WP4: Antibiotic Stewardship Programme (ABS)

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Objectives of WP4

1. To develop **evidence based ABS interventions** to be implemented in the clinical study (baseline and advanced).

2. To assess **effectiveness of ABS interventions** based on patient case mix and most prevalent antimicrobial resistant pathogens.

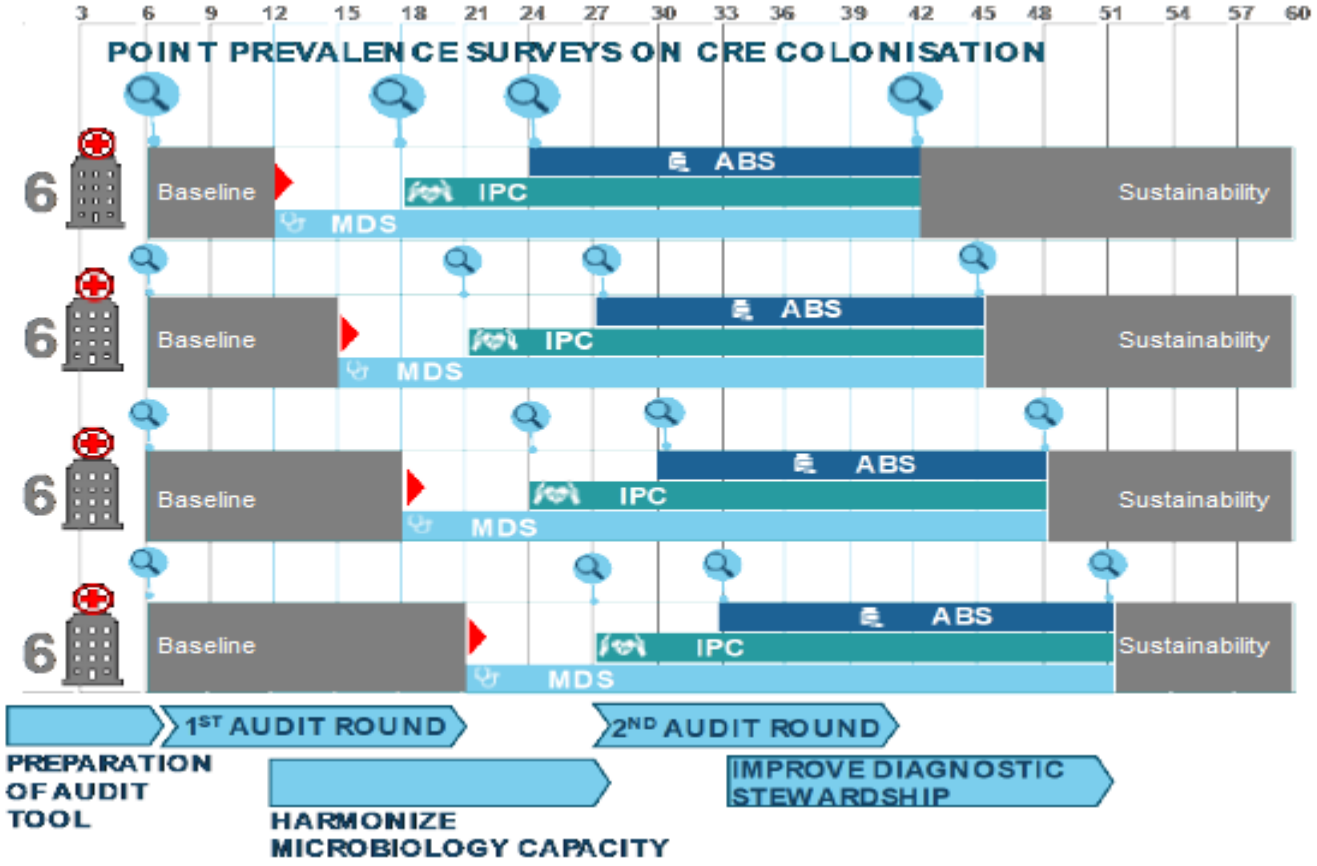
3. To test **integration of ABS recommendations** with measures implemented in the IPC and MDS availability.

4. To develop **recommendations for clinical management strategies** of severe infections caused by antimicrobial resistant bacteria.

5. To provide clinical and epidemiological data **to inform cost modelling to define effectiveness of stewardship modules** by hospital setting and available resources, and define transferability including LMICs.

ABS Programme **REVERSE**

Primary outcome:
Incidence density of HAI due to a composite index of CRE, CRPE, and CRAB combined



Secondary outcomes:

- Quarterly proportions of HAI due CRE, CRPA, and CRAB.
- Incidence density (N/1000 patient-days) of healthcare-associated BSI of any type.
- Incidence density (N/1000 patient-days) and quarterly proportions of HAI due to other clinicallyimportant MDROs (ESBL-KLEPNE, MRSA, VRE).
- Incidence density (N/10'000 patient-days) of *Clostridioides difficile* infection (CDI).
- Process indicators: performed blood culture sets; performed stool tests for *Clostridioides difficile*; consumption of alcohol-based handrub solution per 1000 patient-days**; antimicrobial consumption in DDDs.**
- Antibiotic consumption per 1000 patient-days (WP6).
- **Prevalence of CRE colonisation** before baseline, end of baseline, end of IPC intervention (WP3), **end of ABS intervention (WP4).**
- Resistance-mechanisms of the isolated CRE in the four prevalence surveys.
- Clonality of the isolated CRE in the four prevalence surveys.
- **In-hospital all-cause mortality; 30-day all-cause mortality.**
- **Re-admissions density (N / month) of any type (WP6).**
- **Length of hospital stay for admissions of any type (WP6).**

Power calculation

Estimations calculated for hypothesized effects of the intervention programmes:

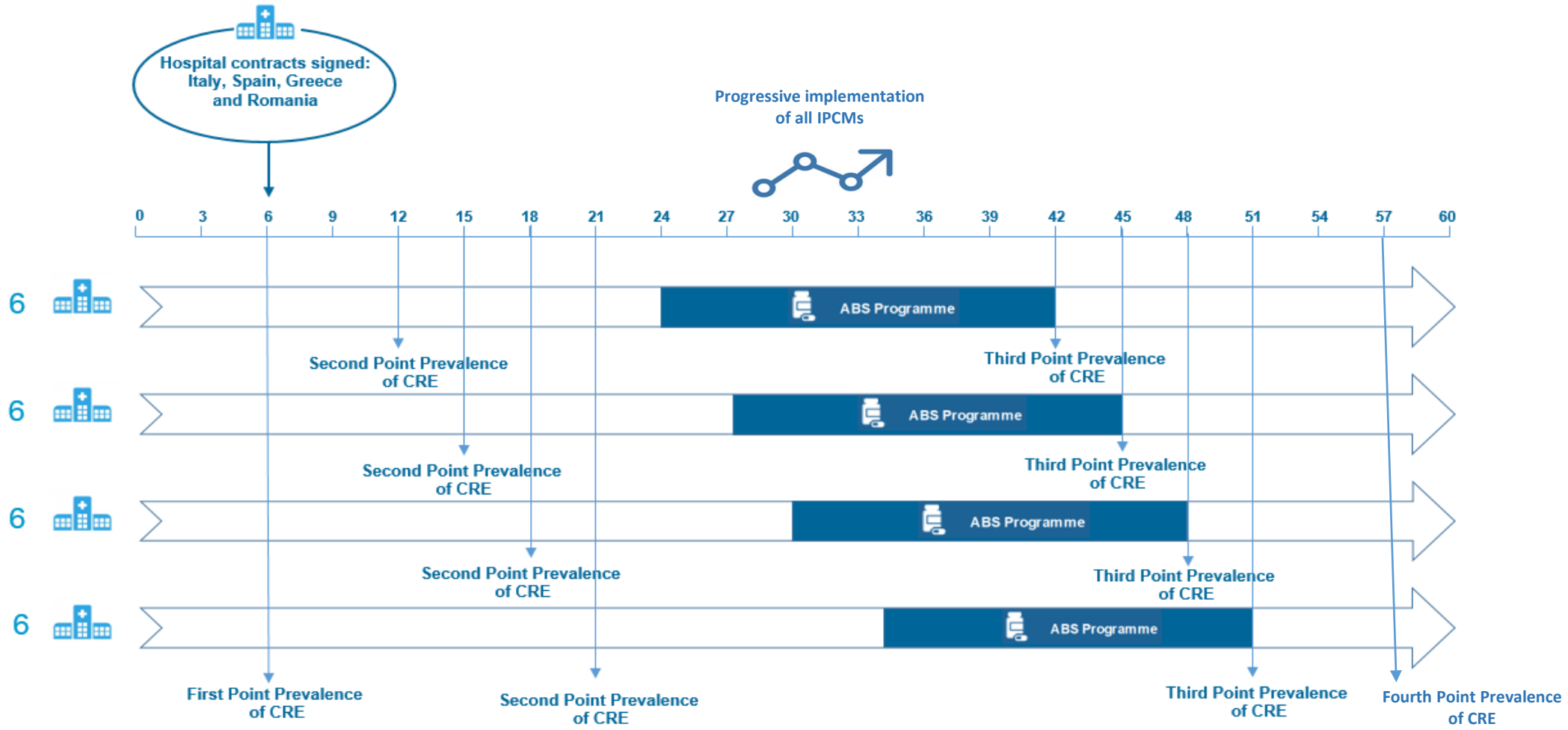
- Reduction of 25% of HAI by IPC alone (IPC compared to baseline)
- **Reduction of 35%** of HAI by **IPC and ABS combined (IPC plus ABS compared to baseline**).
- **Reduction of 10%** HAI by **ABS on top of IPC (ABS compared to IPC**).
- **Reduction of 15%** HAI by enhanced implementation support on top of 35% reduction by **IPC and ABS combined (as compared to basic implementation support**).

***** Mean estimated incidence densities of HAI due to a composite index incorporating CRE, CRPA and CRAB, combined for Greece, Italy, Romania and Spain were **2,99/1000 patient-days 0.73, 0.62, and 0.51, respectively,** based on findings and modelling of the ECDC point prevalence survey of 2016/2017.

Antibiotic Stewardship Interventions

1. Establishment of **multidisciplinary stewardship committee**
2. **Guidance document** on syndrome – specific treatment pathway
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 **2 times a week in high risk settings** (intensive care, haematology-oncology, transplant units)
7. **Pathway** for the 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 BSI and HAP

ABS interventions as described in the project



Preliminary considerations
Re-assessment of interventions

- The hospital selection process underlined a substiantial heterogeneity in terms of IPCM – ATBS – Diagnostics among centers with the same incidence of infections caused by target resistant bacteria
- There is therefore a need to realign DoW with the diagnostic interventions included in the clinical studies (WP2 - WP4)
- Corrective actions started to align tasks (and linked budget) among WPs and different proposals are under assessment

Locally tailored ABS Programme

BASIC CHECKLIST
1. Programme to adhere to national ABS plans (if any)
2. Active multidisciplinary stewardship committees
3. Updated and tailored on local microbiological data of guidance documents on syndrome-specific treatment pathways and dedicated recommendations for new drugs
4. Established training and audit procedures (including feedback) on compliance with local guidelines on antibiotics
5. Established more than one time a week ABS rounds in ICU, transplant units and haemato-oncology
6. Established weekly ABS rounds in areas with high burden of MDRO
7. Periodic reports on hospital antibiotic consumption fed to the ABS team

Baseline or advanced intervention ***«Calibrated approach to ABS»***

Technical interventions (advanced)
1. Molecular characterization of resistance genes in MDRO isolated in BSI to drive target therapy
2. Screening of patients in high-risk areas (intensive care, transplant units, haematology-oncology) to drive empiric therapy of severe infections
3. Personalised surgical prophylaxis in patients colonised by MDR-pathogens before abdominal surgery
4. Rapid molecular testing in patients with hospital-acquired pneumonia in intensive care

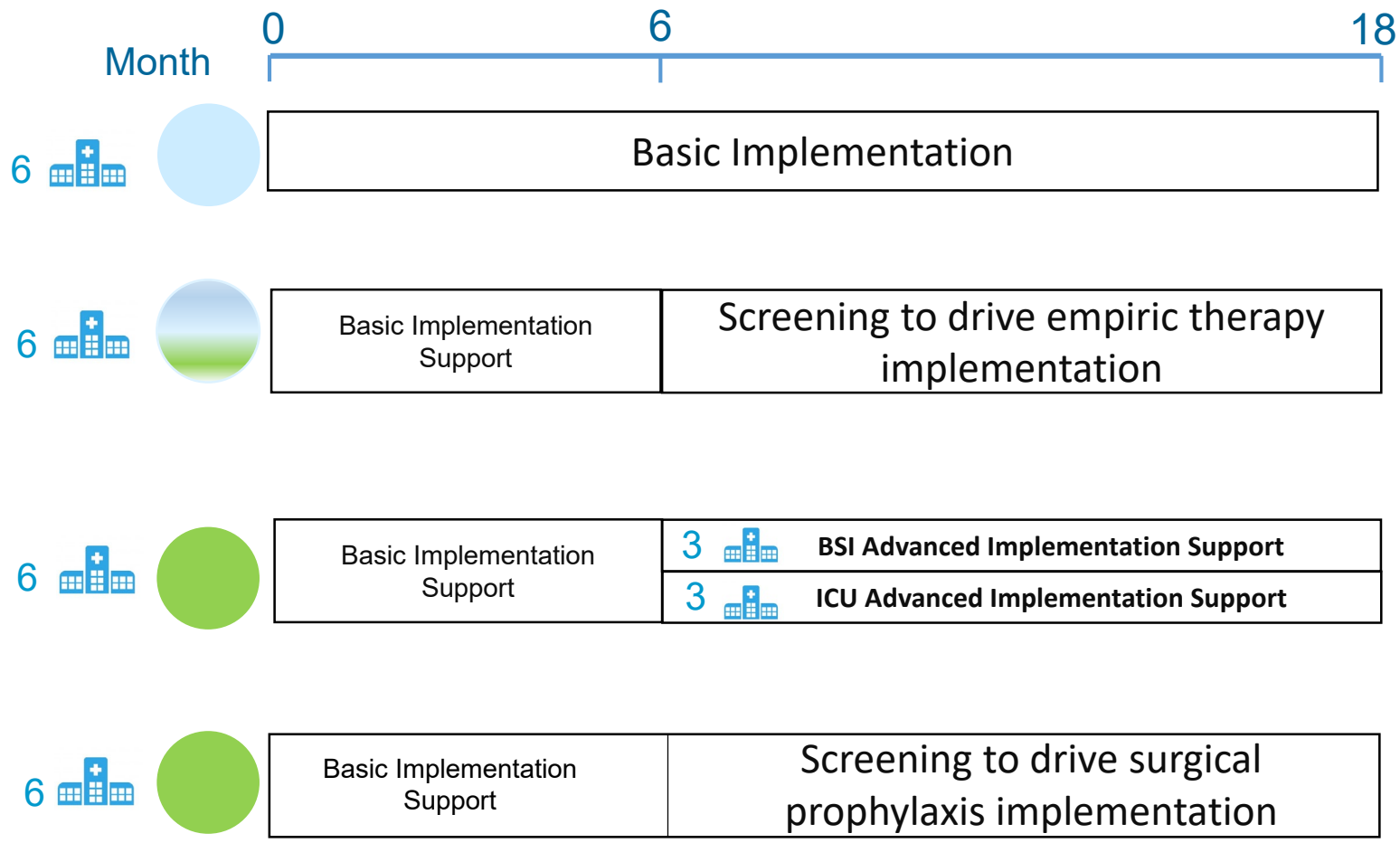
Calibrated Implementation (examples) based on local already active ABS measures

Check-list of the local active measures

Local active «basic» ABS measures	
	No measures active
	Some measures active
	All measures active

Advanced interventions elements

1. Screening to drive empiric therapy
2. Molecular testing in patients with BSI to drive target therapy
3. Rapid molecular test in patients with VAP to improve targeted therapy
4. Personalized surgical prophylaxis



- A preliminary analysis of tasks and available budget with the coordinator and the other WP leaders seems to suggest that the option is feasible
- A final decision can be taken only after the estimation of costs of diagnostics and man-power based on sample size and local epidemiology by the clinical studies

Interactions with other WPs

- WP1: clinical trial (basic and and advanced ABS measures)
- WP2: point prevalence surveys (clinical studies?)
- WP3: clinical studies (screening of high risk patients and pre-surgery)
- WP5: educational meetings during ATB implementation
- WP6: economic assessment (data collection from clinical studies)
  - Need to add involved Partners in the interaction (attributed MM) in the WP4
  - Need to align the due-month of Tasks to the global projects' timelines

1.3.6. WT6 Summary of project effort in person-months

	WP1	WP2	WP3	WP4	WP5	WP6	WP7	WP8	Total Person/Months per Participant
1 - UZH	38	0	0	0	72	0	30		140
2 - UNIVR	5	0	0	97	0	0	0		102
3 - SAS	5	0	0	73	0	0	0		78
4 - UMCU	22	60	0	0	0	0	15		97
5 - TASMC	0	0	34	0	0	0	0		34
6 - UNIGE	10	0	30	0	16.80	0	0	✓	56.80
7 - PHE	0	0	0	0	0	38.60	0		38.60
8 - UOXF	0	0	0	0	0	41	0		41
9 - NKUA	4.80	0	0	0	0	0	0		4.80
10 - UNIFI	0	90	28	0	0	0	0		118
11 - ISGLOBAL	0	0	0	0	0	64	0		64
Total Person/Months	84.80	150	92	170	88.80	143.60	45		774.20

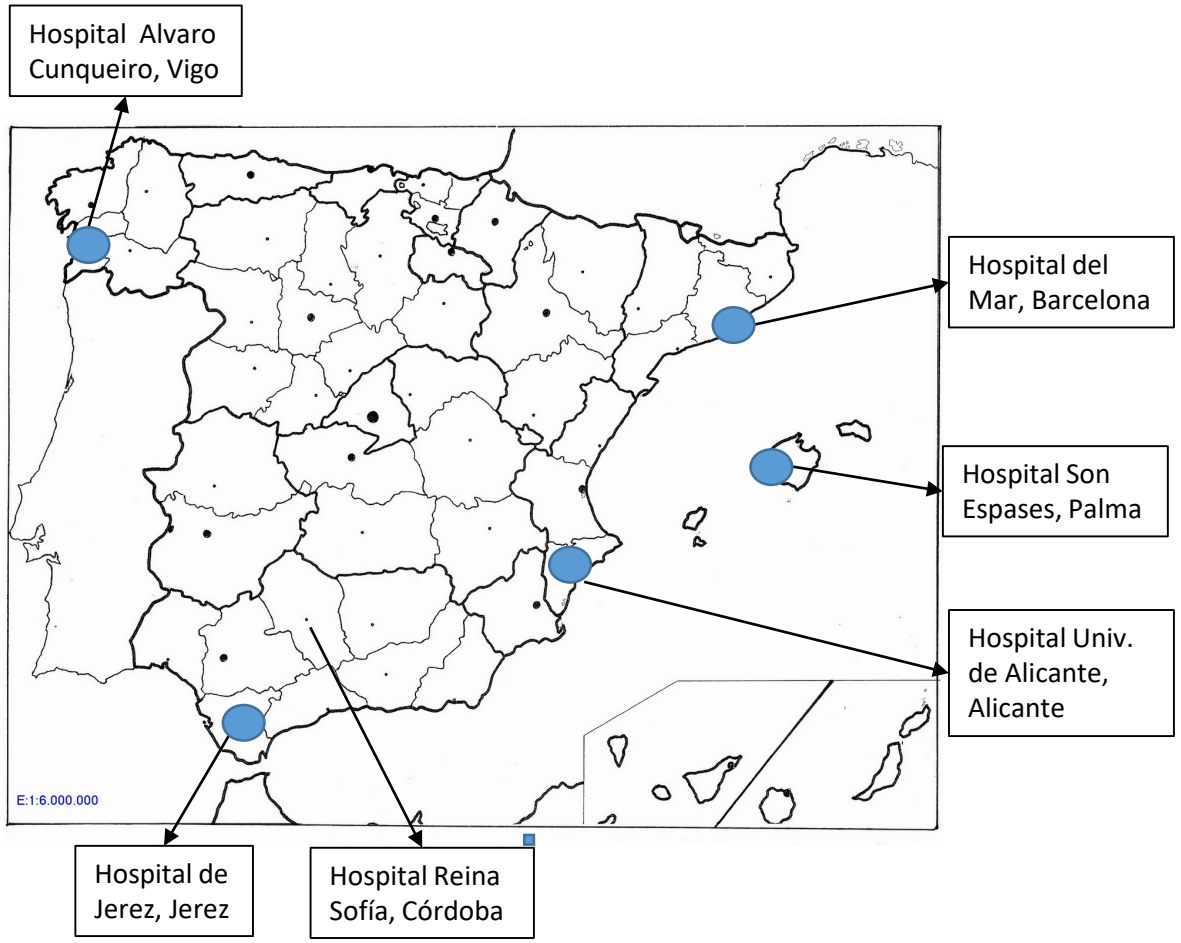
Tasks of WP 4

Task 4.1	**Evaluation of hospitals**	Month 1 - 30	Lead partner: UNIVR Other partners involved: SAS- HUVM, NKUA, UZH, UMCU, UNIFI	AIM: **define** specific interventions calibreted by epidemiological scenario and case-mix of patients.
Task 4.2	**Implementation of basic level of ABS**	Month 24-51	Lead partner: UNIVR Other partners involved: SAS- HUVM, NKUA, UZH	AIM: **apply** interactive processes embedded in multinational approaches to reduce ATC
Task 4.3	**Efficacy of rapid molecular test in driving targeted therapy for BSI**	Month 30 - 57	Lead partner: SAS- HUVM, Other partners involved: UNIFI, and 3 hospitals with highest burden of BSI caused by MDR-bacteria	AIM: **reduce** inappropriete antibiotic use and overall consumption.
Task 4.4	**Efficacy of screening in driving empirical therapy for severe infections in high risk population**	Month 30 – 51	Lead partner: UNIVR Other partners involved: UNIFI, UMCU, 6 hospitals with highest burden of AMR in immunocompromised	AIM: **test** if isolation of MDR-bacteria from screening samples in immunocompromised hosts will increase appropriateness of therapy and reduce the use of broad-spectrum antibiotics.
Task 4.5	**Personalised prophylaxis in patients colonised with ESBL and KPC before abdominal surgical prophylaxis**	Month 30 – 51	Lead partner: UNIVR Other partners involved: UMCU, 6 hospitals with the highest burden of SSI (abdominal surgery) caused by MDR-bacteria	AIM: **reduce** the incidence of surgical site infections, and therefore antibiotic use, in patients colonised with ESBL and KPC-producing bacteria before abdominal surgery by providing personalised surgical prophylaxis.
Task 4.6	**Efficacy of rapid molecular diagnosis in improving targeted therapy in ICU patients with VAP**	Month 30 – 51	Lead partner: UNIFI Other partners involved: 3 hospitals with the highest burden of VAP caused by MDR-bacteria	AIM: **define** effectiveness of implementing rapid molecular tests in patients with HAP in settings with high prevalence of MDR-Gram negative bacteria on the reduction of inappropriate antibiotic use and overall consumption.

WP4 Milestones

Milestone number	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification	Status
MS3	All 6 hospitals in Spain selected	3 - SAS	6 (Jan 2022)	Contracts signed	
MS4	All 6 hospitals in Italy selected	2 - UNIVR	6	Contracts signed	
MS5	All 6 hospitals in Greece selected	9 - NKUA	6	Contracts signed	
MS6	All 6 hospitals in Romania selected	1 - UZH	6	Contracts signed	
MS17	First 6 hospitals commencing ABS programme	2 - UNIVR	24 (July 2023)	WP4 report	
MS19	Second group of 6 hospitals commencing ABS programme	2 - UNIVR	27	WP4 Report	
MS21	Third group of 6 hospitals commencing ABS programme	2 - UNIVR	30	WP4 Report	
MS23	Fourth group of 6 hospitals commencing ABS programme	2 - UNIVR	33	WP4 Report	
MS26	First six hospitals completed all three programmes	1 - UZH	42	WP1 Report	
MS28	Second group of six hospitals completed all three programmes	1 - UZH	45	WP1 Report	
MS29	Third group of six hospitals completed all three programmes	1 - UZH	48	WP1 Report	
MS31	Fourth group of six hospitals completed all three programmes	1 - UZH	51	WP1 Report	

Preliminary selection of Italian and Spanish centers



WP4 Deliverables

Deliverable Number	Deliverable Title	Lead Beneficiary	Type	Dissemination Level	Due Date (in months)	Status
D4.1	Practical recommendation to implement antibiotic stewardship in hospitalized patiens by case mix and income status.	2 - UNIVR	Report	Public	60	-
D4.2	Recommendation on implementation of rapid tests in sepsis and HAP to reduce inappropriate usage and overall consuption.	2 - UNIVR	Report	Public	60	-
D4.3	Recommendation on implementation of screening of immunocompromised patients to drive appropriate empiric therapy of severe bacterial infections.	2 - UNIVR	Report	Public	60	-
D4.4	Recommendation on implementation of personalized surgical prophylaxis in patients colonised by ESBL- producing bacteria and KPC before abdominal surgery.	2 - UNIVR	Report	Public	60	-

“REVERSE” antimicrobial resistance

(p**REV**ention and management tools for r**E**ducing antibiotic **R**esistance in high prevalence **SE**ttings)

Thank you for your attention

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