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Developing the tools to fight drug-resistant bacteria

Submission date	Recruitment status	[X] Prospectively registered
01/11/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[X] Statistical analysis plan
11/11/2021	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
09/04/2024	Infections and Infestations	[_] 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?
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Study website
https://www.reverseproject.eu

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
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

Secondary study design
Cluster randomised trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
See additional files

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 measure
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

Secondary outcome measures
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 pneumonia, methicillin-resistant Stapyhlococcus 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

Overall study start date
01/07/2021

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

Age group
Adult

Sex
Both

Target number of participants
24 centres

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
Via della Pineta Sacchetti 217
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00168

Study participating centre
Policlinico S.Orsola Bologna
Via Giuseppe Massarenti 9
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Study participating centre
ASST Santi Paolo e Carlo Milano
Via Antonio di Rudinì 8
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Italy
20142

Study participating centre
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano
Ospedale Maggiore Policlinico Milano
Via Francesco Sforza 35

Milan
Italy
20122

Study participating centre
IRCCS Ospedale Sacro Cuore Don Calabria
Don A. Sempreboni, 5
Negrar di Valpolicella
Italy
37024

Study participating centre
Hospital Universitario Jerez de la Frontera
Ctra. Trebujena, s/n
Jerez de la Frontera
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11407

Study participating centre
Hospital Universitario Reina Sofía
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Study participating centre
Hospital Universitario Son Espases
Carretera de Valldemossa 79
Palma
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Study participating centre
Hospital del Mar
Passeig Marítim de la Barceloneta 25, 29
Barcelona
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08003

Study participating centre
Hospital General Universitario de Alicante
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Study participating centre
Hospital Álvaro Cunquiero
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115 27

Study participating centre
Ippokrateio General Hospital
Vasilissis Sofias 114
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11527

Study participating centre
AHEPA University Hospital of Thessaloniki
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Greece
546 21

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

Study participating centre
Attikon General Hospital
Rimini 1
Chaidari
Greece
124 62

Study participating centre
Military Hospital Bucharest
Calea Plevnei Nr. 134
Bucharest
Romania
010825

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
Romania
540103

Study participating centre
Sibiu County Emergency Hospital
Bulevardul Corneliu Coposu 2-4

Sibiu
Romania
550245

Study participating centre
Fundeni Hospital
Sos Fundeni Nr. 258, Sector 2
Bucharest
Romania
022328

Study participating centre
Sismanoglio General Hospital
Sismanogliou 37
Marousi
Greece
151 26

Sponsor information

Organisation
University Hospital of Zurich

Sponsor details
Clinic for Infectious Diseases and Hospital Hygiene
Rämistrasse 100
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walter.zingg@uzh.ch

Sponsor type
Hospital/treatment centre

Website
http://www.uzh.ch/index_en.html

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

Publication and dissemination plan
1. Results will be published in peer-reviewed journals with open access policies where possible.
2. Periodic reports will be distributed to stakeholders and the funding agency
3. Participant level data is only collected for the quality of life study (observational). Only hospital-level data or surveys are utilized for the rest of the study. Aggregate data will be available upon request

Intention to publish date
30/01/2027

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?
Participant information sheet	Participants		10/11/2021	No	Yes
Participant information sheet	Representatives		10/11/2021	No	Yes
Protocol file	version 1.1	10/01/2022	16/02/2022	No	No
Participant information sheet	Brochure for participants version 2	06/12/2022	05/02/2024	No	Yes
Protocol file	version 1.4	15/06/2023	05/02/2024	No	No
Statistical Analysis Plan			09/04/2024	No	No