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D2.3 Challenge brief and description of uncovered functionalities

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Deliverable Description
WP2 deliverables are to be considered in an integrated way, because they have been designed, developed, updated, integrated and reviewed in two phases, also to incorporate the contributions provided by the additional buyers that joined the project from December 2017. The Challenge Brief comprises all the outcomes of D2.1 Needs Elicitation through questionnaires and WIBGIs events with end users, D2.2 Business case(s) and prioritized list of common uncovered innovation needs, D3.1 State of the Art and D3.2 Open Market Consultation. The Challenge Brief will constitute the Technical Specifications of the ANTI-SUPERBUGS PCP Invitation To Tender

Revision History			
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ABBREVIATIONS AND ACRONYMS

ASB	"ANTI-SUPERBUGS"
ATPase	Microbiology test able to detect different MDROS
C. diff.	Clostridium difficile
CAUTI	Catheter associated urinary tract infection
CDC	Centers for Disease Control and Prevention (USA)
CDI	Clostridium difficile Infection
CLabsi	Central Line-associated blood Stream infection
CPE	Carbapenemase-producing Enterobacteriaceae
CRE	Carbapenem-resistant Enterobacteriaceae
DDD	Defined daily dose
DoA	Description of the Action
ECDC	European Centre for Disease Prevention and Control
E. coli	*Escherichia coli*
ESBLs	Extended-spectrum beta-lactamases
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
EU/EEA	European Union and European Economic Area
G+	Gram positive
G-	Gram negative
GA	Gran Agreement
GNB	Gram negative bacilli
HAI	Healthcare-Associated Infections
HCP	Healthcare Practitioner
HCW	Healthcare Worker
HH	Hand Hygiene
HW	Hardware
IC	Infection Control
ICU	Intensive Care Unit
IPSec	Internet Protocol Security
KPC	Klebsiella pneumoniae carbapenemase
K. pneumonia	*Klebsiella pneumoniae*
LOS	Length of Stay
LTCFs	Long-term care facilities
MDROs	Multidrug-resistant organisms
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
NI	Nosocomial infection(s)
OR	Operating Room
PCR	Polymerase Chain Reaction
PN	Parenteral Nutrition
S. aureus	*Staphylococcus aureus*
SSI	Surgical Site infection
SW	Sotware
US	United States
VAP	Ventilator-Associated Pneumonia
VOC	Volatile Organic Compound
VRE	Vancomycin-resistant enterococci

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1. INTRODUCTION

Healthcare-associated infections (HAIs), or "nosocomial" and "hospital" infections, are defined as infections acquired in hospital by a patient who was admitted for a reason other than that infection. The European Centre for Disease Prevention and Control (ECDC)[1] estimated that 2,609,911 new cases of HAI occur every year in the European Union and European Economic Area (EU/EEA).

The **uncontrolled transmission of multi-drug resistant organisms** (**MDROs**, aka 'Superbugs') via patient to patient, patient to staff to patient, or patient to surface to patient, is a major problem in healthcare systems. This causes significant morbidity, mortality and increased hospitalization and costs, as well as adversely affecting patient experience. ECDC reports that the **cumulative burden** of the main HAIs is estimated at 501 DALYs (disability-adjusted life years) per 100,000 general population each year in EU/EEA. Pneumonia and primary bloodstream infection impose the highest burden, representing over 60% of the total estimation. Additionally, studies[2] following the indications by the Centres for Disease Control and Prevention (CDC) Network at the US, suggest that the **total annual cost** for the 5 major infections was $9.8 billion (95%CI, $8.3-$11.5 billion).

HAIs are also related to a more pressing problem worldwide: **antimicrobial resistance** (AMR). AMR is responsible for 25,000 deaths and a loss of €1.5 billion in extra costs (treatment and societal costs) every year in the EU alone. Worldwide, 10 million deaths per year are projected between 2015 and 2050 and expected cumulative losses in OECD countries due to AMR will be USD 2.9 trillion by 2050, if current infection and resistance trends are not reversed. AMR accounts for USD 10,000 to 40,000 additional hospital costs per patient in OECD countries and these figures are likely to double if considering other indirect costs[3].

Antimicrobial resistance is linked to **excessive and inappropriate use of antimicrobial medicines and poor infection control practices[4].** The consumption of specific antibiotics used for treatment of multidrug-resistant bacterial infections has almost doubled in Europe from 2010 to 2014, with a high variability of antibiotic consumption across OECD countries. Three of the countries where the ANTI-SUPERBUGS procurers are located – i.e.: UK, Spain

[1] Burden of Healthcare-Associated Infections in Europe (October 2016) PLOS Medicine | DOI:10.1371/journal.pmed.1002150
[2] Health care–associated infections: a meta-analysis of costs and financial impact on the US health care system. (2013) (https://psnet.ahrq.gov/resources/resource/26769/health-care-associated-infections-a-meta-analysis-of-costs-and-financial-impact-on-the-us-health-care-system)
[3] EU factsheet 'AMR: A major European and Global challenge' (https://ec.europa.eu/health/amr/antimicrobial-resistance_en)
[4] EU factsheet 'AMR: A major European and Global challenge' (2017) (https://ec.europa.eu/health/amr/antimicrobial-resistance_en)

and Italy -, have an above average antibiotic consumption when compared to the average from all OECD countries.

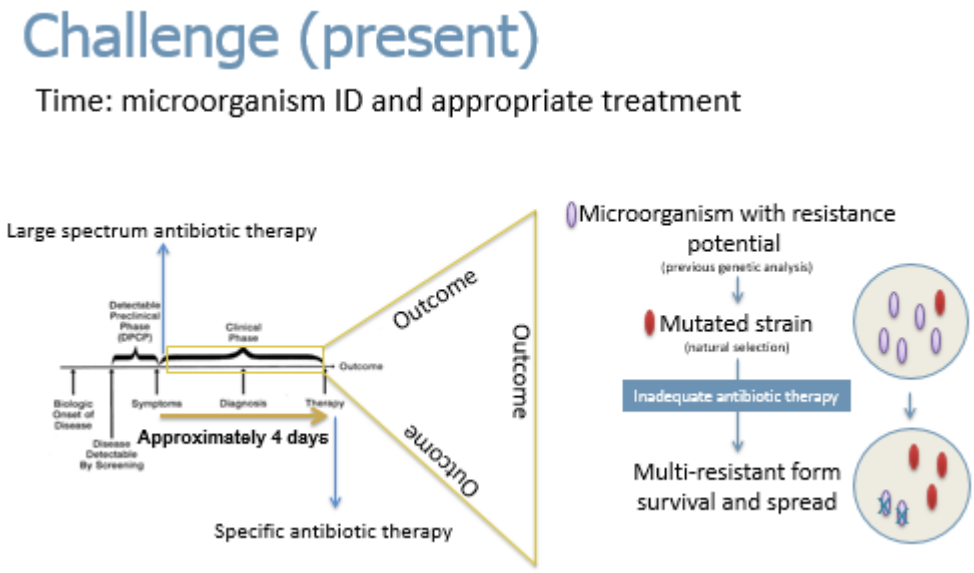


Figure 1 – Present challenge when prescribing antibiotic therapy: the adequacy of the treatment depends on the time taken to correctly diagnose the patient. If an infected patient has resistant strains present in his/her body, then an inadequate antibiotic treatment will maintain those pathogens in the body, allowing for the disease to progress.

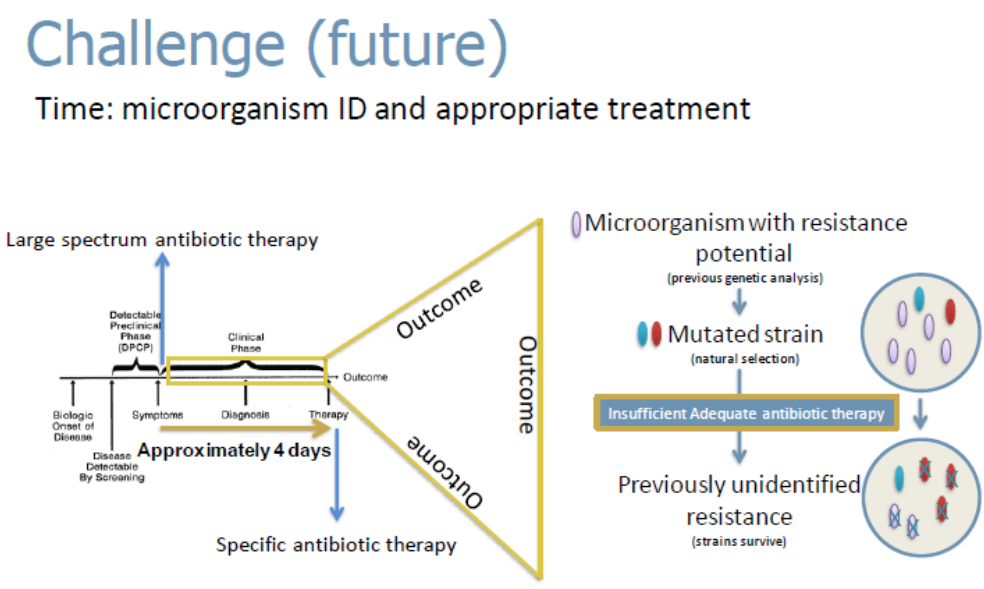


Figure 2 – Future challenge when prescribing antibiotic therapy: independently on the time taken to correctly diagnose the patient, new strains, which laboratories have never previously identified, can appear and make an adequate treatment less effective.

Continuous surveillance has been demonstrated effective[5] to prevent the propagation of specific MDROs infections and to reduce the hospital length of stay. However, continuous surveillance is currently very expensive and not feasible for all organisms. Moreover, the ability of different facilities and different countries to implement it varies widely. Although great effort has been concentrated on admission epidemiology, surveillance and Infection Control, patients continue to acquire MRDOs in hospital and their clinical outcomes are adversely affected compared to their initial prognosis. Currently, the main intervention which healthcare organisations can undertake to prevent the spread of AMR organisms is follow aseptic methods where appropriate, and practicing good hand hygiene.

According to ESCMID guidelines[6] for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients, the **current measures for HAIs prevention** are defined in the areas listed below:

- Hand Hygiene (either for staff, patients and/or visitors)
- Contact Precautions (personal protective equipment)
- Alert coding
- Isolation
- Cohort staff
- Active Screening Cultures
- Environmental Cleaning/decontamination
- Antimicrobial/Antibiotic Stewardship
- Infrastructure and Education

These initiatives and measures differ in application depending on the incidence of the infections (i.e. endemic vs epidemic settings) and in evidence-based level. A harmonized approach based on the application of evidence-based core strategies considering local characteristics and context could be beneficial.

ANTI-SUPERBUGS PCP Buyers' Group - composed by ICO/VINCat and FMT (ES), PAT (IT), Helios and UKA (DE) and STH (UK) -, aims to:

- ✓ **Improve the quality of care processes in hospitals;**
- ✓ **Reduce both the costs and the operational impact resulting from infections caused by MDROs;**
- ✓ **Improve the appropriateness of antimicrobial medicine usage;**
- ✓ **Reduce the community and social care impact of MDROs acquired in hospitals through the procurement of pre-commercial technologies that will transform**

[5] Souverein D, Houtman P, Euser SM, Herpers BL, Kluytmans J, Den Boer JW (2016) Costs and Benefits Associated with the MRSA Search and Destroy Policy in a Hospital in the Region Kennemerland, The Netherlands. PLoS ONE 11(2): e0148175. doi:10.1371/journal.pone.0148175

[6] E. Tacconelli; et al.; ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients; Clinical Microbiology and Infection; 2014, Vol 20, s1; p1-55.

current Surveillance and Infections control systems into new comprehensive systems.

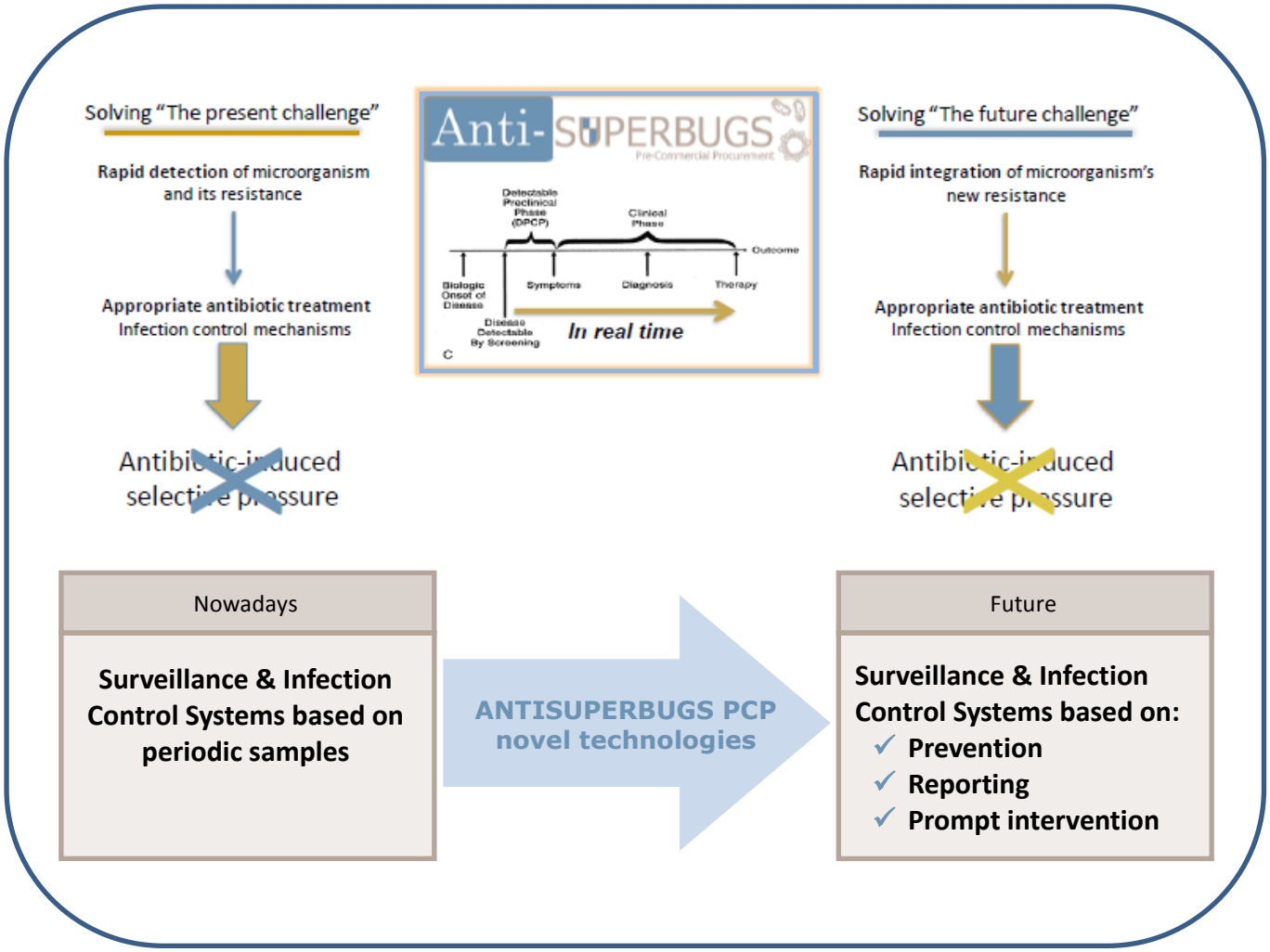


Figure 3 – ANTI-SUPERBUGS PCP Challenge

The new Surveillance & Infection Control Systems of the target microorganisms will allow healthcare practitioners to:

- be aware of the alert coding procedure by the technology's continuous/high frequent screening of fomites and hospital environments;
- start contact precautions procedures from the very first moment they are needed and discontinue them the soonest possible;
- start isolation procedures from the very first moment they are needed and discontinue them the soonest possible;

- prevent further or possible development of antibiotic resistance thanks to the cultures' of the detected microorganisms laboratorial analysis triggered by the results of the continuous/high frequent screening of fomites and hospital environments;
- prevent contamination in accordance to the results of continuous/high frequent screening of fomites and hospital environment;
- promptly define the appropriate treatment plan and prevent antibiotic resistance by means of the swift identification of the possible source of infection; and
- promptly manage epidemic/outbreaks thanks to the analysis of the detected contamination/colonization.

2. OBJECTIVES

This document aims to describe in detail the unmet needs of the buyers' group and their challenge to ensure a full comparability of the competing solutions proposed by the market in view of potential conversion into permanent services.
The description of the need involved the main stakeholders of the public service delivery chain including the final users of ANTI-SUPERBUGS ICT novel solutions.
ANTI-SUPERBUGS PCP challenge does not pre-define any technical solution and is opened to diverse ICT technologies that could address the needs translated into functional and performance-based requirements. At the same time, the performance targets and the expected behaviours are upfront, clearly and unambiguously specified.
To pre-determine a wide potential market (public and private) for the ANTI-SUPERBUGS novel ICT solutions and to enable the desired economies of scale and cost savings, the functional and performance requirements are not hyper-described, customization and personalization requirements are avoided, interoperability and scalability requirements are instead specified.
As pre-commercial procurement, ANTI-SUPERBUGS PCP will not look for research and development efforts aiming to lowest price per units, but aiming to long-term gains in cost efficiencies based on the entire life cycle of the novel solutions (production, delivery, installation, use, management, maintenance and disposal).

3. THE ANTI-SUPERBUGS CHALLENGE DESCRIPTION

3.1 What are the detection capabilities of ANTI-SUPERBUGS ICT novel technologies?

Each resistance found in European regions relates to political, historical, biological, social and geographical characteristics. The ANTI-SUPERBUGS Buyers Group aims to incorporate as many microorganisms in the ICT technology detection capabilities as possible because of these very broad needs. The ANTI-SUPERBUGS novel technologies should be able to easily address these European variables through small modular variations and, therefore, provide a solution to each region, their health system and health centres (no matter the size or targeted demographics).

The surveillance and prevention impact related to the microorganisms and the high probability of commercializing such a technology makes it a very competitive, albeit ambitious, project. The described objectives have been adapted to the needs of the different ANTI-SUPERBUGS buyers including the microorganisms that, because of their prevalence and virulence, are of maximum interest for our health professionals and the population they target.

ANTI-SUPERBUGS novel technologies should be able to detect **the following top priority multi-resistant microorganisms**:

- ***C. difficile*** (gram-positive bacillus) was the 8th most frequently detected microorganism among HAIs in the ECDC point prevalence survey of (HAIs) and antimicrobial use in European acute care hospitals 2011-2012 (ECDC PPS[7]), and is leading cause of diarrhoea among hospitalized patients[8]. Newly emerged hypervirulent ribotypes (e.g. 027) are responsible for a dramatic increase in severity of the disease, higher mortality rates, increased risk of relapse and higher colectomy rates. [9]

- ***Klebsiella pneumonia*** (gram-negative enterobacteriaceae resistant to carbapenems) These bacteria can spread quickly in healthcare facilities, thanks to the presence of carriers that can disseminate the pathogen in absence of disease. Such MDROs

[7] ECDC, Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012 (https://ecdc.europa.eu/en/healthcare-associated-infections-acute-care-hospitals/surveillance-disease-data/report)

[8] Epidemiology and outcome of Clostridium difficile infections in patients hospitalized in Internal Medicine: findings from the nationwide FADOI-PRACTICE study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5101712/)

[9] P. Mastrantonio, M. Rupnik (eds.), Updates on Clostridium difficile in Europe, Advances in Experimental Medicine and Biology 1050, https://doi.org/10.1007/978-3-319-72799-8_2

usually present combined resistance to other antibiotics, and are quickly spreading across some geographic areas such as the Mediterranean basin.
Klebsiella spp. is between the ten most frequently isolated microorganisms in HAIs. According to data by the ECDC[10], in 2011, 22.3% of all *K. pneumoniae* invasive isolates were resistant to at least three antimicrobial classes. A significant increase in resistance to carbapenems in *K. pneumoniae* from 8% to 15% was reported over the period 2005–2010. Remarkably, the 'Global priority list of antibiotic-resistant bacteria' published by the WHO[11] (February 2017) considers the *Enterobacteriaceae* (including *Klebsiella*) within the 'Critical' category, according to the urgency of need for new antibiotics. In some countries, because of resistance, carbapenem antibiotics do not work in more than half of people treated for *K. pneumoniae* infections[12].

- ***Acinetobacter baumannii*** (gram-negative bacterium) is a common causative agent of hospital-acquired infections and a leading cause of infection in patients suffering from fire damage. While there are many types or "species" of Acinetobacter that can cause human disease, *Acinetobacter baumannii* (A. baumannii) accounts for about 80% of reported infections[13]. Acinetobacter can live on the skin and may survive in the environment for several days. Carbapenem-resistant A. baumannii is considered a major public-health threat and has been identified by the WHO as the top priority organism requiring new antimicrobials[11].

- ***S. aureus***, (gram-positive bacillus), is also between the ten most frequently isolated microorganisms in infections, and is included in the 'High-priority' category for new antibiotics needed due to its methicillin resistance (MRSA). Staphylococcus aureus (including MRSA) survives for months on dry surfaces

Most gram-positive bacteria (such as C. difficile and MRSA) and many gram-negative species (such as Klebsiella spp. and Acinetobacter spp.) can survive for months on inanimate surfaces[14]. Moreover, in some cases, evidence exists regarding environment-to-healthcare worker spread[15] (such as C. difficile).

[10] http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=580
[11] *Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiòtics (WHO, Feb 2017) (http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/)*
[12] *Antimicrobial resistance (WHO, Feb 2018) (http://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance)*
[13] *Multidrug-resistant Acinetobacter baumannii (MDRAB) (WHO, Nov 2010)* (*http://www.wpro.who.int/mediacentre/factsheets/fs_20101102/en/)*
[14] How Long do Nosocomial Pathogens Persist on Inanimate Surfaces? A Systematic Review (PDF Download Available). Available from: https://www.researchgate.net/publication/6873698_How_Long_do_Nosocomial_Pathogens_Persist_on_Inanimate_Surfaces_A_Systematic_Review
[15] Contamination, Disinfection, and Cross-Colonization: Are Hospital Surfaces Reservoirs for Nosocomial Infection? Robert A. Weinstein Bala Hota Clinical Infectious Diseases, Volume 39, Issue 8, 15 October 2004, Pages 1182–1189, https://doi.org/10.1086/424667

ANTI-SUPERBUGS novel technologies should also include additional information on the microorganisms (e.g. virulence factors like toxins in C. difficile).

3.2 Where do we want ANTI-SUPERBUGS ICT novel technologies to detect microorganisms?

Depending on the technology and the microorganisms that it is targeting, there can be an independence from human contact or surfaces contacting with these human tissues, allowing for a more environmental detection (e.g. medical objects, inanimate objects and aerial space). Therefore, the technology must be flexible enough to be integrated in both controlled areas, like intensive care units, and open spaces designed for patient and healthcare practitioners (e.g. common areas in healthcare facilities).

3.3 How should the detection be made?

ANTI-SUPERBUGS novel technologies will detect volatile organic compounds (VOC) of the target microorganisms and will not make use of any intrusive or invasive sampling since they can create a risk of infection for the patients.
ANTI-SUPERBUGS novel technologies should autonomously activate a real-time information pathway, integrate the detection in the clinical history of the patient around where detection occurred and create an alarm with the relevant information.

3.4 What are the ANTI-SUPERBUGS potential strategies to address the basic recommendations to prevent MDR-GNB according to the ESCMID?

Basic recommendations to Prevent Spread of MDR-GNB (multidrug-resistant gram-negative bacteria) (ESCMID (European Society of Clinical Microbiology and Infectious Diseases guidelines) Guidelines) [16]			ASB ICT Solution		
	Epidemic setting	**Endemic setting**	**ASB technology can have a role in satisfying recommendation? (Yes, No, in part)**	**Potential impact (0= null , 1=low, 2=medium, 3=high)**	**ASB potential strategies related to recommendation**
Hand Hygiene (HH)	Strong recommendation: Implement HH education programmes to reduce the transmission of ESBL-producing Enterobacteriaceae. MDR-**A. baumannii**, Stenotrophomonas maltophilia (moderate level of evidence); MDR-**K. pneumoniae**, MDR-P. aeruginosa and Burkholderia cepacia (very low level of evidence)	Strong recommendation: Implement HH education programmes to reduce the transmission of extended-spectrum β-lactamase (ESBL)-producing enterobacteriaceae, multidrug-resistant (MDR)-*Klebsiella* ***pneumoniae***, MDR-*Pseudomonas aeruginosa*, MDR-***Acinetobacter baumannii*** (moderate level of evidence); *Stenotrophomonas maltophilia* and *Burkholderia cepacia* (very low level of evidence)	in part	1	ASB ICT Solution interoperates with HIS/LIS/EHR, electronic hygiene control systems and indication-relation control systems sending the screening outcomes and alerts on detections

[16] E. Tacconelli; et al.; ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients; Clinical Microbiology and Infection; 2014, Vol 20, s1; p1-55. https://onlinelibrary.wiley.com/doi/full/10.1111/1469-0691.12427

Contact Precautions	Strong recommendation: Implement contact precautions (CP) for all patients colonized and/or infected with extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, multidrug-resistant (MDR)-***Klebsiella pneumoniae***, MDR-***Acinetobacter baumannii*** (moderate level of evidence); and *Pseudomonas aeruginosa* (very low level of evidence)	Strong recommendation: Implement contact precautions (CP) for all patients colonized with extended-spectrum β-lactamase (ESBL)-Enterobacteriaceae (with the exception of *Escherichia coli*), multidrug-resistant (MDR)–***Klebsiella pneumoniae***, MDR-***Acinetobacter baumannii***, and MDR-*Pseudomonas aeruginosa* (moderate level of evidence)	Yes	2	The ASB ICT Solution reads from the patient Electronic Health Record the patient history (previous infections, hospitalizations). ASB ICT Solution informs in real time the HIS of the risks of infection. ASB VOC detector automatically screens patient environment (e.g.: skin flora, linen, gown, room surfaces, patient potty, etc) The ASB ICT Solution increases staff awareness about MDR microorganisms through early detection and rapid communication. ASB ICT Solution colonization detection geolocalizes an environment that could be a possible place of contamination. ASB ICT Solution triggers an alert regarding possible contamination/colonization and screening outcome. Nurse receives the alert about MDR colonization/contamination and manages the admission of the patient (isolation or cohort isolation) and the CP appropriately. Once the patient and the area are confirmed to have been decolonized/decontaminated, ASB ICT Solution keeps the detection screening of microorganisms allowing healthcare practitioners to decide upon discontinuing contact precautions and isolation/cohort isolation protocols.

Alert code	Strong recommendation: Use alert code to identify promptly patients already known as colonized with ESBL-producing Enterobacteriaceae and MDR-**K. pneumoniae** at hospital/ward admission and perform screening and pre-emptive CP (moderate level of evidence)	Strong recommendation: Use alert code to identify promptly patients already known as colonized with MDR-**A. baumannii** at hospital/ward admission and perform screening and pre-emptive CP (moderate level of evidence)	Yes	3	ASB ICT Solution generates an alert code after MDR detection. A GUI interface enables the professionals to either access patient data or enter the relevant missing data. ASB ICT Solution interoperates with the Hospital Information System (HIS), Laboratory Information System (LIS) and the patient Electronic Health Record (EHR), integrating alert code into LIS and HIS in real time.
Isolation room	Strong recommendation: Isolate colonized and infected patients in a single room to reduce the risk of acquisition of ESBL-producing Enterobacteriaceae, MDR-**K. pneumoniae** (moderate level of evidence); MDR-**A. baumannii** and MDR-P. aeruginosa(low level of evidence)		Yes	2	Nurse receives the alert and manages the admission of the patient (isolation or cohort isolation) appropriately. Patient colonization screening and continuous monitoring allow prompt and effective patient isolation. In case the contamination is detected, the ASB ICT Solution sends an alert to the HIS and the users and stores, in the server patient identifier, the geo-localized room where the patient is staying and the timestamp of the patient screening. Once the patient and the area are confirmed to have been decolonized/decontaminated, the ASB ICT Solution inform about discontinuing isolation. ASB ICT Solution comprises a screening device and a data server for local epidemiological purpose informing promptly if endemic or epidemic colonization/infection levels are in place.

Cohort staff	Strong recommendation: Cohort staff to reduce the risk of acquisition of MDR-**K. pneumoniae** (moderate level of evidence)		in part	1	ASB ICT Solution interoperates with HIS/LIS/EHR, electronic hygiene control systems and indication-relation control systems sending the screening outcomes and alerts on detections
Active Screening Cultures	Strong recommendation: Implement a programme of active screening culture at hospital admission followed by contact precautions to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae, multidrug-resistant (MDR)-***Klebsiella pneumoniae***, MDR-***Acinetobacter baumannii*** (moderate level of evidence); and MDR-*Pseudomonas aeruginosa* (very low level of evidence)		Yes	3	Patient finds that the screening method with ASB ICT Solution does not negatively affect his/her experience and is minimally intrusive. ASB ICT Solution use is associated with the lowest possible patient risk. ASB ICT Solution performs an active screening at patients' admission for the identification of cases needing laboratory culture confirmation.

Environmental Cleaning	Strong recommendation: Monitor cleaning performance to ensure consistent environmental cleaning (EC). Vacate units for intensive cleaning. Implement regular EC procedures and, when available, dedicate non-critical medical items for use on individual patients colonized or infected with extended-spectrum β-lactamase Enterobacteriaceae and multidrug-resistant-***Acinetobacter baumannii*** (moderate level of evidence)	Strong recommendation: Implement regular environmental cleaning (EC) procedures and, when available, dedicate non-critical medical items for use on individual patients colonized or infected with multidrug-resistant-***Acinetobacter baumannii*** (moderate level of evidence)	Yes	3	The ASB ICT Solution allows for the detection of surface colonization of the target microorganisms. ASB ICT Solution screening device automatically screens the environment close to the patient (e.g.: linen, gown, room surfaces, patient potty) collecting information about possible contaminated surfaces and efficacy of contact precaution measures. Environmental inanimate surfaces monitoring allows detection of high rate of repeated contamination/colonization, definition of both cleaning and decontamination procedures.
Antimicrobial Stewardship	Strong recommendation: Implement an antimicrobial stewardship programme to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae (moderate level of evidence)	Strong recommendation: Implement an antimicrobial stewardship programme. Plan interventions of restriction of antibiotic usage to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae (moderate level of evidence)	Yes	2	The ASB ICT Solution enters the ASB screening outcome into the patient Electronic Health Record. The infection disease specialist assesses the patient status and starts promptly treating the patient. Rapid detection of MDR colonization, allows reducing time to clinical diagnosis of MDR and implementation of antimicrobial stewardship.

Infrastructure and Education	Strong recommendation: Conduct educational programmes to ensure that healthcare workers understand why extended-spectrum β-lactamase-Enterobacteriaceae are important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective (moderate level of evidence)	Strong recommendation: Conduct educational programmes to ensure that healthcare workers understand why multidrug-resistant-***Acinetobacter baumannii*** is important epidemiologically, why prevention of spread is critical for control, and which measures for preventing spread have proven to be effective (moderate level of evidence)	Yes	2	The ASB ICT Solution sends the colonization/infection alert asynchronously to the centralized data server for epidemiological purpose. ASB ICT Solution sends the information relevant to the confirmed infection to the central data server and triggers an epidemiologic alert. ASB ICT Solution provides statistics regarding detection of colonization and microorganisms' identification at molecular level (epidemic strains.)

3.5 Specifications and requirements for the ANTI-SUPERBUGS ICT Solution

ASB ICT Solution is an active medical device whose intended use is:

- the volatile organic compound (VOC) **detection of contaminations/colonisations of fomites and inanimate hospital environment on the following:**
  - ***Clostridium difficile* spores and/or microorganism** (including, if possible, the detection of Toxins A and B, and Binary toxin (transferase))
  - **and either *Klebsiella pneumonia*** (including, if possible, the detection of its carbapenem & ESBL production resistances) **or *Acinetobacter baumannii*** (including, if possible, the detection of its carbapenem & ESBL production resistances) **or both**
  - including, if possible, the detection of MRSA, additional Gram-negative pathogens and additional resistances
- The provision of an **alert system to aid in the correct management of contaminated/colonized patients and inanimate hospital environments**
- The provision of a **local Surveillance & Infection Control System of the target microorganism(s)**

ASB ICT Solution comprises a bundle of technologies offering different approaches and outputs at different level of infection management (as surveillance, environmental safety, first patient screening and patient early diagnosis):

- a volatile organic compound (VOC) screening device (hereinafter referred to as **ASB VOC detector**) that determines contaminations/colonisations of fomites and hospital environments on the following:
  - *Clostridium difficile* spores and/or microorganism (spore detection is considered of higher priority)
  - and either *Klebsiella pneumoniae* or *Acinetobacter baumannii* or both
  - and additionally, if possible, of:
    - antibiotic resistances in *Clostridium difficile* (Toxins A and B, and Binary toxin (transferase)) and/or *Klebsiella pneumoniae* (carbapenem & ESBL production) and/or *Acinetobacter baumannii* (carbapenem & ESBL production)
    - MRSA
    - any additional Gram-negative pathogen or any additional resistance
- the software (client and server) for the proper application of the screening device*
- a **local data server acting as**:

- **local Surveillance & Infection Control System** of the target microorganism(s) (repository of all the local contamination/colonization history, dashboards, retrospective analysis based on local data)
- **interoperability engine** to integrate with Hospital Information System (HIS) (SAP, ISH/ISHMED, MEDICO etc.), Laboratory Information System (LIS), patients Electronic Health Records (EHR) and existing software used for epidemiological surveillance, electronic hygiene control systems and indication-relation control systems
- **alert system** – alerts will be triggered based on the information retrieved by the screening device, the HIS/LIS/EHR, the ASB ICT Solution will:

  (1) identify patients at risk of infection after having analysed their health conditions, their patient history, the geolocalised area history and the staff indication-relation compliancy and

  (2) generate alerts to be sent to the HIS/EHR

*No requirement is given regarding whether the screening device software client and server are both installed on the screening device or not

No requirement is given about where the screening device client GUI is made available from: it could be accessible from either the screening device itself or a mobile device or a computer, etc.

No requirement is given about where the screening device server GUI is made available from: it could be accessible from either the screening device itself or the local data server or a dedicated server to be installed at the buyer premises

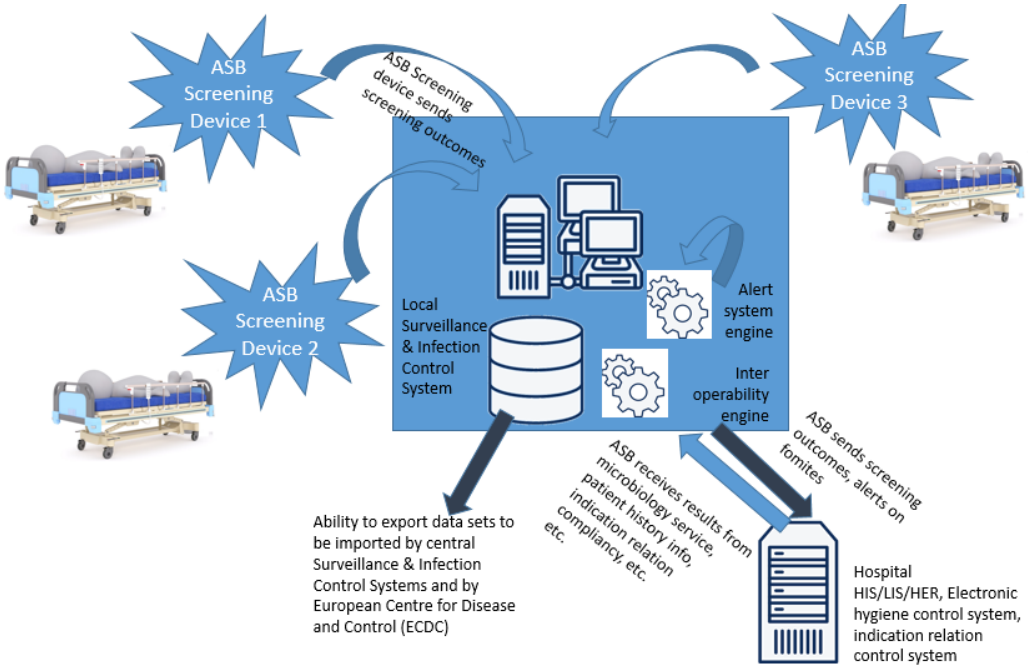


Image 4- Schema of ANTI-SUPERBUGS ICT Solution

MUST HAVE Technical Specifications and Requirements

Life Cycle: Production - Non-functional requirements

- ASB-PROD-001: ASB ICT Solution prototype MUST be produced according to ANTI-SUPERBUGS Pre-commercial Procurement Call for Tender specifications and requirements

Life Cycle: Delivery - Non-functional requirements

- ASB-DELI-001: ASB ICT Solution MUST use existing delivery routes of ANTI-SUPERBUGS Buyers

Life Cycle: Installation - Non-functional requirements

- ASB-INST-001: ASB VOC detector MUST be deployable/installable/ready to be used into existing healthcare environments, facilities and architecture (patient room(s), Intensive care units (ICU), Emergency rooms (ER), Haematology/Oncology clinics, common/crowded areas in healthcare facilities)
- ASB-INST-002: ASB ICT Solution MUST be easy to deploy

Life Cycle: Use

Functional requirements

- ASB-USER-001: Users SHALL securely authenticate and gain access to the ASB ICT Solution
- ASB-USER-002: Users SHALL select the patient
- ASB-USER-003: Users SHALL be able to enter the relevant data (patients identifiers) of the new patients (in case patients selection is not possible)
- ASB-USER-004: Users SHALL be able to manually enter/update into the ASB ICT Solution all the information related to resistant infection episodes detected at the buyer's premise and not detected by ASB (patients identifiers, geo-localized rooms where the patients stayed, timestamp of infection/colonization/contamination detection, timestamp of infection/colonization/contamination confirmation) In such case the system MUST store the identification of the users that enter/update the information
- ASB-USER-005: Users SHALL be able to manually enter into the ASB ICT Solution all the information related to resistant infections episodes

(patients identifiers, geo-localized rooms where the patients stayed and time) of referring healthcare centres/social care centres/ hospitals where infected patients were previously hospitalized

- ASB-USER-006: Users SHALL have access to the relevant data and user interfaces depending on their profiles
- ASB-USER-007: Microbiologists SHALL be able to manually enter the microorganisms identification at molecular level (epidemic strains), the resistance(s) and the degree of virulence in case the infection is confirmed and the HIS cannot push this data to ASB ICT Solution

Non-functional requirements

Performance:

- ASB-PERF-001: ASB ICT Solution MUST be able to identify/geolocalise fomites (including patients and healthcare workers) and inanimate hospital environment
- ASB-PERF-002: ASB ICT Solution MUST detect the contaminations/colonisations of fomites and inanimate hospital environment from:
    - *Clostridium difficile* spores and/or microorganism (spore detection is considered of higher priority)
    - and either *Klebsiella pneumoniae* or *Acinetobacter baumannii* or both

- ASB-PERF-003: ASB ICT Solution MUST integrate with Hospital Information System (HIS) (SAP, ISH/ISHMED, MEDICO etc.), Laboratory Information System (LIS), patients Electronic Health Records (EHR) (linking the infection with the place of detection) and existing software used for epidemiological surveillance, electronic hygiene control systems and indication-relation control systems using interoperability standards (e.g. HL7, FHIR, FHIR XML, IHE XDS, etc.)
- ASB-PERF-004: ASB ICT Solution MUST store all the ASB detected infections and colonization/contamination episodes of the target microorganisms at the buyer's premise (patients identifiers, geo-localized rooms where the patients stayed, timestamp of infection/colonization/contamination detection, timestamp of infection/colonization/contamination confirmation and the source of the information (ASB VOC detector, HIS/LIS, end-user identification, automatic upload from a XML files))
- ASB-PERF-005: ASB ICT Solution MUST store all the infections and colonization/contamination episodes of the target microorganisms manually entered by the users (patients identifiers, geo-localized rooms

where the patients stayed, timestamp of infection/colonization/contamination detection and timestamp of infection/colonization/contamination confirmation)

- ASB-PERF-006: ASB ICT Solution MUST correctly manage all the episodes and enable the merging of duplicate episodes
- ASB-PERF-007: ASB ICT Solution MUST automatically start screening procedure and screen the patient and the room where installed at the frequency defined by the buyer (the screening frequency can be set to continuous)
- ASB-PERF-008: In case the screening frequency is NOT set to continuous, ASB ICT Solution MUST automatically start screening procedure and screen the patient and the room where installed in case a risk of infection is identified after having analysed the patient history (any previous infection, the referring health care/social care centre (if any), previous hospitalizations (if any), etc.)
- ASB-PERF-009: ASB VOC detector MUST allow manual patient screening. In this case, the ASB VOC detector will be handled by one HCW. ASB ICT Solution will store the timestamp of both the screening initiation and completion and the HCW user identifier.
- ASB-PERF-010: ASB ICT Solution MUST inform in real time the HIS of the risks of infection (if any) after having analysed the patient history (any previous infection, the referring health care/social care centre (if any), previous hospitalizations (if any), etc.)
- ASB-PERF-011: ASB VOC detector MUST provide and store in the ASB ICT Solution the geolocalization of the device together with the timestamp
- ASB-PERF-012: ASB ICT Solution MUST send the ASB screening outcome and its timestamp to the HIS/patient EHR.
- ASB-PERF-013: In case the contamination/colonisation is detected, ASB ICT Solution MUST store in the server the relevant data (patient identifier, the geo-localized room where the patient is staying and the timestamp of the patient screening)
- ASB-PERF-014: in case of contamination/colonization detection, ASB VOC detector MUST calculate and store in the ASB ICT Solution the distance of detection, the timestamp and any other data relevant to the detecting action as, for example, the size of the detected area/volume.
- ASB-PERF-015: In case the contamination/colonisation is detected, ASB ICT Solution MUST send an alert to BOTH the HIS AND the users
- ASB-PERF-016: ASB ICT Solution MUST provide multiple user interfaces according to the professional profiles (microbiologist, infection disease specialist, nurse, etc.) Different users should have access to specific content.

- ASB-PERF-017: ASB ICT Solution MUST provide tools to configure the interfaces and the content according to the professional profiles
- ASB-PERF-018: In case the infection is confirmed and HIS can push the data of the microorganisms identification at molecular level (epidemic strains), the resistance(s) and the degree of virulence, ASB ICT Solution MUST receive this information from the HIS and store it together with the timestamp of the confirmation
- ASB-PERF-019: ASB ICT Solution MUST send the information relevant to the confirmed colonization/contamination (patient identifier (if any), the geo-localized room where the patent stays, timestamp of the patient screening, microorganisms identification at molecular level (epidemic strains), resistance(s), the degree of virulence and the timestamp of the microbiology test results) to the local data server
- ASB-PERF-020: At local level, ASB ICT Solution MUST provide dashboards retrospective analysis based on local data, statistics regarding detections of the target microorganisms: (1) number of detections/day/week/month/year, species detected, etc.; (2) Detection and identification of molecular biology (epidemic strains); (3) detect endemic or epidemic colonization/infection levels
- ASB-PERF-021: ASB ICT Solution MUST periodically access any inserted/updated information of the Electronic Health Records inpatients: the frequency will be determined by the buyers ICT policies and it will be, at least, daily; the access will be done according to the buyers ICT policies (either querying directly the EHR database or importing an EHR export file containing all the INSERT/UPDATE relevant to the inpatients)
- ASB-PERF-022: ASB ICT Solution MUST send an alert to the HIS of the risks of infection (if any) after having processed all the inserted/updated information of the Electronic Health Records inpatients together with all the inpatients histories (any previous infection, the referring health care/social care centre (if any), previous hospitalizations (if any), etc.)
- ASB-PERF-023: ASB ICT Solution MUST provide the ability to perform queries and export data in XML format
- ASB-PERF-024: ASB ICT Solution MUST be available 24x7
- ASB-PERF-025: ASB ICT Solution MUST be integrated in the regular healthcare routines
- ASB-PERF-026: ASB ICT Solution MUST be flexible/modular to integrate detection capabilities for additional MRDOs or future proofing or possible evolution of the microorganisms
- ASB-PERF-027: ASB ICT Solution MUST be flexible/modular to integrate detection capabilities for additional clinically relevant HAI microorganisms

Environmental:

- ASB-ENVI-001: ASB VOC detector sensitivity MUST not depend on environmental conditions (temperature, humidity and kinetic saturation) or be negatively affected to a point where the committed relative sensitivity is reduced more than 50%
- ASB-ENVI-002: ASB VOC detector performance capabilities (turn-around time, sensitivity, specificity, distance of detection and accuracy) MUST not be subjected to degradation due to the interference of the devices commonly in use in the hospital premises
- ASB-ENVI-003: ASB VOC detector limitations of use MUST be declared (environment interferences that could reduce VOC detector performance capabilities (turn-around time, sensitivity, specificity, distance of detection and accuracy))

Security and Data Protection:

- ASB-SECU-001: ASB ICT Solution secure authentication MUST be in accordance with the existing methods of the buyers (such as log on (password, barcodes, smartcard, biometric, etc), network access authentication (IPSec, remote, single sign on, etc), etc)
- ASB-SECU-002: data MUST be protected from external misuse (servers MUST be installed according to buyers ICT security procedures (e.g. firewalls))
- ASB-SECU-003: ASB ICT Solution MUST comply with EU General Data Protection Regulation (Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC) (please refer to: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679)

Safety

- ASB-SAFE-001: ASB VOC detector MUST be risk free to the patients
- ASB-SAFE-002: ASB VOC detector MUST be risk free to the users
- ASB-SAFE-003: ASB VOC detector MUST neither include nor generate any toxic material to be handled by the personnel
- ASB-SAFE-004: ASB VOC detector MUST have a self-diagnostic function
- ASB-SAFE-005: Consumables (if any) MUST be non-toxic and ecological
- ASB-SAFE-006: ASB VOC detector MUST not interfere with the devices in use in the hospital premises
- ASB-SAFE-007: ASB ICT Solution MUST comply with EU safety, health, and environmental protection requirements by mean of the provision of conformity assessment of all the products used to build the prototypes and to carry out the pilots (please refer to:

https://ec.europa.eu/growth/single-market/ce-marking/manufacturers_en)

Usability

- ASB-USAB-001: ASB VOC detector MUST be easy to handle, easy to use and comfortable to the users (highly usable user interface)
- ASB-USAB-002: ASB ICT Solution software client GUI MUST be easy to use to the user (highly usable user interface)
- ASB-USAB-003: ASB ICT Solution software client GUI MUST not require any specific academic preparation to be used
- ASB-USAB-004: ASB VOC detector MUST be acceptable and comfortable to the patient
- ASB-USAB-005: ASB VOC detector MUST be considered minimally intrusive by the patient
- ASB-USAB-006: ASB ICT Solution software GUIs MUST be localized and during the pilot the language of ANTI-SUPERBUGS buyers will be provided (Spanish, Italian, German and English)
- ASB-USAB-007: ASB ICT Solution User guide MUST be provided in the language of ANTI-SUPERBUGS buyers (Spanish, Italian, German and English)

Economic

- ASB-ECON-001: The cost-effectiveness MUST be comparable with buyers' patient screening common practice (the analysis will include the structural cost of the clinical validation, the ASB VOC detector operating life costs, the cost of consumables (if any), the forecasted ASB ICT Solution pricing model and the ASB VOC detector range capabilities)

Life Cycle: Maintenance - Non-functional requirements

- ASB-MAIN-001: The covering materials of the overall device MUST be cleanable
- ASB-MAIN-002: ASB VOC detector MUST be environmentally friendly, limited amount of single-use material
- ASB-MAIN-003: ASB ICT Solution MUST be easy to maintain; self-manageable by the responsible maintenance staff
- ASB-MAIN-004: ASB ICT Solution MUST be easy to upgrade and renew
- ASB-MAIN-005: ASB VOC detector MUST require minimal or no recalibration, meaning that ASB VOC detector drift MUST be minimal. In case recalibration is needed, ASB VOC detector MUST be able to warn that the device need to go maintenance tasks to recalibrate.
- ASB-MAIN-006: ASB ICT Solution MUST provide on-line how-to manual with both a quick guide to instruction for use

- ASB-MAIN-007: ASB ICT Solution MUST be integrated in the regular support HCWs/staff routines
- ASB-MAIN-008: ASB ICT Solution data integrity MUST be guaranteed while storing and processing all the collected data by the ASB VOC detector and all the received data by the computerized systems ASB ICT Solution interoperates with
- ASB-MAIN-009: ASB ICT Solution data integrity MUST be guaranteed while exporting to/transmitting between/among all its comprised technologies and the computerized systems ASB ICT Solution interoperates with
- ASB-MAIN-010: ASB ICT Solution data integrity MUST be guaranteed while calibrating and during the maintenance tasks of the different comprised technologies
- ASB-MAIN-011: ASB ICT Solution MUST facilitate, through electronic audit-trail records, the reconstruction of the course of events relating to the creation, modification and deletion of any electronic datum, including the "who, what, when and why"
- ASB-MAIN-012: ASB ICT Solution MUST be compatible with common third party backup software packages
- ASB-MAIN-013: ASB ICT Solution maintenance guide MUST be provided and it MUST include backup and recovery instructions

Life Cycle: Disposal - Non-functional requirements

- ASB-DISP-001: ASB VOC detector MUST use existing disposal routes

NICE TO HAVE Requirements

Life Cycle: Use

Non-functional

Performance requirements:

- ASB-PERF-002a: ASB ICT Solution COULD detect the Toxins A and B, and Binary toxin (transferase) produced by *Clostridium difficile* in the contaminations/colonisations of fomites and inanimate hospital environment from *Clostridium difficile*
- ASB-PERF-002b: ASB ICT Solution COULD detect antibiotic resistances (carbapenem & ESBL production) in the contaminations/colonisations of fomites and inanimate hospital environment from *Klebsiella pneumoniae* and/or *Acinetobacter baumannii*
- ASB-PERF-002c: ASB ICT Solution COULD detect the contaminations/colonisations of fomites and inanimate hospital environment from MRSA

- ASB-PERF-002d: ASB ICT Solution COULD detect the contaminations/colonisations of fomites and inanimate hospital environment from any additional Gram-negative pathogen or any additional resistance
- ASB-PERF-002e: ASB ICT Solution COULD detect nucleic acid-based detection of the target microorganisms using non-invasive sampling

3.6 Use Case scenarios

USE CASE SCENARIO - Clostridium difficile

Nowadays: *A 74-year old patient is admitted at the internal medicine's unit from the ICU with severe community-associated pneumonia to a room shared with another patient. Empirical antibiotic treatment starts with ceftriaxone and levofloxacin during 48h. On the 3rd day, due to the absence of behavioural diagnosis, ceftriaxone is suspended and the patient ends antibiotic treatment with 7 days of levofloxacin. On the 8th day of admission, the patient presents diarrhea (more than 3 stool depositions per day) with resurging of fever and abdominal pain. Stool samples are used to identify the presence of GDH and toxins A and B of* ***Clostridium difficile (within 2-4 hours' time interval)****. On the 9th day, antibiotic treatment with oral vancomycin is initiated after laboratorial analysis reveals the presence of a toxigenic strain. The symptoms disappear in 48h and, on the 11th day, the patient is released. After being released, terminal cleaning of the room is done.*

Future 1: *A 74-year old patient is admitted at the internal medicine's unit from the ICU with severe community-associated pneumonia to a room shared with another patient. In that same room, prior to the arrival of the new patient, the ASB determines the environmental absence of the microorganisms it detects. Empirical antibiotic treatment of the patient with pneumonia starts with ceftriaxone and levofloxacin during 48h. On the 1st day of admission, detection of* ***Clostridium difficile*** *by ASB's detector determines the presence of this microorganism in the pneumonia patient with no environmental spread (suggesting a community-acquired microorganism). On the same 1st day, stool samples are used to readily identify the presence of GDH and toxins A and B of* ***Clostridium difficile*** *(the decision to start antibiotic treatment is based upon medical evaluation) and isolation measures are taken based on the results of the laboratorial analysis. The results come out positive for a toxigenic C. diff strain. Isolation measures are implemented and healthcare practitioners in contact with said room incur on their self-cleaning practices. The early detection and the isolation measures prevent cross infection of the other patient sharing a room with a carrier of a toxigenic C. difficile. In case the patient with toxigenic C. diff. develops CDI (due to presence of spores or the microorganism outside of the ASB detection radius via vectors that interact with the patient), the appropriate antibiotic treatment will be quickly administered. Cleaning measures are taken upon release of the patient. Due to the early detection, isolation and cleaning measures, and environmental constant control, the risk of cross infection and spread is null.*

Future 2: *A 74-year old patient is admitted at the internal medicine's unit from the ICU with severe community-associated pneumonia to a room shared with another patient.*

In that same room, prior to the arrival of the new patient, the ASB determines the environmental presence of the microorganisms it detects*. On the same day, room samples are used to readily identify the presence of GDH and toxins A and B of* ***Clostridium difficile*** *and cleaning measures are taken based on the results of the laboratorial analysis. The results come out positive for a toxigenic C. diff. strain. Cleaning measures are implemented and healthcare practitioners in contact with said room incur on their self-cleaning practices. ASB is used to detect the presence of C. diff. from all patients and healthcare practitioners in this unit. An anal swab is only performed in patients with an ASB positive result. The early detection and the cleaning measures prevent cross infection of the patients being admitted to this room and unit. Due to the early detection, isolation and cleaning measures, and environmental constant control, the risk of cross infection and spread is null.*

Future 3: *A 74-year old patient is admitted at the internal medicine's unit from the ICU with severe community-associated pneumonia to a room shared with another patient. In that same room, prior to the arrival of the new patient, the ASB determines the environmental absence of the microorganisms it detects. Empirical antibiotic treatment of the patient with pneumonia starts with ceftriaxone and levofloxacin during 48h.* ***On the 4th day of admission, detection of Clostridium difficile by ASB's detector determines the presence of this microorganism in the pneumonia patient with no environmental spread, suggesting a hospital-acquired microorganism****. On the same day, stool samples are used to readily identify the presence of an infectious* ***Clostridium difficile*** *strain (the decision to start antibiotic treatment is based upon medical evaluation) and isolation measures are taken based on the results of the laboratorial analysis. The results come out positive for such a C. diff. strain. Isolation measures are implemented and healthcare practitioners in contact with said room incur on their self-cleaning practices. The early detection and the isolation measures prevent cross infection of the other patient sharing a room with a C. difficile carrier. Due to the early detection, isolation and cleaning measures, and environmental constant control, the risk of cross infection and spread is null.*

USE CASE SCENARIO - Klebsiella pneumoniae

Nowadays: *A 68-year old patient is admitted at a hospital for a scheduled colon hemicolectomy due to a detected neoplasm. The surgery happens on May 20th, 2018. As surgical prophylaxis, the patient is prescribed ceftin and metronidazole. A urinary probe is introduced during the surgical procedure. Two days after the surgical procedure, the patient presents fever and suppuration on the surgical opening. The patient is diagnosed with suture unstitching and goes through another surgical intervention. Piperacillin-tazobactam is prescribed to the patient for a duration of 7 days. The surgical cultures show that the gut microbiota enterobacteria present no*

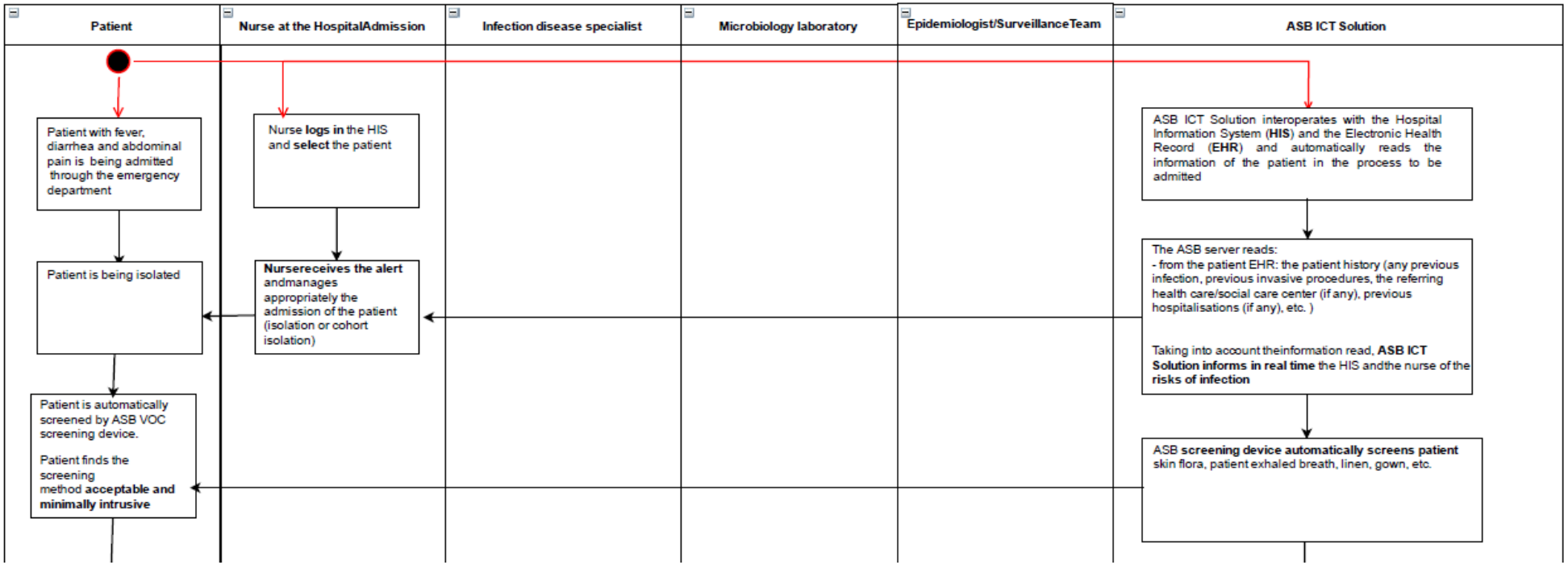
multi-resistance mechanisms. 18 days after the patient's admission, fever and urinary infection related to the urinary probe are diagnosed. Empirical antibiotic treatment with ceftazidime and amikacin is initiated. 18 hours after this diagnosis, the microbiology laboratory informs of a Gram-negative bacterial growth in the hemoculture. 36 hours later, ***Klebsiella pneumonia*** *with KPC production is detected in this patient. An anal swab is collected from all patients admitted to the same unit as this patient and two patients are found to be carriers.*

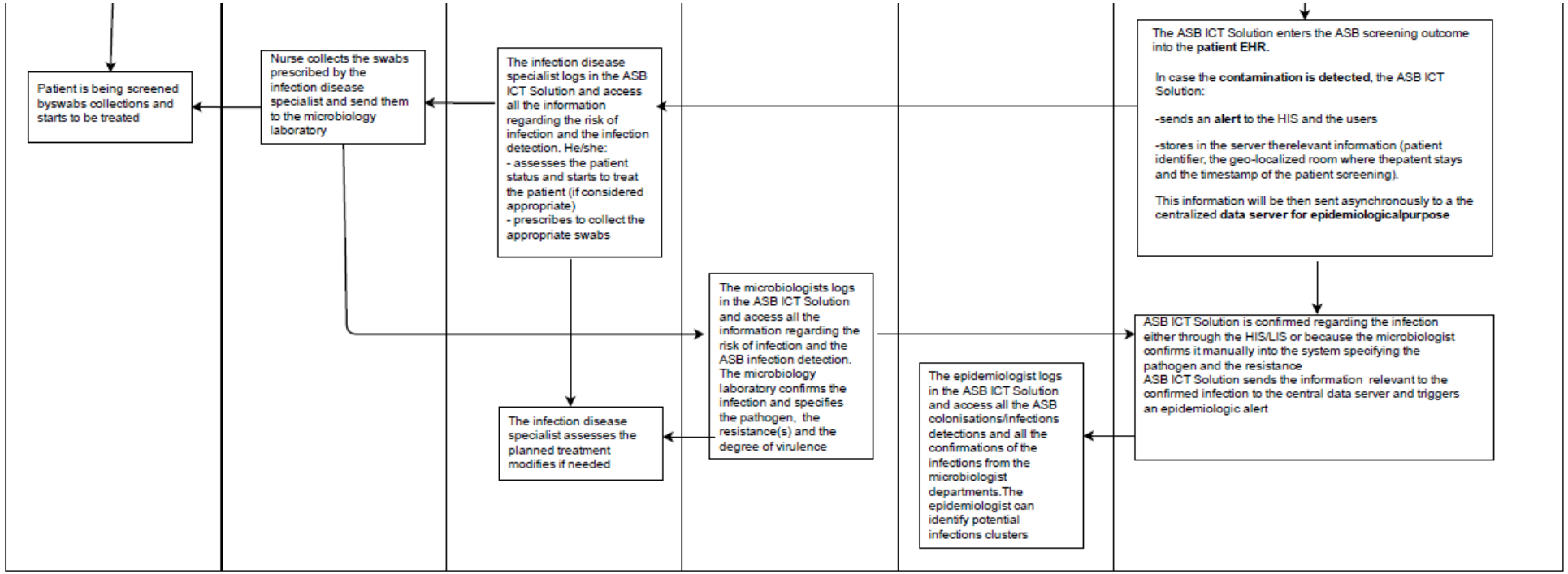
Future: *A 68-year old patient is admitted at a hospital for a scheduled colon hemicolectomy due to a detected neoplasm. In that same room, prior to the arrival of the new patient, the ASB determines the environmental absence of the microorganisms it detects. The ASB technology detects the presence of* ***Klebsiella pneumonia*** *in the admitted patient with no environmental spread. Healthcare practitioners in contact with said room and patient incur on their self-cleaning practices. This patient's samples are gathered in order to verify possible resistances in the microbiology laboratory (other patients are only tested for resistances in case there is a positive ASB response). 36 hours later,* ***Klebsiella pneumonia*** *with KPC production is detected in the admitted patient. Isolation measures are implemented and healthcare practitioners in contact with said room incur on their self-cleaning practices. KPC appropriate prophylaxis antibiotic treatment is immediately started for a resistant form of* ***Klebsiella pneumonia*** *identified via laboratory after the earlier detection of the presence of the microorganism in the patient by the ASB. The surgery happens on May 20th, 2018. As surgical prophylaxis, the patient is prescribed ceftin and metronidazole. A urinary probe is introduced during the surgical procedure. The ASB-related prophylaxis prevents Klebsiella pneumonia-related surgical infection complications. The patient is diagnosed with suture unstitching and goes through another surgical intervention. Antibiotic treatment is prescribed according with previous isolates. The surgical cultures show that the gut microbiota enterobacteria present no multi-resistance mechanisms, meaning that both prophylaxes were successful. ASB is used to detect the presence of Klebsiella pneumoniae in that same unit. A focused anal swab routine is performed in the patients with an ASB positive result, rather than in all the patients that were present in that unit.*

** ASB: ANTI-SUPERBUGS*

3.7 Example of one clinical workflow

Phase: Admission
ASB ICT Solution Screening device Goal: either discard or confirm whether the patient is a fomite or not
Analysed sample: Patient exhaled breath, skin flora and surfaces in contact with the patient (e.g. as linen or gowns)




Patient is being screened byswabs collections and starts to be treated
Nurse collects the swabs prescribed by the infection disease specialist and send them to the microbiology laboratory
The infection disease specialist logs in the ASB ICT Solution and access all the information regarding the risk of infection and the infection detection. He/she:
- assesses the patient status and starts to treat the patient (if considered appropriate)
- prescribes to collect the appropriate swabs
The ASB ICT Solution enters the ASB screening outcome into the patient EHR.
In case the contamination is detected, the ASB ICT Solution:
-sends an alert to the HIS and the users
-stores in the server therelevant information (patient identifier, the geo-localized room where thepatent stays and the timestamp of the patient screening).
This information will be then sent asynchronously to a the centralized data server for epidemiologicalpurpose
The microbiologists logs in the ASB ICT Solution and access all the information regarding the risk of infection and the ASB infection detection. The microbiology laboratory confirms the infection and specifies the pathogen, the resistance(s) and the degree of virulence
ASB ICT Solution is confirmed regarding the infection either through the HIS/LIS or because the microbiologist confirms it manually into the system specifying the pathogen and the resistance
ASB ICT Solution sends the information relevant to the confirmed infection to the central data server and triggers an epidemiologic alert
The infection disease specialist assesses the planned treatment modifies if needed
The epidemiologist logs in the ASB ICT Solution and access all the ASB colonisations/infections detections and all the confirmations of the infections from the microbiologist departments.The epidemiologist can identify potential infections clusters

3.8 Key Performance of indicators

Committed Technical/performance Indicators* (assessed through automatic formulas)

- ASB-INDI-001: Minimum turn-around time of test (task time) *(in seconds)*[1]
- ASB-INDI-002: Maximum relative sensitivity *(%)*[2]
- ASB-INDI-003: Maximum relative specificity *(%)*[3]
- ASB-INDI-004: Maximum distance of detection *(in centimetres) with more than or equal to 50% of relative accuracy* [4]
- ASB-INDI-005: Maximum relative accuracy *(%)*[5]

*No requirement is given regarding the minimums to comply with

Parameters for comparison of ASB ICT VOC detector results with microbiology laboratory/a commercial PCR/ used as reference method in a 2 × 2 error matrix contingency table.

		Microbiology laboratory/PCR	
		Positive	***Negative***
ASB ICT VOC detector	*Positive*	*TP*	*FP*
	Negative	*FN*	*TN*

TP—True positive—Positive sample correctly identified as positive.

TN—True negative—Negative sample correctly identified as negative.

FP— False positive result - Occurs when the alternative method gives a negative result without confirmation when the reference method gives a positive result. This deviation becomes a false negative result when the true result can be proved as being positive.

FN— False negative result - Occurs when the alternative method gives a positive result without confirmation when the reference method gives a negative result. This deviation becomes a false positive result when the true result can be proved as being negative.

[1] **Minimum turn-around time of test (task time)**

Turn-around time of test (task time) is defined as the number of seconds ASB VOC detector takes to identify the sample, analyse it and returns the detection result to both the user and the ASB ICT Solution

[2] **Maximum relative sensitivity**

Relative sensitivuty is defined as the ratio TP/(TP + FN) and describes the proportion of all correctly identified positive samples among all the positive samples. If no FN are detected, then it is 100%. In all other cases, this value is lower than 100%.

[3] **Maximum relative specificity**

Relative specificity is defined as the ratio TN/(TN + FP) and describes the proportion of all correctly identified negative samples among all samples. If no FP are detected, then it is 100%. In all other cases, this value is lower than 100%.

[4] **Maximum distance of detection**

Distance of detection is defined as the maximum distance in centimetres ASB VOC detector reaches its limit of detection (lowest amount of analyte that can be detected with more than or equal to 50% of relative accuracy)

[5] **Maximum relative accuracy**

Relative accuracy is defined as the ratio (TP + TN)/(TP + TN + FP + FN) and describes the proportion of all correctly identified samples among all samples. If no FN and FP are detected, then it is 100%. In all other cases, this value is lower than 100%. From the relative accuracy is also possible to determine the relative error using the formula: relative_error=1-relative_accuracy

Compliancy indicators

- ASB-INDI-006: Compliancy with the specifications and requirements for the ANTI-SUPERBUGS ICT Solution

- ASB-INDI-007: Cost-effectiveness analysis should include (*depending on whether the Buyer is able to measure them*):

  - ASB-INDI-007-001: Length of Stay of target microorganisms-infected patients
  - ASB-INDI-007-002: Period between ‘detection of target microorganisms at the patient admission’ and the ‘consultation of a medical specialist’ (infectiologist, in this case).
  - ASB-INDI-007-003: Period between 'detection of target microorganisms at the patient' to 'treatment'
  - ASB-INDI-007-004: Period between 'detection of target microorganisms at the patient' to 'treatment-adjustment'
  - ASB-INDI-007-005: Period between 'detection of target microorganisms at the patient' to 'patient discharge'
  - ASB-INDI-007-006: Time between 'detection of the target microorganisms at the patient' and 'alert message received by the HIS/LIS/electronic hygiene control systems and indication-relation control systems'
  - ASB-INDI-007-007: Number of cases due to target microorganisms-infected patients
  - ASB-INDI-007-008: Number of cases of target microorganisms-infected patients with resubmission within 28 days due to a reinfection from the target microorganism.
  - ASB-INDI-007-009: Transmission rate of target microorganisms
  - ASB-INDI-007-010: Eradication rate of target microorganisms
  - ASB-INDI-007-011: Patient prognosis due to target microorganism infection

- ASB-INDI-007-012: the structural cost of the clinical validation,
- ASB-INDI-007-013: the ASB VOC detector operating life costs and the forecasted ASB ICT Solution pricing model
- ASB-INDI-007-014: Overall cost of hospital stay per patient/day (either all units or selected depending on Phase 3 plan)
- ASB-INDI-007-015: Overall cost of hospital stay per target microorganisms-infected patient/day
- ASB-INDI-007-016: Cost of antibiotics consumption in case of target microorganisms-infected patient
- ASB-INDI-007-017: Cost of disinfecting products usage for hand hygiene
- ASB-INDI-007-018: Cost of microbiology test(s) related to current infection-surveillance practice

User Experience Indicators (assessed through questionnaires)

- ASB-INDI-008: Level of pilot sites patients' acceptability of ASB technology
- ASB-INDI-009: Level of satisfaction of pilot sites HCWs
- ASB-INDI-010: Level of satisfaction of pilot sites lab professionals
- ASB-INDI-011: Level of satisfaction of pilot sites ICT and maintenance professionals

The full methodology to evaluate tenderers' proposals and contracts compliancy across the different phases of ANTI-SUPERBUGS pre-commercial procurement procedure is described in detail in the Call for Tender.

4. LIST OF REFERENCE REGULATIONS, LEGISLATIONS AND STANDARDS

During the validation of functional requirements and indicators, different regulatory frameworks and standards were identified to be applicable to novel ANTI-SUPERBUGS solutions at a general scale.

In other terms, ***'The 'ASB' ICT solution shall comply with:'***

- ✓ EU **safety, health, and environmental protection** requirements by mean of the provision of **conformity assessment** of all the products used to build the prototypes

and to carry out the pilots to test the performance of the developed technologies (refer to: https://ec.europa.eu/growth/single-market/ce-marking/manufacturers_en)

- Specific sector legislation (e.g. new Regulations on medical devices entered into force on 25 May 2017)[17]
  - Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0745) and REGULATION (EU) 2017/746 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU **(**https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32017R0746&from=EN **)**
  - DIRECTIVE 2007/47/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32007L0047)
  - European Commission Medical Device regulation and legislation – MEDDEVs (http://ec.europa.eu/growth/sectors/medical-devices/guidance_en)
  - ISO Standards Catalogue 11.040.01 - Medical equipment in general (https://www.iso.org/ics/11.040.01/x/)

[17] EU Regulatory Framework for Medical devices
http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en

- ISO Standards Catalogue 11.100.20 - Biological evaluation of medical devices (https://www.iso.org/ics/11.100.20/x/)
- Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice (2016)

- General Product Safety Directive 2001/95/EC (GPSD): complements sector specific legislation and requires Member States to have laws with specific requirements ensuring a high level of product safety. Thus, national/regional transposed regulations shall be considered. E.g. Catalonia (Llei 22/2010 de 20 de juliol, del Codi de consum de Catalunya [18]), UK (NHS Digital Network Security Standards [19]).
- EU Products Safety Standards[20]: e.g. Healthcare engineering; Measuring technology; Electric and electronic engineering; Energy efficiency. Although defined as voluntary by the EU, but can be very relevant to prove safety of a product.
- 2016/C 272/01 Commission Notice — The 'Blue Guide' on the implementation of EU products rules 2016 (http://ec.europa.eu/DocsRoom/documents/18027/)

✓ Ethical Standards and procedure for Research:

- Nuremberg Code (1947)
- Declaration of Helsinki (1964) with all its amendments (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)
- The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (1979) (https://videocast.nih.gov/pdf/ohrp_appendix_belmont_report_vol_2.pdf)
- European Code of Conduct for Research Integrity (https://ec.europa.eu/research/participants/data/ref/h2020/other/hi/h2020-ethics_code-of-conduct_en.pdf)

[18] Catalan Regulation for Product Safety
http://consum.gencat.cat/ca/empreses/requisits-obligatoris/seguretat-del-productes/
[19] NHS Medical devices regulation and safety
(https://www.gov.uk/topic/medicinesmedicaldevicesblood/medicaldevicesregulationsafety)
[20] EU Products Safety Standards:
https://ec.europa.eu/info/business-economy-euro/product-safety-and-requirements/consumer-product-safety/standards-and-risks-specific-products_en#productsafetystandardsintheeu

- Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants (http://apps.who.int/iris/bitstream/handle/10665/44783/9789241502948_eng.pdf;jsessionid=34314927842E93FD8CAAF6F962FEFBA1?sequence=1)

- ✓ **EU General Data Protection Regulation** (Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing **Directive 95/46/EC**) (refer to: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32016R0679).
- ✓ Local/regional regulation requirements (e.g. ISO, IEC standards, IEEE norms, etc.). E.g.:
  - ISO/IEC IS 17799-1 - Information security management - Part 1: Code of practice for information security management – Standard and BS7799-2 - Information security management systems - Specification with guidance for use.
  - ISO/IEC TR 13335 – Information Technology
  - Safety mechanisms standardized by ISO / IEC / JTC1 / SC27
- ✓ Local/regional regulation requirement on the Hospital Information Systems/Electronic Health Record interoperability standards (e.g. HL7, FHIR, FHIR XML, IHE XDS, etc.): HL7 standards specifically highlighted by some procurers (HELIOS, FMT)
- ✓ Secure authentication of users implemented at Buyers' premises and to be complied by ASB ICT solutions (e.g. log on (password, smartcard, biometric, etc.), network access authentication (IPSec, remote, single sign on, etc.)

Bidders are required to identify the full list of the regulation, legislations, standards and guidance documents relevant to their offers across the different PCP phases and comply with them.

5. THE VALIDATED ASSUMPTION FOR ANTI-SUPERBUGS PCP

5.1 Business case

The uncontrolled transmission of multi-drug resistant organisms (MDROs, aka 'Superbugs') in hospitals - via patient to patient, patient to staff to patient, or patient to surface to patient -, is a major problem in healthcare systems. This cause significant morbidity, mortality and increased hospitalization and costs, as well as adversely affecting patient experience.
However, it is difficult to put a firm figure on the cost of AMR infections:

- **Antibiotics** are relatively cheap and therefore reductions in usage have a relatively low cost saving potential compared with the potential costs of untreated infection.

- The treatment of patients with AMR organisms can greatly **complicate clinical practice** with the **need to isolate** the patient and **prevent the transmission** of infection to other patients.
- AMR infection can also result in **extended hospital stays** - and therefore additional cost - and poorer outcomes for the patient. Extended length of stay (LOS) is considered the main driver of costs for HAIs.
- There is an ongoing **cost in terms of the routine monitoring** of AMR in patients and the environment and in **effectively decontaminating** the near patient environment and medical instruments.
- A hard to calculate but not to be neglected cost is the **lost income** resulting **if** it is **necessary to close a hospital ward** or ICU unit.
- **Colonisations** with MDRO can have an impact on clinical outcome and can result in **prolonged length of stay** (LOS) seeing as infections with MDROs occurred in approximately one-third of all colonized patients. [21]

The lost income due to prolonged LOS of MRDOs infected patients is the main factor used to build ANTI-SUPERBUGS business case and to highlight the opportunity. ANTI-SUPERBUGS consortium estimates that the novel technologies to be developed within the pre-commercial procurement are an opportunity to address:

- the **overall annual income loss of approximately 36 millions of Euros due to the missed admissions because the prolonged LOS and the isolation of the patients infected by the target MDROs**

ICO-VINCAT (Hospitals of the Catalan health System, SISCat)

Calculations based in data from VINCat, Catalan Health System and literature references

APPROXIMATED TOTAL INCOME LOSS RELATED TO IMPACT ON POTENTIAL ADMISSIONS LOSS DUE TO MOST RELEVANT MDROs (ICO-VINCat)	**36.408.791,25**	**€/year**

- the **annual extra costs of approximately 11 millions of Euros due to the LOS excess of the patients infected by the target MDROs**

HELIOS

(Data from 13 Helios' clinics in the North-Rhine Westphalia region, 2017)

Average Cost of patient/day	649 €		
Total costs of the no. of cases that represent a significant extension of the LOS compared to the LOS reimbursed by the insurer	No. of cases/year	Extesion of LOS (days)	**Total extra cost/ year**
Clostridium difficile	1308	3	**€ 2.546.676,00**
Klebsiella pneumoniae (ESBL & Klebsiella Aerogenes production)	356	3	**€ 462.088,00**
Acinetobacter baumanii (MDR)	50	0	
Methicillin Resistant Staphylococcus Aureus (MRSA)	6481	2	**€ 8.412.338,00**
	8195		**€ 11.421.102,00**

[21] Mutters NT, Günther F, Sertic B, Mischnik A, Frank U. Control of multidrug-resistant organisms by cross-country transfer of patients. BMC Infectious Diseases. 2015;15:466. doi:10.1186/s12879-015-1173-8

PAT (Data from input provided by procurers)

Average Cost of patient/day [a]	831,5	€	
Total costs of the no. extension of the LOS compared to average LOS/patient	No. of cases/year (2016) [b]	Extesion of LOS (days) [c]	Total extra cost/ year
Clostridium difficile	25	3	€ 62.362,29
Klebsiella pneumoniae (ESBL & carbapenemase production)	29	2	€ 48.226,84
Acinetobacter baumanii (MDR)	2	0	€ -
Methicillin Resistant Staphylococcus Aureus (MRSA)	36	2	€ 59.867,80
	Total extra cost of C.diff. & K. Pneumoniae due to increased LOS		170.456,93
	Total extra cost/ case		€ 1.852,79

5.2 *Expected impact of released and deployed ANTI-SUPERBUGS ICT Solutions on buyers' indicators*

The goal of ANTI-SUPERBUGS pre-commercial procurement procedure is to complete the research and development process up to the prototypes validation. Once ANTI-SUPERBUGS ICT Solutions will be fully productized, released, servitized and deployed, they are expected to impact the following buyers' indicators:

Impact on the Prevalence/Incidence of the 'Superbugs'

- Overall Prevalence of Nosocomial Infections (given specific time-frame)
- Prevalence of Nosocomial Infections related to target microorganisms (given specific time-frame)
- No. of patients with C. Difficile
- No. of patients with bacteraemia due to C. Difficile
  And either
  - No. of patients with K. Pneumoniae

- No. of patients with bacteraemia due to K. Pneumoniae

Or

- No. of patients with Acinetobacter baumannii
- No. of patients with bacteraemia due to Acinetobacter baumannii

Or both

And

- No. of patients with any of the additional Gram-negative pathogen or any additional resistance bidders commit to detect
- No. of patients with bacteraemia due to any of the additional Gram-negative pathogen bidders or any additional resistance commit to detect

In case of detection of antibiotic resistances

Extended-spectrum beta-lacatamase-producing Klebsiella pneumoniae (ESBL-producing K. pneumoniae)

- No. of patients with ESBL-producing *K. pneumoniae*
- No. of patients with bacteraemia due to ESBL-producing *K. Pneumoniae*
- No. of patients with bacteraemia due to *K. Pneumoniae*

Carbapenemase-producing Klebsiella pneumoniae

- No. of patients with carbapenemase-producing *K. pneumoniae*
- No. of patients with bacteraemia due to carbapenemase-producing *K. Pneumoniae*

Extended-spectrum beta-lacatamase-producing Acinetobacter baumannii (ESBL-producing Acinetobacter baumannii)

- No. of patients with ESBL-producing *Acinetobacter baumannii*
- No. of patients with bacteraemia due to ESBL-producing *Acinetobacter baumannii*
- No. of patients with bacteraemia due to *Acinetobacter baumannii*

Carbapenemase-producing Acinetobacter baumannii

- No. of patients with carbapenemase-producing *Acinetobacter baumannii*
- No. of patients with bacteraemia due to carbapenemase-producing *Acinetobacter baumannii*

MRSA (Methicillin-resistant Staphylococcus aureus):

- No. of patients with MRSA
- No. of patients with S. aureus
- No. of episodes of bacteraemia due to MRSA
- No. of episodes of bacteraemia due to S. aureus

Other epidemiological indicators

- Reproductive ratio of the infections
- Mortality rate related to Healthcare-associated infections

- Mortality rate related to healthcare-associated infections due to target microorganisms

6. THE DESCRIPTION OF THE INNOVATION GAP

Today, larger companies dominate the market of instrumentation for central bacteriological laboratories; for identification of microorganisms and detection of their (potential) resistance to antibiotics. In general, many of these instruments or systems are optimized to be used in a large laboratory and can analyse many samples in parallel. With this approach the input of man-power, and cost, can be held at a minimum. Thus, most of the technologies are therefore difficult to directly transfer into a POC solution where relatively few samples will be handled at a time by non-laboratory personnel.

In conclusion, central laboratories are well equipped for sophisticated analyses where both identity of bacteria, and their complete antibiotic resistance profile, can be characterized. However, these technologies are often dependent on initial isolation of bacterial colonies before identification/resistance determination. This procedure takes time even if the following analyses for bacterial ID and resistance profiling might be relatively fast. In addition, sending a sample for characterization in the central laboratory also adds to the total time to get results.

Current worldwide research and development effort either go after the microbial target (genotype/phenotype) or streamlining the detection methodology.

On the other hand, VOC, Volatile Organic Compounds-based diagnostics has the potential to become a screening tool for early detection of infectious agents. A fast and disseminated VOC-based diagnostics could, thus, be used for infectious disease management.
There are several alternative detection technologies for VOC available on the market today that could be applied for detection of VOC profiles from air samples. With an acquired VOC profile, it is possible to compare it to databases of known VOC profiles and thus detect presence of specific bacteria, such as C. difficile, A. baumannii, or K. pneumonia. Today, the VOC sample is normally acquired from exhaled breath or head space over a sample of blood, urine or feces.

According to the Prior Information Notice published in October 2017 at the Official Journal of the EU, on December 2017 ANTI-SUPERBUGS open market consultations started. The market consultation was carried out through four different events and the collection of structured information through a questionnaire made available on the project's web page.

The main issue detected by the participants for the development of an ASB ICT Solution was related to the sample collection. The possibility of collecting an early sample for the detection of MRDOs is the challenge that posed the most concern.

The non-invasiveness aspect of the sample collection was an additional constraint that some industrial stakeholders viewed as complex or difficult to achieve, especially depending on the types of bacteria involved.

7. ANNEX 1 – GLOSSARY

Accuracy: it represents the maximum deviation between the actual value of the physical stimulus and the value that the sensor is reporting

Audit trail: An audit trail is a process that captures details such as additions, deletions, or alterations of information in a record, either paper or electronic, without obscuring or over-writing the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its media, including the "who, what, when and why" of the action. Computer-generated audit trails shall retain the original entry and document the user ID, time/date stamp of the action, as well as a reason for the action, as required to substantiate and justify the action (WHO).

Backup: a backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (for example, in the event of a system crash or corruption of a disk). Back-up copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically over-written (WHO).

Calibration: the set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established (WHO).

Data integrity: Data integrity is the degree to which a collection of data is complete, consistent and accurate throughout the data lifecycle. The collected data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices (WHO).

Data lifecycle. A planned approach to assessing and managing risks to data in a manner commensurate with potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the process by which data is created, processed, reviewed, analysed and reported, transferred, stored and retrieved, and continuously monitored until retired (WHO).

Drift: a degradation of the sensor performance over time so that the output will vary even in the presence of the exact same stimulus. Drift is often reported as a change in the unit of measure per unit of time

Functional Requirements: Functional requirements are those requirements which deal with what the system should do or provide for users.

- Describes the behavior of the system as it relates to the system's functionality.
- Includes the description of the required functions, outlines of associated reports or online queries, and details of data to be held in the system.
- Specified by users themselves.

GUI- The graphical user interface, is a type of user interface that allows users to interact with electronic devices through graphical icons and visual indicators such as secondary notation, instead of text-based user interfaces, typed command labels or text navigation.

ICT - Information and communication technology, covers all technical means used to handle information and aid communication. This includes both computer and network hardware, as well as their software. Examples are Micro-Nanoelectronics, Smart Systems Integration, Robotics, Internet of Things, Photonics, Smart Textile, Big Data, and Artificial Intelligence.

Limit of detection Applied to qualitative microbiological tests and expressed in parts-per-million or in parts-per-billion. The lowest number of microorganisms that can be detected, but in numbers that cannot be estimated accurately.

Limit of determination Applied to quantitative microbiological tests. The lowest number of microorganisms within a defined variability that may be determined under the experimental conditions of the method under evaluation

Linearity: it represents the consistency of the sensor to translate a change in stimulus to a change in the output. An ideal sensor has a 1:1, or linear relationship, between a unit change in the stimulus to a unit change in the output signal across the entire supported range. In reality, this is not possible, and thus many sensors require designs that employ a variety of methods to correct for the typical non-linear relation of stimulus to output.

Medical device means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:
— diagnosis, prevention, monitoring, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
— investigation, replacement or modification of the anatomy or of a physiological process,
— control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

(Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices)

Non Functional Requirements: Non-functional requirements are those requirements which elaborate the performance characteristic of the system and define the constraints on how the system will do so.

- Defines the constraints, targets or control mechanisms for the new system.
- Describes how, how well or to what standard a function should be provided.
- Specified by technical peoples e.g. Architect, Technical leaders and software developers.
- They are sometimes defined in terms of metrics (something that can be measured about the system) to make them more tangible.
- Identify realistic, measurable target values for each service level.
- These include reliability, performance, service availability, responsiveness, throughput and security.

Operating Life: Sensors have a life expectancy after which their performance degrades and must be replaced.

Precision The degree of agreement among individual results (WHO).

Range: it represents the minimum and maximum physical attribute that can been detected

Reference cultures Collective term for reference strain and reference stocks.

Reference material: material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process (WHO).

Reference method: a method which has been validated as being fit for purpose, with which an alternative method may be compared.

Reference stocks: a set of separate identical cultures obtained by a single subculture from the reference strain (ISO 11133-1:2000).

Reference strains: microorganisms defined at least to the genus and species level, catalogued and described according to its characteristics and preferably stating its origin (ISO 11133-1:2000). Normally obtained from a recognized national or international collection.

Repeatability: closeness of the agreement between the results of successive measurements of the same measure and under the same conditions of measurement (adjusted from ISO).

Reproducibility: it expresses precision between laboratories (WHO)

Resolution: it represents the smallest increment of change in the stimulus that can be detected

Response Time: it represents how quickly the output signal changes in response to a change in the physical stimulus.

Robustness (or ruggedness): the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions (WHO).

Sensitivity: It represents the smallest amount of change of physical stimulus that will result in a change in the sensor output.