European wide Innovation Procurement in Health and Care

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Deliverable

D6.1: Common challenge definition and business case

WP	**6**	Future PPI - Call writing
Task	**6.1**	Common challenge definition and business case

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[1] Dissemination level: **PU**: Public; **CO**: Confidential, only for members of the consortium (including the Commission Services); **EU-RES**: Classified Information: RESTREINT UE (Commission Decision 2005/444/EC); **EU-CON**: Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC); **EU-SEC** Classified Information: SECRET UE (Commission Decision 2005/444/EC)
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Deliverable abstract

The Business case aims to present the burden imposed by the hospital-acquired lower respiratory tract infections and the expected impact that the desired innovative solutions may have in this burden, with specific focus in economic terms.

Deliverable Review

	Reviewer #1: Yves Verboven			Reviewer #2: NA		
	Answer	Comments	Type*	Answer	Comments	Type*
Is the deliverable in accordance with						
the Description of Action?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
the international State of the Art?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
Is the quality of the deliverable in a status						
that allows it to be sent to European Commission?	☒ Yes ☐ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
that needs improvement of the writing by the originator of the deliverable?	☐ Yes ☒ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a
that needs further work by the Partners responsible for the deliverable?	☐ Yes ☒ No		☐ M ☐ m ☐ a	☐ Yes ☐ No		☐ M ☐ m ☐ a

* Type of comments: M = Major comment; m = minor comment; a = advice

ABBREVIATIONS AND ACRONYMS

AMR	Antimicrobial Resistant
COPD	Chronic obstructive pulmonary disease
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
GA	Grant Agreement
HAI	Hospital-Acquired Infections
LOS	Length Of Stay
MRSA	Methicillin-Resistant Staphylococcus Aureus
NIMV	Non-invasive mechanical ventilation
PO	Procurement Organisation
PCP	Pre-Commercial Procurement of Innovation
PPI	Public Procurement of Innovation
VAP	Ventilator-Associated Pneumonia
WP	Work Package

Table of Content

1. Executive Summary

A 'business case is an argument, usually documented, that is intended to convince a decision maker to approve some kind of financial, economic or social action to articulate a clear path to an attractive return on investment (ROI) in either financial or social benefit terms, or preferably both' (extract from INSPIRE Project, 'D3.1 Economic Determinants of PCP'; GA: 611714).

This document aims to present the potential impact that a rapid diagnosis tool, composed of innovative solutions and technologies to be procured for antibiotic stewardship of Ventilator Associated Pneumonia (VAP), could represent for the cross-border Buyer's Group and at an overall scale. Several fields are considered in order to provide a comprehensive overview (i.e. clinical pathway and operational framework to be addressed within the health care systems, economic dimension).

From the economic perspective, estimated figures are provided in order to exemplify the burden that HAIs and AMR impose on institution (hospitals), patients and society, as well as the potential benefits of the incorporation of rapid diagnostic test to innovate the care delivery and management for ventilated patients at the ICU. The main burden and expenditure is driven due to the complications, including toxicity of antibiotic treatment, time to recovery and the excess time in ICU and hospital stay. In addition, there is a indirect consequence due to the build up of anti microbial resistance.

Lastly, important potential boundaries to adopt the solutions are considered, along with an exercise of risk identification and management.

2. Introduction

According to the deliverable *D4.2 Final Procurement Demands*, appropriate antibiotic therapy needs to be based on the pharmacokinetics and -dynamics, adequate dosages with enough penetration in lung tissue and adapted to local antibiotic susceptibility profile [1]. It is also recommended that the de-escalation of therapy start as soon as the patient is stable and/or microbiology data are available. Both European and USA guidelines prefer to treat a patient for 7-8 days.

Each treatment of VAP patients starts currently with empiric treatment and is continued unless low clinical susceptibility or negative culture. This treatment should be based on the local pathogens presents, antibiotic resistance pattern, risk factors of the patient and the type of care.

Clinical decision tree

Based on the currently available guidelines UAntwerp defined two clinical decision trees, focusing on diagnosis and stewardship. In these trees, UAntwerp identified several needs, such as the presence of epidemiology data and the absence of useful prognostic biomarkers. Considering the clinical symptoms, there is a lack of specificity and sensitivity; and most likely, these symptoms alone are not enough for adjusting the antibiotic treatment. Microbiology should be an important step in these decision trees, although the current techniques are slow and different methods having similar outcomes are available. It is also important to assess how the diagnosis will guide stewardship, especially to avoid overuse of antibiotics.

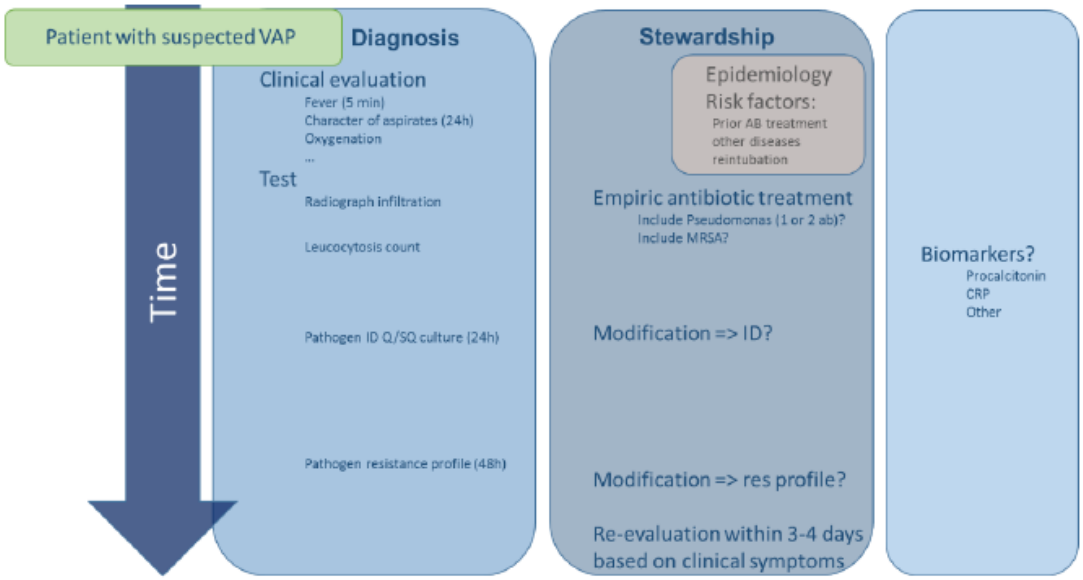

Figure 1. Current clinical decision tree for VAP

After the literature review, it has been defined a new clinical decision tree, where a rapid diagnostic test will improve the clinical diagnostic pathway of VAP (Figure 2). The diagnostic test will have an important impact on the decision tree where the pathogen identification and resistance profile will be determined sooner compared to the current clinical decision tree. This data was presented during a break out session in the kick-off meeting in Brussels; all partners provided their input on this topic.

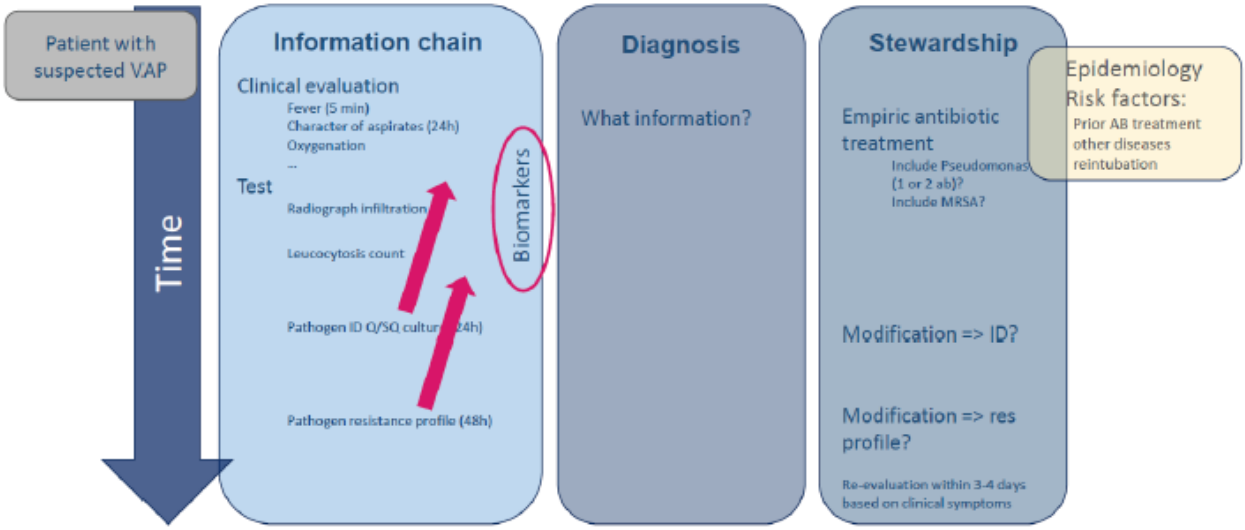

Figure 2. New clinical decision tree for VAP

To define the ideal and minimum acceptable product specifications for rapid diagnostic tests the two algorithms were being considered. The first algorithm focuses on antibiotic stewardship of VAP by early detection of the presence of pathogens and their antibiotic resistance/susceptibility patterns. Such early detection might allow to alter treatment or de-escalation strategies and can thus impact on mortality and morbidity rates, the length of stay and overall costs and reduce the development of antibiotic resistance. The second algorithm considers a diagnostic test that would allow prevention strategies, reduce pathogen transmission and avoid VAP infections. These strategies were presented during a meeting in Antwerp with the WP4 partners (12/2/2019).

When comparing the importance of the specification between the two pathways, the detection of colonization was scored with lower importance compared to the stewardship pathway. Given this fact, **stewardship pathway was selected as the procurement objective in rapid diagnostics field.**

Stewardship pathway

It has been witnessed the emergence of new diagnostic tools over the last few years that might allow to promptly initiate antibiotic therapy or rapid de-escalation after the initial dose. These diagnostic tools are capable of guiding antibiotic treatment, particularly in the case of broad-spectrum antibiotics in Intensive Care Units. Current recommendations for management of VAP in patients at risk of multi-drug resistant pathogens call for prompt broad-spectrum empirical treatment, including dual Gram-negative coverage. This recommendation is supported by consistent findings that delayed appropriate antibiotic therapy in multi-drug resistant pneumonia is associated with increased mortality. However, the definition of "patients at risk for multi-drug resistant pathogens" is very broad and results in massive overtreatment with broad-spectrum antibiotics. Kett et al showed that adherence to empirical treatment of these patients was associated with increased mortality [2]. A potential explanation for this increased mortality was the antibiotic-specific toxic effects of colistin, aminoglycosides and fluoroquinolones. ATS-IDSA guidelines recommend that the broad-spectrum empirical treatment is de-escalated when possible, based on clinical response and microbiological data. The goal of de-escalation is to limit the emergence of resistance and to reduce costly complications including mortality.

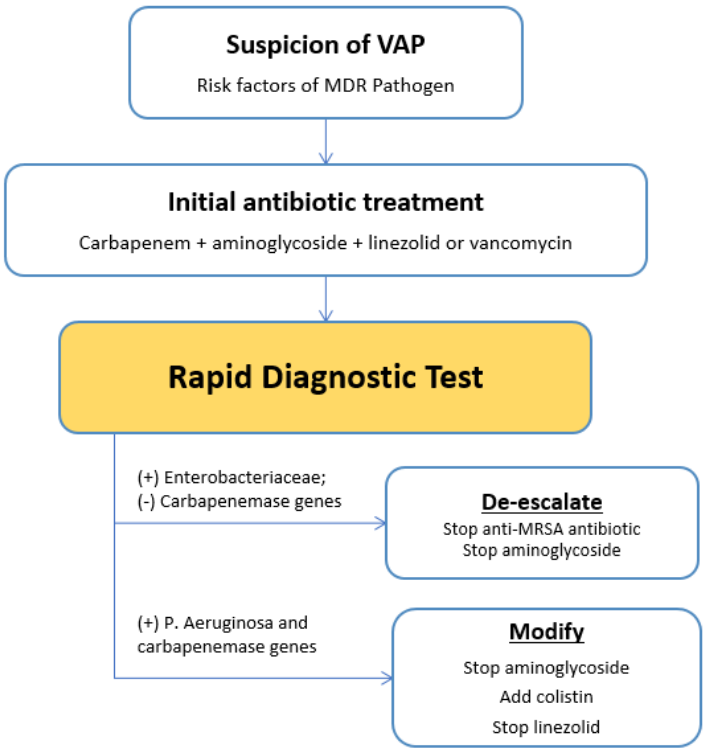

Figure 3. An example of an stewardship aproach algorithm

Based on the conclusions from the deliverable D4.2 on WP4 and the results obtained in the two OMC conclusions on WP5, a set of Key Functional Requirements were defined in the deliverable *D6.2 Functionalities and technical prescriptions*

The solution should comply with nine Rapid Diagnosis Key Functional Requirements (RDKFR) that will be described in a potential tender specification's sheet. As mentioned previously, procurement organisations will be responsible to determine whether these requirements end up being considered as key functional requirements that the solution MUST HAVE and/or would be OF ADDED VALUE TO HAVE. In case first scenario is contemplated, the presented requirements will be considered as Knock-Out (KO) criteria, meaning that if any presented offer that does not respect them, will be automatically excluded. In case the minimum is reached, it will be scored based on both a value function.

In the second scenario (OF ADDED VALUE TO HAVE), the fact that the solution does not meet the requirements will have an impact on the scoring, but not on the exclusion of the offer.

From the Adapted MEAT VBP Framework to Rapid Diagnosis, all defined RDKFR will have a direct impact on both patients and health care professionals (HCPs) and healthcare delivery. However, they will also lead to outcomes that can have an effect at a hospital level as well as on the affordability and at a socio-economic level. As observed in the next section, the business case of EURIPHI-CSA on Rapid diagnosis tool for antibiotic stewardship of VAP wants to satisfy both definitions putting emphasis on both the financial and social benefits that the future Buyers' Group aim to achieve.

3. Objectives

According to EU FP7 funded project INSPIRE (GA: 611714) a 'business case is an argument, usually documented, that is intended to convince a decision maker to approve some kind of action (…) has to articulate a clear path to an attractive return on investment (ROI) in either financial or social benefit terms, or preferably both' (extract from INSPIRE 'D3.1 Economic Determinants of PCP') and 'a business case should clearly articulate the current situation and an extrapolation of the current situation, e.g. 5 years into the future. This gives the 'do nothing' baseline against which the envisaged future (achieved by introducing the solution into the care delivery and management through PCP or PPI procedures) can be compared' (extract from INSPIRE the '*D2.4 Toolkit*').

The **business case** of EURIPHI-CSA on Rapid diagnosis tool for antibiotic stewardship of VAP wants to satisfy both definitions putting emphasis on both the financial and social benefits that the future Buyers' Group aim to achieve. To this end, it aims to provide:

- **The Problem statement from a Societal-Economic Perspective and Cost-of-Care Estimation**: quantification of the cost in part of or the full care pathway in the management of VAP (over a defined period and within a defined geographical area) of delaying or not proceeding with the intended investment, extrapolating the future based on predictive data and/or model based analysis

- **Opportunities of areas to impact and Specific Needs - Value analysis**: Identification of improvements in safe, high quality care resulting in improved quality of life and benefits valued in line with the values put forward by health authorities, institution and health care professionals. The Value analysis will also assess the cost drivers in the care delivery and the economic value to be obtained.

- **Risk-Uncertainly identification and management**: assessment of the expected risks to which the innovative care delivery will be exposed through needed investment and transformative changes and outline a plan to manage these uncertainties and risks.

4. EURIPHI Problem Statement using a Societal-Economic Perspective

Multi-Drug Resistant Organisms (MDROs)

The uncontrolled transmission of multi-drug resistant organisms (MDROs) in hospitals - via patient to patient, patient to staff to patient, or patient to surface to patient -, is a major problem in health care systems. This cause significant morbidity, mortality and increased hospitalization and costs, as well as adversely affecting patient experience.

The prevalence of hospital-acquired infections by either viral, bacterial, and fungal pathogens in Europe is around 7.1%, with more than 4 million patients affected by approximately 4.5 million episodes of per year. These entail an **additional 16 million days of hospital stay and 37,000 attributable deaths**. According to reports issued by the WHO and the European Centre for Disease Prevention and Control (ECDC), the four main infections due to multi-drug resistant bacteria **cost approximately 7 billion euros a year in Europe**, taking into account only the costs direct. In US hospitals, the overall annual direct medical costs of HAIs ranges from $28.4 to $45 billion (depending on cost adjustments)[4].

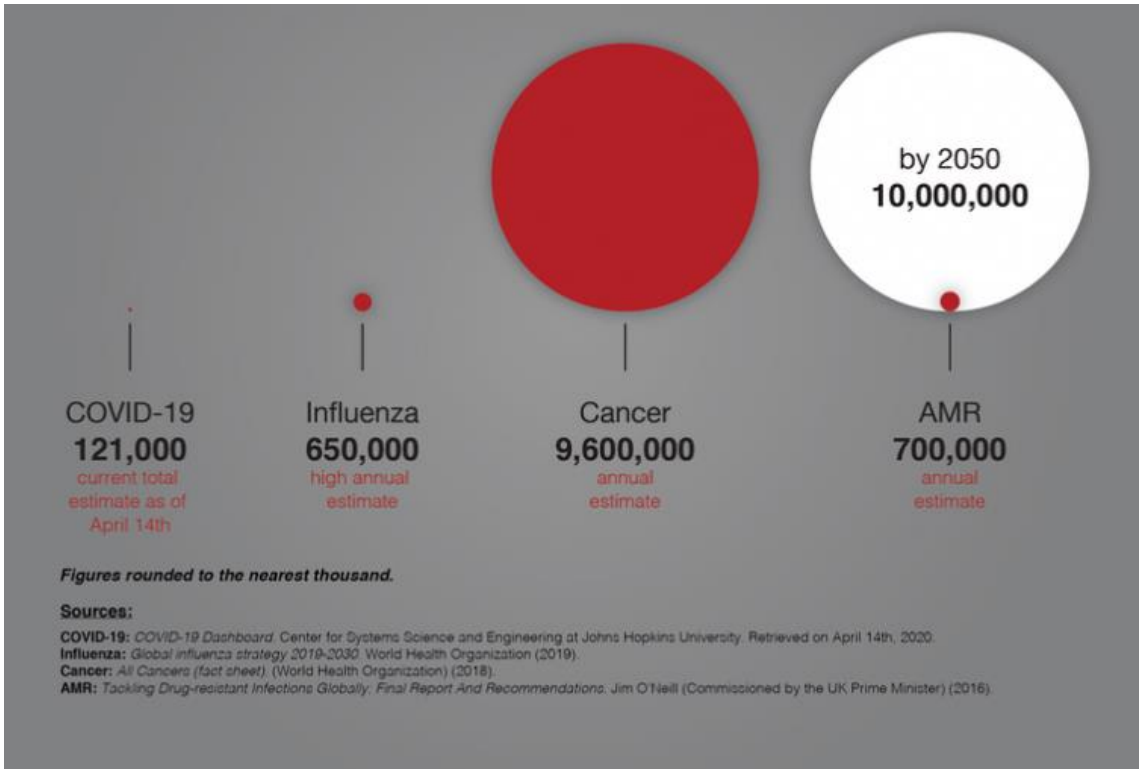

Figure 4. Global deaths caused by COVID-10, Influenza, and cancer compared to the projected deaths attributable to antimicrobial resistance

When considering the **burden of main HAIs** (i.e. ventilated-associated pneumonia (VAP), healthcare-associated pneumonia (HAP), urinary tract infection (HA UTI), surgical site infection (SSI), Clostridium difficile infection (HA CDI), and primary bloodstream infection (BSI)), literature reports that the more

[4] R. Douglas Scott II; The Direct Medical costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention; ECDC report; 2009.

than 2.5 million cases of HAI occurring in the European Union and European Economic Area (EU/EEA) each year, correspond to **approximately 2.5 million disability-adjusted life years (DALYs)**[5].
The same study that estimates 2,609,911 new cases of HAI every year in the EU/EEA, has a cumulative burden of the main **HAIs estimated at 501 DALYs per 100,000 general population**. HAP and primary BSI were associated with the highest burden and represented more than 60% of the total burden - because of their high severity -, with 169 and 145 DALYs per 100,000 total population, respectively. HA UTI, SSI, HA CDI, and HA primary BSI ranked as the third to sixth syndromes in terms of burden of disease. The **cumulative burden of the main HAIs was higher than the total burden of all other 32 communicable diseases** included in the Burden of Communicable Diseases in Europe (BCoDE) 2009-2013 study.

In turn, the worldwide pressing problem of antimicrobial resistance (AMR) is responsible for 25,000 deaths and **a loss of €1.5 billion in extra costs every year in the EU alone**. Wide-reaching, 10 million deaths per year are projected between 2015 and 2050 and expected cumulative losses in OECD countries due to AMR will be **2.59 trillion € by 2050, if current infection and resistance trends are not reversed**.[6].

Economic burden related to AMR is referred to costs primarily due to the increase in hospital LOS, additional discharge costs to facilities, extra medical care needed and productivity loss. According to literature reviewed, these factors present a high variability. The table below, published by WHO (2014), summarizes some of the ranges of this burden.

Country	Additional Costs	Additional Hospital LOS
USA[60,61,62,63,64,65,66]	US$ 10 276 – 50 896/patient	4.3 – 16 days/patient
Spain[67,68,69]	€1 205.75 – 5 614/patient	2 – 29 days/patient
Europe9,[70]	€1.5 billion total (societal cost)	2.5 million days total

Figure 5. Summary of economic ranges related to AMR (WHO, 2014)

As reported by the ECDC, due to the huge economic benefits of avoiding infections, **screening, isolation and/or decolonisation strategies are likely to be cost-effective**. In general, the results of the evaluations reviewed by the ECDC for the report suggested that screening upon admission to hospital followed by isolation/decolonisation is cost effective[7].

Ventilator-Associated Pneumonia (VAP)

Ventilator-associated pneumonia (VAP) is the second most common health care-associated infections (HAI) in the United States and is responsible for 25–42% of all infections that occur in intensive care units (ICUs). Among those patients requiring mechanical ventilation, mortality rates are 46% in patients with VAP. [6][7][8] Patients with VAP have significantly increases the length of hospital stay and thus healthcare costs.

[5] Cassini et al. Burden of Six Healthcare-Associated Infections on European Population Health: Estimating Incidence-Based Disability-Adjusted Life Years through a Population Prevalence-Based Modelling Study. PLoS Med 13(10): e1002150. doi:10.1371/journal. pmed.1002150

[6] EU factsheet 'AMR: A major European and Global challenge' https://ec.europa.eu/health/amr/antimicrobial-resistance_en

[7] *European Centre for Disease Prevention and Control. Economic evaluations of interventions to prevent healthcare - associated infections.Stockholm: ECDC; 2017.*

Ventilator-associated pneumonia (VAP) is the leading cause of nosocomial infection in intensive care unit (ICU) patients. While the international nosocomial infection control consortium (INICC) data suggests that the incidence of VAP is as high as 13.6/1000 mechanical ventilator (MV) days [9], the occurrence of VAP in Asian countries is much higher and ranges from 3.5 to 46 infections/1000 MV days [10]. In US hospitals, VAP is the second most costly nosocomial infection **at $40,144 (95% CI, $36,286—44,220)** [11]. Similarly, in developing countries, the total costs attributed to patients with VAP infections are nearly five-fold higher than those of other patients [12]

Among the various causative factors of VAP, Klebsiella pneumoniae (Kp) is one of the most common gram-negative bacteria that causes hospital infections, especially several notoriously fatal infections. [13]

The **Spanish Society Of Intensive Medicine Criticism And Coronary Units (SEMICYUC)** recently published a national surveillance study of nosocomial infection in services of intensive medicine[8]., where 27,514 patients under surveillance had been admitted to the ICU from 185 hospitals participants in the study (April 1st to June 30th, 2018). Relevant results on VAP are included below and on Annex I.

	Incidence Rate
Number of VAP X 100 / total ICU acquired infections..... *497 x 100 / 1.631= 30,47% infections per 100 patients*	**30,47%**
Number of VAP X 100 / total ICU patients ..... *497 x 100 / 27.514 = 1,81 infections per 100 patients*	**1,81%**
Number of VAP X 100 / total patients with mechanical ventilation..... *497 x 100 / 11.259 = 4,41 Infections per every 100 ventilated patients*	**4,41%**
Number of VAP X 1000 / total stays (monthly factor table)..... *497 x 1000 / 191.429 = 2,60 Infections per thousand days of stay*	**2,60‰**
Number of VAP X 1000 / total days with mechanical ventilation..... *497 x 1000 / 84.626 = 5,87 Infections per thousand days of mechanical ventilation*	**5,87‰**
Utilization ratio (days of mechanical ventilation / total stays)..... *84.626 x 1000 / 191.429 = 0,44*	**0,44**

5. Assessment of current costs and potential benefits

According to EU FP7 funded project INSPIRE (GA: 611714) a '***business case is an argument, usually documented, that is intended to convince a decision maker to approve some kind of action (…) has to articulate a clear path to an attractive return on investment (ROI) in either financial or social benefit terms, or preferably both***' (extract from INSPIRE 'D3.1 Economic Determinants of PCP') and 'a business case should clearly articulate the current situation and an extrapolation of the current situation, e.g. 5 years into the future. This gives the 'do nothing' baseline against which the envisaged future (achieved by enacting the PCP or PPI) can be compared' (extract from INSPIRE the '*D2.4 Toolkit*').

[8] http://hws.vhebron.net/envin-helics/Help/Informe%20ENVIN-UCI%202018.pdf

Assessment of current costs and dimension of the problem. Potential benefits.

High economic burden of HAIs can be referred to increased co-morbidity and mortality resulting in prolonged hospital **length of stay (LOS) as the main cost driver**.[9] Even in some specific MDROs pathogens, colonization can have an impact on clinical outcome that can also result in prolonged LOS.[10]

Other cost sources to consider could be diagnose and treatment complexity (cost of broad spectrum antibiotics *vs.* cost of reserved antibiotics), screening hygiene and isolation procedures, re-admission costs, reduction of hospital operational capacity and patient and staff indirect costs (e.g. productivity loss). Impact on hospital revenues will be conditional upon the payment methods defined by the insurer (i.e. payment per discharge; payment related to results vs. re-admission; payment per procedure; payment per day/patient; etc.).

Lastly, the Adapted MEAT-VBP Framework to Rapid Diagnosis developed in WP2, can also be applied as a tool to the complement the identification of the (most) relevant expenditure elements/levers regarding the costs-elements of the business case.

A report published in 2015 by **VINCat**[11] (ICO) in collaboration with AQuAS, aimed to assess the economic impact of main nosocomial infection in Catalonia. Results estimated that in 2013, the potential cost of the five most important nosocomial infections was in excess of € 30 million (Table 7) for the Catalan Health System. Among them, the ones with greater costs were the central line-associated bloodstream infections (CLABSI) and the Surgical Site infections (SSI) related to colorectal interventions (12.709.289 € and 8.869.939 €, respectively). The third highest cost infection would be the **Ventilation-Associated Pneumonia (VAP), with a cost of 5.389.455€.**

A further study by VINCat[12], assessing the impact of HAIs in patients that underwent a colo-rectal surgery, estimated that **the average length of stay was 3 fold higher in patients with infection**.

[9] Hübner, C., Flessa, S. (2016), Reimbursement for Hospital-acquired Infections with Multidrug Resistant Organisms in German DRG System, Economics and Sociology, Vol. 9, No 3, pp. 111-118. DOI: 10.14254/2071-789X.2016/9-3/10

[10] Mutters, N. T., Günther, F., Sander, A., Mischnik, A., & Frank, U. (2015). Influx of multidrug-resistant organisms by country-to-country transfer of patients. *BMC Infectious Diseases*, *15*, 466. http://doi.org/10.1186/s12879-015-1173-8

[11] Gudiol F, Limón E, Pujol M, Almirante B, Freixas N, Valles J, Lopez-Contreras Gonzalez J. Estimació econòmica dels costos derivats de les infeccions nosocomials a Catalunya (Programa VINCat), número 14. Barcelona: Agència de Qualitat i Avaluació Sanitàries de Catalunya. Departament de Salut. Generalitat de Catalunya; 2015.

[12] Shaw et al.: 'Cost of organ/space infection in elective colorectal surgery. Is it just a problem of rates?' Antimicrobial Resistance and Infection Control 2015 4(Suppl 1):P77.

Estimació dels costos derivats de cinc infeccions nosocomials

Infeccions	Nombre d'hospitals participants	Casos d'infecció 2013	Cost per infecció 2015	Cost total 2015
Bacterièmia de catèter venós central[a]	47	405	31.381 €	12.709.289 €
Pneumònia associada a ventilació mecànica[b]	29 (UCI)	196	27.497 €	5.389.455 €
ILQ de recanvi protètic total de genoll[c]	58	173	14.237 €	2.462.998 €
ILQ de recanvi protètic total de maluc[c]	57	82	14.237 €	1.167.432 €
ILQ en cirurgia colorectal[c]	61	623	14.237 €	8.869.639 €
Cost total	-	-	-	30.598.812 €

a. 45,814.00 USD 2012 = 31.381 € 2015; b. 40.144 USD 2012 = 27.497 € 2015; c. 20,785.00 USD 2012 = 14,237 € 2015.
ILQ: infecció de localització quirúrgica.

Table 1. Estimation of cot of main nosocomial infections in Catalonia (VINCat, 2015)

EURIPHI targets to reduce both the costs and the operational impact of Ventilation-Associated Pneumonia infections acquired in hospitals. EURIPHI-VAP technologies should allow procurers to improve the quality of care and the appropriateness of antimicrobial therapies related to VAP, thus reducing the LOS of the patients in their facilities.

On the basis of above premises, an estimation of economic losses imposed by VAP caused by MDROs has been performed. According to data available from VINCat, surveillance program representing over 60 hospitals of the Catalan Health System (SISCat) and with reimbursement received according to no. of hospital discharges, **opportunity-cost of inaction** was estimated. based on the different multirresistant pathogen.

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

No. of cases/year[1]	2012	2013	2014	2015	2016
Clostridium difficile	660	702	1098	1206	**1173**
ESBL K.pneumoniae					**1965**
CP K. Peumoniae					**223**
MRSA			338	304	**337**

[1] VINCAt surveillance report 2016[13]

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

Table 2 – Business case estimates for ICO (VINCat)

[13] Annual VINCat Surveillance report (2016). Available here: http://catsalut.gencat.cat/ca/proveidors-professionals/vincat/programa/infeccions-nosocomials-catalunya/

Clostridium difficile infection (CDI)		
Average Length of Stay - patient without infection [a]	6,1	days
Average Length of Stay - patient with CDI [b]	**19,75**	days
Productivity loss (Patients not admitted per case of CDI, due to extension of LOS) [c]	4,24	patients/ HAIs case
Annual CDI cases in Catalonia (2016) [d]	1.173	cases
Annual productivity loss (Approximate no. of patients "not admitted"/year) [e]	4.970,83	patients
Average payment per discharge - public insurer fees [f]	2.095,47	€
Income loss related to impact on potential admissions loss due to CDI [g]	**10.416.220,67**	**€/year**

[a] Data reported by the Catalan Health system (SISCAT, 2015)

[b] Average calculation on data reported from 106 infected patients in 2 Spanish tertiary hospitals (2015)[14]

[c] Calculation done considering the Average LOS, the extended LOS due to HAIs and that isolation of infected patients forces to have 1 patient/room instead of 2 as planned.

[d] VINCat surveillance report (2016)

[e, g] Calculation

[f] According to legislation by Catalan Government (ORDRE SLT/150/2017)[15]

ESBL K. penumoniae infection		
Average Length of Stay (patient without infection) [a]	6,1	days
Average Length of Stay patient with ESBL *K. pneumonia* infection [b]	**16,67**	days
Productivity loss (Patients "not admitted" per case of ESBL K. pneumoniae, due to extension of LOS) [c]	4,55	patients/ HAIs case
Annual ESBL K. pneumoniae cases in Catalonia (2016) [d]	1965	cases
Annual productivity loss (Approximate no. of patients "not admitted"/year) [e]	8.994,51	patients
Average payment per discharge - public insurer fees [f]	2.095,47	€
Income loss related to impact on potential admissions loss due to ESBL K. pneumoniae[g]	**19.485.466,36**	**€/year**

[a] Data reported by the Catalan Health system (SISCAT, 2015)

[b] Average from reference sources *(LIMITATION ACKNOWLEDGED: LOS data due to MRDOs as reported in literature with high variability)*:

[b.i.] Tertiary care; Nosocomial EC & KP infections (USA 2001)[16]

[14] Asensio A., Di Bella S., Lo Vecchio A. et al. The impact of *Clostridium difficile* infection on resource use and costs in hospitals in Spain and Italy: a matched cohort study. International Journal of Infectious Diseases Vol 36, July 2015, pp. 31-38 https://www.ijidonline.com/article/S1201-9712(15)00121-6/fulltext

[15] Ordre SLT/150/2017 by the Catalan Government to set up reimbursement fees for hospitals providing public service during 2017 *http://cido.diba.cat/legislacio/7160771/ordre-slt1502017-de-7-de-juliol-per-la-qual-es-determinen-per-a-lany-2017-els-preus-unitaris-per-a-la-contraprestacio-de-latencio-hospitalaria-i-especialitzada-departament-de-salut*

[16] Lautenbach E., Baldus Patel J., Bilker W.B., Et al.; Extended-Spectrum β-Lactamase-Producing Escherichia coli and Klebsiella pneumoniae: Risk Factors for Infection and Impact of Resistance on Outcomes. Clinical Infectious Diseases, Vol 32, Issue 8, 15April2001, Pp. 1162–1171, https://doi.org/10.1086/319757

[b.ii.] Tertiary care; Non-Urinary tract infection EC & KP (USA, 2006) [17]

[b.iii.] Large cohort; BSI KP & EC (Germany, 2014) [18]

[c] Calculation done considering the Average LOS, the extended LOS due to HAIs, and that isolation of infected patients forces to have 1 patient/room instead 2 as planned.

[d] VINCat surveillance report (2016)

[e, g] Calculation

[f] According to legislation by Catalan Government (ORDRE SLT/150/2017)[19]

Carbapenem-resistant (CP) K. pneumoniae		
Average Length of Stay (patient without infection) [a]	6,1	Days
Average Length of Stay patient with CP *K. pneumoniae* [b]	**17,9**	Days
Productivity loss (Patients "not admitted" per case of CP K. pnemoniae, due to extension of LOS) [c]	4,93	patients/ HAIs case
Annual cases in Catalonia (2016) [d]	223	Cases
Annual productivity loss (Approximate no. of patients "not admitted"/year) [e]	1.100,38	Patients
Average payment per discharge - public insurer fees [f]	2.095,47	€
Income loss related to impact on potential admissions loss due to CP K. pneumoniae [g]	**2.305.807,10**	**€/year**

[a] Data reported by the Catalan Health system (SISCAT, 2015)

[b] Average from reference sources:

[b.i.] Hospital BSI CP K.Pnemoniae[20]

[b.ii.] HAIS, acute care hospitals (Greece, 2017)[21]

[b.iii.] CP GNB 206 hospitals (USA,2017)[22]

[c] Calculation done considering the Average LOS and the extended LOS due to HAIs

[d] VINCat surveillance report (2016)[23]

[e, g] Calculation

[f] According to legislation by Catalan Government (ORDRE SLT/150/2017)[24]

[17] Su Young Lee, Srividya Kotapati, Joseph L. Kuti, Charles H. Nightingale. Impact of Extended-Spectrum β-Lactamase–Producing Escherichia coli and Klebsiella Species on Clinical Outcomes and Hospital Costs: A Matched Cohort Study; Vol. 27, Issue 11; Nov2006 , pp. 1226-1232; https://doi.org/10.1086/507962

[18] Leistner R, Gürntke S, Sakellariou C, et al.; Bloodstream infection due to extended-spectrum beta-lactamase (ESBL)-positive K. pneumoniae and E. coli: an analysis of the disease burden in a large cohort.; Infection. 2014 Dec;42(6):991-7. doi: 10.1007/s15010-014-0670-9. Epub 2014 Aug 7.

[19] Ordre SLT/150/2017 by the Catalan Government to set up reimbursement fees for hospitals providing public service during 2017 *http://cido.diba.cat/legislacio/7160771/ordre-slt1502017-de-7-de-juliol-per-la-qual-es-determinen-per-a-lany-2017-els-preus-unitaris-per-a-la-contraprestacio-de-latencio-hospitalaria-i-especialitzada-departament-de-salut*

[20] O. Zarkotou, S. Pournaras, P. Tselioti, et al.; Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment Clin Microbiol Infect 2011;17 : 1798–1803; 10.1111/j.1469-0691.2011.03514.x

[21] Kritsotakis, E. I., Kontopidou, F., Astrinaki, E., el al. (2017). Prevalence, incidence burden, and clinical impact of healthcare-associated infections and antimicrobial resistance: a national prevalent cohort study in acute care hospitals in Greece. *Infection and Drug Resistance*, *10*, 317–328. http://doi.org/10.2147/IDR.S147459

[22] Bin Cai, Roger Echols, Glenn Magee, Juan Camilo Arjona Ferreira; et al.; Prevalence of Carbapenem-Resistant Gram-Negative Infections in the United States Predominated by *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, *Open Forum Infectious Diseases*, Volume 4, Issue 3, 1 July 2017, ofx176, https://doi.org/10.1093/ofid/ofx176

[23] VINCat Report 2016 http://catsalut.gencat.cat/web/.content/minisite/vincat/documents/informes/Informe-2016.pdf

[24] Ordre SLT/150/2017 by the Catalan Government to set up reimbursement fees for hospitals providin públic service.during 2017 *http://cido.diba.cat/legislacio/7160771/ordre-slt1502017-de-7-de-juliol-per-la-qual-es-determinen-per-a-lany-2017-els-preus-unitaris-per-a-la-contraprestacio-de-latencio-hospitalaria-i-especialitzada-departament-de-salut*

Methicillin-Resistant Staphylococcus Aureus (MRSA)		
Average Length of Stay (patient without infection) [a]	6,1	days
Average Length of Stay patient with MRSA [b]	**16,8**	days
Productivity loss (Patients "not admitted" per case of MRSA, due to extension of LOS) [c]	4,75	patients/ HAIs case
Annual MRSA cases in Catalonia (2016) [d]	337	cases
Annual productivity loss (Approximate no. of patients "not admitted"/year [e]	1.602,13	patients
Average payment per discharge - public insurer fees [f]	2.095,47	€
Income loss related to impact on potential admissions loss due to MRSA [g]	**3.357.217,76**	**€/year**

[a] Data reported by the Catalan Health system (SISCAT, 2015)

[b] Average from reference sources:

[b.i.] Data published European review, corresponding to EU ICUs (2014)[25]

[b.ii.] EU resistance burden (BURDEN study Group) [26]

[c] Calculation done considering the Average LOS, the extended LOS due to HAIs, and that isolation of infected patients forces to have 1 patient/room instead of 2 as planned.

[d] VINCat surveillance report (2016)

[e, g] Calculation

[f] According to legislation by Catalan Government (ORDRE SLT/150/2017)[27]

As observed, from the approximately 36 millions of income loss related to impact on potential admissions loss due to most relevant MDROs by ICO-VINCat, more than the half income loss is due to ESBL K. Pneumoniae infection (53,5%), followed by Clostridium difficile infection (CDI) with a 28,6% of the total.

Methicillin-Resistant Staphylococcus Aureus (MRSA) and Carbapenem-resistant (CP) K. pneumoniae have a less impact on the income loss related to potential admissions loss, with a 9,22% and 6,33%, respectively.

[25] Chastre J. Blasi F, et al. European perspective and update on the management of nosocomial pneumonia due to methicillin-resistant Staphylococcus aureus after more than 10 years of experience with linezolid; Clinical Microbiology and Infection; Vol. 20, Supplement 4, April 2014, pp. 19-36

[26] Marlieke E. A. de Kraker, Peter G. Davey, Hajo Grundmann, on behalf of the BURDEN study group; Mortality and Hospital Stay Associated with Resistant Staphylococcus aureus and Escherichia coli Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe; PLOS Medicine;2011; https://doi.org/10.1371/journal.pmed.1001104

[27] Ordre SLT/150/2017 by the Catalan Government to set up reimbursement fees for hospitals providin públic service.during 2017 *http://cido.diba.cat/legislacio/7160771/ordre-slt1502017-de-7-de-juliol-per-la-qual-es-determinen-per-a-lany-2017-els-preus-unitaris-per-a-la-contraprestacio-de-latencio-hospitalaria-i-especialitzada-departament-de-salut*

6. Expected Areas of Impact

Impact on Workflow

The work undertaken under EURIPHI project has enabled to move from a rapid diagnostic test procurement on VAP towards management of hospital-acquired respiratory infections, where all elements along the rapid diagnosis care pathway are taken into consideration. This change of perspective will lead to better advancement and broader impact that will be described along de section. This is shown in the Pathway to Impact developed under WP4:

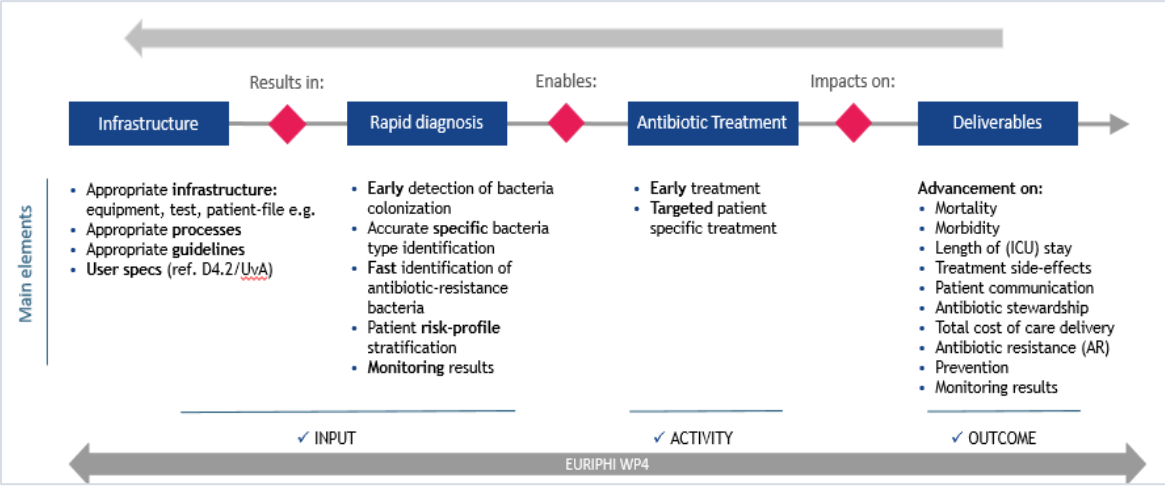

Figure 6. From a rapid diagnostic test on VAP towards management of hospital-acquired respiratory infections

The Pathway to Impact is a visual representation showing the sequence of related events (e.g., inputs, activities, outcomes, impact) that connect the need for a planned activity or set of activities with the desired outcomes and results[28]. In order to move towards management of hospital-acquired respiratory infections, appropriate facilities, as well as processes and guidelines, are need in order to respond to user needs and specifications.

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) provides medical guidance and recommendations to tackle infectious diseases at a broad level, also including the management of MDROs, HAIs and antibiotic prescription. However, ESCMID reports high variability of the application of these guidelines in the different centres and regions, thus requiring a more harmonized approach to tackle the AMR challenge at a global scale. The guidelines for infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients[14]

The current business case aims to evidence that a properly defined infrastructure will result into a faster diagnosis, enabling an **early and more accurate detection** of bacteria colonization. Consequently, healthcare professionals will effectively **monitor patient risk-profile stratification** and **detect the presence of pathogens and their antibiotic resistance/susceptibility patterns**. Such early detection might allow to alter **treatment or de-escalation** strategies and can thus **impact**

[28] https://pclive.peacecorps.gov/pclive/index.php/pclive-resources/resource-library/2325-small-grants-programme-resources-for-small-grants/file

on mortality and morbidity rates, the length of stay and overall costs and reduce the development of antibiotic resistance and their associated infections in VAP.

Consequently, taking action along the whole pathway (specially strengthening INPUT elements) will lead to relevant impact and benefits. According to Adapted MEAT VBP Framework to Rapid Diagnosis (available at Annex 1), several outcomes can be achieved at different levels:

- **Patient Level**
- **Health-care professional level**
- **Healthcare provider benefits**
- **Broader impact on society**
    - *Innovation*
    - *Sustainability*
    - *Socio-economic impact*

Impact in ESCMID basic recommendations to prevent MDR-GNB

The **European Society of Clinical Microbiology and Infectious Diseases (ESCMID)** provides medical guidance and recommendations to tackle infectious diseases at a broad level, also including the management of MDROs, HAIs and antibiotic prescription. However, ESCMID reports high variability of the application of these guidelines[29] in the different centres and regions, thus requiring a more harmonized approach to tackle the AMR challenge at a global scale. The guidelines define infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients.

The requirements depicted for the rapid diagnosis tool for antibiotic stewardship of VAP are re-examined to understand how the novel technologies will fit to increase the capacity of the WP6 partners to address the recommendations, while providing a certain degree of practice homogeneity.

The table below (Table 1) shows the expected degree of impact of the EURIPHI Technology in the operational framework; according to the initial analysis performed by AQuAS with WP6 partners. In all, the business case showcase that EURIPHI-VAP technology will also have a direct impact in the capacity of the buyers to address most of the European recommendations, which lead in a direct impact on the **management of MDROs, VAP and antibiotic prescription.**

[29] 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.

Area	EURIPHI TECHNOLOGY		
	EPIDEMIC SETTING	Can EURIPHI technology have a role in satisfying recommendation? (Yes, No, In part)	Potential impact (0 = null, 1 = low, 2 = medium, 3 = high)
Hand Hygiene	***Strong recommendation:*** Implement hand hygiene (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)	Yes	High
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)	Yes	High
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)	Yes	Medium/High
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	Medium/High
Cohort staff	***Strong recommendation:*** Cohort staff to reduce the risk of acquisition of MDR-K. pneumoniae (moderate level of evidence)	In-part	Low

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)	In-part	Low/Medium
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)	Yes	Medium
Antimicrobial Stewardship	***Strong recommendation:*** Implement an antimicrobial stewardship programme to reduce the spread of extended-spectrum β-lactamase-producing Enterobacteriaceae (moderate level of evidence)	Yes	High
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)	In-part	Medium

Table 3. Preliminary assessment of the impact of EURIPHI solutions to address ESCMID guidelines for MDR GNB

Use Case

Two use cases have been used to trigger discussions with relevant stakeholders and to provide practical scenarios of the interaction of the rapid diagnosis solutions in the clinical pathway on VAP, as well as their potential outcomes.

A first version to illustrate a potential use case for the procurement of innovative solutions has been defined by consensus within Enric Limon – Advisory Board member from VINCat (Nosocomial Infections Surveillance program from Catalunya), AQuAS and Fundació Parc Tauli:

Use Case Scenario 1 : *Clostridicoides difficile - Pseudomonas auroginosas*

Currently: A 74-year-old patient, resident in a Socio-Health Center, suffers from a respiratory infection and requires his emergency assistance. He is a chronic COPD patient and respiratory infection implies the need to be admitted in the semi-critical plant in an intensive care unit in a medium complexity hospital, from where he is discharged after 7 days. Two days later, in the Socio-health Center, he is admitted at a multipurpose ICU unit from a high complexity hospital with severe pneumonia associated with ventilation acquired in the medium complexity hospital. The intensive care unit has 8 single beds and its occupancy is 80% during the winter months.
The empirical antibiotic treatment that is administered upon arrival in the emergency room begins with amoxi-clavulance for 48 hours. On the third day, upon being informed by the microbiology laboratory of the presence of **Pseudomonas auroginosas**, amoxy-clavulanate was suspended and the patient was prescribed antibiotic treatment with 7 days of levofloxacin. On the 4th day, due to his ventilatory improvement, he is transferred to a semi-critical unit where he remained for three more days under observation before being transferred to the internal medicine hospitalization plant. The semicritic plant has 6 boxes and is always at its maximum capacity because it is used both as drainage from the intensive care unit and to keep patients with severe hemodynamic changes in other units under observation. On the eighth day of admission, already in the internal medicine unit and sharing a room with another patient, he presented diarrhea (more than 3 stools per day) with a resurgence of fever and abdominal pain. Stool samples are used to identify the presence of GDH and Clostridicoides difficile toxins A and B (within the 2-4-hour time interval). On the ninth day, treatment with oral vancomycin antibiotics is started after laboratory analysis reveals the presence of a toxigenic strain. Preventively he is isolated individually after taking samples from his roommate and that he was negative for the presence of clostridium.
The symptoms disappear in 48 hours and, on the 11th, the patient is discharged. After being discharged, the terminal cleaning of the room is carried out. From the microbiology service, the preventive medicine service is notified that three positive cases have appeared for the same toxigenic strain, two in the critical units and one in the semi-critical unit. The appearance of these three cases suggests an outbreak of clostricoides difficile due to cross dissemination, possibly due to the presence of environmental spores. Environmental controls are required in the units where cases have been detected, screening patients with symptoms and isolating patients who have tested positive. The protocol against outbreaks by clostricoides difficile is activated and the cleaning and disinfection protocol against spores is started.

Future with EURIPHI-VAP technology: A 74-year-old patient, resident in a Socio-Health Center, suffers from a respiratory infection and requires his emergency assistance. He is a chronic COPD patient and respiratory infection implies the need to be admitted in the semi-critical plant in an intensive care unit in a medium complexity hospital, from where he is discharged after 7 days. Two days later, in the Socio-health Center, he is admitted at a multipurpose ICU unit from a high complexity hospital with severe pneumonia associated with ventilation acquired in the medium complexity hospital. Upon admission, the detection of **Clostridium difficile** through the EURIPHI-VAP detector determines the presence of this microorganism in the patient with pneumonia without environmental spread.

On the same first day, stool samples are used to easily identify the presence of GDH and Clostridium difficile toxins A and B (the decision to start antibiotic treatment is based on a medical evaluation) and isolation measures are taken depending on the laboratory results. The test carried out by the early detection system in the emergency department shows the presence of **Pseudomonas aeruginosa**. The doctor has the microbiological diagnosis with the microorganism causing the respiratory infection in the first hours, in addition to having information on the presence of clostricoides, which makes him a patient at risk of transmission to other patients and therefore requires preventive isolation. The preventive service is notified to take the necessary preventive measures, it is isolated, and the receiving unit is informed that this patient is isolated. Risk factors for **P. aeruginosa** infection are recent hospitalization, institutionalization, administration of antibiotics in the previous 3 months or more than 4 times a year, FEV1 <30%, previous treatment with oral corticosteroids, the presence of bronchiectasis and the colonization or previous isolation of P. aeruginosa. These risk factors are similar to those of **Clostricoides difficile**, so having these data avoids nosocomial transmission of both pathogens and prescribed treatment is prescribed. Early detection and isolation measures prevent cross infection in other patients who share a room with a carrier of toxigenic C. difficile. In case the patient with C. diff. Toxigenic. develop CDI (due to the presence of spores or microorganisms outside the detection range of EURIPHI-VAP through vectors that interact with the patient), appropriate antibiotic treatment will be administered quickly. Cleaning measures are taken when the patient is discharged.
Due to early detection, isolation and cleaning measures, and constant environmental monitoring, the risk of cross infection and spread is nil.

Use Case Scenario 2: *Staphylococcus aureus – Klebsiella pneumoniae*

Currently: A 65-year-old male patient, with a good previous quality of life despite having the following history: HT, diastolic heart failure, COPD, benign prostatic hypertrophy.
The reason for hospital admission was a respiratory superinfection and decompensation of heart failure, for which he had to receive diuretic, hypotensive and antibiotic treatment for one week (specifically, amoxicillin-clavulamic). Subsequently, a peripherally inserted central catheter bacteremia was diagnosed by **Staphylococcus aureus**, with no complications at a distance and a transthoracic echocardiogram without notable alterations that suggested the diagnosis of endocarditis. The patient receives empirical treatment with vancomycin for 48 hours, after which he switches to cefazolin after learning about methicillin sensitivity, which he will receive until completing 14 days of treatment.
Iron deficiency anemia, secondary to intestinal losses and paroxysmal ACXFA, is also detected during admission, which will end up requiring tests and prolonging your hospital stay. After performing a colonoscopy with a biopsy of three polyps, the patient presented an acute abdomen. An abdominal CT scan detects a perforation in the transverse colon. The patient ends up entering the critical care unit, requiring vasoactive drugs and intubation. Upon admission to the ICU, colonization screening was performed for MRSA and enterobacteriaceae producing wide-spectrum beta-lactamases or carbapenemases. Both screens are negative.
The patient is intubated for 5 days. Two days after weaning, respiratory failure begins acutely. The chest X-ray shows a left basal infiltrate. The patient requires re-intubation. Bronchoalveolar lavage and blood cultures are collected and antibiotic treatment with meropenem and linezolid is started.
After 72 hours, from microbiology we are informed of the growth of a Gram-negative bacillus in blood cultures and bronchoaspirate identified as a K pneumoniae. Treatment with meropenem is maintained, since the evolution is being favorable, although the patient continues febricular. The next day, we are informed of the production of carbapenemases and probably of extended spectrum beta-lactamases (ESBLs). They want to confirm the result, which will require replanting the samples. Antibiotherapy is changed to ceftazidime-avibactam. Finally, the microbiological diagnosis of ESBL and KPC-producing Klebsiella pneumoniae is confirmed and treatment is maintained.
Meanwhile, the rest of the patients admitted to the unit are screened using a rectal smear and respiratory samples. In total 20 patients, among whom a patient colonized by K pneumoniae is detected, in this case, by a non-beta-lactamase-producing strain. 35 surface samples are also obtained, in which K pneumoniae is not detected in any of the samples obtained outside the index case room.

Future with EURIPHI-VAP technology: A 65-year-old male patient, with a good previous quality of life despite having the following history: HT, diastolic heart failure, COPD, benign prostatic hypertrophy.
The reason for hospital admission was a respiratory superinfection and decompensation of heart failure, for which he had to receive diuretic, hypotensive and antibiotic treatment for one week (specifically, amoxicillin-clavulamic). Subsequently, peripherally inserted central catheter bacteremia was diagnosed by methicillin-sensitive Staphylococcus aureus detected by the EURIPHI-VAP detector. The patient receives treatment with cefazolin until completing 14 days of treatment.
Iron deficiency anemia, secondary to intestinal losses and paroxysmal ACXFA, is also detected during admission, which will end up requiring tests and prolonging your hospital stay. After performing a colonoscopy with a biopsy of three polyps, the patient presented an acute abdomen. An abdominal CT scan detects a perforation in the transverse colon. The patient ends up entering the critical care unit, requiring vasoactive drugs and intubation. Upon admission to the ICU, colonization screening by MRSA and enterobacteriaceae producing wide-spectrum beta-lactamases or carbapenemases was performed using the EURIPHI-VAP detector. Both screens are negative.
The patient is intubated for 5 days. Two days after weaning, respiratory failure begins acutely. Chest x-ray shows left basal infiltrate. Bronchoaspirate and blood cultures are collected. Antibiotic treatment with meropenem and linezolid is started, but after the first dose the identification of carbapenemase-producing K pneumoniae and extended spectrum betalactamases (ESBL) is now available thanks to detection using EURIPHI-VAP. Antibiotherapy is changed to ceftazidime-avibactam.
Meanwhile, the rest of the patients admitted to the unit have been screened using a rectal smear and respiratory samples. In total 20 patients, among whom a patient colonized by K pneumoniae is detected. The EURIPHI-VAP detector already reports the absence of resistance mechanisms, so it is not necessary any type of additional contact measurement to the standard ones with the second patient. 35 surface samples are also obtained, in which the EURIPHI-VAP detector does not detect K pneumoniae in any of the samples obtained outside the index case room.

7. Needs-Value Analysis Methodology and Tools

The process defined in EURIPHI's methodology ensures that all the key steps are present and at the same time adds overlapping temporal windows among the different stages, allowing a major efficiency in the PPI scope definition.

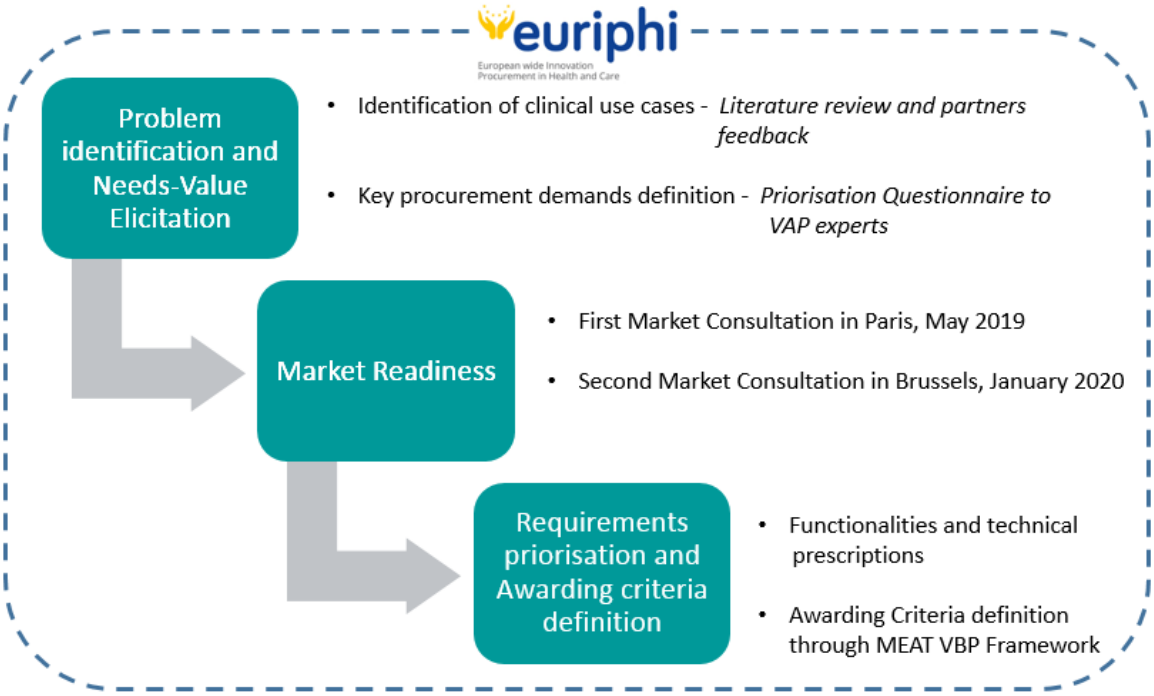

Figure 7. EURIPHI Needs-Value Assessment Methodology

Going through each of the steps:

Problem Identification and Needs-Value Elicitation

WP4 aimed to translate multidisciplinary requirements specifications into procurement demands. The clinical perspectives were matched with the currently available innovative diagnostics based on the algorithms defined in D4.1.

Hospital-acquired lower respiratory tract infections, such as Ventilator-Associated Pneumonia (VAP) served as an example of how the demand side from a clinical perspective can be matched with the currently available innovative diagnostics, as discussed in D4.1 report. It was first analyzed online available VAP guidelines and compared the diagnostic parameters and treatment options for VAP. VAP clinical scoring systems were also revised. Secondly, clinical decision trees for VAP were defined based on these guidelines. The UAntwerp developed a questionnaire to identify the product specifications for the selection of a rapid diagnostic test for the two VAP algorithms (antibiotic stewardship and prevention). With the support of the European Respiratory Society (ERS), seven VAP experts were invited to fill out this questionnaire. Next, the different outcomes were identified that could be linked to these technical specifications. It resulted in a clear picture of the diagnostic test key requirements to be used in the proposed pathway for the diagnosis of VAP (i.e., for the technical specification). Finally, UAntwerp constructed a database with variables for landscaping diagnostic tests for detection of microbial and host biomarkers for diagnosis of respiratory tract infections. This landscaping is a joint initiative with another EU funded Marie Curie project (New Diagnostics for Infectious Diseases). Information collected further included information of criteria as: intended use, setting, performance,

patient type, method, target, analysis, detection, detected pathogens, detected antimicrobial resistance (AMR), storage conditions, shelf life, kit components, volume/amount required, test preparation, sample processing, controls, calibration, maintenance, hands on time, results readout, time to result, instrumentation, instrument specifications, connectivity, waste disposal, samples per run, patient population, sensitivity, specificity, PPV, NPV, reproducibility, limit of detection, cross-reactivity, interference, training, required, on-site training, cost of kit (€), instrument availability in Europe, cost of instrument (€)/leasing possibility, calibration, maintenance/support, stage of development, market region, regulatory approval, and CLIA complexity.

Additionally, a PPO skype session was performed on September 2019 in order to gather input from the WP4 participating public procurement organisations (PPOs) on the project's scope and next steps. Based on the minutes of the meeting, the general opinion seems to be that the scope should not be limited to just buying a (rapid) test delivering a faster test result, but should also take into account clinical pathway, associated machines and other consumables. Moreover, besides fast detection, also early detection and identification of the kind of bacteria are regarded important.

As a result, there might be an interest to procure rapid diagnostic test for use within a given clinical pathways or to see a solutions to innovate the care delivery an perform a rapid diagnosis and management.

Market Readiness

A first Open Market Consultation (OMC) was performed on May 2019. At the EURIPHI OMC, procurement organizations, partners and members of EURIPHI, seek to obtain an overview of the latest information on innovative rapid diagnostic test available on the market or in development.

The industry had the opportunity to enter into dialogue with procurement organizations and experts through 1:1 dialogue session. The companies could present and discussed their innovation and value propositions. Value proposition which responded to the needs of patient and shortcoming of current care delivery but as well of expected interest of the actors in health care and society. The economic benefits and consequences were as well highlighted and possible interest in value-based agreement expressed.

Participating companies receive a description of identified awarding criteria and evaluation as a basis for discussion. These guided by user requirements and application of the MEAT Value Based Procurement Framework.

Despite the Paris Open Market Consultation on the RD test, it seems yet unclear to what extend the market can be provide a comprehensive solution. A broader scope (rapid diagnosis instead of rapid diagnostics) was define for the (second) pre-tender market consultation, which was performed on January 2020. This time, the number of companies was higher (7) and better conclusions were obtained. As a result, EURIPHI got to understand the current state of the art on the rapid diagnosis tools on antibiotic stewardship on VAP and what is currently available on the market.

The results from both OMC confirmed the opportunity to develop a solution, through a rapid diagnosis, might allow to promptly initial antibiotic therapy or rapid de-escalation after the initial dose. Given the « ambitious » minimal requirements identified by VAP experts, the OMC results determined that obligation of meeting them should be decided by each procurement organisation when publishing the Tender.

Requirements prioritisation and Awarding Criteria definition

Taking into account the conclusions from the deliverable D4.2 on WP4 and the two OMC conclusions performed under WP2 and WP5, the tasks expected on WP6 were accomplished.

On the one hand, solution requirements were defined: The solution should comply with nine Rapid Diagnosis Key Functional Requirements (described in D6.2) that will be described in a potential tender specification's sheet. As mentioned above, procurement organisations will be responsible to determine whether these requirements end up being considered as key functional requirements that the solution MUST HAVE or would be OF ADDED VALUE TO HAVE. In case first scenario is contemplated, the presented requirements will be considered as Knock-Out (KO) criteria, meaning that if any presented offer that does not respect them, will be automatically excluded. In case the minimum is reached, it will be scored based on both the value function and performance value.

On the Task 6.3, a first approach of user-centred framework was defined on rapid diagnosis tools for antibiotic stewardship of VAP. As part of the framework, a coherent and first version of awarding criteria was defined, according to MEAT Value Based Procurement Framework, to be part of the tender documentation on a potential procurement. The work performed on previous work packages (WP2, WP3, WP4 and WP5) has enabled the definition of a first approach in order to be implemented in this potential tender and using the cross-border model with localised decision-making.

The procurement organisations (PO) will be eventually responsible to take the obtained results and adapt them, if considered, according to their innovation ecosystem, their specific needs and local legislation. With his aim, each PO will be responsible to adapt the defined criteria, as well as the assigned weight and performance measurement description.

8. Risk – Uncertainty identification and management

During the validation of functional requirements and indicators (D6.2), different regulatory frameworks and standards were identified to be applicable, at a general scale, to the rapid diagnosis innovative solution for antibiotic stewardship of VAP.

In other terms, 'The EURIPHI Rapid Diagnosis VAP 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).[30]
    - 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[31]), UK (NHS Digital Network Security Standards[32]).
    - EU Products Safety Standards[33]: 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.

- ✓ 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). MOH is also aligned with EU regulations.

- ✓ 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.
    - 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.).

- ✓ Secure authentication of users implemented at your own site to be complied by EURIPHI Rapid Diagnosis VAP solutions (e.g. log on (password, smartcard, biometric, etc.), network access authentication (IPSec, remote, single sign on, etc.)

[30] EU Regulatory Framework for Medical devices
http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework_en
[31] Catalan Regulation for Product Safety
http://consum.gencat.cat/ca/empreses/requisits-obligatoris/seguretat-del-productes/
[32] NHS Medical devices regulation and safety
https://www.gov.uk/topic/medicinesmedicaldevicesblood/medicaldevicesregulationsafety
[33] 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

9. Conclusions

For Europe and rest of the world, MDROs is evolving to be problematic leading to harmful diseases. The Ventilator-Associated Pneumonia (VAP) is the second most common Hospital-Acquired Infection (HAI) and a leading infection in ICUs, which is resulting in million infections and thousands of deaths every year in Europe. Its consequent burden is not only affecting to societal health and wellbeing, but also to health system and economy given patient's treatments needs and toxic effects, length of stay and income loss related to slow of any recovery.

Current situation claims to an urgent action to attempt and mitigate the harm that both MDROs and VAP are causing nowadays in Europe, as based on scientific evidence estimations, which will get worse by an increasing yearly prevalence and incidence, leading to even more harmful infections and, consequently even deaths and significant increase in cost and length of care.

The present business case aims to serve as an argument to convince decision makers from health authorities and procurement organisations (POs) to engage in a cross-border collaborative value driven innovation procurement actions that will articulate a clear path on a rapid diagnosis innovative solution procurement that will lead, to relevant and valued impacts at all levels guided by the Adapted MEAT VBP Framework of Rapid Diagnosis,

EURIPHI-VAP rapid detection innovative solution will enable an early and more accurate detection of bacteria colonization and antibiotic stewardship. Consequently, healthcare professionals will be able to effectively monitor patient risk-profile stratification and be informed on the presence of pathogens and their antibiotic resistance/susceptibility patterns. Such early information might allow to and early start-up, alter treatment or de-escalation strategies and can thus impact on mortality and morbidity rates, the length of stay and overall costs and reduce the development of antibiotic resistance and their associated infections in VAP.

In addition, EURIPHI-VAP technology will have a direct impact in the capacity of the POs to address most of the recommendations provided by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), resulting in improvements on the management of MDROs, VAP and antibiotic prescription.

Lastly, assessment of the expected risks to which the innovative care delivery will be exposed through needed investment and transformative changes are outlined through a plan to manage these uncertainties and risks.

Annex 1. Relevant Data on VAP

A) General results in VAP patients

UNDERLYING PATHOLOGY	N	%	Average Stay	APACHE II[34]	Exitus (%)	Incidence Ratio (*)
Coronary	32	0,12	30,03	21,73	40,63	1,46
Medic	243	0,88	32,20	21,15	35,80	2,52
Surgical Program	47	0,17	32,94	19,32	46,81	1,84
Urgent Surgical	59	0,21	33,61	21,16	33,90	2,71
Traumatological	82	0,30	26,60	18,17	15,85	5,28

URGENT SURGERY	N	%	Average Stay	APACHE II	Exitus (%)	Incidence Ratio (*)
Yes	125	0,45	32,99	21,11	31,20	4,11
No	338	1,23	30,69	20,18	34,32	2,24

AGE	N	%	Average Stay	APACHE II	Exitus (%)	Incidence Ratio (*)
< 40	43	0,16	26,88	16,71	11,63	2,72
40 - 59	152	0,55	30,70	19,23	26,32	2,99
60 - 69	121	0,44	32,68	20,28	36,36	2,74
70 - 74	62	0,23	31,65	22,88	35,48	2,27
75 - 79	55	0,20	34,78	21,69	49,09	2,38
> 79	30	0,11	28,17	25,04	56,67	1,46

(*) Number of pneumonias related to mechanical ventilation for every 1,000 days of stay.

[34] APACHE II ("Acute Physiology And Chronic Health Evaluation II") is a severity-of-disease classification system (Knaus et al., 1985), one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to an intensive care unit (ICU): an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death

APACHE II	N	%	Average Stay	Exitus (%)	Incidence Ratio (*)
0 - 5	5	0,02	25,00	0	0,62
6 - 10	39	0,14	29,54	12,82	1,42
11 - 15	85	0,31	33,74	28,24	2,27
16 - 20	92	0,33	33,38	27,17	2,57
21 - 25	103	0,37	29,17	43,69	3,76
26 - 30	45	0,16	28,11	60,00	2,99
> 30	52	0,19	35,08	34,62	4,57

RELATED PNEUMONIA INCIDENCE RATE WITH VENTILATION MECHANICS

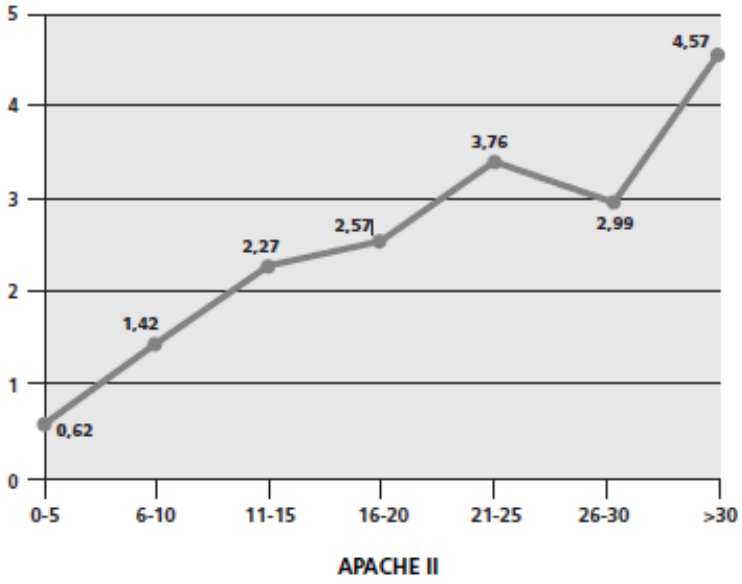

Figure 8. Severity (APACHE II) related to Ventilation-Associated Pneumonia (expressed in incidence ratio)

EXITUS	N	%	Average Stay	APACHE II	Incidence Ratio (*)
Yes	155	0,56	24,56	22,42	6,31
No	308	1,12	34,71	19,42	1,97

(*) Number of pneumonias related to mechanical ventilation for every 1,000 days of stay.

B) Risk factor in VAP patients

Risk factors	N	% total patients	% patients with VAP
Antibiotherapy prior to ICU admission	128	0,47	27,65
Antibiotic treatment in the ICU	451	1,64	97,41
Previous surgery (30 days prior to admission)	156	0,57	33,69
Urgent surgery (during ICU stay)	125	0,45	27,00
Central venous catheter	440	1,60	95,03
Mechanic ventilation	**463**	**1,68**	**100**
Urinary catheter	452	1,64	97,62
External ventricular derivation	43	0,16	9,29
Extrarenal clearance	76	0,28	16,41
Parenteral nutrition	112	0,41	24,19
ECMO	7	0,03	1,51
Neutropenia	15	0,05	3,24

Previous comorbidities in patients with VAP

Risk Factor	N	% total patients	% patients with VAP
Diabetes	89	0,32	19,22
Renal insufficiency	50	0,18	10,80
Immunosuppression	52	0,19	11,23
Neoplasia	73	0,27	15,77
Cirrhosis	29	0,11	6,26
EPOC	58	0,21	12,53
Malnutrition - Hypoalbuminemia	52	0,19	11,23
Solid organ transplant	9	0,03	1,94

Colonization / Infection, by:

Risk factor	N	%(1)	%(2)	Pior	%(1)	%(2)	Ongoing	%(1)	%(2)
Acinetobacter spp R-Imipenem	16	0,06	3,46	4	0,01	0,86	12	0,04	2,59
Multirresistant GNB	26	0,09	5,62	4	0,01	0,86	22	0,08	4,75
Enterobacteria-BLEE	63	0,23	13,61	17	0,06	3,67	46	0,17	9,94
Multirresistant *Pseudomonas*	47	0,17	10,15	4	0,01	0,86	43	0,16	9,29
Vancomycin resistant enterococcus	3	0,01	0,65	0	0	0	3	0,01	0,65
MRSA	27	0,10	5,83	12	0,04	2,59	15	0,05	3,24
Tuberculosis	6	0,02	1,30	5	0,02	1,08	1	0	0,22
BGN-carbapenemasa	26	0,09	5,62	5	0,02	1,08	21	0,08	4,54
Clostridium difficile	8	0,03	1,73	2	0,01	0,43	6	0,02	1,30

(1):% of total patients (2):% of patients with VAP

C) Isolated Microorganisms in VAP

MICROORGANISM	TOTAL		≤ 7 days		> 7 days		≤ 4 days		> 4 days	
	n	%	n	%	n	%	n	%	n	%
Pseudomonas aeruginosa	97	23,83	23	13,37	74	31,49	6	10,91	91	25,85
Staphylococcus aureus	48	11,79	26	15,12	22	9,36	10	18,18	38	10,80
Escherichia coli	37	9,09	20	11,63	17	7,23	7	12,73	30	8,52
Klebsiella pneumoniae	34	8,35	14	8,14	20	8,51	3	5,45	31	8,81
Enterobacter cloacae	25	6,14	15	8,72	10	4,26	3	5,45	22	6,25
Haemophilus influenzae	25	6,14	19	11,05	6	2,55	10	18,18	15	4,26
Stenotrophomonas maltophilia	17	4,18	5	2,91	12	5,11	0	0	17	4,83
Serratia marcescens	15	3,69	6	3,49	9	3,83	2	3,64	13	3,69
Acinetobacter baumannii	11	2,70	2	1,16	9	3,83	1	1,82	10	2,84
Enterobacter aerogenes	10	2,46	4	2,33	6	2,55	2	3,64	8	2,27
Streptococcus pneumoniae	8	1,97	4	2,33	4	1,70	3	5,45	5	1,42
Klebsiella oxytoca	8	1,97	5	2,91	3	1,28	2	3,64	6	1,70
Aspergillus fumigatus	7	1,72	2	1,16	5	2,13	0	0	7	1,99
Staphylococcus aureus meticilín resistente	7	1,72	5	2,91	2	0,85	3	5,45	4	1,14
Proteus mirabilis	7	1,72	4	2,33	3	1,28	0	0	7	1,99
Enterococcus faecalis	5	1,23	3	1,74	2	0,85	0	0	5	1,42
Enterococcus faecium	4	0,98	2	1,16	2	0,85	0	0	4	1,14
Moraxella catarrhalis	3	0,74	1	0,58	2	0,85	1	1,82	2	0,57
Citrobacter freundii	3	0,74	3	1,74	0	0	0	0	3	0,85
Candida albicans	3	0,74	0	0	3	1,28	0	0	3	0,85
Herpes simplex	3	0,74	0	0	3	1,28	0	0	3	0,85
Burkholderia cepacia	3	0,74	0	0	3	1,28	0	0	3	0,85
Other bacteria	3	0,74	0	0	3	1,28	0	0	3	0,85
Staphylococcus epidermidis	2	0,49	1	0,58	1	0,43	1	1,82	1	0,28
Streptococcus anginosus	2	0,49	1	0,58	1	0,43	0	0	2	0,57
Morganella morganii	2	0,49	1	0,58	1	0,43	0	0	2	0,57
Citrobacter spp	2	0,49	1	0,58	1	0,43	0	0	2	0,57
non-fermenter GNB	1	0,25	0	0	1	0,43	0	0	1	0,28
Providencia stuartii	1	0,25	1	0,58	0	0	0	0	1	0,28
Citomegalovirus	1	0,25	0	0	1	0,43	0	0	1	0,28
Candida parapsilosis	1	0,25	0	0	1	0,43	0	0	1	0,28
Candida tropicalis	1	0,25	0	0	1	0,43	0	0	1	0,28
Candida krusei	1	0,25	0	0	1	0,43	0	0	1	0,28
Streptococcus agalactiae	1	0,25	1	0,58	0	0	0	0	1	0,28
Acinetobacter lwofii	1	0,25	0	0	1	0,43	0	0	1	0,28
Burkholderia spp	1	0,25	1	0,58	0	0	0	0	1	0,28
Chlamydia pneumoniae	1	0,25	0	0	1	0,43	0	0	1	0,28
Pseudomonas otras	1	0,25	1	0,58	0	0	0	0	1	0,28
Hafnia alvei	1	0,25	1	0,58	0	0	1	1,82	0	0
HIV 1	1	0,25	0	0	1	0,43	0	0	1	0,28
Corynebacterium jeikeium	1	0,25	0	0	1	0,43	0	0	1	0,28
Haemophilus parainfluenzae	1	0,25	0	0	1	0,43	0	0	1	0,28
Aspergillus spp	1	0,25	0	0	1	0,43	0	0	1	0,28
TOTAL	**407**		**172**		**235**		**55**		**352**	

D) More frequent microorganisms in VAP

Gram positives

MICROORGANISMS	TOTAL		≤ 7 days		> 7 days		≤ 4 days		> 4 days	
	n	%	n	%	n	%	n	%	n	%
Staphylococcus aureus	48	11,79	26	15,12	22	9,36	10	18,18	38	10,80
Streptococcus pneumoniae	8	1,97	4	2,33	4	1,70	3	5,45	5	1,42
Staphylococcus aureus meticilín resistente	7	1,72	5	2,91	2	0,85	3	5,45	4	1,14
Enterococcus faecalis	5	1,23	3	1,74	2	0,85	0	0	5	1,42
Enterococcus faecium	4	0,98	2	1,16	2	0,85	0	0	4	1,14
Staphylococcus epidermidis	2	0,49	1	0,58	1	0,43	1	1,82	1	0,28
Streptococcus anginosus	2	0,49	1	0,58	1	0,43	0	0	2	0,57
Streptococcus agalactiae	1	0,25	1	0,58	0	0	0	0	1	0,28
Corynebacterium jeikeium	1	0,25	0	0	1	0,43	0	0	1	0,28
TOTAL	**78**		**43**		**35**		**17**		**61**	

Gram negatives

MICROORGANISMS	TOTAL		≤ 7 days		> 7 days		≤ 4 days		> 4 days	
	n	%	n	%	n	%	n	%	n	%
Pseudomonas aeruginosa	97	23,83	23	13,37	74	31,49	6	10,91	91	25,85
Escherichia coli	37	9,09	20	11,63	17	7,23	7	12,73	30	8,52
Klebsiella pneumoniae	34	8,35	14	8,14	20	8,51	3	5,45	31	8,81
Enterobacter cloacae	25	6,14	15	8,72	10	4,26	3	5,45	22	6,25
Haemophilus influenzae	25	6,14	19	11,05	6	2,55	10	18,18	15	4,26
Stenotrophomonas maltophilia	17	4,18	5	2,91	12	5,11	0	0	17	4,83
Serratia marcescens	15	3,69	6	3,49	9	3,83	2	3,64	13	3,69
Acinetobacter baumannii	11	2,70	2	1,16	9	3,83	1	1,82	10	2,84
Enterobacter aerogenes	10	2,46	4	2,33	6	2,55	2	3,64	8	2,27
Klebsiella oxytoca	8	1,97	5	2,91	3	1,28	2	3,64	6	1,70
Proteus mirabilis	7	1,72	4	2,33	3	1,28	0	0	7	1,99
Otros	21	5,16	10	5,81	11	4,68	2	3,64	19	5,40
TOTAL	**307**		**127**		**180**		**38**		**269**	

Fungi

MICROORGANISMS	TOTAL		≤ 7 days		> 7 days		≤ 4 days		> 4 days	
	n	%	n	%	n	%	n	%	n	%
Aspergillus fumigatus	7	1,72	2	1,16	5	2,13	0	0	7	1,99
Candida albicans	3	0,74	0	0	3	1,28	0	0	3	0,85
Candida parapsilosis	1	0,25	0	0	1	0,43	0	0	1	0,28
Candida tropicalis	1	0,25	0	0	1	0,43	0	0	1	0,28
Candida krusei	1	0,25	0	0	1	0,43	0	0	1	0,28
Aspergillus spp	1	0,25	0	0	1	0,43	0	0	1	0,28
TOTAL	**14**		**2**		**12**		**0**		**14**	

E) Germs types

GROUP	N	%
GNB	307	75,43
Gram +	78	19,16
Fungis	14	3,44
Others	8	1,97
TOTAL	**407**	

F) Inflamatory response in VAP

Inflamatory Response	N	%
No sepsis	56	11,27
Sepsis	324	65,19
Septic shock	117	23,54
TOTAL	**497**	

F) Antibiotic treatment in VAP

ANTIBIOTIC TR.	N	%
Yes	459	92,35
No	20	4,02
Missing	18	3,62
TOTAL	**497**	

F) Proper Antibiotic treatment in VAP

PROPER ANTIBIOTIC TREATMENT	N	% total antibiotic treatment	% of total VAP cases
Si	315	68,78	63,38
No	65	14,19	13,08
Not applicable	78	17,03	15,69
TOTAL	**459**	**100**	**92,15**

Missing = 1

Annex 2. MEAT VBP Framework adapted to Rapid Diagnosis

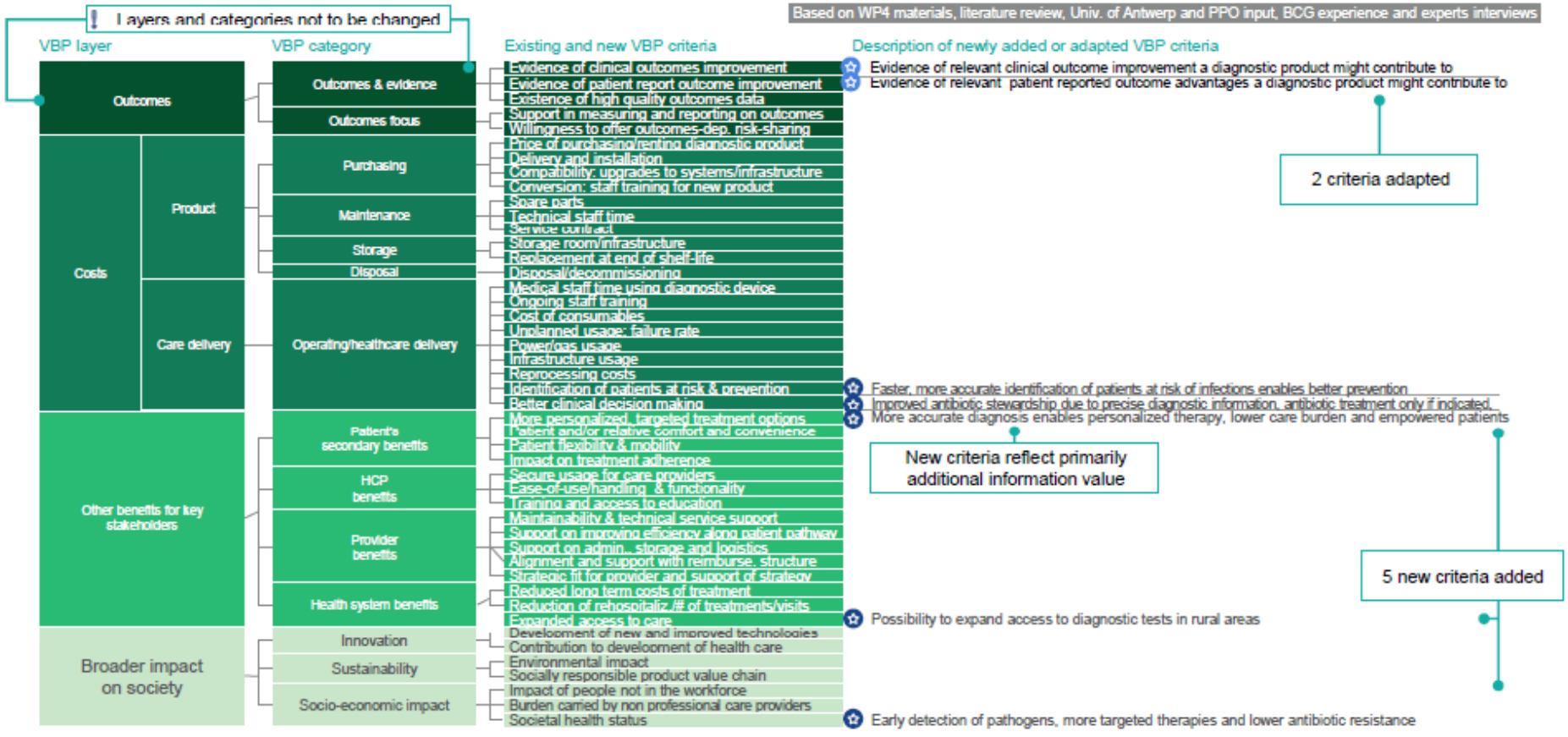

Figure 9. MEAT VBP Framework adapted to Rapid Diagnosis

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