pREVention and management tools for rEducing antibiotic Resistance in high prevalence SEttings

REVERSE

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WP1 Clincial study

1.1 Identifier

pREVention and management tools for rEducing antibiotic Resistance in high prevalence Settings (REVERSE) – Work package 1

1.2 Study design and endpoints

1.2.1 Study design

The study is a prospective multi-centre, cluster-randomised, stepped-wedge trial in 24 hospitals of four European countries (Greece, Italy, Romania, Spain) to evaluate the effectiveness of diagnostic stewardship, infection prevention and control, and antibiotic stewardship programmes on antimicrobial resistance in acute care. The hospitals are high prevalence settings for multidrug-resistant microorganisms, particularly carbapenem-resistant Gram-negative bacteria.

The intervention programmes are implemented as bundles, with professional implementation support; they are multifaceted and tiered in best practice procedures and technology interventions. All hospitals will benefit from all interventions. Control is provided by the stepped-wedge design.

Although this is a clinical trial, randomisation is on the hospital level and the interventions address institutions as a whole and health professionals in particular.

1.2.2 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)

1.2.3 Relevant guidance documents

Not applicable

1.3 Regulatory status and activities

1.3.1 Regulatory / ethics status

The REVERSE clinical trial will be submitted to local ethical committees with the purpose to obtain a waiver of individual informed consents from patients because REVERSE is a quality improvement project.

1.3.2 Scientific advice / protocol assistance

Not applicable.

1.3.3 Qualification advice

Not applicable.

1.4 Subjects/population(s)

REVERSE is a quality improvement study and outcomes are based on routine samples, except for four prevalence surveys on rectal/peri-anal CRE-colonisation. We expect to have 2.5 million adult patients minimum , hospitalized in 24 hospitals in Greece, Italy, Romania and Spain, to analyse the primary outcome (25,000 admissions per year; study duration of 51 months).

For assessing CRE-colonisation we enroll 24,000 patients to have a perianal swab taken for microbiology analysis and whole-genome sequencing.

All adult inpatients in the participating hospitals and hospitalized in intensive care, internal medicine, haematology-oncology, and surgery (including transplant units) are included in the study. Exclusion criteria are patients in settings other than mentioned above and children, infants or neonates.

1.5 Statistical analysis plan(ning) and power calculation

Generalized mixed-effects models with log-link function will be considered for the analysis of the primary outcomes. The fixed effects will be the interventions, the country and the time to account for the partial confounding of the interventions with time. A cluster-specific random effect will be considered to model the repeated measurements on the same cluster. In the presence of over-dispersion, negative-binomial mixed-effects models with the same parametrization will be used instead. Model-based intervention effects will be reported. Supportive analyses considering more complex random effects structures will also be investigated. (e.g. time within clusters, wards within

hospitals). The interaction between time and interventions will also be added as a fixed effect to model a possible time-varying intervention effect.

Based on findings and modelling of the ECDC point prevalence survey of 2016/2017, mean estimated incidence densities of HAI due to a composite index incorporating CRE, CRPA and CRAB combined for Greece, Italy, Romania, Spain, were 2.99/1000 patient-days, 0.73, 0.62, and 0.51, respectively. Taking into account the lowest incidence density of 0.5/1000 patient-days, an intra-cluster correlation of 0.9, four randomisation steps, and 25'000 admissions per year in average, the following estimations were calculated for hypothesized effects of the intervention programmes:

- Reduction of 25% of HAI by IPC alone (IPC compared to baseline): 2.3 required hospitals
- Reduction of 35% of HAI by IPC and ABS combined (IPC plus ABS compared to baseline): 1.1 required hospitals
- Reduction of 10% HAI by ABS on top of IPC (ABS compared to IPC): 19.9 required hospitals
- Reduction of 15% HAI by enhanced implementation support on top of 35% reduction by IPC and ABS combined (as compared to basic implementation support): 9.8 required hospitals

Twenty-four acute care hospitals from high AMR prevalence areas provide sufficient power to perform all relevant comparisons for the primary outcome as specified by REVERSE: 1) IPC to baseline; 2) ABS to IPC; 3) IPC and ABS combined to baseline; and 4) enhanced implementation support to basic implementation support.

1.6 Cumulative safety and efficacy information

1.6.1 Cumulative safety information

Not applicable

1.6.2 Cumulative efficacy information

Not applicable

1.7 Conduct

1.7.1 Schedule for study conduct including timelines for key study milestones

All 24 hospitals start their baseline period in month 7. After a baseline of 6 months, 6 participating hospitals will be randomised to start with the first programme, until all 24 hospitals have started the intervention 9 months later. Randomisation is stratified by country. Three multifaceted intervention programmes will be implemented sequentially and building on each other: microbiology and diagnostic stewardship (MDS), infection prevention and control (IPC), and antimicrobial stewardship (ABS). The total observation time is 45 months.

Start of trial: M7
First 6 hospitals start MDS programme: M13
Last 6 hosptials start MDS programme: M22
First 6 hospitals start IPC programme: M19
Last 6 hosptials start IPC programme: M28
First 6 hospitals start ABS programme: M25
Last 6 hosptials start ABS programme: M34
End of trial: M51

1.7.2 Description of recruitment strategy

Hospitals will be recruited by national focal points (UNIVR, SAS-HUVM, NKUA), using their own network, but also the COMBACTE network.

1.7.3 Description and assignment of intervention

This will be an observational quality improvement study. There are no direct interventions on patients. Three multifaceted intervention programmes will be implemented sequentially in the participating hospitals: microbiology and diagnostic stewardship (MDS), infection prevention and control (IPC), and antimicrobial stewardship (ABS). Interventions address insitutions as a whole, and health professionals in particular. All hospitals will get all intervention programmes.

1.7.4 Study management, study monitoring, data and sample management

- Trial management is with WP1. Communication between participating hospitals and REVERSE occurs primarily across the national focal points (UNIVR, SAS-HUVM, NKUA) and WP1. All intervention programmes are facilitated by the national focal points and WP1.
- In month 6, a kick-off meeting with all participating hospitals will be organised. This meeting will take place at UNIGE. For centres that cannot travel due to COVID-19 or other reasons, it will be transmitted by videoconferencing.
- A total of eight workshops will be organised with participating hospitals: a first set (before the IPC interventions) at months 17, 20, 23, and 26; a second set (before the ABS intervention) at months 23, 26, 29, and 31. Every hospital will participate twice, before the IPC intervention and before the ABS intervention. The first 4 workshops will be organised in collaboration with WP2 (MDS) and WP3 (IPC), the second 4 workshops will be organised in collaboration with WP2 (MDS) and WP4 (ABS). All workshops will be organised in collaboration with WP5 (Implementation). These workshops can be organised as videoconferences.
- In close collaboration with WP2, WP3, WP4 and WP5, and the national focal points, the three interventions on MDS, IPC and ABS will be implemented as per randomisation (see above). WP1 will function as the direct partner of the participating hospitals.
- Quarterly videoconferences with the participating hospitals and national focal points will support implementation. Twelve randomised hospitals will receive tailored support by the WP5 team (see WP5).
- In month 52, a wrap-up meeting with all participating hospitals will be organised. This meeting will take place at UNIGE. This last meeting will gather all partners of REVERSE together with national and international stakeholders in healthcare, and particularly infection prevention and control and antimicrobial resistance.
- WP1 does not plan visits to the hospitals, but audits will be performed by local focal points in collaboration with WP2 (to check on microbiological capacity), WP3 (for education and training in IPC), and WP4 (to establish local ABS groups). Twelve of the 24 participating hospitals will also have visits by WP5. These visits will all report back to the project management of WP1.

- Data collection is done by study nurses using the REDCap platform (https://www.project-REDCap.org/). REVERSE finances 1 FTE study nurse per participating hospital. Data are located centrally at UNIGE.
- REDCap allows surveillance on data collection activity. Quarterly checks on data completeness with feedback to the centres will be organised. Delays or errors of data collection will be discussed in the quarterly videoconferences with the hospitals.

1.7.5 Sponsor, coordinating centre(s) and committees

Not applicable

1.7.6 Study medication

Not applicable

1.7.7 Clinical centres

Hospitals qualify for inclusion if the incidence density of healthcare-associated infections due to CRE, CRPA and CRAB combined is >0.5 per 1000 patient-days (e.g. 75 cases per year for an acute care hospital with 25'000 yearly admissions and a mean length-of-stay of 6 days); if their microbiology has the capacity of testing CRE, CRPA and CRAB correctly; and if they have an automated system for blood culture testing.

1.8 Orphan designation

Not applicable

1.9 'Unit costs per patient' for clinical trials / studies / investigations

REVERSE will finance one FTE of a study nurse for 4 years and an infectious disease doctor for 2 years per participating site. Per prevalence survey of CRE-colonisation, a total of 4800 patients will be tested (24,000 in total). We expect a prevalence of 6% in the first round, which will decrease to 4% in the last round. The overall prevalence is expected to be around 5% (Approximately 1000 strains), which brings the total amount of for isolation and whole-genome sequencing to 268,000 EUR (168,000 EUR for swabs, enrichment broth, shipping and culture; 100,000 for whole genome sequencing of the positive samples).