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| ProtocolThe VRESIST Study CA cluster randomised controlled trial to reduce inappropriate antibiotic use in district health facilities in Vietnam |
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| title page |

**Trial Sponsor:** *The Woolcock Institute of Medical Research*

**Funding Agency:** *The Australian Department of Foreign Affairs and Trade*

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VERSION HISTORY

**Version 1.0, 17/01/2022**

**Version 2, 14/2/2022**

# PROTOCOL SYNOPSIS

This protocol presents the methods for a randomised controlled trial being performed in district health facilities in Vietnam.

VRESIST Study C

This cluster randomised controlled trial aims to evaluate the effectiveness of a multi-faceted, Antimicrobial Stewardship (AMS) intervention on overall antibiotic use, and appropriate antibiotic use, in district health facilities. The unit of randomisation (cluster) is the district clinic. The intervention will be implemented by research staff in cooperation with healthcare workers in district facilities, pharmacists, academic and community partners.

The intervention will be delivered over a four-month period in the intervention group. After the intervention period the intervention will also be implemented in control sites. The co-primary outcomes will be measured before and after the intervention period. The co-primary outcomes are:

1. The difference in the proportion of patients treated with appropriate antimicrobials according to a clinical audit of patient files, before and after the four-month intervention period, assessed using a locally-adapted version of the Australian National Antimicrobial Prescribing Survey (NAPS) tool, in the intervention group compared to the control arm.
2. The difference in Defined Daily Doses (DDD) of antibiotics per 1,000 bed-days prescribed for inpatients, before and after the four-month intervention period, in the intervention group compared to the control arm.

Table 1: Abbreviations and definition of terms

| **Abbreviation or special term** | **Definition** |
| --- | --- |
| AE | Adverse event |
| AMR | Antimicrobial resistance |
| AMS | Antimicrobial stewardship - Antibiotic stewardship (AMS) is defined as a coherent set of actions designed to promote the use of antibiotics responsibly in ways that ensure sustainable access to effective therapy1 |
| CI | Chief investigator |
| CRF | Case Report Form (electronic/paper) |
| DDD | Defined daily dose - “the assumed average maintenance dose per day for a drug used for its main indication in adults.” 2 |
| DOT | Days of therapy |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| GCP | Good Clinical Practice |
| MoH | Ministry of Health, in Vietnam |
| NAPS | National Australian Prescriber Survey |
| NHMRC | National Health and Medical Research Council |
| PI | Principal Investigator  |
| URTI | Upper respiratory tract infection |

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# OVERVIEW

**Title:** A cluster randomised controlled trial to reduce inappropriate antibiotic use in the district health facilities in Vietnam: VRESIST Study C.

**Study investigators**

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| **Associate Investigators** |  |  |
| Dr Jaslyn Doshi | PhD Student | The University of Sydney |

# Position Descriptions

### Chief investigators’ committee

The Chief Investigators’ Committee will:

* Provide guidance regarding study design, protocol development and implementation of the study
* Support engagement within the Vietnamese health care system
* Support ethical approval procedures within Australia and Vietnam
* Provide guidance into the analysis of data
* Participate in site visits, monitoring and evaluation
* Contribute to dissemination of research findings

Principal investigator

The Principal Investigator will be responsible for the following:

* Development of the final study protocol, in consultation with all relevant parties
* Provide approval of all forms and manuals of procedures, prior to their use
* Obtain relevant ethical approval from the University of Sydney Human Research Ethics Committee
* Conduct monitoring visits to evaluate data integrity and compliance with protocols and regulations
* Oversee the data analysis of the study, and preparation of data for reporting
* Approve budgets that have been developed by project staff.

Project Management Committee

The Project Management Committee will be responsible for:

* Overseeing the day to day management of the trial
* Development of Manuals of Procedures and study documents (including case report forms, data monitoring forms, public documents)
* Providing input into training materials
* Monitoring the expenditure in line with approved project budgets
* Reviewing Adverse Events and ensuring reporting of those events is performed in a timely fashion
* Providing input into communications material for stakeholders (e.g. newsletters)
* Developing Terms of Reference for study staff
* Meeting every 1-2 weeks with Project Staff to review trial progress, and develop strategies to improve recruitment, follow up and adherence to trial protocols

Country Director (Woolcock Institute, Hanoi)

* + Oversee the Project Coordinator in implementing the project in Vietnam, including weekly meetings (in person or by teleconference).
	+ Approve budgets prepared by the Project Coordinator, according to office financial policies.
	+ Approve all forms and manuals of ­procedures, prior to submission to the Principal Investigator for final approval.
	+ Support the Project Coordinator in liaising with Vietnamese government partners, and its affiliated health care facilities to implement the project.
	+ Ensure the project complies with all relevant legal and ethical guidelines.

Project Coordinator (Woolcock Institute, Hanoi)

The Project Coordinator will fulfil the following key roles:

* Work collaboratively with study staff and leaders to implement the project
* Develop a manual of procedures, forms, data management processes, monitoring and evaluation processes, training materials and participant information
* Organise for translation of study documents
* Conduct training of local staff as required.
* Oversee data collection and entry, ensuring that data is entered electronically in an accurate and timely way.
* Ensure that any adverse events or activities undertaken in the Project that could harm the reputation of the research organizations, sponsors or any individuals are clearly documented and promptly reported to the Country Director.
* Maintain the equipment for the study, and ensure it is properly accounted for according to institutional policies.

Provincial Project Officer (Woolcock Vietnam), in each Province

The Provincial Project Officer (Woolcock) will fulfil the following roles:

* + Engagement with Vietnamese partners within all the participating facilities
	+ Support training of Vietnamese staff
	+ Prepare monthly progress reports for the Principal Investigator
	+ Work with other Project Officers and the Project Coordinator to obtain local approvals
	+ Work with other Project Officers to conduct regular monitoring and evaluation

Provincial Coordinator (Provincial Department of Health)

In each Province, an employee of the Provincial / City hospital involved in the management of antimicrobial stewardship will be responsible for supporting the study in all communes participating in the study. Roles include:

* + Obtaining support for the study within the Province
	+ Supporting the training
	+ Conduct monitoring visits, with the Research Officers
	+ Providing advice about the suitability of the Manual of Procedures and other study documents, during the localisation process.

# BACKGROUND

Vietnam is a hotspot for the emergence of drug resistant disease 3, epitomising the regional challenges facing health systems in combating antimicrobial resistance (AMR) 4. Deregulation of the pharmaceutical industry following the country’s “Đổi Mới” economic reforms in the 1980s has contributed to widespread over-use of antibiotics 4,5. One third of antibiotics are thought to be taken inappropriately, predominantly due to overuse – particularly within the lower levels of the health system 6. At the same time, Vietnam continues to experience a high prevalence and incidence of infectious diseases, with substantial associated morbidity and mortality 3,7. This combination of factors has contributed to selective pressure upon microorganisms, leading to high rates of drug resistance in a range of pathogens including *M. tuberculosis* 7, pneumococcus 8, gram negative bacteria 4 and malaria 9. **Although Vietnam has established regulations to address this issue, their impact upon antibiotic use and on AMR has been very limited 4. Therefore, additional policy responses are urgently needed.** Factors linked to the rising rates of antimicrobial resistant infections in Vietnam include inappropriate antibiotic use, poor quality of medications, inadequate AMR surveillance, poor community awareness, inadequate regulation, excessive use in agriculture and perverse financial incentives that result in over-servicing 4,10. The problem is not limited to Vietnam. Regional economic, educational and tourism networks mean that **the emergence of resistant infections in Vietnam has serious adverse implications for whole Indo-Pacific region.**

**The Vietnamese Government is responding. It has recognised Antimicrobial resistance (AMR) as a top health security priority** 11,12, reflecting the growing burden that it places on individuals and the health system 13. The Vietnam **Global Health Security Agenda 2015-2025** outlines a comprehensive strategy to promote national health security, with AMR listed as the first among eleven health security priorities 11. Accompanying this strategy, the **National Action Plan on Antibiotic Resistance** (NAPAR) lays out a detailed plan for strengthening the control of AMR in the country, as well as calling for enhanced research capacity to address the challenges of drug resistance 10.

**The overall aim** of the VRESIST series of projects is to develop, implement and evaluate the effectiveness of AMS interventions to reduce inappropriate antimicrobial use in the local community, and within district health facilities, in Vietnam.

# VRESIST STUDY C OVERVIEW

### Study hypothesis and objectives

**Hypotheses**: We hypothesise that a multi-faceted, Antimicrobial Stewardship (AMS) intervention based upon audit and feedback as well as health promotion amongst patients based in District Hospitals will: (a) improve appropriateness of antibiotic use in the intervention arm compared to the control arm, and (b) reduce overall antibiotic consumption.

Table 2: Summary of Objectives and Outcome measures for VRESIST Study C

| # | **Objective** | **Outcome measures** |
| --- | --- | --- |
|  | **Co-primary objectives** | Outcomes will be compared between the intervention and control groups: |
| 1 | To evaluate the effect of the AMS intervention upon the appropriateness of antimicrobial use, assessed by clinical file audit. | The proportion of patients with infectious diseases treated with appropriate antimicrobials according to a clinical audit of patient files, comparing the antimicrobial use in the period before and after the intervention period, assessed using an adapted version of Australian National Antimicrobial Prescribing Survey (NAPS) tool. |
| 2 | To determine the effect of an integrated AMS intervention upon the Defined Daily Doses (DDDs) of antibiotics per 1,000 bed-days among inpatients in the intervention compared to the control group  | The reduction in Defined Daily Doses (DDD) of antibiotics per 1,000 bed-days (or DOT for paediatric cohort) among inpatients attending district health facilities comparing the period before and after the intervention period, in the intervention compared to the control group. |
|  | **Secondary objectives** |  |
| 3 | To evaluate the effect of the AMS intervention upon healthcare worker knowledge. | To evaluate differences in healthcare worker knowledge regarding appropriateness of antibiotics and avoidance of antibiotics for common viral infections, as assessed by standardized surveys, after compared to before the intervention period in the intervention compared to control group. |
| 4 | To determine the incremental cost-effectiveness of the AMS intervention. | The incremental health system cost per DDD of antibiotics per 1,000 inpatients averted during the intervention period, in the intervention compared to the control group. |
| 5 | To determine the effect of the intervention upon clinical outcomes for inpatients in the intervention period | The difference in 30-day all-cause mortality among inpatients, comparing mortality for patients admitted at baseline versus the end of the intervention period, in the intervention compared to the control group |
|  | **Process outcomes in intervention sites only** |  |
| 6 | To determine the proportion of clinical staff participating in training programs | The proportion of clinical staff employed at District clinics attending one or more training workshops during the intervention period. |
| 7 | To evaluate campaign awareness and message recall | Awareness of the key messages to the inpatients as part of the community health promotion program for AMS based upon a survey, following the intervention. |
| 8 | Perceived value and quality of the campaign among patients and healthcare workers | The proportion patients reporting awareness of the AMS campaign. |

### Study design

This is a cluster randomised controlled trial (RCT) of an integrated AMS intervention to reduce inappropriate antibiotic use in district healthcare facilities. The intervention will be carried out over four months. The study will be conducted in two Provinces of Vietnam (Hanoi and Ca Mau Provinces). All health facilities and people attending district health facilities within clusters (districts) allocated to the intervention group will be offered the same general types of intervention.

Clusters

The cluster comprises a district health facility, located with a district in one of the two provinces. Outcomes measured in clusters that receive the intervention will be compared to outcomes measured in clusters that do not receive the intervention.

In this study, we are evaluating the combined effectiveness of two interventions:

Each participating cluster will be randomly allocated to one of two groups

* Intervention group: a hospital-based AMS program involving:
	+ Establishment of approved guidelines for antibiotic use
	+ Implementation of periodic antibiotic use audit and feedback
	+ Healthcare worker education
	+ Provision of health promotion material for patients that are admitted in hospital, regarding antibiotic use
* Control group: No interventions.

Control sites will not receive the intervention during the four-month intervention period. At the completion of the intervention, there will be a cross-over period when control sites will also receive the intervention.

Figure 1 summarises the overall schema of VRESIST Study C.

Figure 1: Overview of activities in the Intervention Group

4 weeks

Localisation of guidelines and stakeholder engagement

~ 8 weeks

Measure process indicators

**MEASUREMENTS**

**PRE-INTERVENTION PHASE\***

**INTERVENTION PHASE+**

2 weeks

16 weeks

2 weeks

Outcome measurements

Month 4 NAPS audit

DDD dispensed

Baseline antibiotic use (NAPS) audit survey.

KAP survey for healthcare workers.

Calculation of DDDs dispensed at baseline.

Training of local staff.

Implement AMS interventions

Audit and feedback at month 0 (baseline) and months 1, 2 and 3 months

Feedback to local stakeholders

Work with stakeholders to sustain the intervention

**ACTIVITIES**

**POST-INTERVENTION PHASE**

Figure 2: Overview of activities in the Control Group

4 weeks

Localisation of guidelines and stakeholder engagement

~ 8 weeks

**MEASUREMENTS**

**PRE-INTERVENTION PHASE\***

**INTERVENTION PHASE+**

2 weeks

16 weeks

2 weeks

Collect data about antimicrobial use

Outcome measurements

Month 4 NAPS audit

DDD dispensed

Baseline antibiotic use (NAPS) audit survey (no feedback).

KAP survey for healthcare workers.

Calculation of DDDs dispensed at baseline.

Training of local staff.

Implement NAPS survey and audit and feedback.

Provide feedback to facility

**ACTIVITIES**

**POST-INTERVENTION PHASE**

### Site selection

The study will be conducted in 16 clusters (District Health Facilities). The unit of randomisation is the District Health Facility (Hospital). Each hospital will be randomly allocated to either the intervention or control group after sites have agreed to participate in the study.

Selection of Districts

Districts are the second level administrative units of government in Vietnam. The eligibility criteria for districts in this study are:

1. Located within one of the two participating Provinces (Hanoi and Ca Mau); AND
2. The location of the public Health Centre within that District is less than 2 hours travel time by road from the Provincial Centre (as defined by Google Maps; [www.maps.google.com](http://www.maps.google.com), Google);

Each District has a District Health Facility. Eligibility criteria for District Health Facilities to be included in this study will be:

1. A government-run District Health Facility (Hospital)
2. The leader of the facility agrees to participate, and agrees for the facility to adopt standardised guidelines for antimicrobial use for the duration of the study.
3. The facility has a pharmacy present on site.

Exclusion criteria for District Health Facilities:

1. The facility cannot be accessed by study staff due to COVID-19 restrictions.

Eligibility criteria for inclusion of departments within each facility are listed in Table 3:

Table 3: Eligibility criteria for departments within participating health facilities

|  |  |
| --- | --- |
| **Inclusion criteria** | **Exclusion criteria** |
| 1. A department or ward that has inpatients
2. Located in an eligible District Health Facility
 | 1. Deparmtents where antibiotics are not available.
2. Departments in which the hospital leader or Head of Department does not give approval to conduct the research
3. Wards or departments that will be closed for at least 8 weeks during the intervention period.
 |

Selection of District Health Facilities

Members of the AMS Committee will approach the district health facilities to engage hospital administrators and gain consent for participation in the study. A survey to describe the general capacity of their respective hospitals including pharmacy, microbiology services and information technology. Once the leaders of each facility agree to participate, participating wards in each of the facilities will be selected.

Prior to commencing the study, study staff will meet with senior administrators and clinicians within the health facility. They will explain the objectives of the study, including the study design and implications if sites are chosen to carry out the intervention.

One senior hospital administration staff member will complete a survey regarding the general capacity of the hospital, including pharmacy, microbiology services and information technology.

Permission will be obtained to conduct the study in the health facility. Once the leaders of each facility agrees, participating wards in that facility will be selected.

### Randomisation of District Health Facilities

Once approval has been obtained from the leader of each eligible healthcare facility, sites will be randomised to either the intervention or control groups. Randomisation will be stratified by province, to ensure balance between the number of intervention and control groups.

Once cluster eligibility has been confirmed, clusters will be randomised to either the intervention or control group. The randomisation sequence will be stratified by province. Because the number of inpatients beds is different between clinic sites, a total of 1000 randomisation sequences will be generated using a computer program. These 1000 sequences will be examined to verify if the number of inpatient beds are approximately equal between the two arms. Randomisations that result in reasonable balance will be chosen, and subsequently one of these sequences will be selected from the subgroup of balanced randomisation sequences. Randomization will be performed by a person who is not otherwise engaged in the implementation process, and who is blinded to the identity of the sub-districts.

Owing to the nature of the intervention, group allocation will not be blinded to stakeholders in each cluster.

**Steps to avoid contamination effects between intervention and control sites**

A contamination effect can occur if components of the intervention have an effect in the control sites. It is important to minimise contamination between intervention and control arms at all stages during the study. This means that health practitioners working in control sites must not participate in training or engage with other health promotion material that may influence their behaviour, and therefore the measured effect of the intervention.

Steps taken to minimise contamination will include:

1. Collecting outcome data from medical files, and minimising interaction of research staff with the health facility staff in the control group.
2. Not holding a workshop for control sites until the cross-over period.
3. Educating all study staff about the importance of minimising contamination effects between clusters
4. Informing local stakeholders about the importance of confining interventions to intervention sites only

### Development of standardised antimicrobial use guidelines

Standardised guidelines will be developed in consultation with national and provincial authorities, that specify the valid options for antimicrobial use in different clinical scenarios. This development work has been undertaken within the VRESIST Study B (Pilot study), described separately.

### Development of AMS training materials

Training materials for appropriate antibiotic will be developed for doctors and pharmacists. They include use of guidelines, purpose of audit and feedback as well scenario based learning of appropriate antibiotic prescribing. Training will be provided to all doctors and pharmacists across all intervention site

### Development of health promotion material

Health promotion material regarding appropriate antimicrobial use has been developed in consultation with the VRESIST group of studies. This will be used to educate patients and healthcare workers in participating health facilites. This material will include:

1. Posters regarding antimicrobial use (Posters 1-4)
2. Brochures regarding management of common conditions that do not require antimicrobial use (including viral upper respiratory tract infections and acute diarrhoea) (Leaflets 1-4)
3. Sketch videos to be played on facility televisions
4. An audio jingle to be played locally

These will be given to patients and healthcare workers in the participating intervention hospitals, according to a Health Promotion Plan.

Establishment of an AMS advisory committee

The trial AMS advisory committee will include local and international pharmacists as well as local and international infectious diseases physicians. The committee will meet every fortnight and will

* Oversee protocol development and submission of ethics approval in Vietnam
* Oversee the development of guidelines and strategies in the AMS intervention
* Work with local partners to determine acceptability of intervention
* Oversee the implementation of the intervention across health districts
* Oversee the AMS teams in each health facility
* Evaluate and provide feedback in the follow up period

Arm 1: intervention sites

### **Pre-intervention phase**

After the development phase, each hospital in the intervention arm will undertake a pre-intervention phase.

### Step 1: Formation of the health facility AMS team

The leader of the health facility will nominate members to participate in an AMS team. These members will participate in a training course, performed at the health facility. The training will address:

* The rationale and evidence for the clinical guidelines for the management of common infections
* Skills in counselling health workers
* Skills in performing audit of patient charts using the NAPS audit tool and providing feedback to clinicians
* Practice delivering training sessions for staff
* Skill in patient counselling when pharmacists dispensing antibiotics at outpatient dispensaries

The training activities for staff will focus upon the rationale for guideline implementation, monitoring and feedback on compliance with the AMS guidelines.

The AMS team will be trained in details of how to implement the required activities, including health promotion and audit and feedback.

### Step 2: Baseline pharmacy dispensing calculation

The study team will work with site pharmacists to calculate total pharmacy antibiotic dispensing will be performed over a 1 month) prior to the commencement of activities at all sites. The Defined Daily Doses (DDD) of antibiotics per 1,000 patient bed days will be calculated using WHO endorsed gold standard measurement ATC/DDD methodology.23 In the case of paediatric patients, days of therapy (DOT) will be calculated.23 Results will be stratified by department and class of antibiotics. This will form the measure for comparison at the end of the intervention.

We will use the outcome of DDD per 1000 bed-daysDDD gives an estimate of the number of days for which each patient is, on average, treated per unit of time.2 Defined daily dose: “The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose. DDDs provide a fixed unit of measurement independent of price, currencies, package size and strength enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups.” 2 DDDs will be defined according to the ATC codes included in the WHO Guidelines for ATC classification and DDD assignment 2019. Category J01 refers to antibacterials for systemic use, J02 antimycotics for systemic use, J04 antimycobacterials and J05 antivirals for systemic use (Table 8).

### Step 3: Baseline antibiotic knowledge, attitudes and practices (KAP) surveys and antibiotic audits among healthcare workers and patients

1. For prescribers: All prescribers who attend training meetings will complete a Knowledge, Attitudes and Practices survey (CRF 1, with PIS HCW) prior to the intervention period. The survey will aim to assess their knowledge, attitudes and practice around antibiotic prescribing and antimicrobial resistance.
2. For other healthcare workers: A similar survey assessing nurses and pharmacists’ knowledge and attitudes around antibiotic use will also be carried out (CRF 2).
3. A questionnaire about patient knowledge, attitudes and practices (CRF 3) will be administered to a random sample of 30 inpatients in each intervention hospitals on one randomly selected day:
	1. Prior to the intervention period
	2. In the third month after the beginning of the intervention period.

### Step 4: Training of the AMS team

The AMS team in each facility will be trained to conduct the Australian National Antibiotic Prescribing (NAPS) Audit. This intervention involves a cross-sectional survey of the medical files of all inpatients admitted to selected wards at a specified time on one selected. The audit may be conducted over one to three days, but eligibility is based upon the patient being present on the ward at the start of the selected day.

This will apply the antibiotic audit processes developed by the Australian NAPS tool. This is described below. Medical files will be assessed for clinical appropriateness of the antibiotic use using a proforma alongside instructions on how to fill it.

The [National Antimicrobial Prescribing Survey](http://www.naps.org.au/) (NAPS) (CRF 4) is a standardised auditing tool that is designed to assist healthcare facilities to assess the quantity and quality of local antimicrobial prescribing. It has been implemented widely in Australia and some countries around the world and has been shown to improve antimicrobial prescribing14.

### **Intervention phase**

### Step 1: District facility workshops

Workshops will be performed at baseline in intervention district health facilities and after 1-2 months to train clinical staff at each health facility in wards / departments that will participate in the intervention. This will include doctors, nurses and pharmacists, to train them regarding the treatment guidelines and the components of the AMS intervention. This training will be co-led by the Study staff and members of the AMS Stewardship team.

Content of the staff workshops will include:

* Presenting Ministry of Health guidelines regarding appropriate antibiotic use
* Education regarding the standardised antimicrobial guidelines
* Role play / practice in the audit and feedback process
* Health promotion regaring the importance of appropriate antimicrobial use
* Questions and answers from staff.

### Step 2: Implementation of health promotion and training about AMS guidelines

The AMS intervention is run over a four-month period in District Health Facilities in the intervention group. This will comprise the following steps.

The study AMS committee will work with the AMS team at each district facility to implement the AMS intervention, including:

1. **Ongoing health promotion regarding appropriate antimicrobial**  throughout the intervention period. This will include:
	1. Display of posters in public areas
	2. Use of written material for patients who have viral illnesses that do not require antibiotics
	3. Antimicrobial stewardship jingle played in health facilities
	4. Presentation about antimicrobial use at clinical meetings.
2. **Implementation of appropriate treatment guidelines** for common viral infections (including URTIs, viral diarrhoea) and bacterial infections (including pneumonia, urinary tract infections, cellulitis, prophylaxis against surgical infections). The implementation will include:
	1. Availability of written copies of the guidelines in each ward
	2. Training of clinicians by the local AMS Committee during the audit and feedback process (below)
	3. Training in guidelines (described in step 5, above).
3. **Dissemination of health promotional materials to patients visiting out**-patient departments as well as inpatients

### Step 3: Implementation of monthly audit and feedback

The AMS team will peform an audit of the medical files of all inpatients present in the hospital on a specified day at baseline, month 1, month 2 and month 3. The team will provide de-identified feedback to the clinicians at the hospital. This will follow the NAPS survey tool, applying a locally adapted version of the Australian audit process.

Eligibility for files to be audited are:

1. Patient is an inpatient in selected wards on the day selected for audit (at a specific time chosen by the Study Coordinator)
2. Medical record is available for review
3. Regardless of whether an antibiotic was used (i.e. can be reviewed if an antibiotic is used, or not)\*.

A log book will be completed during the NAPS audit, that will include a summary of:

1. Patient’s age and gender
2. Whether antibiotics were used
3. Ward/department name
4. Whether a NAPS audit has been undertaken (completed on a detailed NAPS Audit form).

The NAPS audit will follow the approach of the Australian National Antimicrobial Prescribing Service (NAPS), comprising the use of a pro-forma for each file review (CRF 4), with accompanying instructions (Audit instructions)24. For each eligible, the team will complete an audit proforma, that allows them to evaluate the appropriateness of antibiotic use.

Within two weeks of the completion of the audit, feedback about prescribing in each department will be provided to: (a) the head of department, and, (b) clinical staff in a departmental meeting or grand round setting Clinicians will be informed about their compliance with the guidelines in a way that is de-identified. Any feedback in a group setting will not identify the name of the clinician.

Feedback will include:

* A structured evaluation process
* Clear and respectful communication about any discrepancies.
* Constructive feedback about strategies for improving appropriateness of antimicrobial use.
* Methods to motivate staff.

In addition, once a month a “Antimicrobial Champion” certificate will be awarded to highly-performing wards / staff.

Data collected on audited inpatients will include:

* Age, gender, insurance type, antibiotic allergies, date
* Microbiological test results.
* Measures of kidney (creatinine, eGFR) and liver function (bilirubin, AST, ALT), if available (to allow appropriateness of dosing to be assessed).
* Whether the indication for use of antibiotics is documented in the medical record.
* A list of the name, dose, frequency (how many times per day) and duration (number of days, as of the day of audit) of antimicrobials. This will involve any oral or intravenous antimicrobial agent given during the whole period of hospitalisation, from the patient’s day of admission up to the date of audit.

Audits will be validated by a random repeat review of at least 5% of randomly selected audited charts, selected by convenience sampling. The review will be performed by study staff - independent of the District Health Facility AMS team.

Audits will not involve individual patient consent. A waiver of consent will be requested, due to the very low risk to participants and alignment with standard clinical quality assurance processes.

If recommended process for audit are not followed by the District AMS team, then additional chart audits will be performed. If >10% of the audits are not performed appropriately, re-training of the AMS team will be performed by study staff.

**Audit reports:** A written summary of the findings of the auditwill be submitted every time a periodic audit is performed to a senior leader of the District Health Facility and study staff.

**Feedback to staff:** Feedback will be provided via meetings and written feedback to staff in the health facilities.

Table 7 summarises the AMS interventions and the expected outputs of those interventions.

Table 4: Outputs of antimicrobial stewardship interventions

| **Component** | **Objective** | **Outputs** |
| --- | --- | --- |
| Clinical guidelines for management of infectious diseases | To develop treatment guidelines for infectious diseases suitable for District Health Facilities | * Simple printed guidelines for clinicians at District hospitals regarding evidence-based management of commonly treated infectious diseases (including viral upper respiratory tract infections, lower respiratory tract infections, viral diarrhoea, urinary tract infections, prophylaxis against surgical infections etc)
* Feedback from doctors, nurses and pharmacists regarding these guidelines (through documentation of feedback in meetings, or in writing from these staff).
 |
| Develop working guidelines for District AMS committees | To develop and pilot locally applicable framework for introduction of AMS programs within District level health facilities | * Guidelines for start-up of AMS committees within local healthcare facilities.
* Identification of core and flexible elements of guidelines for AMS to be undertaken
* Feedback from doctors and pharmacists regarding the guidelines.
 |
| Develop educational material for district doctors, nurses and pharmacists | To develop training material for local health workers regarding appropriate antibiotic use | * Staff training materials developed
* Testing of training materials with feedback from participants in participating facilities
 |
| Develop educational material for inpatients  | To develop training material for patients regarding appropriate antibiotic use only when necessary | * Patient educational materials developed
* Testing of training materials with feedback from participants in participating facilities
 |
| Measuring appropriateness of antibiotic use within health facilities  | Standardised tools for evaluating:(a) DDDs / 1000 bed-days of antibiotics given to inpatients(b) Periodic audit tools to assess appropriate antibiotic use within health facilities, using the National Antimicrobial Prescribing Survey tool | * Completed surveys
* Pilot testing of standardised methodology for calculation of DDD per 1000 bed days.
* Comparison of appropriateness of antibiotic use after the intervention, compared to before the intervention, measured using a locally-adapted audit tool.
 |

### **Post-intervention phase**

### Step 1: End of intervention antibiotic dispensing survey

A survey of total pharmacy dispensing will be performed by study staff over one month period after *the intervention period*. The Defined Daily Doses of antibiotics per 1000 bed days will be calculated according to WHO methodology 23 The final antibiotic audit survey for appropriateness of antimicrobial use will also be collected post intervention and compared to the baseline.

### Step 2: Measurement of outcome measures after 4 months

The primary and secondary outcomes will be measured after 4 months of the intervention (see below). The appropriateness will be based upon a NAPS audit, based upon the patients who are inpatients at 9am (or an alternate time selected by local staff) on a single day.

The measurement of DDDs will be collected based upon pharmacy dispensing data over a month after the completion of the intervention period.

A repeat survey to test staff Knowledge, Attitudes and Practices (CRFs 1 and 2) will be conducted among healthcare workers after the intervention period.

### **Long-term sustainability of appropriate antimicrobial prescribing**

### Step 1: 6 month post-intevention follow-up

If funding permits, we will repeat the cross-sectional survey in intervention sites 6 months after the intervention period. This will establish whether the effects of the intervention are sustained over time.

Arm 2: Activities in control sites

**No intervention activities** will be performed at control sites for the four-month intervention period. At the conclusion of the four-month period, the primary outcome measure will be performed. Training will not be undertaken for staff at this time.

### **Pre-intervention phase**

### Step 1: Baseline external Antimicrobial stewardship audit

An external AMS team trained to conduct the National Antibiotic Prescribing (NAPS) Audit, will perform an audit on the medical files of all inpatients in selected wards presenting to the health facility on one weekday (selected for convenience) using antibiotic audit form adapted from the Australian NAPS tool. Medical files will be assessed for clinical appropriateness of the antibiotic use using a proforma alongside instructions on how to fill it. **Feedback will not be provided to individual clinicians or to the heads of department**.

### Step 2: Baseline pharmacy dispensing calculation

The study team will work with site pharmacists to calculate total pharmacy antibiotic dispensing will be performed over 1 month prior to the commencement of activities at all sites. The Defined Daily Doses (DDD) of antibiotics per 1,000 patient bed days will be calculated using WHO endorsed measurement ATC/DDD methodology.23 In the case of paediatric patients, days of therapy (DOT) will be calculated.23 Results will be stratified by department and class of antibiotics. This will form the measure for comparison at the end of the intervention.

### Step 3: Baseline antibiotic knowledge, attitudes and practices (KAP) surveys and antibiotic audits

KAP surveys will be given to all prescribers at a meeting during the baseline period to assess their knowledge, attitudes and practice around antibiotic prescribing and antimicrobial resistance. A similar survey assessing nurses and pharmacists’ knowledge and attitudes around antibiotic use will also be carried out.

### **Intervention phase**

No activities will be conducted in the Control District Health Facilities during the 4 month intervention phase.

### **Post intervention phase**

### Step 1: End of intervention antibiotic dispensing survey

After four months, a survey of total pharmacy dispensing will be performed by study staff over a 1 month period. The Defined Daily Doses of antibiotics per 1000 bed days will be calculated according to WHO methodology 23 The final antibiotic audit survey for appropriateness of antimicrobial use will also be collected post intervention and compared to the baseline

The external AMS team will perform the audit on the medical files of all inpatients in selected wards who are inpatients at the selected time. The survey will follow the audit form adapted from the Australian NAPS tool.

### Step 2: Cross-over (post intervention)

In the post-intervention period (once the outcomes have been measured), a cross-over will be undertaken in the control sites. During this period, the intervention (audit and feedback and health promotion and staff training) will be introduced to all control sites. This includes: (a) pre-intervention (step 1 and step 4), described in the intervention group above, and (b) intervention activities (steps 1, 2, and 3).

Training workshops will be conducted for staff at baseline, and after 1 month.

# Health economic analysis

For both the intervention and control sites, we will calculate the cost of the antimicrobials used during the pre-intervention period and at the end of the 4 months. The cost of antimicrobials will be estimated, using a survey of the pharmacy cost of purchasing antibiotics. The total antimicrobial costs will be calculated before and after. These data will be used to calculate the cost-effectiveness of the intervention.

The economic impact on hospital bed days will also be calculated using patient hospital length of stay.

# Statistical Analysis

Outcome measures expressed as a difference in proportions will be calculated with 95% confidence intervals for each of the primary and secondary clinical outcomes. The sample size calculation, for determining the number of individuals included in the pre- and post-intevention surveys, is described below.

# Dissemination of research findings

At the completion of the study, findings will be presented to local government leaders and district facility managers. Key findings will be summarised, and recommendations regarding potential scale of the intervention will be made. We will conduct a dissemination workshop in each district facility presented by study staff and local and national government leaders.

The findings of the study will be reported to the Vietnam Ministry of Health. The findings of this pilot study and the main study will be published in a peer reviewed international scientific journal. The findings will be provided to the Ministry of Health, for which the outcomes will be valuable information for developing future policies.

# Timeline for VRESIST Study C

|  |  |  |
| --- | --- | --- |
|  | 2021 | 2022 |
| 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7  | 8 | 9 | 10 |
| **PROTOCOL DEVELOPMENT** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Develop interventions |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ethics approval |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **PRE-INTERVENTION** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stakeholder engagement |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Develop health promotion materials |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **INTERVENTION** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Baseline survey in intervention sites |   |   |   |   |   |   |   |   |  |  |  |  |  |
| Training workshops |  |  |  |  |  |  |  |  |   |  |  |  |  |
| Audit feedback |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Health communication |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **POST INTERVENTION** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Post intervention surveys in all sites |  |  |  |  |  |   |   |   |  |  |  |  |  |
| Cross-over |  |  |  |  |  |  |   |   |  |  |  |  |  |
| Data analysis |  |  |  |  |  |  |  |   |   |  |  |  |  |

Statistical issues

**Sample size for survey to measure defined daily doses (DDD)**

We expect that the intervention will reduce the proportion of antibiotics inappropriately prescribed from 66% (based upon baseline evaluation) to 52% (a 14% improvement). We expect the intraclass correlation coeffient to be up to 0.048 (ranged from 0.005 to 0.048 in a study of an AMS intervention among primary health providers) 15. Therefore, the sample size in the final audit that is required to detect this difference will be a total of 380 (including both intervention and control groups). When adjusted to account for intraclass correlation 15, with a design effect of 5.7, the total number will be at least 1900 patients across all districts, ie. approximately 120 people per district clinic.

For each randomisation unit, the number of inpatients will be between 100 and 400 people at any time. The expected DDDs per 1000 bed days was 81116. We expect the intervention will be associated with a reduction in the co-primary outcomes of: (a) reduction in DDD per 1000 bed-days of 25% 17 Assuming an intra-class correlation coefficient of up to 0.048, and an average number of inpatients of 150, we need 118 patients in total be able to detect a difference in DDD per 1000 bed-days of 25% ithout accounting for intraclass correlation. With a design effect of 5.7, the minimum sample size will be 672.

Therefore, the total number of people who will participate in the final survey will be 1900.

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