Innovazione nella diagnostica a supporto della *stewardship* antimicrobica

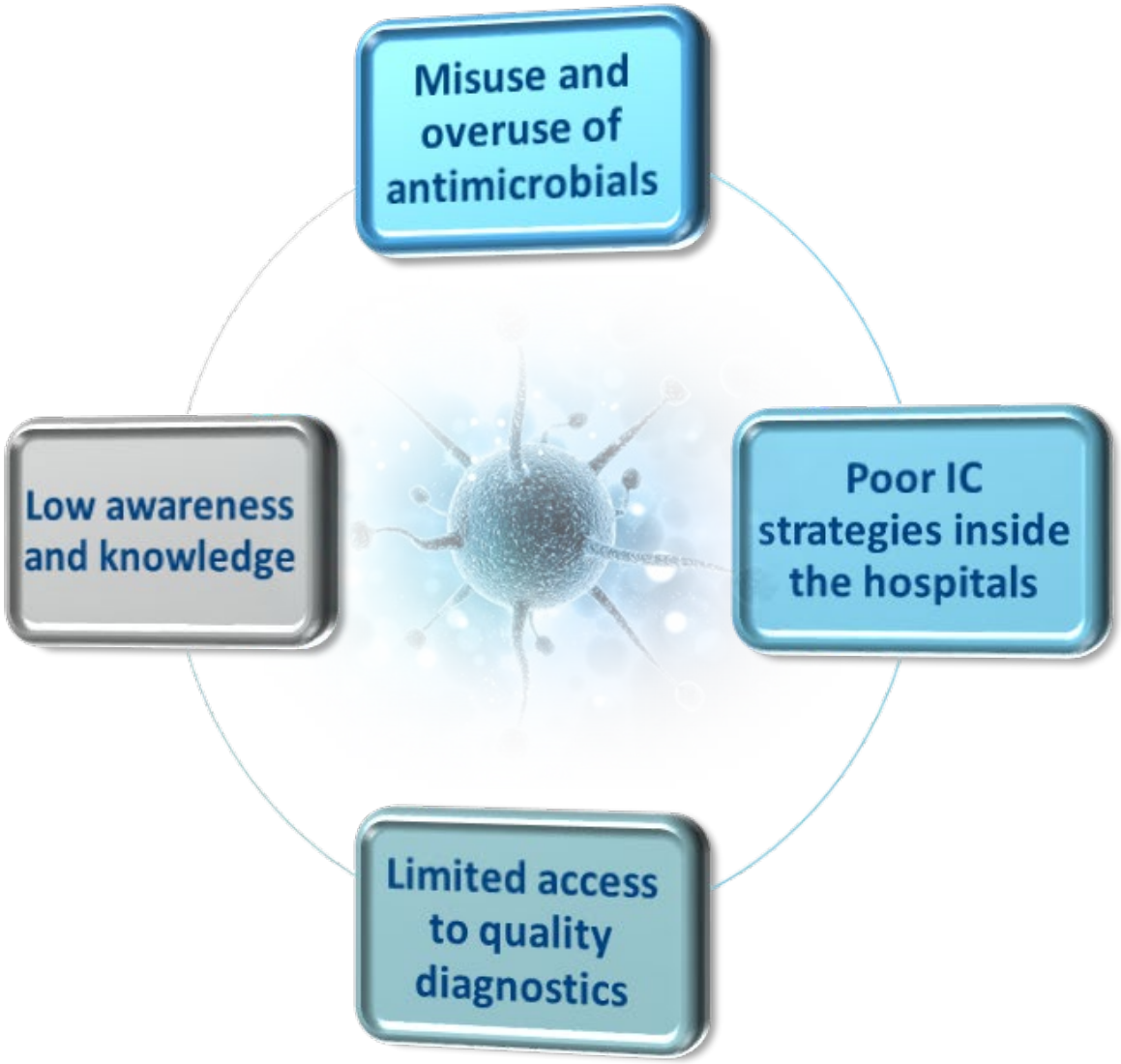
Valeria Zucchelli

Adriatic Medical Affairs Director

bioMérieux

PIONEERING DIAGNOSTICS

What accelerates the most the emergence and spread of AMR?



Adapted from O'Neill 2014, Review on Antimicrobial Resistance.

How to Slow Down and Reverse AMR Trend

Adapted from O'Neill 2014, Review on Antimicrobial Resistance.

How to Slow Down and Reverse AMR Trend

Four Core Actions to Prevent AMR

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

1 PREVENTING INFECTIONS, PREVENTING THE SPREAD OF RESISTANCE

Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

2 TRACKING RESISTANCE PATTERNS

data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

Optimized Use of ABs

3 IMPROVING ANTIBIOTIC PRESCRIBING/STEWARDSHIP

Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe.

> *"High-income countries should make it mandatory that by 2020 the prescription of antibiotics will need to be informed by data and testing technology wherever it is available."*

O'Neill 2014, Review on Antimicrobial Resistance.

bioMérieux Commitment to Fighting AMR

+55
Years of microbiology expertise

1,800
People are **employed in R&D**

12-13%
of net Sales invested in R&D

80%
of **clinical products** contribute **to overcome AMR challenge**

80%
of **R&D budget** dedicated to **AMR research**

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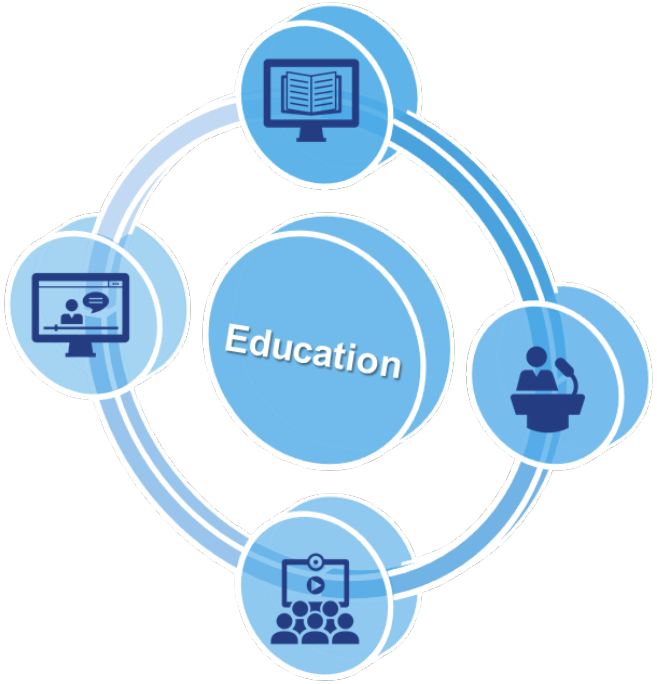
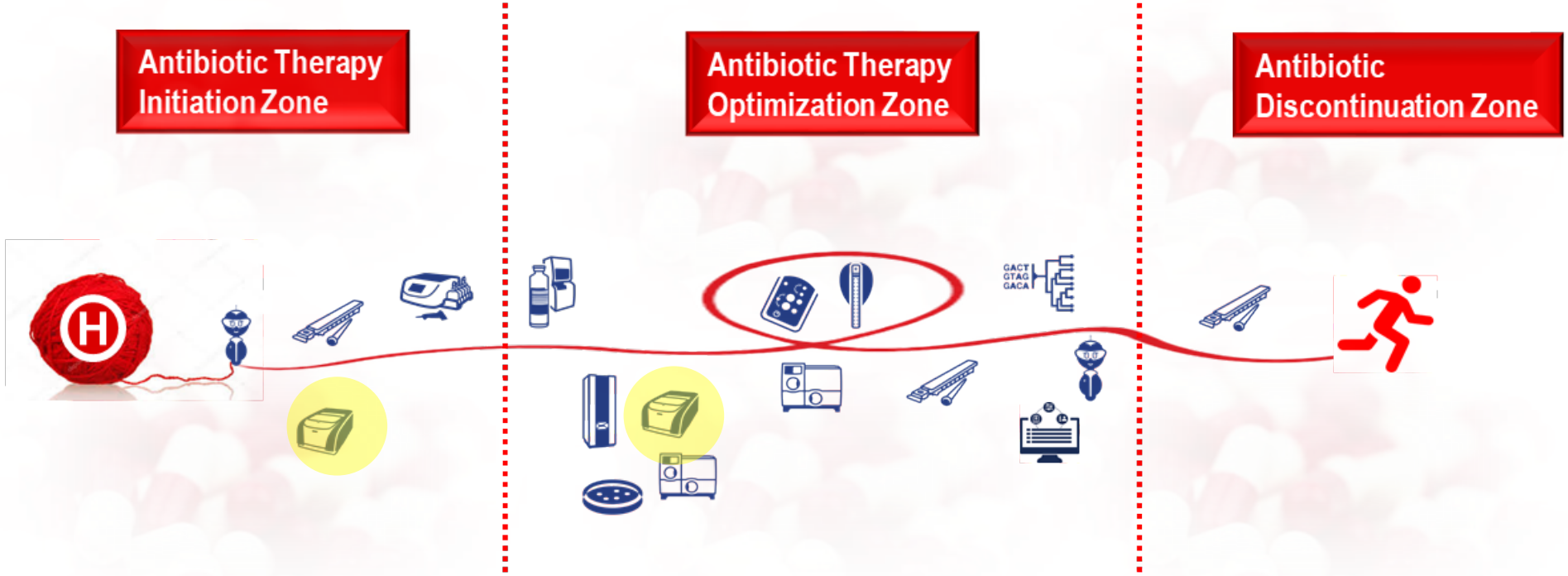


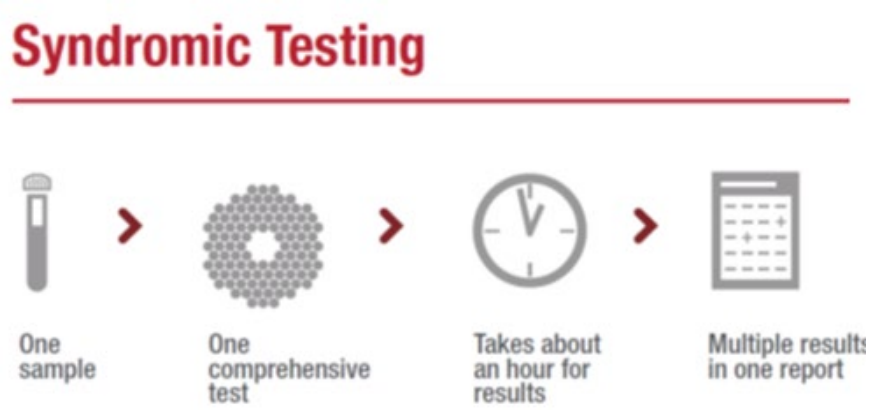
AMS is the *file rouge* that links most of bioMérieux products together - optimized use of antibiotics at each step of the prescription workflow.



"**mPCR tests** (also known as '**syndromic' panels**) combine tests for numerous pathogens and AMR genes into a single test, and have changed how we diagnose infections, leading to improved patient care and clinical workflow.

These syndromic panels have the **ability to impact IC, AMS, and patient outcomes by significantly reducing time to diagnosis and clinical decision making**." (*J Antimicrob Chemother* 2021; 76 Suppl 3: iii4–iii11)

Syndromic Approach to the Management of Infectious Diseases



Symptom-driven broad grouping of probable pathogens into one, rapid test that **maximizes the chance of getting the right answer in a clinically relevant timeframe.**

Advantages for Patients, Hospitals and Healthcare Systems

Provide more timely and effective treatment

Limit the use of unnecessary antibiotics

Prevent secondary spread of infection

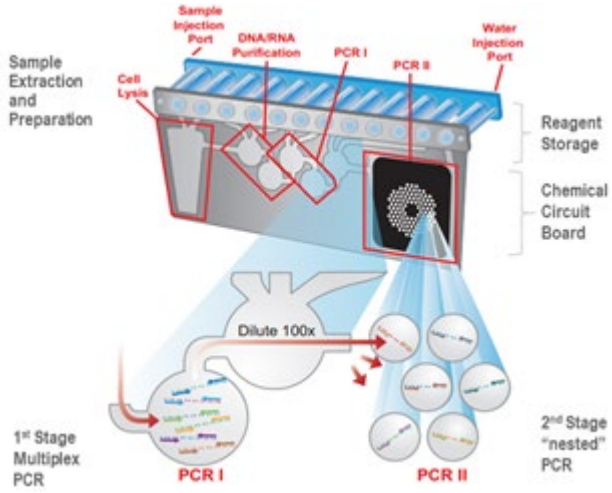
Reduce unnecessary tests

Better triaging patients in ER

Shorten hospital stays

Advanced Syndromic Screening for the Diagnosis of Infections

Multiplex PCR platforms that integrates sample preparation, amplification, detection and analysis into **one closed system**, that requires **2 min** of **hands-on time** with a total **run time** of about **1 hour.**



Respiratory Panel 2.1 *plus* Panel

23 Targets

- 4 bacteria
- 19 viruses

Blood Culture Identification 2 Panel

43 Targets

- 26 bacteria
- 7 yeast
- 10 antibiotic resistance genes

Gastro-intestinal Panel

22 Targets

- 13 bacteria
- 5 viruses
- 4 parasites

Meningitis/ Encephalitis Panel

14 Targets

- 6 bacteria
- 7 viruses
- 1 fungus

Pneumonia *plus* Panel

34 Targets

- 18 bacteria
- 9 viruses
- 7 antibiotic resistance genes

Practical Comparison of the BioFire FilmArray Pneumonia Panel to Routine Diagnostic Methods and Potential Impact on Antimicrobial Stewardship in Adult Hospitalized Patients with Lower Respiratory Tract Infections

Blake W. Buchan,[a] Sam Windham,[a] Joan-Miquel Balada-Llasat,[b] Amy Leber,[c] Amanda Harrington,[d] Ryan Relich,[e] Caitlin Murphy,[f] Jennifer Dien Bard,[g] Samia Naccache,[g] Shira Ronen,[a] Amanda Hopp,[a] Derya Mahmutoglu,[a] Matthew L. Faron,[a] Nathan A. Ledeboer,[a] Amanda Carroll,[b] Hannah Stone,[b] Oluseun Akerele,[b] Kathy Everhart,[c] Andrew Bonwit,[d] Christina Kwong,[d] Rebecca Buckner,[e] Del Warren,[e] Randal Fowler,[f] Sukantha Chandrasekaran,[h] Holly Huse,[h] Shelley Campeau,[h*] Romney Humphries,[h*] Corrin Graue,[i] Angela Huang[a,j]

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BACTERIOLOGY

A total of 259 BAL specimens were collected from inpatients aged 18 years and older with symptoms of LRTI at 8 US hospitals.

Chart review was conducted to determine type and duration of antibiotic therapy for each subject and assess the potential impact of BioFire Pneumonia Panel on AB utilization.

Panel Menu

BACTERIA

Semi-Quantitative Bacteria

- *Acinetobacter calcoaceticus-baumannii* complex
- *Enterobacter cloacae* complex
- *Escherichia coli*
- *Haemophilus influenzae*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
- *Moraxella catarrhalis*
- *Proteus* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

ATYPICAL BACTERIA

Qualitative Bacteria

- *Chlamydia pneumoniae*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

VIRUSES

- Adenovirus
- Coronavirus
- Human Metapneumovirus
- Human Rhinovirus/Enterovirus
- Influenza A
- Middle East Respiratory Syndrome Coronavirus (MERS-CoV)
- Influenza B
- Parainfluenza Virus
- Respiratory Syncytial Virus

ANTIMICROBIAL RESISTANCE GENES

Carbapenemases

- IMP
- KPC
- NDM
- OXA-48-like
- VIM

ESBL

- CTX-M

Methicillin Resistance

- *mecA/C* and MREJ (MRSA)

Sample Type: Sputum (including ETA) and BAL (including mini-BAL)
CE-marked and US FDA-cleared

Buchan BW *et al*. Journal of Clinical Microbiology. July 2020 Volume 58 Issue 7 e00135-20.

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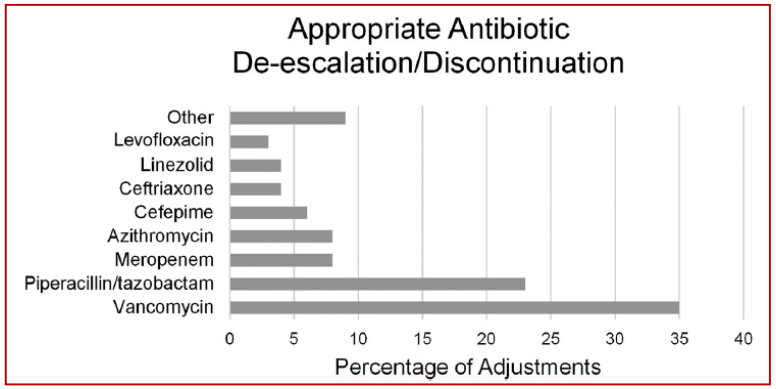
Chart review was conducted to determine type and duration of antibiotic therapy for each subject and assess the potential impact of BioFire Pneumonia Panel on AB utilization.

Potential modification	No. of antimicrobials	No. of patients (%)	No. of hours
Culture-confirmed de-escalation/discontinuation	206	122 (48.2%)	18,284.07
Culture-confirmed escalation/discontinuation	11	11 (4.3%)	184.66
Culture-discrepant de-escalation/discontinuation*	4	4 (1.6%)	-
Culture-discrepant escalation or continuation**	42	42 (16.6%)	-
No change	-	74 (29.3%)	-
Unable to assess	-	16	-



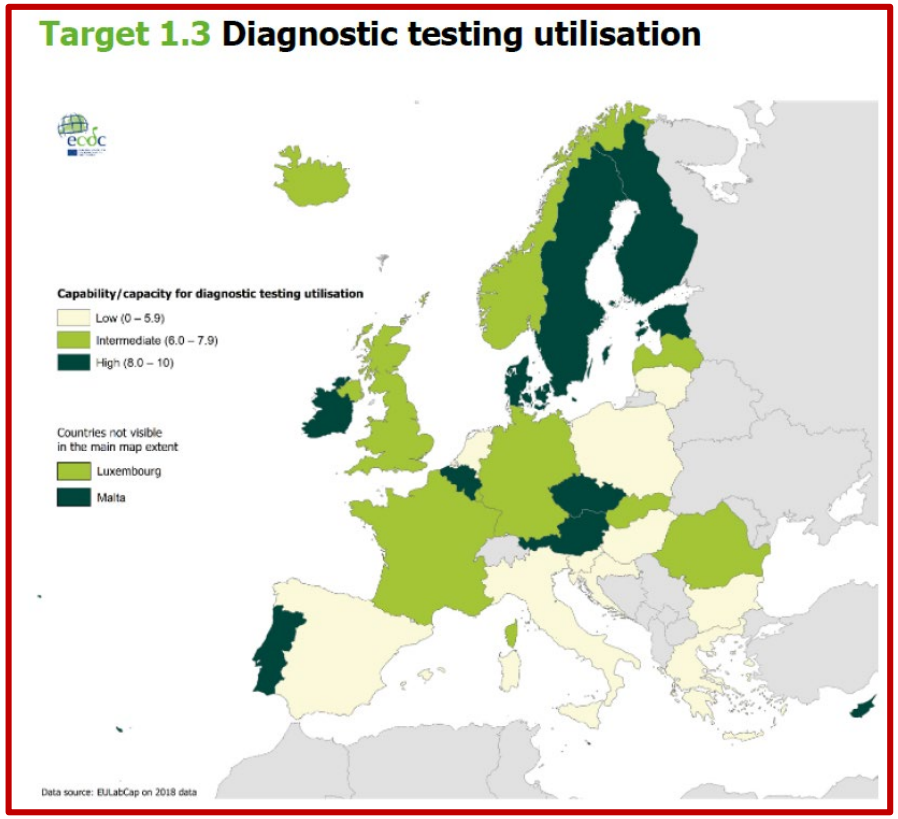
*Potential antibiotic adjustments based on the PN panel results were considered appropriate only if PN panel and SOC results were in positive or negative agreement.

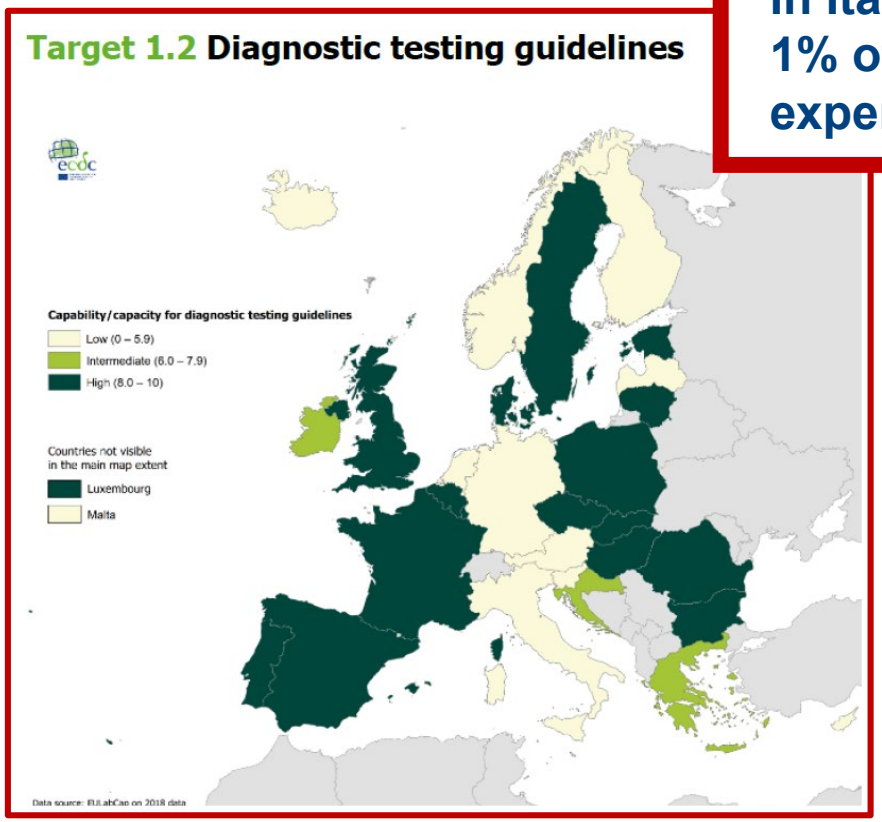
- **Potential for AB adjustments for 179/253 (70.8%) of evaluable patients;**
- **Most common potential intervention was appropriate antibiotic de-escalation/discontinuation;**
- **BioFire Pneumonia results enabled >18.000 antibiotic hours saved (avg. 6.2 d/patient, 3.8 d/AB).**

Buchan BW *et al*. Journal of Clinical Microbiology. July 2020 Volume 58 Issue 7 e00135-20.

Capability and Capacity of Microbiology Labs across Europe

- **As many as 70% of clinical decisions are informed by data from the Laboratory** (Hallworth, *Ann Clin Biochem* 2011; 48: 487-8), **but still low score for**
  - **Availability of National primary diagnostic and screening testing guidelines *(who to test, how to test*, and *when to test*);**
  - **Diagnostic testing utilization.**





In Italy, IVD accounts for 1% of total healthcare expenditure.

EU Laboratory Capability Monitoring System (EULabCap), 2018. *www.ecdc.europa.eu*.

European Journal of Clinical Microbiology & Infectious Diseases (2021) 40:429–434
https://doi.org/10.1007/s10096-020-04031-2

BRIEF REPORT

How are rapid diagnostic tests for infectious diseases used in clinical practice: a global survey by the International Society of Antimicrobial Chemotherapy (ISAC)

Stephen Poole[1] · Jennifer Townsend[2] · Heiman Wertheim[3] · Stephen P. Kidd[4] · Tobias Welte[5] · Philipp Schuetz[6] · Charles-Edouard Luyt[7] · Albertus Beishuizen[8] · Jens-Ulrik Stæhr Jensen[9,10] · Juan González del Castillo[11] · Mario Plebani[12] · Kordo Saeed[13,14]

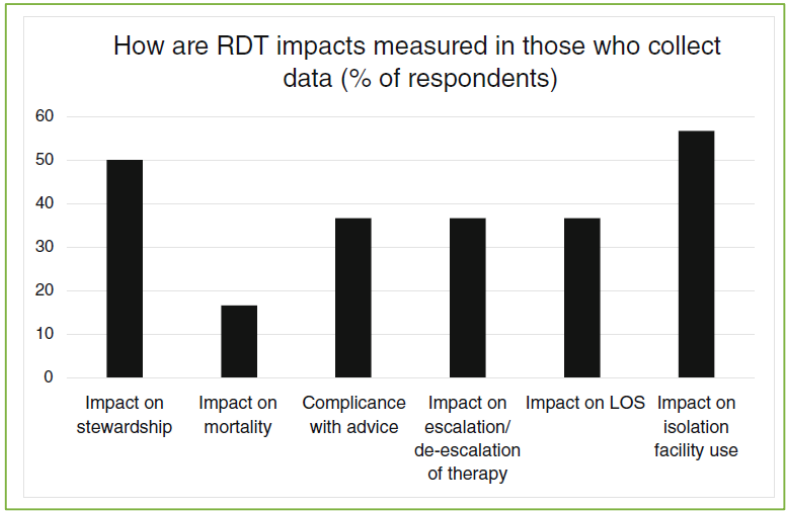
An electronic survey was devised by ISAC to assess the current patterns of use of RDTs around the world, understand whether or not their impact is measured, identify issues for successful implementation and suggest best practice advice on how to introduce new tests.

- **13/81 (16%) respondents reported no available RDTs;**
- **The main barrier reported for not adopting RDTs was financial (64%);**
- **Only 37% of those with RDTs reported measuring the impacts of their tests in any way.**

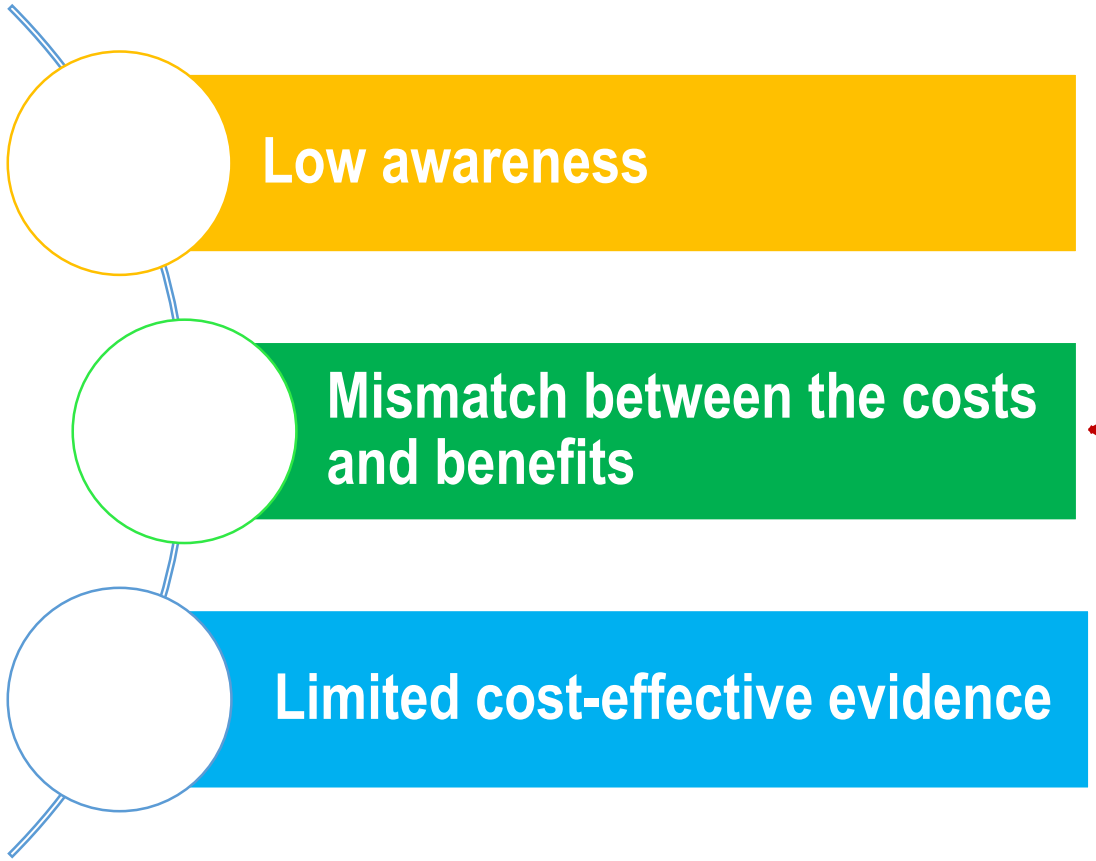
Fig. 1 Resident countries of specialists responding to survey (dark grey)

Table 1 Best practices for RDT implementation

Clinical scenario	Identify what scenario the test will impact. Assess the number of patients that the test will impact per year.
Test requirements	Determine relevant patient outcome(s) for measuring impact. Consider what turnaround time can usefully influence clinical decision making to achieve tangible improvements in this outcome(s). Ascertain the acceptable sensitivity and specificity, after taking account for likely pre-test probability of disease. Identify a suitable source of funding, and consider ongoing financial requirements for support and reagents.
Logistics and reporting	Decide on siting of RDT (laboratory vs POCT). Provide rapid reporting method which integrates with existing reporting mechanisms. Explore need for clinical specialist reporting or result interpretation. If wider public health consideration of RDT target organism(s), ensure results can be readily compiled for appropriate agencies (e.g. influenza or *Legionella* reporting). Consider need for material for additional studies, such as confirmatory testing, internal validation, laboratory research and development, or strain characterization.
Quality control and Governance	Decide responsible body governance body. Identify source of suitable QC materials (particular consideration in highly multiplexed RDTs). Instigate regular internal quality assurance programme. Set up external quality assurance programme, preferably with inter-laboratory comparison. Achieve and maintain reliable technical competency with the RDT. Set up regular audit cycles which capture RDT benefit.



Limitations to Implementation of Rapid Diagnostic Technologies

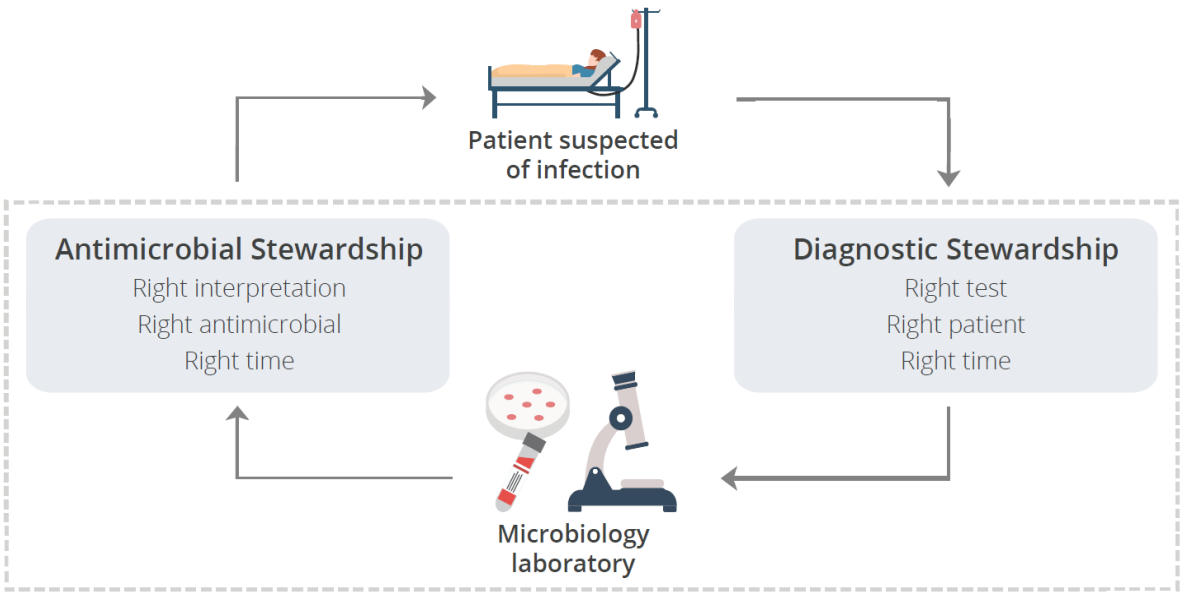


Budget silos **– Benefit of using clinically effective tests does not accrue to the Lab where the cost was incurred.**

Existing *reimbursement structures* often disincentivise the uptake of new innovative technology.

White Paper on Rapid Diagnostic Technologies to Tackle AMR, Health First Europe, 2017.

"Diagnostic and antimicrobial stewardship are necessary to ensure rapid technologies conserve, rather than consume, health care resources and optimally impact patient care."



- **Diagnostic *stewardship*** is needed to implement appropriate tests for the clinical setting and to **direct testing toward appropriate patients;**

- **Antimicrobial *stewardship*** should ensure prompt appropriate clinical action **to translate diagnostic faster test results in the Lab into improved outcomes at the bedside.**

"A functioning, collaborative partnership between Lab and clinical side is essential for the successful implementation of rapid diagnostic technologies."

Messacar K et al. Implementation of Rapid Molecular Infectious Disease Diagnostics: the Role of Diagnostic and Antimicrobial Stewardship. Journal of Clinical Microbiology 2017; 55 (3): 715-23.

Diagnostic Stewardship

Right test
Right patient
Right time

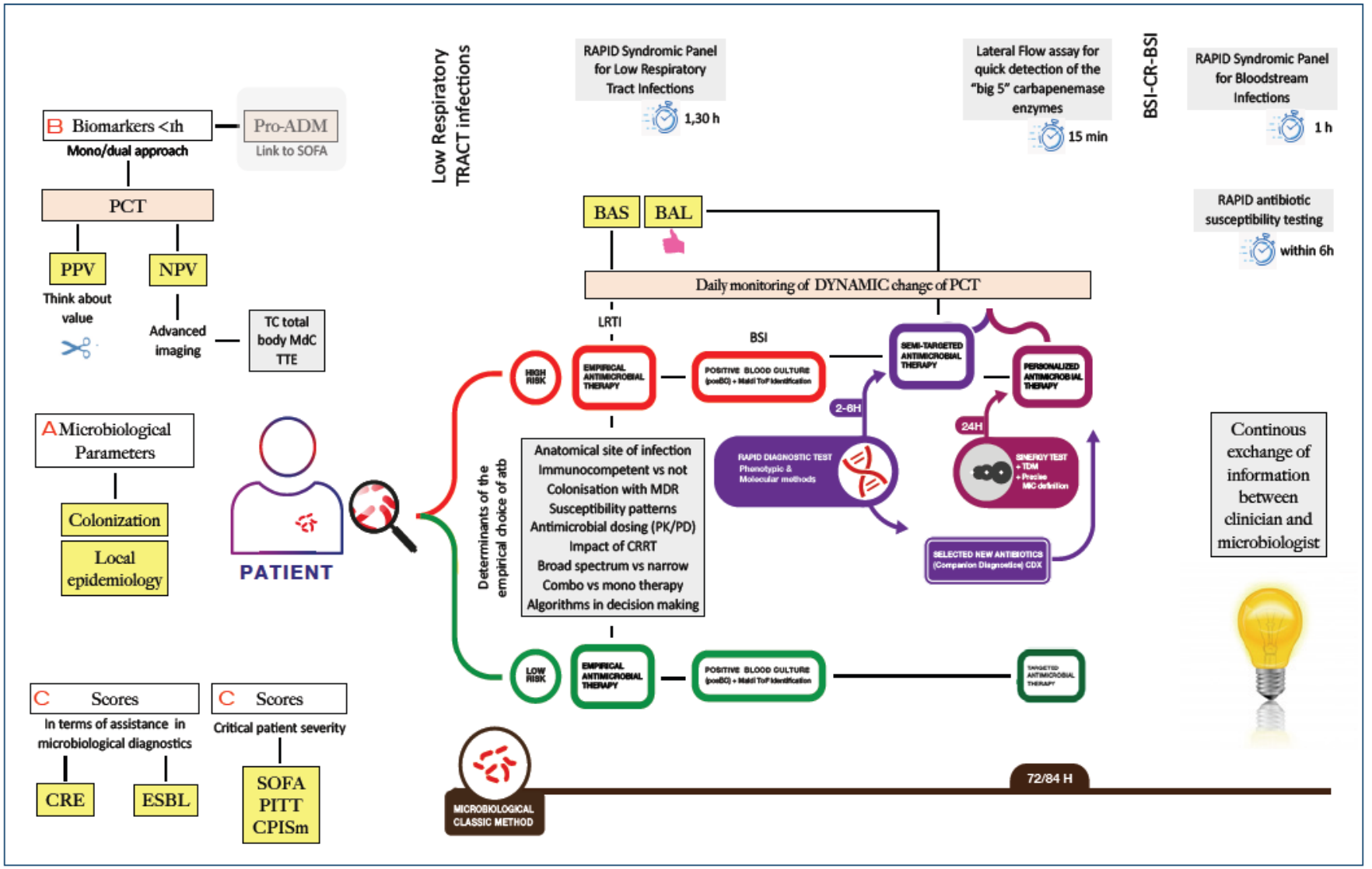


Figure 3. *Bioscore model: tool to support the best diagnostic-therapeutic pathway for the management of the critically ill patient with severe MDR infection. It answers the question "who goes to rapid diagnostics?"*

Antimicrobial Stewardship

Right interpretation
Right antimicrobial
Right time

Antimicrobial *stewardship* should ensure prompt appropriate clinical action **to translate diagnostic faster test results in the Lab into improved outcomes at the bedside.**

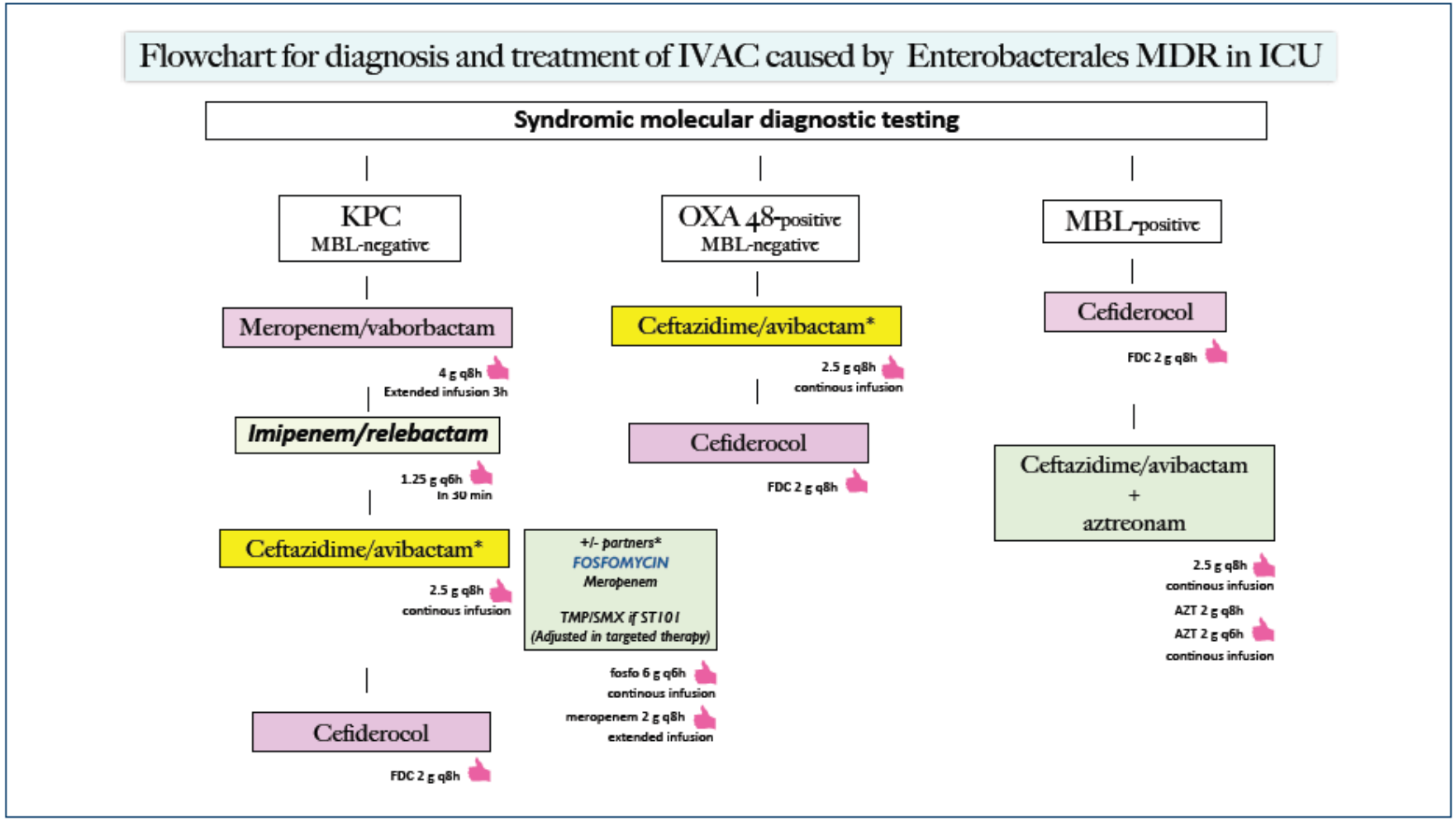


Figure 21. *Diagnostic/therapeutic decision algorithm for the treatment of ventilator-associated pneumonia due to KPC, OXA-48 and MβL-producing Enterobacterales.*

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+55
Years of microbiology expertise

1,800
People are **employed in R&D**

80%
of **clinical products** contribute **to overcome AMR challenge**

80%
of **R&D budget** dedicated to **AMR research**

bioMérieux Commitment to Fighting AMR

Education

- Improve awareness about AMR;
- Promote expert-driven behavioral change;
- Raise knowledge about the importance of diagnostics in combatting AMR and their pivotal role within ASP efforts.

2021

- **> 25** 3rd party and company-sponsored **educational events**, in collaboration with **Scientific Societies** and/or **pharma companies;**

AMCLI associazione microbiologi clinici italiani · SITA · SIAARTI · MSD · SHIONOGI

- **> 3.000 attending HCPs.**

2019

- **120** hospital-based **multi-disciplinary Round Tables;**
- **> 1.000 attending HCPs.**

bioMérieux Commitment to Fighting AMR

MERIDIANO SANITÀ *Le coordinate della salute*

The European House Ambrosetti

Advocacy

Il Think Tank di The European House - Ambrosetti nato nel 2005 con l'obiettivo di elaborare riflessioni strategiche, stimolare il dialogo sul futuro della sanità in Italia e individuare azioni di miglioramento del nostro sistema sanitario con il fine di tutelare la salute e il benessere delle persone.

Stimulate the dialogue among key healthcare stakeholders (Government, Nat'l institutions, industry and PAGs) about

- **The AMR challenge as public health priority, and the value of vaccination and diagnostics in tackling AMR;**
- **The role of strategic public-private collaborations at national level;**
- **The role of research and innovation in improving health status of population and Country's competitiveness and growth.**

In questo senso, il comparto della diagnostica in vitro ha apportato un contributo determinante nel contrasto all'AMR[13]. Negli ultimi anni, infatti, l'industria IVD ha sviluppato una serie di tecnologie diagnostiche innovative, a partire dai test rapidi molecolari, che hanno semplificato l'uso delle strumentazioni IVD e reso più rapido il processo di identificazione della potenziale infezione, garantendo una sensibilità analitica equivalente se non superiore a quella della diagnostica tradizionale. Un ulteriore elemento di innovazione è rappresentato dall'approccio sindromico di alcuni test diagnostici molecolari, consistente nella loro capacità di testare simultaneamente un ampio spettro di patogeni, massimizzando la possibilità di produrre risultati completi e accurati in un tempo che abbia rilevanza clinica rispetto all'infezione da curare.

Al fine di assicurare l'accesso più ampio possibile ai dispositivi IVD innovativi, che dispongono di una diagnosi in poche ore (contro i 2-3 giorni delle strumentazioni tradizionali) e possono ridurre gli eventi avversi degli antibiotici e le resistenze, ma anche la mortalità, e migliorare gli outcome di salute, è indispensabile promuovere uno scambio continuo tra reparto e laboratorio, attraverso lo sviluppo di percorsi che prevedano la completa integrazione tra stewardship diagnostica e antimicrobica.

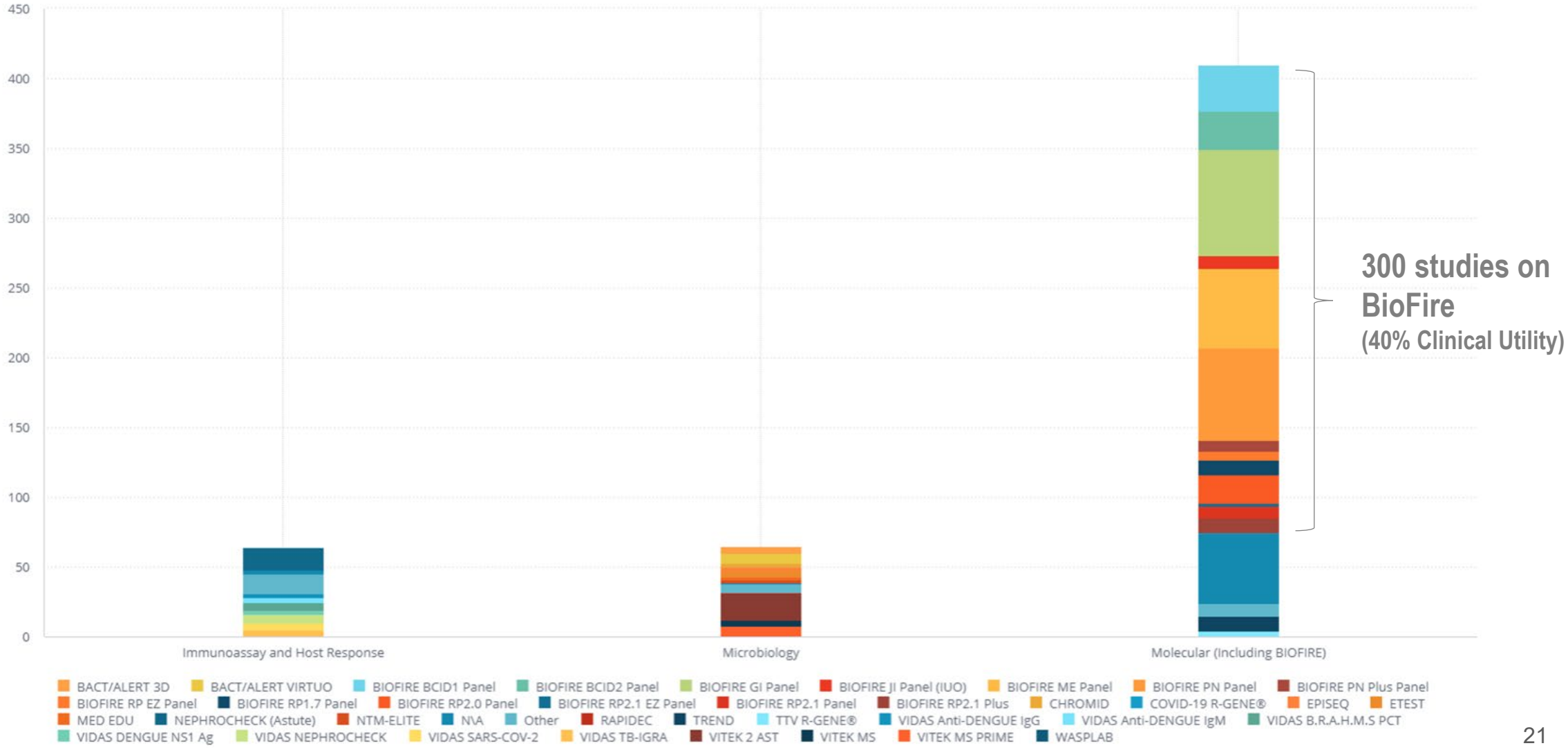
A fronte di una domanda crescente da parte dei clinici, sempre più frequentemente, all'interno dei programmi ospedalieri integrati di antimicrobial e diagnostic stewardship, sono inserite strategie di companion testing, che mirano al corretto inserimento in terapia di nuove molecole antimicrobiche. In particolare, i companion test sono dispositivi di diagnostica molecolare rapida, il cui uso consente l'applicazione sicura di una terapia antimicrobica: attraverso questa azione preventiva, che subordinando la scelta di una nuova molecola al risultato di un test consente di sfruttare tutto il potenziale della stessa in termini di efficacia, si evitano gli effetti indesiderati o la totale inefficacia a seguito dell'insorgenza di fenomeni di resistenza e/o infezioni.

Per concludere, le innovazioni introdotte nel campo della diagnostica in vitro hanno apportato benefici a tutti i player coinvolti nell'assistenza: dai pazienti, che ricevono cure sempre più appropriate e personalizzate, ai clinici, che anticipano la decisione terapeutica ottimale, riducendo il ricorso a terapie empiriche ad ampio spettro. In aggiunta, anche il management ospedaliero ottiene un risparmio complessivo di risorse, grazie all'ottimizzazione stessa della gestione del paziente, e il personale di laboratorio, in virtù della semplificazione e della velocizzazione del lavoro, può rendere il servizio più efficiente. Negli ultimi due anni, il progresso tecnologico nei dispositivi medico-diagnostici in vitro è stato anche un argine importante alla diffusione del COVID-19, in particolare grazie allo sviluppo dei test diagnostici (cosiddetti tamponi).

bioMérieux Commitment to Fighting AMR

Evidence Generation

Overall number of studies (all ranges)



Encouraging a new approach to the use of diagnostic technologies. What's missing?

- **Active *Antimicrobial Stewardship Programs*** across hospitals, **with dedicated resources and funding.**
- **Transformation of the microbiology lab role in ASP into a vital component**.
- **National Clinical Practice Guidelines** for the management of different IDs with principles on
  - **Rational use of antimicrobial agents;**
  - **Appropriate adoption of rapid syndromic testing.**
- **Educational programs** around **the importance of diagnostics in combatting AMR** and their pivotal role within ASP efforts.
- **Hospital-based criteria for the adoption of innovative technologies.**
- High **need for reform and modernization of Laboratory services** (i.e. full service, 24/7), in order to better suits the benefits of new technologies.
- **Alternative reimbursement systems for rapid diagnostics** .
- **Evidence-based studies**, **to assess the health and economic benefits** of existing and new diagnostic systems.
- **Monitoring program to track** implementation, **use and outcomes of rapid diagnostic tools**.

The right drug for the right bug.
AMS is blind without diagnostics.