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Short description of REVERSE and Eligibility criteria

REVERSE (pREVention and management tools for rEducing antibiotic Resistance in high prevalence Settings) is a European Horizon 2020 project with the objective of "reverting" emerging healthcare-associated infections due to multidrug-resistant Gram-negative bacteria such as carbapenem-resistant enterobacteriales (**CRE**) and carbapenem-resistant non-fermentative bacilli (*Pseudomonas* spp. [**CRPA**], *Acinetobacter baumannii* [**CRAB**]).

REVERSE aims to achieve this goal by implementing a tiered, comprehensive and interactive programme of evidence-based and cost-effective interventions to improve microbiology capacity, infection prevention and control and the judicious use of antimicrobials

Three interventions will be offered to acute care hospitals located in high prevalence areas of MDRO-Gram-negative bacteria in Europe:
1) microbiology and diagnostic stewardship (MDS),
2) an infection prevention and control (IPC) programme, and
3) an antibiotic stewardship (ABS) programme.

All participating hospitals will receive all interventions.

The **clinical study of REVERSE (WP1) starts in January 2022 with a baseline of 6 months for all hospitals.** After this time, 6 hospitals will be randomized every three months to start with the first intervention, followed by the second and the third, always following the same sequence. The implementation phase of each intervention is 6 months.

Primary and secondary endpoint(s)
Primary outcome:

Incidence density (N/1000 patient-days) of healthcare-associated infections (HAIs) due to carbapenem-resistant enterobacteriales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB), combined in a composite index; measured during baseline and during the infection prevention and control- and antibiotic stewardship programmes.

Secondary outcomes:
- Quarterly proportions of HAI due CRE, CRPA, and CRAB
- Incidence density (N/1000 patient-days) of healthcare-associated bloodstream of any type (to obtain a proxy for the overall burden of HAI)
- 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 (to assess the overall impact of the interventions on HAI)

- Incidence density (N/10'000 patient-days) of *Clostridium difficile* infection (as a proxy for the consumption of broad-spectrum antibiotics)
- Performed blood culture sets per 1000 patient-days (to assess detection bias for HAI)
- Performed stool tests for *Clostridioides difficile* per 1000 patient-days (to assess detection bias for *Clostridioides difficile* infection)
- Consumption of alcohol-based handrub solution per 1000 patient-days (to assess compliance with the infection prevention and control programme)
- Antimicrobial consumption in daily-defined doses (to assess compliance with the antibiotic stewardship programme)
- Prevalence of CRE colonisation before baseline, at the end of baseline, at the end of the infection prevention and control programme, and at the end of the antibiotic stewardship programme (to assess impact on antimicrobial resistance outside HAI)
- Resistance-mechanisms of the isolated CRE in the four prevalence surveys (to understand CRE spread)
- Clonality of the isolated CRE in the four prevalence surveys (to understand CRE spread)
- In-hospital all-cause mortality (to assess harmlessness of the antibiotic stewardship programme)

Methodology for the MDS programme

This WP will perform audits to assess microbiological capacity and stewardship in REVERSE hospitals, and where needed, to support establishing microbiological assays to reliably identify CRE, CRPA and CRAB in clinical samples. An internal REVERSE quality control programme on correctly identifying CRE, CRPA and CRAB will be established. The rate of blood culture sampling will be assessed, and where positivity ratios are >10% or performance is below 25/1000 patient-days, hospitals will be encouraged to increase the rate based on predefined sampling criteria. This WP also performs 4 point prevalence surveys on CRE colonisation of inpatients with clonal relatedness analysis and identification of resistance genes.-A total of 250 swabs will be included per time point per centre, from patients screened for CRE by applying a perianal swab. Sampling will be performed at four time points: before baseline, at the end of baseline, at the end of the IPC intervention, and at the end of the ASP intervention.

Methodology for the IPC programme

The basic best practice intervention bundle of the IPC-module will include the following elements:
- 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)
- Regular point prevalence surveys to detect previously unknown MDRO carriers and identify hidden hot spots of MDRO transmission in the concerned institution in collaboration with WP2
- Reinforced basic environmental hygiene
- Targeted MDRO screening at admission for selected high-risk populations (e.g. previously known MDRO carriers)

- Audits and feedback on the basic IPC components in regular time intervals

Methodology for the ABS Programme

The ABS programme will be stratified into two programmes: 1) a best practice programme focusing on organisation, structure and available microbiology; and 2) technical interventions. The basic best practice intervention bundle of the ABS-module will include the following elements: assessment of adherence to national ABS plans, if any; assessment of presence and work of multidisciplinary stewardship committees; development of guidance documents on syndrome-specific treatment pathways and dedicated recommendations for new drugs; training and audit and feedback on compliance with local guidelines in collaboration with WP5. Local ABS stewardship teams will be established and linked with an expert ABS team within WP4 to support the local ABS teams and to troubleshoot problems and local implementation.

ABS rounds will be established two times a week in intensive care, transplant units and haemato-oncology.

In addition, weekly ABS rounds will be established outside high-risk areas in wards with high burden of MDR-pathogens. Antibiotic consumption will be fed back to the ABS teams regularly.

What REVERSE offers to your hospital:

-REVERSE will finance a study nurse for four years and a physician (preferably an infectious disease physician or clinical microbiologist) for two years for data collection and intervention implementation.

-Multi-faceted interventions to improve infection prevention and control and judicious use of antimicrobials (education, training, tools, audits, local support)

-Implementation support

-Networking with other hospitals in the country and in Europe

-Data on the transmission of MDRO Gram-negative bacteria by repeated whole genome sequencing

At the end of the project, participating hospitals are invited to build a national reference network of competency centres to reduce antimicrobial resistance.

Eligibility

The hospital has the following specialties: **internal medicine, haematology-oncology, surgery, UTI**

- The hospital is **medium to large size**, has **20'000 yearly admissions** or more in acute care,
- Has an **incidence density of healthcare-acquired infections due to MDRO Gram-negative bacteria of more than 0.5 per 1000 patient-days (75 infections or more in an average acute care hospital with 25'000 yearly admissions)**, and

- **Sufficient capacity of antimicrobial resistance testing** (state-of-the art methodologies and an automated system for blood culture testing eg BACTEC)
- The local ethical committee must accept the REVERSE trial as a quality improvement project and to waive individual written informed consent by patients

Abrevieri

ABHR = alcohol-based hand rub
ABS= antibiotic stewardship
IPC = infection prevention and control
MDS = microbiology and diagnostic stewardship
CRE = carbapenem-resistant *Enterobacterales*
CRPA = carbapenem-resistant *Pseudomonas aeruginosa*
CRAB = carbapenem-resistant *Acinetobacter*
CDI = *Clostridioides difficile* infection
BSI = blood stream infection
MDRO = multi drug resistant organisms
WP = work package
HAI = hospital-acquired infection