ISRCTN10957189 https://doi.org/10.1186/ISRCTN10957189

A global low- and middle-income country primary care antimicrobial stewardship trial using the WHO AWaRe system – the AWaRe 1 Trial

Submission date
01/08/2024

Recruitment status
Recruiting

Registration date
14/08/2024

Overall study status
Ongoing

Last Edited
11/03/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
The global rise in inappropriate antibiotic use is a threat to population health. Over 90% of human use is in primary care (PC), with rapidly increasing use of broad-spectrum oral Watch antibiotics in low- and middle-income countries (LMICs). A core component of antibiotic stewardship is improvement in clinical treatment decision-making by frontline health workers. The overall aim of this proposal is to develop and test a framework for future surveillance, benchmarking and population-based interventional trials of optimal antibiotic use in LMIC PC settings. We will pilot new methods of estimating patterns of antibiotic exposure (WS1), develop a new AMS intervention (WS2) and evaluate it in a paradigmatic clinical trial (WS3). Novel methods of measuring antibiotic exposure will be designed to facilitate surveillance, benchmarking and improved outcome capture in LMIC PC clinical trials. The educational and organisational intervention will be based on the 2022 WHO Essential Medicines List (EML) AWaRe (Access – Watch – Reserve) Book. The pragmatic global cluster randomised trial will be performed in countries across Asia and Africa to determine the effectiveness and safety of an AWaRe system-based intervention on appropriately reducing total and oral Watch antibiotic prescribing and will be designed as a blueprint for future population-based PC trials.

Who can participate?
Participants capable of giving informed consent, or if appropriate, participants having an acceptable individual capable of giving consent on the participant's behalf, over the age of one, attending one of the primary healthcare facilities we are studying with symptoms of acute respiratory illness. Healthcare workers who prescribe antibiotics from some of facilities will also have the opportunity to participate.

What does the study involve?
Exit Interviews: a 15 minute discussion on current symptoms, treatment received or prescribed. Telephone follow-up: asked how symptoms have changed, what treatments were taken, any other treatments received, and what the associated costs were.

Observations and patients involved in qualitative interviews: A researcher will observe and record the consultation with the healthcare worker.
Qualitative interviews with staff: An audio recorded 60-minute discussion following a topic guide covering expectations of, and preferences for, different treatments for their illness; their awareness of antimicrobial resistance and alternatives to antimicrobial treatment; their experience of the care they received; and the information they received and want from clinicians. Topics covered in interviews with health professionals will include their knowledge and experience of antimicrobial treatment and resistance; factors influencing their treatment choices; communication with patients about treatment options; and their experiences and preferences regarding the AWaRe book and the training they received.

What are the possible benefits and risks of participating?
The intervention will entail minimal risk to participants because it is an educational intervention. As it is delivered at the facility level, the small risk that the patient may not receive an antibiotic they would benefit from, will be the same for all patients regardless of whether they participate or not. Those participating in qualitative interviews may be compensated for their time, up to $10, depending on the country and local regulations.

Where is the study run from?
St George's, University of London (UK)

When is the study starting and how long is it expected to run for?
April 2024 to February 2027

Who is funding the study?
Wellcome Trust (UK)

Who is the main contact?
Miss Jennifer Martin, jmartin@citystgeorges.ac.uk
Prof. Michael Sharland, msharlan@sgul.ac.uk

Contact information

Type(s)
Scientific, Principal investigator

Contact name
Prof Michael Sharland

ORCID ID
https://orcid.org/0000-0001-8626-8291

Contact details
St George’s, University of London
Institute for Infection and Immunity
Jenner Wing
Cranmer Terrace
London
United Kingdom

SW17 0RE
+44 (0)208 725 5382
msharlan@sgul.ac.uk

Type(s)
Public

Contact name
Miss Jennifer Martin

Contact details
City St Georges, University of London, Cranmer Terrace
London
United Kingdom
SW17 0RE
+44 20 8725 5382
jmartin@citystgeorges.ac.uk

Additional identifiers

Protocol serial number
2024.0179, WT 228140/Z/23/Z

Study information

Scientific Title
The AWaRe1 pragmatic cluster-randomised trial, economic and process evaluation of antibiotic stewardship in primary healthcare of acute respiratory infections in low- and middle- income countries using the WHO AWaRe system

Acronym
AWaRe1

Study objectives
The global rise in inappropriate antibiotic use is a threat to population health because it is making bacteria resistant to those antibiotics, which makes them ineffective. Over 90% of human antibiotic use is in primary healthcare, with rapidly increasing and inappropriate use of antibiotics seen in low- and middle-income countries (LMICs).
The AWaRe1 project has three workstreams;
• WS1 –AWaRe1-Surveillance
• WS2 – AWaRe1-Education
• WS3 – AWaRe1-Trial
WS1 will contribute to the development and validation of novel and scalable methods of surveillance for antibiotic use in LMIC primary healthcare.
WS2 (AWaRe1-Education) will develop an educational and organisational intervention for primary healthcare, based on the 2022 WHO Essential Medicines List AWaRe (Access – Watch – Reserve) Book. The intervention will be localised in each country. It will then be delivered, at facility level, to frontline (patient-facing) healthcare professionals working in intervention arm primary healthcare facilities.
The AWaRe1-Trial (WS3) aims to develop and test a framework for population-based

interventional trials to promote optimal antibiotic use in primary healthcare settings. We will develop a new intervention focussing on improving the quality of antibiotic use in primary healthcare and evaluate it in a pragmatic cluster randomised trial.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 04/07/2024, St. George's Research Ethics Committee (Joint Research and Enterprise Services Ground Floor, Jenner Wing, St. George's, University of London, Cranmer Terrace, London, SW17 0RE, United Kingdom; +44 20 8672 9944; sgulrec@sgul.ac.uk), ref: 2024.0179

2. notYetSubmitted 02/08/2024, Oxford Tropical Research Ethics Committee (Research Services, University of Oxford, University Offices, Wellington Square, Oxford, OX1 2JD, United Kingdom)

Study design
Pragmatic parallel arm multi-country cluster randomized superiority trial

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Optimising antibiotic use in patients presenting to primary healthcare facilities with acute respiratory tract infection symptoms

Interventions
This will be a pragmatic parallel arm multi-country cluster randomised superiority trial. The clusters will be primary healthcare centres and eligible patients attending them. Clusters will be randomised to either receive the AWaRe intervention ("intervention facilities") or to continue with usual standard of care ("control facilities"). Clusters will be randomised in a 1:1 ratio to intervention and control groups after completion of the baseline survey and before the intervention begins to be delivered in each country. Randomisation will be in blocks of four and will be carried out by the trial statistician, after completion of the baseline surveys and before the start of the intervention in each country.

The intervention package will be an educational and organisational intervention intended to change healthcare workers' and patients' behaviour around antibiotic use, localised to each country. It will focus on supporting the optimal use of antibiotics for acute respiratory infections through improved clinical guidance and health education for patient and healthcare worker. This will include 'no antibiotic' and symptomatic care for non-severe presentations and low-risk patients. The intervention and trial will focus on acute respiratory infections because they are the most common reason for antibiotic prescribing in LMICs. Interventions will be delivered at cluster level and targeted at intervention facilities and the frontline (patient-facing) health workers working in them who are responsible for diagnosis and treatment of individual patients.

Before the randomisation, 30 patients at each facility will complete an exit interview. The purpose of the baselines survey is a) to enable randomisation to be stratified by levels of antibiotic prescribing (to help ensure comparability of intervention and control facilities, b) to

assess comparability of participants in intervention and control facilities before delivery of the intervention, and c) to enable statistical adjustment of outcomes if facilities turn out to be unbalance.

Six months after the intervention began, a new cohort of 30 patients at each facility will complete an exit interview. They will be asked about the presence, type, and duration of symptoms of acute respiratory infection, and asked about the treatments or prescriptions with which they were provided. They will also be asked questions relevant to their costs of illness, such as healthcare received, expenditure, and loss of income. These patients will be followed up by telephone two weeks and four weeks after the initial interview, when they will be asked about their current illness, their general health, other treatments received, other healthcare received, and other costs of illness.

Twelve months after the start of the intervention, a further 30 new patients will be interviewed when they will be asked if they received or were given a prescription for any antibiotic and what the category of that antibiotic is.

Intervention Type
Other

Primary outcome(s)
Receipt of, or prescription for, any antibiotic during facility visit (measured at exit interview six months after intervention began)

Key secondary outcome(s))
Measured at exit interviews at 6 and 12 months, and telephone interviews 14 and 28 days after the 6-month exit interview:
1. Receipt of, or prescription for, antibiotics
2. Category of antibiotics
3. Completion of antibiotic treatment
4. Receipt of any additional antibiotic after the facility visit
5. Respiratory symptoms including severity and days until recovery
6. Health-related quality of life
7. Healthcare utilisation and healthcare expenditure
8. Safety indicators
9. Cost and cost-effectiveness of the intervention
10. Process of intervention delivery and its effects

Completion date
15/02/2027

Eligibility

Key inclusion criteria
Male or female adult or child aged over 1 year attending a primary healthcare facility with symptoms of acute respiratory illness:
1. Cough with or without fever
2. Chest symptoms (sputum, wheezing)
3. Ear, nose, sinus, or throat symptoms:
- Rhinitis (nasal discharge or blocked nose)
- Sore throat

- Ear pain
- Facial pain

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
All

Lower age limit
1 years

Sex
All

Key exclusion criteria
1. Respiratory symptoms have persisted for more than 14 days (that is, symptoms not acute)
2. Undifferentiated fever (without any respiratory symptoms)
3. Referred from another primary healthcare facility for management of the same problem

Date of first enrolment
15/03/2025

Date of final enrolment
15/01/2027

Locations

Countries of recruitment
Bangladesh

Indonesia

Nigeria

Viet Nam

Study participating centre
International Centre for Diarrheal Disease Research, Bangladesh
68 Shaheed Tajuddin Ahmed Sarani, Mohakhali
Dhaka
Bangladesh
1212

Study participating centre
Universitas Gadjah Mada
Bulaksumur, Caturtunggal, Depok, Sleman Regency
Yogyakarta
Indonesia
55281

Study participating centre
Lagos State University College of Medicine
Ishaga Rd, beside Lagos University Teaching Hospital, Idi-Araba
Lagos
Nigeria
101233

Study participating centre
Hanoi Medical University
1 P. Tôn Tht Tùng, Kim Liên, Đng Đa
Hà Ni
Viet Nam
116001

Sponsor information

Organisation
St George's, University of London

ROR
https://ror.org/040f08y74

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the study will be available upon request from Prof Michael Sharland (msharlan@sgul.ac.uk)

IPD sharing plan summary
Available on request