

# Developing the tools to fight drug-resistant bacteria

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| <b>Submission date</b><br>01/11/2021   | <b>Recruitment status</b><br>No longer recruiting        | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol            |
| <b>Registration date</b><br>11/11/2021 | <b>Overall study status</b><br>Ongoing                   | <input checked="" type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                       |
| <b>Last Edited</b><br>23/10/2025       | <b>Condition category</b><br>Infections and Infestations | <input type="checkbox"/> Individual participant data<br><input checked="" type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Antibiotic resistance is one of the foremost concerns of modern medicine. While antibiotics have saved countless lives, emerging resistant bacteria (for which many antibiotics do not work) are endangering the well-being of future generations. We need to take action to reduce the effects of these infections. The EU-funded REVERSE project will develop a framework to help prevent, manage, and limit the impact of drug-resistant bacteria. The project will use expertise from many different disciplines in a combined action plan for hospitals. This will also help to develop new strategies to fight resistant bacteria and reduce their effect on health and the European economy.

### Who can participate?

Adult inpatients in intensive care, internal medicine, haematology-oncology, and surgery (including transplant units) at hospitals in four European countries with high rates of infections caused by resistant bacteria.

### What does the study involve?

Three programmes will be started one after the other to try and reduce these infections. All hospitals will start the programmes but at different times. Some of the hospitals will also have additional help to make sure these programmes are put in place. Some of the data collected include hospital antibiotic use, hand sanitizer use, and hospital infection numbers. The researchers will also do a cost analysis to look at whether these programmes saved money by preventing infections. For this, some patients in the hospital will be asked questions about their quality of life after they leave the hospital.

### What are the possible benefits and risks of participating?

There is no additional risk to patients beyond that of a regular hospital admission. The potential benefits to patients include reduced rates of infection with resistant bacteria.

### Where is the study run from?

University of Zurich (Switzerland)

When is the study starting and how long is it expected to run for?  
July 2021 to June 2026

Who is funding the study?  
European Union Horizon 2020 research and innovation programme

Who is the main contact?  
Ashlesha Sonpar  
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## Contact information

**Type(s)**  
Scientific

**Contact name**  
Dr Ashlesha Sonpar

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## Additional identifiers

**Clinical Trials Information System (CTIS)**  
Nil known

**ClinicalTrials.gov (NCT)**  
Nil known

**Protocol serial number**  
965265

## Study information

**Scientific Title**  
pREvention and management tools for rEducing antibiotic Resistance in high prevalence SEttings

**Acronym**  
REVERSE

**Study objectives**

Rationale: Develop and implement cost-effective strategies and tools for the prevention and clinical management of healthcare-associated infections due to multidrug-resistant pathogens, and to reduce the burden of antimicrobial resistance in high prevalence care settings.

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Approved 07/01/2022, Kantonale Ethikkommission (Stampfenbachstrasse 121, 8090 Zürich, Switzerland; +41 (0)43 259 79 70; info.kek@kek.zh.ch), ref: AO-2021-00078

### **Study design**

Hybrid type 2 effectiveness-implementation study; prospective multi-centre cluster-randomized stepped-wedge trial with nested cohort study

### **Primary study design**

Interventional

### **Study type(s)**

Prevention

### **Health condition(s) or problem(s) studied**

Antimicrobial resistance

### **Interventions**

Three bundled programmes will be sequentially implemented after a minimum 6-month baseline monitoring period - microbiology and diagnostic stewardship (MDS), infection prevention and control (IPC), and antimicrobial stewardship (ABS). These interventions target the institutions and health professionals. The data will be collected throughout the baseline and intervention periods. The details of the MDS, IPC, and ABS interventions are as follows (please note: not all interventions within a programme will start immediately):

#### **MDS:**

1. Guidance document on the usage of diagnostics for suspected bacterial infection
2. Audit and feedback on compliance to guidance
3. Universal screening in high-risk settings and abdominal surgery patients (intensive care, haemato-oncology, transplant units);
4. Molecular characterization of blood cultures and samples from lower respiratory tracts (HAP) to inform ABS
5. Rapid tests if molecular tests are unavailable (e.g. CARBA-5 or beta-LACTA)
6. Molecular characterization of isolated CRE from repetitive colonisation surveys to inform IPC.

#### **IPC:**

1. Enhanced standard precautions (e.g., use of gloves for contacts with wounds and body fluids) and hand hygiene, with special emphasis on the use of alcohol-based hand rub (ABHR)
2. Regular point prevalence surveys to detect previously unknown multidrug-resistant organism (MDRO) carriers and identify hidden hot spots of MDRO transmission in the concerned institution in collaboration with WP2MDS
3. Reinforced basic environmental hygiene
4. Targeted MDRO screening at admission for selected high-risk populations (e.g., previously known MDRO carriers)

5. Audits and feedback on the basic IPC components in regular time intervals
6. Enhanced, universal MDRO screening at admission in ICUs and other high-risk units
7. Reinforced contact precautions for identified MDRO carriers
8. Enhanced cleaning in high-risk settings with point prevalence sampling surveys
9. Improved information transfer on MDRO's carriage status within the hospital and along the referral pathways
10. Root-cause analysis of newly detected cases to direct infection control measures
11. Setup and implementation of advanced cohorting facilities for selected highly resistant MDROs (e.g., CRE)
12. Dedicating nursing staff for patient care with highly resistant MDROs
13. Decolonization or decontamination of colonized patients or patients in high-risk units using chlorhexidine body wash
14. Molecular analysis and sequencing of isolates for outbreak investigation (please see 3.4.4 for details)
15. The organisational and pharmaceutical interventions will be started with the basic best practices bundle.

**ABS:**

1. Establishment of a multidisciplinary stewardship committee
2. Guidance document on syndrome-specific treatment pathways
3. Dedicated recommendations for new drugs
4. Training on judicious antibiotic prescription
5. Audit and feedback on compliance to guidance on antibiotic use
6. Stewardship rounds two times a week in high-risk settings (intensive care, haematology-oncology, transplant units)
7. Pathways for integration of antibiotic consumption reporting to the stewardship policies
8. Weekly stewardship rounds in wards other than high-risk, but with a high prevalence of AMR
9. Integration of screening results in the decision-making process for empiric therapy for severe bacterial infections in immunocompromised patients
10. Integration of screening results before abdominal surgery for personalised prophylaxis
11. Integration of molecular characterization of cultures to drive targeted therapy of bloodstream infections and hospital-acquired pneumonia

All centres will have a point prevalence survey for CRE colonization at three predefined time points. Positive swabs may be sequenced to assess for clonality and to establish transmission links. At two timepoints in the study, an audit will be done to assess microbiology capabilities.

In addition, before the IPC module, hospitals will be randomised to either basic implementation support (12 BASIC study sites) or enhanced implementation support (12 ENHANCE study sites) as part of the hybrid approach. This randomisation applies only to the implementation part of this study. The hospitals will be stratified by country and cluster-randomized in a stepped wedge design.

A cost-effectiveness analysis will be done at the end to assess the feasibility of expanding such an initiative. Part of this cost-effectiveness analysis includes a cohort study comparing the quality of life post-discharge of patients with hospital-acquired multi-drug resistant infections to patients without such infections. The cohort study will use validated questionnaires at baseline, 1, 3, 6, and 12 months post-discharge. There will be detailed costing data obtained from the hospitals to accurately estimate the investment required to sustain these initiatives.

**Intervention Type**

Other

### **Primary outcome(s)**

Incidence density (N/1000 patient-days) of healthcare-acquired infections due to carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant enterobacteriales (CRE), and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), measured by prospective surveillance using laboratory and chart information every 3 months starting at baseline and continuing until the end of the study

### **Key secondary outcome(s)**

1. Quarterly proportions of HAI due to CRE, CRPA, and CRAB measured by prospective surveillance using laboratory and chart information every 3 months starting at baseline and continuing until the end of the study
2. Incidence density (N/1000 patient-days) of healthcare-associated bloodstream infection of any type measured using existing surveillance in hospitals every 3 months starting at baseline and continuing until the end of the study
3. Incidence density (N/1000 patient-days) and quarterly proportions of HAI due to other clinically important multidrug-resistant organisms (such as ESBL-producing *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci) measured using existing surveillance in hospitals every 3 months starting at baseline and continuing until the end of the study
4. Incidence density (N/10,000 patient-days) of *Clostridium difficile* infection (as a proxy for the consumption of broad-spectrum antibiotics) measured using existing surveillance in hospitals every 3 months starting at baseline and continuing until the end of the study
5. Performed blood culture sets per 1000 patient-days measured using laboratory data every 3 months starting at baseline and continuing until the end of the study
6. Performed stool tests for *Clostridioides difficile* per 1000 patient-days measured using laboratory data every 3 months starting at baseline and continuing until the end of the study
7. Consumption of alcohol-based handrub solution per 1000 patient-days measured using administrative data every 3 months starting at baseline and continuing until the end of the study
8. Antimicrobial consumption in daily-defined doses over the last 3 months measured using administrative data every 3 months starting at baseline and continuing until the end of the study
9. Prevalence of CRE colonisation measured via rectal swabs at the beginning of the infection prevention and control programme (IPC), at the end of the IPC programme, and at the end and at the end of the antibiotic stewardship programme
10. Resistance mechanisms of the isolated CRE in the three prevalence surveys, assessed using molecular techniques at the beginning of the infection prevention and control programme (IPC), at the end of the IPC programme, and at the end and at the end of the antibiotic stewardship programme
11. Clonality of the isolated CRE in the three prevalence surveys assessed using whole-genome sequencing at the beginning of the infection prevention and control programme (IPC), at the end of the IPC programme, and at the end and at the end of the antibiotic stewardship programme
12. In-hospital all-cause mortality over the last 3 months measured using administrative data every 3 months starting at baseline and continuing until the end of the study
13. Re-admissions density (N / month) of any type measured using administrative data every 3 months starting at baseline and continuing until the end of the study
14. Length of hospital stay for admissions of any type, reported as the average length of stay over the last 3 months, measured using administrative data every 3 months starting at baseline and continuing to the end of the study

15. Intervention (MDS, IPC and ABS) fidelity, acceptability, feasibility, and sustainability measured through surveys of healthcare personnel after workshops or at the end of the intervention period

**Completion date**

30/06/2026

## Eligibility

**Key inclusion criteria**

All adult inpatients in participating centers in intensive care, internal medicine, haematology-oncology, and surgery (including transplant units)

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Sex**

All

**Key exclusion criteria**

1. Patients in settings other than mentioned above
2. Children, infants, or neonates

**Date of first enrolment**

01/03/2022

**Date of final enrolment**

30/09/2022

## Locations

**Countries of recruitment**

Greece

Italy

Romania

Spain

**Study participating centre**

**Azienda Ospedaliera Universitaria Integrata Verona**

Piazzale L.A. Scuro, 10

Verona

Italy

37134

**Study participating centre**

**Policlinico Universitario A. Gemelli Rome**

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**Study participating centre**

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**Study participating centre**

**ASST Santi Paolo e Carlo Milano**

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**Study participating centre**

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Milan

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20122

**Study participating centre**

**IRCCS Ospedale Sacro Cuore Don Calabria**

Don A. Sempredoni, 5

Negrar di Valpolicella

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**Study participating centre**  
**Hospital Universitario Jerez de la Frontera**  
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11407

**Study participating centre**  
**Hospital Universitario Reina Sofia**  
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**Study participating centre**  
**Hospital Universitario Son Espases**  
Carretera de Valldemossa 79  
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**Study participating centre**  
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**Hospital Álvaro Cunqueiro**  
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36213

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**Laiko General Hospital**  
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115 27

**Study participating centre**  
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**AHEPA University Hospital of Thessaloniki**  
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546 21

**Study participating centre**  
**University Hospital of Ioannina**  
Niarxou Avenue  
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Greece  
45500

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**Attikon General Hospital**  
Rimini 1  
Chaidari  
Greece  
124 62

**Study participating centre**  
**Military Hospital Bucharest**  
Calea Plevnei Nr. 134  
Bucharest  
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**Study participating centre**  
**University Emergency Hospital Bucharest**  
Splaiul Independenței 169  
Bucharest  
Romania  
050098

**Study participating centre**  
**Timisoara Municipal Clinical Emergency Hospital**  
Strada Daliei Nr. 17  
Timisoara  
Romania  
300254

**Study participating centre**  
**Targu Mures County Hospital**  
Str. Gh. Marinescu Nr. 1  
Targu Mures  
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540103

**Study participating centre**  
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**Study participating centre**  
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**Study participating centre**  
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## Sponsor information

**Organisation**  
University Hospital of Zurich

**ROR**  
<https://ror.org/01462r250>

## Funder(s)

**Funder type**  
Government

**Funder Name**  
Horizon 2020

**Alternative Name(s)**  
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

**Funding Body Type**  
Government organisation

**Funding Body Subtype**  
National government

**Location**

## Results and Publications

### **Individual participant data (IPD) sharing plan**

The following applies to persons outside of the REVERSE consortium. The data will be available after publication. The project email can be used to contact the coordinating team regarding data

requests (reverse@usz.ch). Data will be made available where possible to support further research under FAIR principles, except for data that are confidential or cannot be shared under the GDPR regulations. De-identified hospital-level data (e.g.: data on hospital-acquired infection rates, antimicrobial use, ABHR use, or cost data) needed to verify the results will be available for approximately 5 years after the project ends. De-identified and aggregate data from the cohort study needed to verify results will also be available for approximately 5 years after the project ends. Please note, participant-level data from the cohort study will not be available due to patient-level confidential information. The researchers will share data electronically with other research groups conducting meta-analyses or reviews on IPC, ABS, or MDS interventions. This adheres to the data-sharing rules outlined in the Grant Agreement with the European Commission.

## IPD sharing plan summary

Available on request

### Study outputs

| Output type                                   | Details                             | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|-------------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Protocol article</a>              |                                     | 16/10/2025   | 23/10/2025 | Yes            | No              |
| <a href="#">Participant information sheet</a> | Participants                        |              | 10/11/2021 | No             | Yes             |
| <a href="#">Participant information sheet</a> | Representatives                     |              | 10/11/2021 | No             | Yes             |
| <a href="#">Participant information sheet</a> | Brochure for participants version 2 | 06/12/2022   | 05/02/2024 | No             | Yes             |
| <a href="#">Protocol file</a>                 | version 1.1                         | 10/01/2022   | 16/02/2022 | No             | No              |
| <a href="#">Protocol file</a>                 | version 1.4                         | 15/06/2023   | 05/02/2024 | No             | No              |
| <a href="#">Statistical Analysis Plan</a>     |                                     |              | 09/04/2024 | No             | No              |
| <a href="#">Study website</a>                 | Study website                       | 11/11/2025   | 11/11/2025 | No             | Yes             |