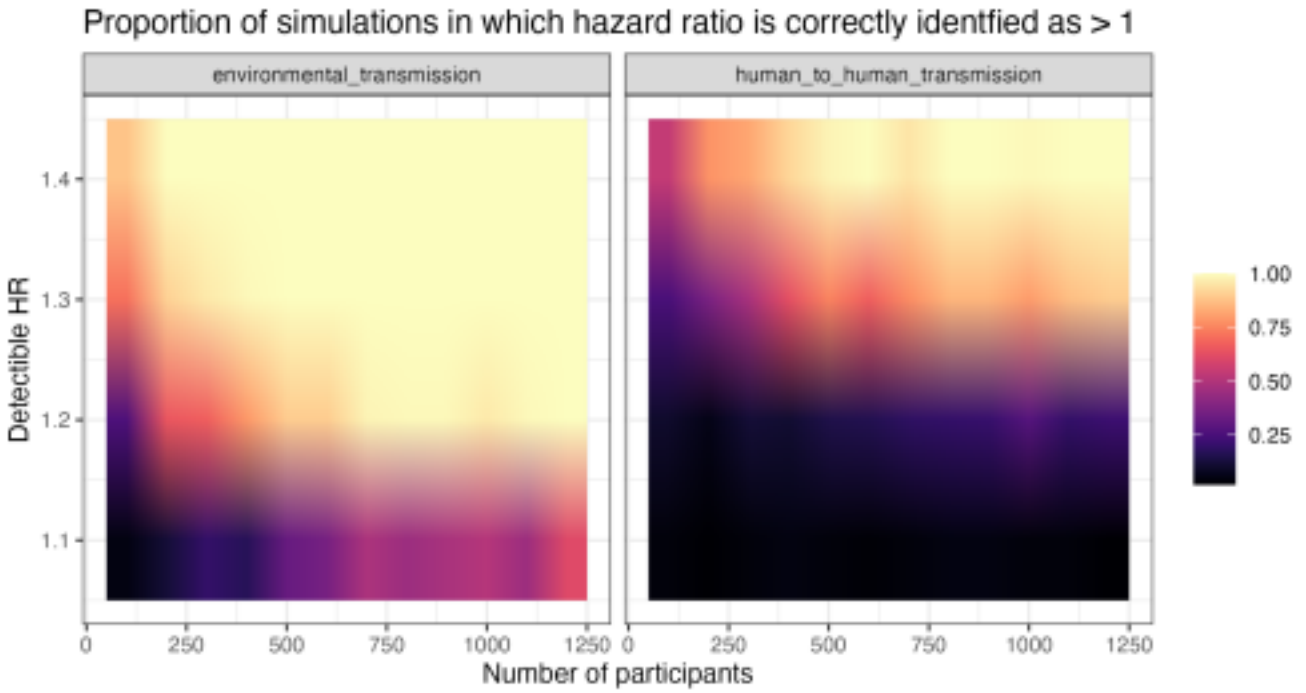


Figure 3: Sample size calculation using a simulation-based approach. Multistate models were constructed with an instantaneous rate of colonisation or decolonisation given by (0.01, 0.005) day^{-1} respectively, based on values from our previous study[18]. Other colonised patients and the environment on the ward act to increase the rate of colonisation via a force of infection with a hazard ratio HR_1 or HR_2 respectively per 10% increase in proportion of colonised patients/ environmental sources. Initial ward patient colonisation proportion was drawn from a Uniform (0,0.1) distribution and environmental colonisation drawn from Uniform (0,0.8). 12 wards were considered, varying the number of recruited participants (n) and the values of HR_1/HR2, with 100 simulations for each combination of parameter values. Multistate models were fit using the msm package in R, simulating collecting samples for each patient at days 0, 3 and 7. The proportion of simulations in which the estimate of a given HR was correctly found to have 95% confidence intervals > 1 (i.e. a measure of the power of the study) are shown as heatmaps for environmental (left panel) and human-to-human (right panel) transmission; n > 500 is likely (~ > 80% of simulations) identify HR equal to or greater than 1.3.

7.1.3 INTERCEPT-intervention

Our general analytical approach will be developmental and iterative, in that data collection and analysis will be undertaken concurrently; knowledge generated in the early interviews and focus groups will be reviewed and compared with and built on in subsequent interviews and observational ethnography. This approach will provide an opportunity to establish initial findings and build on these as data collection evolves. We will develop summary tables of emerging findings and continuously discuss these within the wider research team. This will enable initial findings to be challenged, revealing relevant gaps that will make subsequent data collection efficient.

The qualitative interview, focus group and observational data will be managed and analysed in NVivo 12 software based on a framework approach. Framework analysis provides a systematic approach to distilling themes from qualitative data through five steps: familiarization; identifying a thematic framework; indexing; charting; and mapping and interpretation(6). This analytic approach enables relevant data from different sources on the same topic to be synthesised and compared (6). We will first develop a coding framework based on the research questions, initial observations from the interviews and other data sources, and the specific data needs while retaining greater flexibility in the

framework to accommodate emerging new themes as the analysis evolves. Once the initial coding framework has been developed, the transcripts and field notes will be carefully scrutinised to identify portions that are relevant to the a priori themes/issue on the framework; relevant codes will be developed and categorised to form meaningful themes. Once we identify a theme, we will further search the transcripts and other data sources for related information, employing constant comparison to develop or complicate these themes. We will continually seek to retain the richness of respondents' experiences, documenting atypical cases, conflicts, and contradictions within the data.

7.2 Primary outcome for quantitative analyses

INTERCEPT-transmission: parameters governing acquisition of carbapenem-resistant bacteria from Markov multistate models

INTERCEPT-bacteraemia: description of clinical and microbiologic features of Gram-negative bacteraemia

7.3 Procedure(s) to account for missing or spurious data

Where appropriate, missing data in quantitative analysis will be accounted for by multiple imputation or joint Bayesian modelling of missing data.

8 DATA MANAGEMENT

8.1 Data collection tools and source document identification

8.1.1 INTERCEPT-transmission and INTERCEPT-bacteraemia

For INTERCEPT-transmission and INTERCEPT-bacteraemia, electronic case report forms (CRFs) will be used to capture data using the REDcap (Research Electronic Data Capture) platform and tablet devices. Data will be automatically pushed via cellular data connections to secure servers at the Liverpool School of Tropical Medicine (LSTM). Data entered directly into these eCRFs will be considered source data. Source data will be stored securely on LSTM servers (see below).

Participant identifiable data will not be stored in this database, to avoid international transportation of personally identifiable data. This data will be necessary to allow follow up of participants in INTERCEPT-transmission inpatients only. This will be stored in study recruitment logs securely in Diopnegoro university.

8.1.2 INTERCEPT-intervention

Interviews and group discussions will be recorded as audio recordings with contemporaneous field notes. Recordings and field notes relating to each participant will be given a unique study number and transferred to the LSTM server as soon as possible after the recording session. Audio recordings will then be transcribed into word and anonymised. Reflexive diaries will be uploaded to the secure server weekly from password protected tablets. All data will be managed using Nvivo software.

8.2 Data handling and record keeping

8.2.1 INTERCEPT-transmission and INTERCEPT-bacteraemia

CRFs and databases for INTERCEPT-transmission and INTERCEPT-bacteraemia will be developed and managed by the experienced data team at LSTM, with SOPs for the use of the system, and audit trail for data changes, using the REDcap platform. REDcap is a secure, web-based software platform

designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Data will be stored on secure LSTM servers based in the UK with regular backup, and access restricted to the data team and study team members. Participants will be identified by an unambiguous study code which will allow identification of all the data for each participant.

8.2.2 INTERCEPT-intervention

Interview and focus group recordings will be saved on the LSTM secure server as soon as possible after the interviews and focus groups and the original recording deleted from the audio capture device. Audio recordings will be transcribed verbatim, to allow for detailed nuances about respondents' experiences, opinions and attitudes to be captured as clearly as possible. Transcription will be performed by the interviewer, with a second study researcher checking the transcript for accuracy. All idiosyncratic features that add no meaning to the transcript will be removed along with any identifying statements. Participants will be assigned unique ID numbers to protect their identity. Raw audio data files will be password-protected and stored on a secure server at LSTM. Field notes will be typed out and transferred into the computer with the transcripts. Reflexive diaries will be uploaded to the secure server weekly from password protected tablets. Informed consent forms will be scanned, named, saved and the paper copies stored in a GCP compliant space.

8.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections- in line with participant consent.

8.4 Archiving

Archiving will be authorised by the Sponsor following submission of the end of study report. All archived documents (source data, CRFs, study databases) will be stored on secure LSTM servers for a minimum of five years following completion of the study.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Research Ethics Committee (REC) review & reports

- Before the start of the study, approval will be sought from a REC in the UK and REC in each study site in Indonesia for the study protocol, informed consent forms and other relevant documents. Substantial amendments that require review by REC will not be implemented until UK and Indonesian REC grants a favourable opinion for the study.
- All correspondence with the REC will be retained in the Trial Master File/ Investigator Site File.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the study.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

9.2 Public and Patient Involvement

Multiple stakeholders will be engaged as part of INTERCEPT-intervention and a public involvement strategy will be developed as part of this study

9.3 Protocol compliance

Accidental protocol deviations can happen at any time. They will be adequately documented on the protocol deviation forms and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

9.4 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or

(b) the scientific value of the study

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

9.5 Data protection and participant confidentiality

All investigators and study site staff will comply with the requirements of the UK Data Protection Act 1998 and the Indonesian Personal Data Protection Law (Law No. 27 of 2022) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles. Personal information will be collected via REDcap eCRF and stored securely on LSTM servers. It will be linked to a pseudonymised study ID i.e. the creation of coded, depersonalised data where the participant’s identifying information is replaced by an unrelated sequence of characters. Links between study ID and personal data will be stored in separate locations using encrypted and password protection. Access will be limited to the minimum number of individuals necessary for quality control, audit, and analysis. Data will be stored for a minimum of five years following study completion; personally identifiable information will be stored for a maximum of 12 months and will be destroyed once it is no longer required for analysis.

The data custodian will be the CI of the study. Access to relevant datasets will also be made available to Indonesian co-investigators in accordance with capacity-building and equitable data-sharing principles.

9.6 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall study management

No study team members have any competing interests that might influence study design, conduct, or reporting

9.7 Indemnity

LSTM (the research sponsor) has an insurance policy in place which covers all research activity.

9.8 Amendments

The CI is responsible for a decision to amend the protocol if necessary, to ensure achievement of the study objectives. The CI and sponsor will decide if a proposed amendment is substantial or non-substantial and the revised protocol will be submitted to the REC. Substantive changes will be communicated to relevant stakeholders by the study team. All study documents will be version controlled to identify the most recent protocol version (see appendix 2).

9.9 Access to the final study dataset

Those study team members with responsibility for analysis will have access to the full study dataset, as will members of the LSTM data team with responsibility for database administration. Indonesian site investigators will have access to site-specific data and opportunities to co-analyse and co-publish the results in alignment with equitable partnership principles.

9.10 Serious Adverse Events

Adverse events related to study procedures may include mild rectal bleeding or discomfort following rectal swab. Any serious adverse events (i.e. related to study procedures and unexpected) are very unlikely but will be reported to the REC as per guidelines for non-CTIMP studies.

9.11 Participant Reimbursement and Compensation

Participants in Indonesia will be reimbursed for time, inconvenience, and transportation costs associated with participation in the study, in accordance with local ethics committee guidance. The amount and form of compensation will be approved by the Indonesian Health Research Ethics Committee prior to recruitment. This compensation will not constitute inducement and will be disclosed in the participant information sheet.

10 DISSEMINATION POLICY

10.1 Dissemination policy

Upon receipt of a favourable opinion from the REC, this study protocol will be published in a peer reviewed journal. On completion of the study, the data will be analysed and tabulated and a Final Study Report prepared, which will be circulated to relevant stakeholders. Study findings will be published as preprints on preprint servers (e.g. BioRxiv) and in peer reviewed journals and presented at scientific conferences. Funding bodies will be acknowledged but will have no role in analysis or preparation of reports. Results of analysis will be presented to study sampling locations (to residents and staff of hospital wards, care homes) and participants will be invited to participant analysis feedback days where results will be presented. Following publication of results, anonymised data and code to reproduce results will be published in data and code repositories (e.g. zenodo, GitHub) without any preconditions for access. Sequence data will be deposited into publicly accessible repositories following publication (e.g. European Nucleotide Archive).

10.2 Authorship eligibility guidelines and any intended use of professional writers

It is anticipated that multiple publications will arise from the data generated by this study. The

ICMJE (International Committee of Medical Journal Editors) criteria will be used to determine

eligibility for authorship for any given report:

- Substantial contributions to the conception or design of the work; or the acquisition,
- analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND]
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Use of professional writers is not planned.

12 REFERENCES

1. Murray, CJ et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet 399, 629–655 (2022).

2. WHO. WHO Bacterial Priority Pathogens List, 2024

3. Lewnard, JA et al. Burden of bacterial antimicrobial resistance in low-income and middle-income countries avertible by existing interventions: an evidence review and modelling analysis. The Lancet (2024) doi:10.1016/

S0140-6736(24)00862-6.

4. WHO. GLASS | Country profiles: Indonesia.

5. Saharman, YR et al. Clinical impact of endemic NDM-producing Klebsiella pneumoniae in intensive care units of the national referral hospital in Jakarta, Indonesia. Antimicrob Resist Infect Control 9, 61 (2020).

6. Duerink, DO et al. Preventing nosocomial infections: improving compliance with standard precautions in an Indonesian teaching hospital. Journal of Hospital Infection 64, 36–43 (2006).

7. Indonesia: Second National Action Plan on Antimicrobial Resistance Indonesia 2020-2024.

8. Xu Y, et al. Epidemiology of carbapenem resistant Enterobacteriaceae (CRE) during 2000-2012 in Asia. J Thorac Dis. 7(3):376-85 (2015)

9. Kuntaman, K. et al. Occurrence and characterization of carbapenem-resistant Gram-negative bacilli: A collaborative study of antibiotic-resistant bacteria between Indonesia and Japan. Int J Urol 25, 966–972 (2018).

10. Perdana, MA., et al. Characteristics and susceptibility pattern of catheter-associated urinary tract infections (CAUTI) bacteria in Indonesia: A study in a national reference hospital of Sumatra region 2020–2021. Narra J 3, e436 (2023).

11. Wardhana, A., et al. Bacterial and antimicrobial susceptibility profile and the prevalence of sepsis among burn patients at the burn unit of Cipto Mangunkusumo Hospital. Ann Burns Fire Disasters 30, 107–115 (2017).

12. WHO. GLASS | Country profiles: Indonesia.

13. Severin, JA. et al. Faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae among humans in Java, Indonesia, in 2001-2002. Trop Med Int Health 17, 455–461 (2012).

14. Rosantia, S. et al. Characterization of CTX-M-type-extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae isolated from Indonesian undergraduate medical students of a university in Surabaya, Indonesia. J Infect Chemother 26, 575–581 (2020).

15. Puspandari, N. et al. Extended spectrum beta-lactamase-producing Escherichia coli surveillance in the human, food chain, and environment sectors: Tricycle project (pilot) in Indonesia. One Health 13, 100331 (2021).

16. Weingarten, RA. et al. Genomic Analysis of Hospital Plumbing Reveals Diverse Reservoir of Bacterial Plasmids Conferring Carbapenem Resistance. mBio 9, 10.1128/mbio.02011-17 (2018).

17. Santosaningsih, D., et al. Prevalence and Abundance of Beta-Lactam Resistance Genes in Hospital Wastewater and Enterobacterales Wastewater Isolates. Tropical Medicine and Infectious Disease 8, 193 (2023).

18. Lewis, JM. et al. Colonization dynamics of extended-spectrum beta-lactamase-producing Enterobacterales in the gut of Malawian adults. Nat Microbiol 1–12 (2022) doi:10.1038/s41564-022-01216-7.

19. Bridgen, JR. et al. A Bayesian approach to identifying the role of hospital structure and staff interactions in nosocomial transmission of SARS-CoV-2. medRxiv 2023.09.11.23295353 (2023).

20. Mäklin, T. et al. Bacterial genomic epidemiology with mixed samples. Microbial Genomics 7, 000691 (2021).

21. Cocker, D. et al. Drivers of Resistance in Uganda and Malawi (DRUM): a protocol for the evaluation of One-Health drivers of Extended Spectrum Beta Lactamase (ESBL) resistance in Low-Middle Income Countries (LMICs). https:// doi.org/10.12688/wellcomeopenres.17581.1 (2022).

22. Rimella, L. et al. Inference on Extended-Spectrum Beta-Lactamase Escherichia coli and Klebsiella pneumoniae data through SMC^2. Preprint at https://doi.org/10.48550/arXiv.2208.11331 (2022).

23. Ludden, C. et al. Defining nosocomial transmission of Escherichia coli and antimicrobial resistance genes: a genomic surveillance study. The Lancet Microbe 2, e472–e480 (2021).

24. De Maio, N., et al. SCOTTI: Efficient Reconstruction of Transmission within Outbreaks with the Structured Coalescent. PLoS Comput Biol 12, e1005130 (2016).

25. Worby, CJ. et al. Reconstructing transmission trees for communicable diseases using densely sampled genetic data. Ann Appl Stat 10, 395–417 (2016).

26. Gweon, HS. et al. The impact of sequencing depth on the inferred taxonomic composition and AMR gene content of metagenomic samples. Environmental Microbiome 14, 1–15 (2019).

27. Tonkin-Hill, G. et al. Pneumococcal within-host diversity during colonisation, transmission and treatment. 2022.02.20.480002 https://doi.org/10.1101/2022.02.20.480002 (2022).

28. Khawaja, T. et al. Escherichia Coli Colonisation Diversity and Impact of Antibiotic Use in Punjab, Pakistan: A Cross Sectional Genomic Cohort Study. SSRN https://doi.org/10.2139/ssrn.4683844 (2024).

29. Anggraini, D. et al. Multicenter Study of the Risk Factors and Outcomes of Bloodstream Infections Caused by Carbapenem-Non-Susceptible Acinetobacter baumannii in Indonesia. Trop Med Infect Dis 7, 161 (2022).

30. Tauran, PM. et al. Excess mortality attributable to antimicrobial-resistant bacterial bloodstream infection at a tertiary-care hospital in Indonesia. PLOS Glob Public Health 2, e0000830 (2022).

31. Cane, J., et al. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci 7, 37 (2012).

32. WHO. Global action plan on antimicrobial resistance. (2015).

33. Lester R, et al. Sustained Reduction in Third-generation Cephalosporin Usage in Adult Inpatients Following Introduction of an Antimicrobial Stewardship Program in a Large, Urban Hospital in Malawi. Clin Infect Dis. 3;71(9):e478-e486 (2020)

34. Supriadi, IR. et al. Infection prevention and control in Indonesian hospitals: identification of strengths, gaps, and challenges. Antimicrob Resist Infect Control 12, 1–11 (2023).

35. Saharman, YR. et al. Multimodal intervention to reduce acquisition of carbapenem-non-susceptible Gram-negative bacteria in intensive care units in the National Referral Hospital of Indonesia: An interrupted time series study. J Crit Care 64, 237–244 (2021).

36. Limato, R. et al. Optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention. Lancet Reg Health Southeast Asia 2, 100013 (2022).

37. Limato, R., et al. Qualitative study of barriers to antimicrobial stewardship in Indonesian hospitals: governance, competing interests, cost, and structural vulnerability. Antimicrob Resist Infect Control 11, 1–10 (2022).

38. Carattoli, A. Plasmids and the spread of resistance. International Journal of Medical Microbiology 303, 298–304 (2013).

39. Roberts, AP., et al. Gene transfer in bacterial biofilms. in Methods in Enzymology (ed. Doyle, R. J.) vol. 336 60–65 (Academic Press, 2001).

40. Tansirichaiya, S et al. Capture of a novel, antibiotic resistance encoding, mobile genetic element from Escherichia coli using a new entrapment vector. Journal of Applied Microbiology 130, 832–842 (2021).

41. Goodman, RN., et al. Intracellular Transposition of Mobile Genetic Elements Associated with the Colistin Resistance Gene mcr-1. Microbiology Spectrum 11, e03278-22 (2022).

42. Tansirichaiya, S. et al. Intracellular Transposition and Capture of Mobile Genetic Elements following Intercellular Conjugation of Multidrug Resistance Conjugative Plasmids from Clinical Enterobacteriaceae Isolates. Microbiology Spectrum 10, e02140-21 (2022).

13 APPENDICES

13.1 Appendix 1 – Schedule of Procedures

13.1.1 INTERCEPT-transmission

Table 7: Schedule of procedures for INTERCEPT-transmission

	Day 0	Day 3	Day 7	weekly until discharge	Final week of sampling period
Arm 1: hospitalised inpatients					
Questionnaire	x				
Stool/rectal swab	x	x	x	x	
Arm 2: community members					
Questionnaire	x				
Stool/rectal swab	x				
Arm 3: staff members					
Questionnaire	X				
Nasopharangeal swab/ hand swab / clothing swab	x				x

13.2 Appendix 2 - Protocol Amendments

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.

Amendment date	Protocol version	Changes
04 December 2025	V1.3	Add arm 3 – staff member – recruitment and staff sampling Clarify that bacteraemia participants can be recruited throughout the study (not just during 6 week sampling periods).