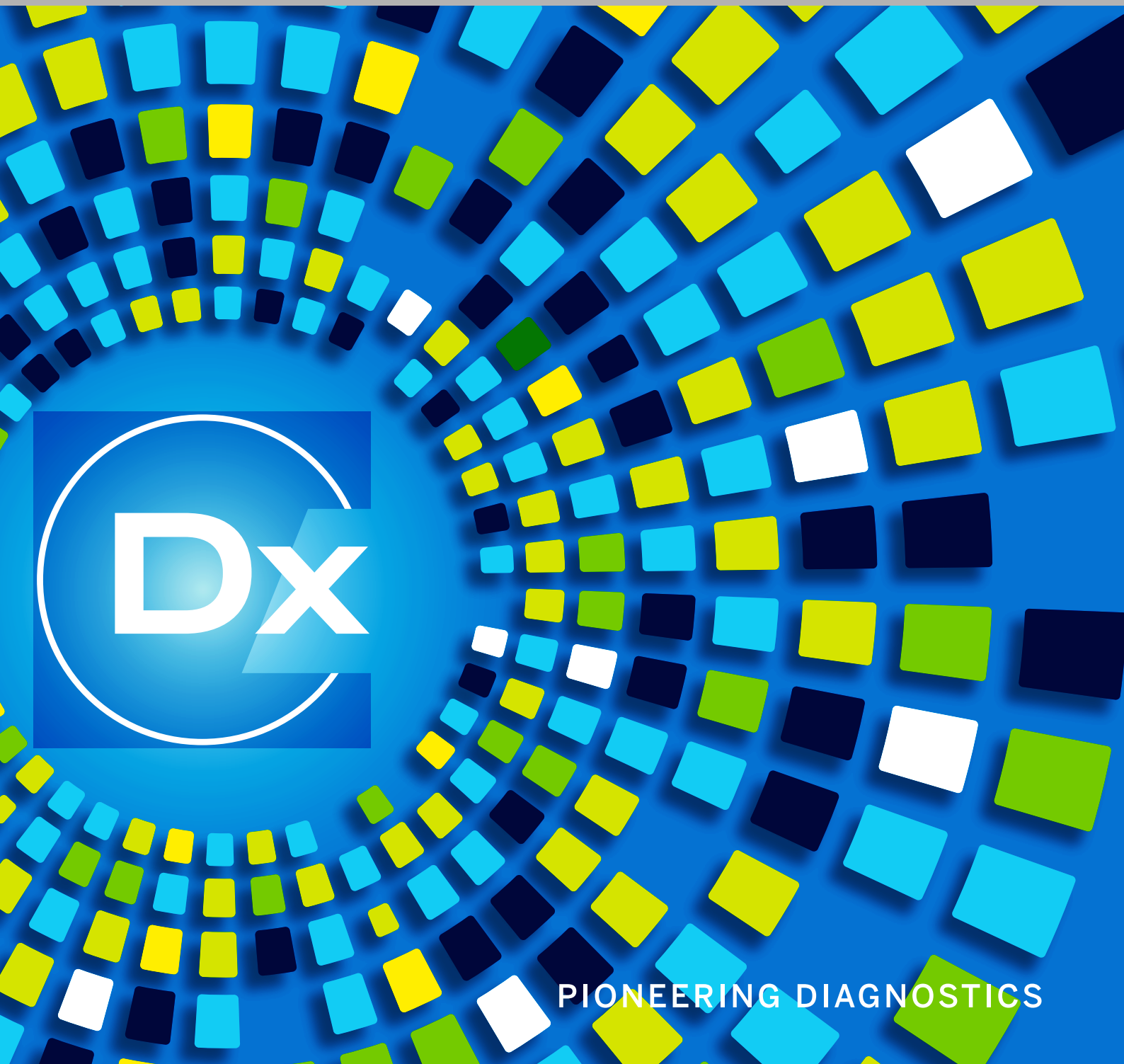
BIOMÉRIEUX

EVIDENCE-BASED DIAGNOSTICS FOR ANTIMICROBIAL STEWARDSHIP

Selection of publications

2024 EDITION



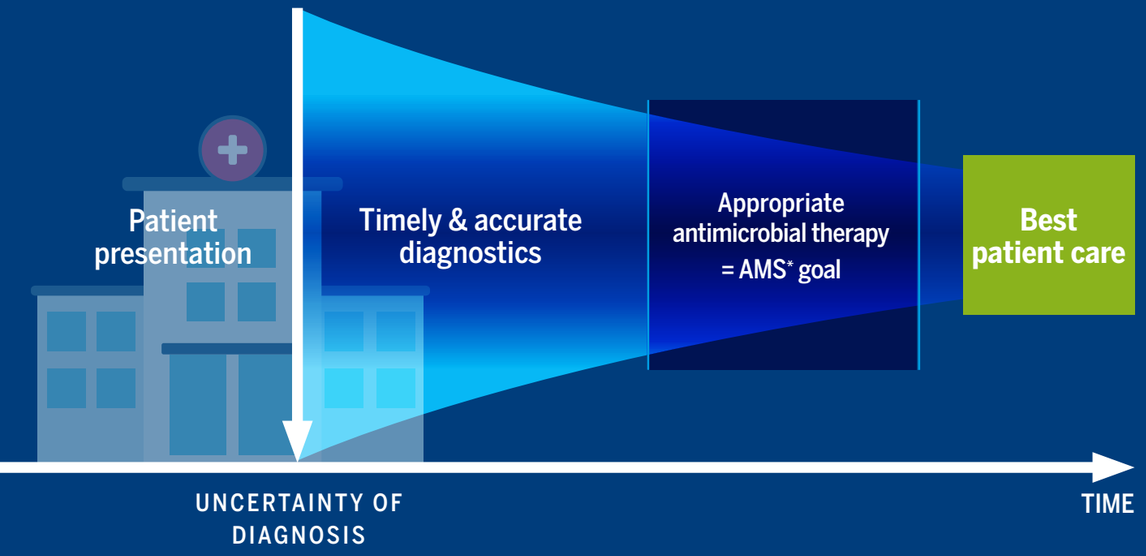
How can Appropriate Antimicrobial Therapy be defined?

> **“ The right antibiotic for the right patient, at the right time, with the right dose, and the right route, causing the least harm to the patient and future patients.[1] ”**

What is the Value of Diagnostics-guided Antimicrobial* Prescribing?

The sooner the appropriate therapy, the better the patient outcome.
By reducing the window of clinical uncertainty, rapid diagnostic test results support earlier prescription of the appropriate antimicrobial therapy.

DIAGNOSTICS CONTRIBUTE TO HIGHER MEDICAL VALUE LEADING TO BETTER PATIENT CARE [2]



* AMS: antimicrobial stewardship

1. Grissinger M. The Five Rights: A destination without a map. *Pharmacy and Therapeutics*. 2010;35(10):542.
2. bioMérieux.

** In this document, the term "antimicrobials", encompassing antibiotics, antifungals and antiviral drugs, will be frequently replaced by "antibiotics", which represent the most commonly prescribed therapy.*

PREFACE

Antimicrobial resistance (AMR) has been increasingly on national and international public health agendas for many years. Whilst the political declaration by the United Nations General Assembly on antimicrobial resistance in 2016[1] brought AMR up the agenda for many governments, enabling traction for the WHO Global Action Plan[2] on AMR, and stimulating nations to develop their own National Action Plans (NAPs) on AMR, progress has been varied. Indeed, an analysis of existing NAPs for AMR[3] identified great international variability, highlighting gaps and opportunities to further optimize antimicrobial use.

With the drivers of AMR known for many years, and with increasing evidence behind each factor, and greater understanding of how these relatively affect global AMR[4], strategies to best implement **antimicrobial stewardship (AMS)** continue to be developed. **Antimicrobial stewardship programs (ASPs)** should clearly focus on minimizing suboptimal use of antimicrobials in human and animal health, and diagnostics have a key role to play in achieving this objective, even though evidence generation to support this has historically been slow[5]. Indeed, whilst at the individual patient level, diagnostics are core to accurate diagnoses and optimized treatment, diagnostics were only named as core enablers in the management of infections in 28 (26%) of 108 NAPs[3].

With the significant **potential of diagnostics to impact patient care** at the individual level (both patient outcomes and AMS goals), it is important to reflect on the utility and applicability of diagnostic tools across the spectrum of infectious diseases. Whilst specific diagnostic tools will vary between regions and nations, many aspects are applicable to both high-resource and low-and-middle-income (LMIC) countries[5]. Yet when potential enablers and barriers to increased diagnostics use are considered[6], there are key areas where clinicians, laboratory practitioners, and policy makers alike should focus. These include ensuring access to diagnostics, integrating diagnostics into patient pathways, developing expertise in their use, and allocating appropriate resources to diagnostics within wider healthcare budgets.

The articles summarized in this **Selection of Publications** provide real-world evidence and scientific data to support the effectiveness of ASPs, and demonstrate the key role diagnostics play in defining and prescribing responsible and appropriate therapy to improve ASP goals.

We hope that this document will be a useful, informative resource to encourage and support healthcare professionals in their pursuit of optimal antimicrobial prescribing practices.

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1. United Nations (UN). Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance : draft resolution / submitted by the President of the General Assembly (71st sess. : 2016-2017). Accessed on Nov 23, 2023 https://digitallibrary.un.org/record/842813?ln=en
2. World Health Organization (WHO). Global action plan on antimicrobial resistance. 2016. Accessed on Nov 23, 2023 https://www.who.int/publications/i/item/9789241509763
3. Charani E, Mendelson M, Pallett SJC, *et al.* An analysis of existing national action plans for antimicrobial resistance-gaps and opportunities in strategies optimising antibiotic use in human populations. *Lancet Glob Health.* 2023;11(3):e466-e474. doi:10.1016/S2214-109X(23)00019-0
4. Holmes AH, Moore LS, Sundsfjord A, *et al.* Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet.* 2016;387(10014):176-87. doi:10.1016/S0140-6736(15)00473-0
5. Apisarnthanarak A, Bin Kim H, Moore LSP, *et al.* Utility and Applicability of Rapid Diagnostic Testing in Antimicrobial Stewardship in the Asia-Pacific Region: A Delphi Consensus. *Clin Infect Dis.* 2022;74(11):2067-2076. doi:10.1093/cid/ciab910
6. Moore LSP, Villegas MV, Wenzler E, *et al.* Rapid Diagnostic Test Value and Implementation in Antimicrobial Stewardship Across Low-to-Middle and High-Income Countries: A Mixed-Methods Review. *Infect Dis Ther.* 2023;12(6):1445-1463. doi:10.1007/s40121-023-00815-z

ABBREVIATIONS & ACRONYMS

ABX	antibiotics
ADE	adverse drug events
AMR	antimicrobial resistance
AMS	antimicrobial stewardship
ARI	acute respiratory infection
ART	antimicrobial resistance testing
ASI	antimicrobial stewardship intervention
ASP	antimicrobial stewardship program
AST	antimicrobial susceptibility testing
BAL	bronchoalveolar lavage
BPA	best practice alert
BSI	bloodstream infection
CAP	community-acquired pneumonia
CDSS	clinical decision support system
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPE	carbapenemase-producing *Enterobacterales*
CRE	carbapenem-resistant *Enterobacterales*
CTX	cefotaximase
DDD	daily defined dose
DOT	duration of therapy
EMR	electronic medical record
EPEC	enteropathogenic *Escherichia coli*
ESBL	extended spectrum beta-lactamase
GNB	gram-negative bacteria
HAI	healthcare-associated infections
HAP	hospital-acquired pneumonia
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
ID	identification
IPTW	inverse probability treatment weighting
LMIC	low- and middle-income countries
LOS	length of stay
LRTI	lower respiratory tract infection
MALDI-TOF	matrix-assisted laser desorption / ionization-time of flight
MDRO	multi-drug resistant organism
MIC	minimum inhibitory concentration
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
MTB	multi-test bundle
NAP	National Action Plan
NICU	neonatal intensive care unit
NPV	negative predictive value
OR	odds ratio
PCR	polymerase chain reaction
PCT	procalcitonin
PK/PD	pharmacokinetics / pharmacodynamics
PNA-FISH	peptide nucleic acid fluorescent *in situ* hybridization
POCT	point of care testing
PPS	point prevalence survey
PPV	positive predictive value
QALY	quality-adjusted life-year
RCT	randomized control trial
RDT	rapid diagnostic test
RSV	respiratory syncytial virus
RTI	respiratory tract infections
SA	septic arthritis
SOC	standard of care
TDM	therapeutic drug monitoring
TTAT/TTET	time to appropriate/effective therapy
TTR	time to result
VAP	ventilator-associated pneumonia
VRE	vancomycin-resistant enterococci

GLOSSARY

ANTIMICROBIAL THERAPY

Empiric therapy: educated decision based on patient presentation and local antibiogram

Targeted/oriented therapy based on initial rapid testing results providing evidence of the nature of the infectious micro-organism (none, bacteria, fungus, virus, parasite) and sometimes resistant determinants

Appropriate therapy (optimal, effective, definitive therapy): microbiologically active therapy based on antimicrobial susceptibility testing and antibiotic sustainability

Personalized therapy: optimizing antimicrobial exposure in selected patient populations (using biomarkers, PK/PD targets, MIC,...)

MEDICAL INDICATORS AND OUTCOMES

When considering the impact of different AMS interventions, it is necessary to take into account a range of indicators and outcomes, in order to determine the beneficial impact or unintended consequences. Furthermore, when specifically considering a diagnostic test as a potential tool for AMS, it is important to consider at what point in the patient journey that diagnostic device could have impact, in order to select relevant outcome metrics. Otherwise, the impact of diagnostics can be underestimated.

ANTIMICROBIAL PRESCRIBING INDICATORS

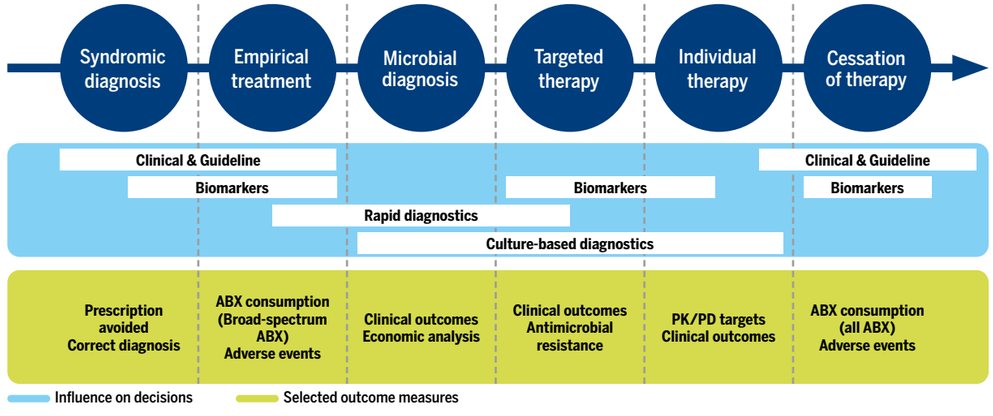
- Antibiotic therapy initiation rate
- Time to appropriate therapy
- Proportion of appropriate antibiotic therapy
- Antibiotic exposure (duration & quantity of antibiotic used during a course of treatment)
- Length/duration of therapy
- Antibiotic de-escalation/escalation
- Time to oral switch
- Reduction in antimicrobial usage: days of therapy (DOT), defined daily dose (DDD)

PATIENT OUTCOMES

- Microbiological eradication
- Clinical resolution/cure rate
- Length of stay (LOS)
- Morbidity
- 30-day mortality
- Time to discharge
- Re-admission at 30 days
- Patient safety
- Adverse effects (HAI, *C. difficile*, acute kidney injury)
- Quality of life post-care

Figure 1. Understanding how diagnostics influence antimicrobial prescribing decisions and potential outcome measures.

Reproduced with permission from Elsevier. Rawson TM, Moore LSP. Clin Microbiol Infect. 2023;29(6):666-669. doi: 10.1016/j.cmi.2023.03.010.



A SELECTION OF ANTIMICROBIAL STEWARDSHIP RESOURCES

■ GUIDELINES

CDC Guidelines: Core Elements of Hospital Antibiotic Stewardship Programs
https://www.cdc.gov/antibiotic-use/core-elements/hospital.html

IDSA/SHEA Guidelines: Implementing an antibiotic stewardship program
https://www.idsociety.org/practice-guideline/implementing-an-ASP/

Guide to Infection Control in the Healthcare Setting by International Society for Infectious Diseases (ISID)
https://isid.org/guide/amr/

NICE guideline: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use.
https://www.nice.org.uk/guidance/ng15

EU-Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI): Guidelines, tools and implementation methods for antibiotic stewardship
https://eu-jamrai.eu/increasing-prudent-use-of-antibiotics-human-health/

Pan American Health Organization (PAHO) / Florida International University (FIU) Recommendations for Implementing Antimicrobial Stewardship in Latin America and the Caribbean: Manual for Public Health Decision-Makers
https://www.paho.org/en/documents/recommendations-implementing-antimicrobial-stewardship-programs-latin-america-and

■ AMR/AMS REPORTS

Global antimicrobial resistance and use surveillance system (GLASS) report
https://www.who.int/glass/resources/publications/early-implementation-report-2020/en/

Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022;399(10325):629-655
doi:10.1016/S0140-6736(21)02724-0 Erratum in: Lancet. 2022 Oct 1;400(10358):1102.

■ POINT PREVALENCE SURVEY RESOURCES

WHO Point Prevalence Survey (PPS) methodology
https://apps.who.int/iris/bitstream/handle/10665/280063/WHO-EMP-IAU-2018.01-eng.pdf?ua=1

Global Point Prevalence Survey (Global-PPS) initiative led by the University of Antwerp
https://www.global-pps.com/

■ REPOSITORIES / DATABASES

ECDC Global and European repository on AMS
https://www.ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/prudent-use-antibiotics/antimicrobial

CIDRAP-ASP (Center for Infectious Disease Research and Policy) web-based resource: Antimicrobial stewardship project with emphasis on news, commentary, webinars, podcasts, etc.
http://www.cidrap.umn.edu/asp

BSAC Antimicrobial Resistance Centre (ARC): resource database for guidelines, MOOC courses, publications, research papers, etc.
http://www.bsac-arc.com

■ ON-LINE COURSES

WHO - Antimicrobial stewardship: a competency- based approach
https://openwho.org/courses/AMR-competency

CDC - Antibiotic Stewardship Training Series
https://www.train.org/cdctrain/training_plan/3697

The role of Diagnostics in the Antimicrobial Resistance Response
https://www.futurelearn.com/courses/role-of-diagnostics-in-the-amr-response

BSAC with University of Dundee and FutureLearn – Massive Open Online Courses (MOOCs)

Antimicrobial Stewardship: Managing Antibiotic Resistance (available in English, Mandarin, Spanish, Russian, and Portuguese translations) Region-specific AMS modules are also available.
https://www.futurelearn.com/courses/antimicrobial-stewardship

■ E-BOOKS / TOOLKITS / PRACTICAL GUIDANCE

Antimicrobial Stewardship (AMS), Volume 2, 1st Edition.
https://www.elsevier.com/books/antimicrobial-stewardship/pulcini/978-0-12-810477-4

WHO Practical Toolkit: Antimicrobial Stewardship Programmes in Healthcare Facilities in Low- and Middle-Income Countries
https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-eng.pdf

Antimicrobial stewardship: a practical guide to implementation in hospitals; and other educational booklets
https://www.biomerieux.com/en/education/antimicrobial-resistance-antimicrobial-stewardship/educational-materials

CONTENTS

DISCONTINUATION OF ANTIBIOTIC THERAPY

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis. A Randomized Trial. 60

Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, *et al.*
AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 2021;203(2):202-210.

ANTIMICROBIAL RESISTANCE SURVEILLANCE

Epidemiology of Antimicrobial Resistance Among Blood and Respiratory Specimens in the United States Using Genotypic Analysis From a Cloud-Based Population Surveillance Network. 64

Timbrook TT, Olin KE, Spaulding U, *et al.*
OPEN FORUM INFECTIOUS DISEASES 2022;9(7):ofac296.

ADDITIONAL RECOMMENDED READING

ERS/ESICM/ESCMID/ALAT Guidelines for the Management of Severe Community-Acquired Pneumonia.

Martin-Loeches I, Torres A, Nagavcj B, *et al.*
EUROPEAN RESPIRATORY JOURNAL 2023;61:2200735.

Utility and Applicability of Rapid Diagnostic Testing in Antimicrobial Stewardship in the Asia-Pacific Region: A Delphi Consensus.

Apisarnthanarak A, Kim HB, Moore LSP, *et al.*
CLINICAL INFECTIOUS DISEASES 2022;74(11):2067-2076

Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations From the IDSA's Diagnostics Committee.

Hanson KE, Azar MM, Banerjee R, *et al.*
CLINICAL INFECTIOUS DISEASES 2020:712744-2751.

Combining Procalcitonin and Rapid Multiplex Respiratory Virus Testing for Antibiotic Stewardship in Older Adult Patients With Severe Acute Respiratory Infection.

Lee C-C, Chang J C-Y, Mao X-W, *et al.*
JOURNAL OF THE AMERICAN MEDICAL DIRECTORS ASSOCIATION 2020;21:62-67.

MEDICAL BENEFITS OF ANTIMICROBIAL STEWARDSHIP

Figure 1. Goals of antimicrobial stewardship programs (ASPs)
Source: bioMérieux

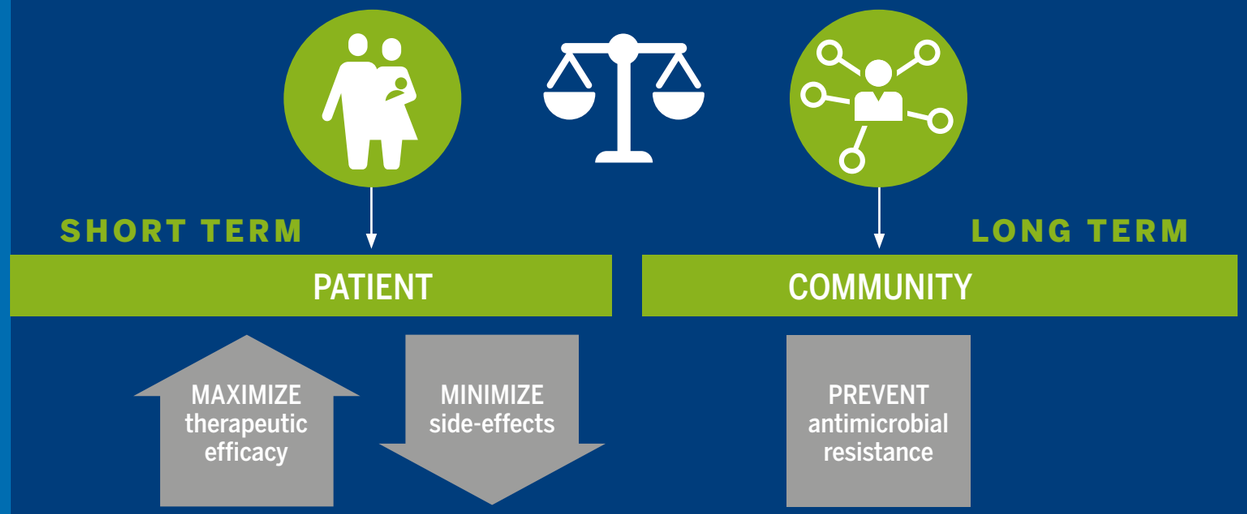
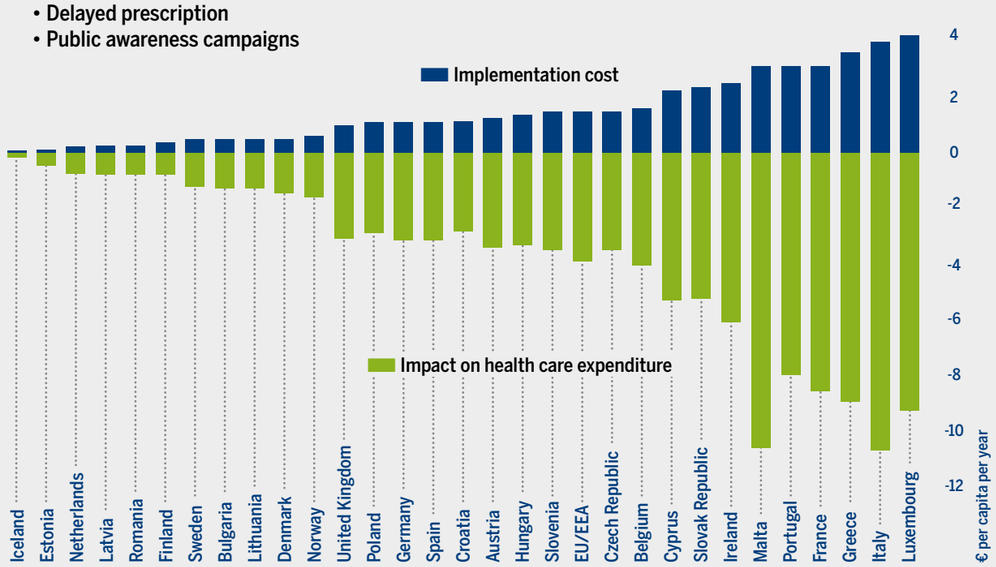


Figure 2. Economic assessment* of the "mixed-intervention" package: just a few euros more produce substantial savings in health care expenditure
Reproduced with permission from OECD. OECD Policy Brief: Stemming the Superbug Tide: Just a Few Dollars More. 2018

"MIXED-INTERVENTION" PACKAGE:
- **Improve hospital hygiene** (starting with hand hygiene)
- **Antimicrobial stewardship**
- **Rapid diagnostic tests** (bacterial *vs*. viral infection)
- **Delayed prescription**
- **Public awareness campaigns**



* Including effects on susceptible infections.

MEDICAL BENEFITS OF ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship (AMS) involves the careful and responsible management of antimicrobial prescribing practices and use in hospitals and healthcare settings worldwide.

AMS efforts are generally led by a dedicated multi-disciplinary team which develops and implements an **antimicrobial stewardship program (ASP)**.

The main objective of ASPs is to achieve the prescription of the **most appropriate antimicrobial therapy** with both short-term and long-term goals (**Figure 1**).

- **SHORT-TERM GOAL** improve individual patient outcomes through optimal therapy.
- **LONG-TERM GOAL** support public health and modern medicine by reducing antimicrobial resistance and sustaining the efficacy of existing antibiotics.

Indirectly, appropriate prescribing also **generates cost-savings**, by enabling, for example, shorter length of stay, lower 30-day readmission rates and optimized hospital resource management. Reports[1,2] have demonstrated that investing 1.5 Euros or 2 USD per capita per year in a package of mixed public health measures, would avoid about 27,000 deaths per year in EU/EEA* countries and about 47,000 deaths annually in OECD** countries (**Figure 2**). Furthermore, such a public health package could pay for itself within just one year and end up **saving about 1.4 billion Euros per year in EU/EEA countries**, and **4.8 billion USD per year in OECD countries**.[2]

ASPs positively impact antimicrobial prescribing practices globally, although implementation is more challenging in low- and middle-income countries (LMICs). Investment in basic infrastructure, the development of affordable, rapid diagnostics with more robust systems for their procurement, supply and storage as well as overall quality assurance are essential to successfully implement ASPs in these settings.

The publications in this section demonstrate how antimicrobial stewardship programs improve patient safety and outcomes, decrease antimicrobial resistance and generate cost-savings. The specific challenges and levers for action in LMICs are also addressed in a position statement by the International Society for Infectious Diseases (ISID).[3]

* EU/EEA: European Union/European Economic Area
** OECD: Organisation for Economic Co-operation and Development
1. OECD/ECDC Briefing Note for EU/EAA Countries. 2019 Antimicrobial Resistance: Tackling the Burden in the European Union.
2. OECD Policy brief. 2018 Stemming the Superbug Tide: Just a Few Dollars More.
3. Pierce J, Apisarnthanarak A, Schellack N, *et al.* Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries: A position statement for the international society for infectious diseases. *Int J Infect Dis.* 2020;96:621-629.

CLICK TO ACCESS ARTICLE

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES
2019;357(2):103-110

Impact of Delayed Appropriate Antibiotic Therapy on Patient Outcomes by Antibiotic Resistance Status from Serious Gram-negative Bacterial Infections.

Bonine NG, Berger A, Altincatal A, Wang R, Bhagnani T, Gillard P, Lodise T.

OBJECTIVE

This study consisted of the retrospective analysis of a large in-patient hospital database to assess the clinical and economic burdens associated with delayed receipt of appropriate therapy among patients with infections due to Gram-negative bacteria, stratified by antibiotic resistance status.

STUDY DESIGN

This analysis studied data from the Premier Hospital Database from over 56,000 patients treated in 150 hospitals throughout the United States. The study population included adult patients admitted from July 2011 to September 2014 with evidence of complicated urinary tract infection, complicated intra-abdominal infection, hospital-acquired pneumonia, or bloodstream infection who also had (1) a positive culture for gram-negative bacteria from a site consistent with the infection type and (2) a length of stay (LOS) of ≥1 day. Patients were divided into two groups based on the antibiotic susceptibility profile of the infecting pathogen (resistant or susceptible).

The group with GNB-resistant infections included patients showing evidence of infection with one or more of the following pathogens: carbapenem-resistant *Enterobacterales* (CRE), carbapenem-resistant *Pseudomonas* sp, multidrug-resistant *P. aeruginosa* and extended spectrum beta-lactamase producing *Enterobacterales*.

Therapy was defined as timely and appropriate when used antibiotics had relevant microbiological activity (matching identification and susceptibility based on culture) and were administered within 2 days of the index date. Appropriate therapy was considered to be delayed when antibiotics with relevant microbiological activity were administered beyond 2 days of the index date.

RESULTS

A total of 56,357 patients with GNB infections were included in the analysis: 6,055 with infections caused by resistant GNB and 50,302 with infections caused by susceptible GNB.

Delayed appropriate therapy was received by 2,800 patients out of 6,055 (46.2%) with resistant infections and 16,585 patients out of 50,302 (33.0%) with susceptible infections **(Table 1)**.

Delayed appropriate therapy was associated with:

a) significantly longer duration of antibiotic therapy (+4.5 days, $p<0.01$);

b) longer LOS (+4.9 days, $p<0.01$);

c) higher in-hospital costs (+$11,508, $p<0.01$).

CONCLUSIONS

Firstly, these study findings show that delays in delivering appropriate therapy are linked to worse clinical and economic outcomes among patients with gram-negative infections, regardless of resistance status.

Secondly, ensuring timely initial therapy has a greater influence on clinical and economic outcomes than does the difference between the resistant or susceptible status of the pathogen.

Thirdly, the negative impact of delayed appropriate therapy was similar on outcomes of infections caused by both resistant and susceptible organisms. Consequently, this study also highlights the importance of rapid pathogen identification to prescribe the appropriate antibiotic(s) as early as possible in the treatment pathway.

Timely availability of identification and susceptibility data can help practitioners streamline therapy and minimize the duration of broad-spectrum antibiotic use to reduce growing antimicrobial resistance and sustain antibiotic efficacy.

ANTIMICROBIAL STEWARDSHIP – PATIENT OUTCOME BENEFITS

Table 1. Association of delayed appropriate therapy *vs.* timely appropriate therapy with infection-related outcomes.

Reproduced with permission from Elsevier. Bonine NG, *et al. The American Journal of the Medical Sciences* 2019;357(2):103-110

Outcome[a]	Serious infections due to resistant pathogens (CRE, CRP, MDRP or ESBL)		Serious infections due to susceptible pathogens	
	Delayed appropriate therapy (n=2,800)	Timely appropriate therapy (n=3,255)	Delayed appropriate therapy (n=16,585)	Timely appropriate therapy (n=33,717)
Mean (95% CI) duration of antibiotic therapy, days	12.7 (12.4-13.0)[b]	8.2 (8.0-8.4)	11.3 (11.2-11.4)[b]	6.4 (6.4-6.5)
Mean (95% CI) LOS, days	13.6 (13.3-14.0)[b]	8.7 (8.5-9.0)	12.1 (12.0-12.2)[b]	6.6 (6.5-6.6)
Mean (95% CI) total in-hospital costs to hospital to render care, $	32,518 (31,491-33,579)[b]	21,010 (20,348-21,695)	21,852 (21,648-22,058)[b]	12,345 (12,231-12,460)
Multivariate OR (95% CI)				
Discharged home	0.7 (0.6-0.8)		0.7 (0.6-0.7)	
In-hospital death or discharged to hospice	1.2 (1.1-1.3)		1.2 (1.2-1.3)	

CI, confidence interval; CRE, carbapenem-resistant *Enterobacterales*; CRP, carbapenem-resistant *Pseudomonas* sp; ESBL, extended spectrum beta-lactamase producing *Enterobacterales*; LOS, length of stay; MDRP, multi-drug-resistant *Pseudomonas* sp; OR, odds ratio.

[a] All values were estimated from the index date to discharge; in all instances, reference group was patients who received timely appropriate therapy. Each outcome was adjusted for variables that were included in the inverse probability weighting: age, Charlson Comorbidity Index score, preindex LOS, resource intensity cost index, complicated urinary tract index, complicated intra-abdominal infection index, admission type, sex, asthma, congestive heart failure, chronic pulmonary disease, myocardial infarction+coronary heart disease, hemiplegia/paraplegia, immunocompromising conditions, cancer, malnutrition, peripheral vascular disease, chronic renal disease, type diabetes, community-acquired infection *vs.* other source of infections, healthcare-associated infection, nosocomial infection, culture drawn in the intensive care unit, infection-related hospitalizations in prior 3 months.

[b] $p<0.01$

"Results of these analyses therefore suggest that better methods of early pathogen identification can reduce time to appropriate therapy, thereby improving outcomes and reducing in-hospital costs among hospitalized patients with serious infections due to gram-negative bacteria."

KEY FINDINGS

- **Incidence of delayed appropriate therapy for adult patients hospitalized for serious GNB infections is relatively high in both antibiotic-susceptible and antibiotic-resistant cases.**
- **In both cases, outcomes for patients with GNB infections improve significantly when timely appropriate therapy is provided.**
- **Improved early pathogen identification methods (diagnostics) make it possible to reduce time to appropriate therapy, contributing to lower costs and better outcomes for patients at risk for serious GNB infections.**

CLICK TO ACCESS ARTICLE

CLINICAL MICROBIOLOGY AND INFECTION
2022;28(4):479-490

Estimating Daily Antibiotic Harms: an Umbrella Review with Individual Study Meta-Analysis (Systematic Review).

Curran J, Lo J, Leung V, Brown K, Schwartz KL, Daneman N, Garber G, Wu JHC, Langford BJ.

OBJECTIVE

The study objective was to estimate antibiotic-associated harms across different indications, by quantifying the incremental daily risk of adverse events, superinfections and antimicrobial resistance in patients receiving shorter versus longer antibiotic therapy for common infections.

STUDY DESIGN

The study was an umbrella review with individual study meta-analysis. The researchers searched three major databases to retrieve systematic reviews from 2000 to 30 July 2020 in any language. Systematic reviews were required to evaluate shorter versus longer antibiotic therapy with fixed durations between 3 and 14 days. Randomized controlled trials included for meta-analysis were identified from the systematic reviews.

The primary outcomes were:

1. **adverse events,** defined as any undesirable effect attributed to antibiotic use;
2. **superinfections,** defined as new or recurrent infections caused by resistant or opportunistic pathogens;
3. **antimicrobial resistance,** defined as the presence or emergence of resistant microorganisms in clinical specimens.

The daily odds ratio (OR) of antibiotic harm was estimated and pooled using random effects meta-analysis.

RESULTS

- A total of 23,174 patients, adults and pediatrics, were evaluated for antibiotic-associated harms in 71 studies.
- Studies most commonly evaluated duration of therapy for respiratory tract (n= 36, 50.7%) and urinary tract (n = 29, 40.8%) infections.
- The most frequently used antibiotics were penicillins (n = 28, 39%), fluoroquinolones (n = 21, 30%), and cephalosporins (n = 18, 25%).
- A total of 4,565 antibiotic-associated harm events were reported (19.6%).
- Out of these, adverse drug events were the most common harm reported in 19.9% (n = 4,039/20,345), followed by antimicrobial resistance in 10.6% (n = 246/2,330) and superinfections in 4.81% (n = 280/5,776) of patients **(Figure 1).**
- Each additional day of antibiotic therapy was associated with a 4% increased odds of adverse events (OR 1.04, 95% CI 1.02 -1.07).
- The daily odds of severe adverse effects also increased by 9% (OR 1.09, 95% CI 1.00 -1.19).
- No association was found between days of antibiotic therapy and the daily risk of superinfections (OR 0.98, 95% CI 0.92-1.06).
- The daily incremental odds of antimicrobial resistance were OR 1.03 (0.98 -1.07).

CONCLUSIONS

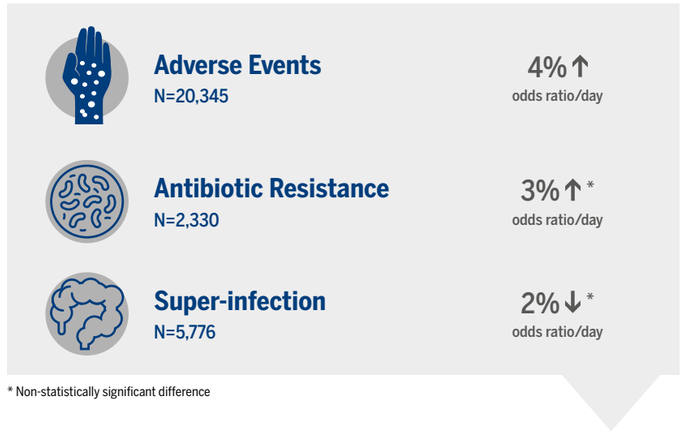
The study highlights the potential harms of prolonged antibiotic therapy and the benefits of prescribing shorter courses of therapy. These findings may provide additional context for clinicians when weighing the benefits versus risks of prolonged antibiotic therapy, and may also inform clinical guideline and policies related to antibiotic prescribing and stewardship.

"Each additional day of antibiotic therapy is associated with measurable antibiotic harm, particularly adverse events."

ANTIMICROBIAL STEWARDSHIP – PATIENT OUTCOME BENEFITS

Figure 1. Antibiotic-associated harm events

Reproduced with permission from Elsevier. Curran J, *et al. Clinical Microbiology and Infection* 2022;28(4):479-490



KEY FINDINGS

- 20% of patients developed an antibiotic-associated harm event. Each additional day of antibiotic therapy was associated with a 4% per day increased odds of adverse events and 9% per day increased odds of serious adverse events.
- This study highlights the importance of using antibiotics judiciously and for the shortest duration possible to minimize the risk of adverse effects, superinfections, and antimicrobial resistance.
- Clinicians should consider the potential harms of prolonged antibiotic therapy when weighing the benefits versus risks of treatment.

CLICK TO ACCESS ARTICLE

ANTIMICROBIAL RESISTANCE AND INFECTION CONTROL
2019;8:35

Value of Hospital Antimicrobial Stewardship Programs [ASPs]: a Systematic Review.

Nathwani D, Varghese D, Stephens J , Ansari W, Martin S, Charbonneau C.

OBJECTIVE

Hospital antimicrobial stewardship programs (ASPs) are primarily designed to improve patient outcomes and safety, and promote appropriate antimicrobial prescribing to fight antimicrobial resistance (AMR). Demonstrating the cost-effectiveness of such a program is, however, also an important factor to ensure adoption and implementation of ASPs. This systematic review aimed to assess the economic and clinical impact of ASPs.

STUDY DESIGN

The study took as its starting point a previous systematic literature review conducted by J-W Dik *et al*., providing an assessment of methods used for published economic evaluations of hospital ASP studies, 2000-2014.

For the present study, the authors conducted a systematic review on Embase and Medline, using the same framework used by Dik *et al*., and limiting their review to primary research studies from September 2014 to December 2017. Following ASP implementation, various criteria were evaluated, including length of stay (LOS), antimicrobial costs and total hospital costs (including ASP implementation and operational costs).

RESULTS

A total of 146 primary research studies were reviewed, originating from North America (49%), Europe (25%) and Asia (14%). A majority of the studies were conducted in hospitals with 500 to 1,000 beds.

Overall, after implementation of ASPs, 92% of studies showed a reduction of antibiotic costs, and 85% a reduction in LOS. LOS was the key driver of cost savings. The mean cost reduction varied by hospital size and geographic region. Hospitals with comprehensive ASPs, including therapy review and antibiotic restrictions, reported higher cost savings.

Outcomes were classified into three categories:

- **ANTIMICROBIAL OUTCOMES**
  - 68% of relevant studies reported changes in antibiotic use, including defined daily dose, days of therapy, and proportion of patients on antimicrobial treatment.
  - Overall antibiotic use decreased in most studies.
  - 61% of the 18 statistically-significant studies measuring antimicrobial resistance found a significant change in AMR post-ASP implementation after a mean interval period of 24.5 months (range 6-36 months).
- **PATIENT OUTCOMES**
  - 85% of studies saw a reduction or no change in LOS, ranging from 0 to 22 days after ASP implementation.
  - An average decrease in LOS of 3.24 days or 20.6% per patient following ASP intervention was noted for statistically significant studies.
  - Among studies that reported significant changes in mortality rates, there was an average decrease of 10.5% in all-cause mortality rates and 11.3% in infection-related mortality rates following an ASP intervention.
- **ECONOMIC OUTCOMES**
  - Antibiotic expenditure: 97% of studies showed a decrease in antimicrobial costs, averaging 36%.
  - LOS costs: all three studies documenting this point showed reductions ranging from $18,300 in a small hospital to 970,397 kr (Swedish Krona) and $1.95M for 2 large-sized hospitals.
  - Overall aggregated hospital costs associated with patient treatment for bacterial infection, typically including LOS, diagnostics, treatment, and ASP costs were documented in 1/3 of all studies (49) and all generated cost savings.
  - Cost savings averaged $435,000 (range: $9,110 to $2 million) per year for the hospital, or $732 per patient (range: $2.50 to $2,640) in studies measuring costs in USD.
  - Cost savings averaged €41,500 (range: €19,000 to €66,200) per year for the hospital, or €198 (range: €40 to €529) per patient for data in EUR. In particular, in Europe the proportion of a bed stay saved through ASP represents 60-80% of the cost of a bed stay **(Table 1)**.
  - Higher cost savings were generated at hospitals implementing comprehensive ASPs with therapy review and antibiotic restrictions.

ANTIMICROBIAL STEWARDSHIP – ECONOMIC BENEFITS

CONCLUSIONS

The economic and clinical value of hospital antimicrobial stewardship programs is supported by this systematic review, which analyzes specific beneficial health outcomes achieved per dollar spent **(Figure 1)**. The review indicates that the cost of implementing ASPs can be offset by subsequent savings. For a full critical appraisal of the value of ASPs, more research is needed, in particular real-world studies in diverse resource settings and geographies.

Table 1. Cost savings compared with bed day costs around the world.

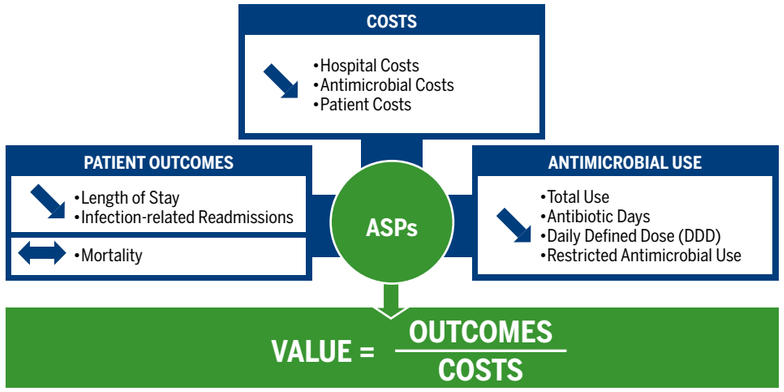
Reproduced from Nathwani D, *et al*. *Antimicrobial Resistance and Infection Control* 2019;8:35. Open Access Licence CC-BY

	United States	European Union	United Kingdom
Annual Per Patient Cost Savings with ASP	$732.00	€198.00	£304.00
Average Hospital Bed Day Cost, 2015	$2,271 [2]	€328.64 [154, 155][a]	£375.86 [154, 155][a]
Estimated Cost Offset as a Bed Day Saved Annually	32%	60%	80%

[a]Original WHO 2008 costs in US$ were inflated to 2015 costs and converted to Euro or Pound Sterling

Figure 1. Value framework for ASP implementation.

Adapted from Nathwani D, *et al*. *Antimicrobial Resistance and Infection Control* 2019;8:35



" The findings [...] suggest that costs associated with start-up and implementation of ASPs are potentially offset by subsequent cost-savings."

KEY FINDINGS

Economic benefits of ASP interventions:

- **85% of relevant studies showed a decrease in LOS (3.24 days on average). Shorter LOS was a key driver in cost savings.**
- **92% of relevant studies showed a decrease in spending on antimicrobials. Cost savings were higher in hospitals with comprehensive ASPs focused on therapy review and antibiotic restrictions.**
- **Mean cost savings in the US were $435,000 per hospital per year.**
- **Initial investment in an ASP can be paid off by the cost-savings generated.**

MEDICAL VALUE OF DIAGNOSTICS IN ANTIMICROBIAL STEWARDSHIP

Figure 1. Role of diagnostics to support responsible antibiotic prescribing
Reproduced with permission from the American Society of Microbiology (ASM). Messacar *et al*. *Journal of Clinical Microbiology* 2017;55:715-723

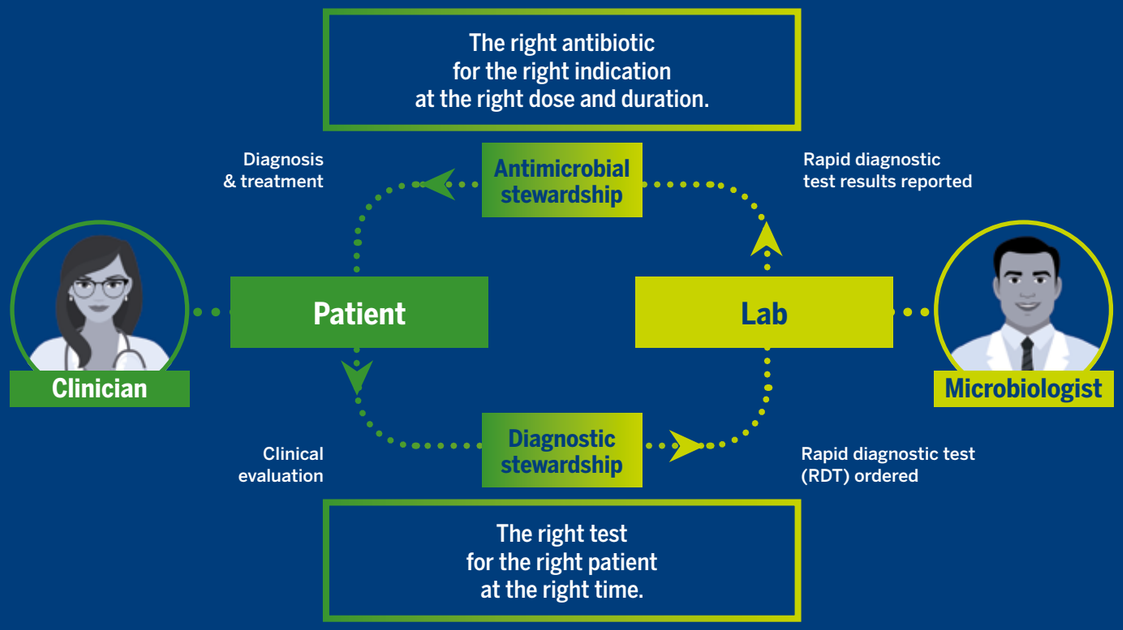


Figure 2. The "Optimal Equation" for appropriate antimicrobial prescribing
Source: bioMérieux

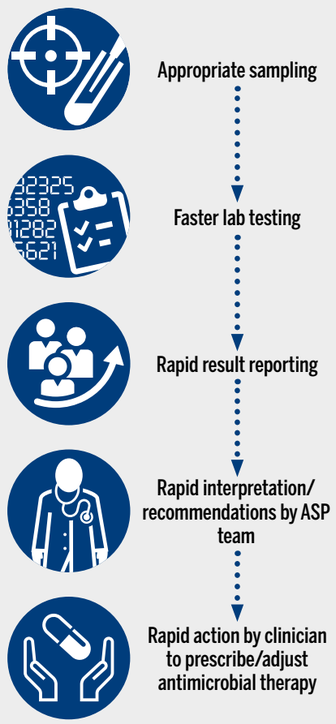
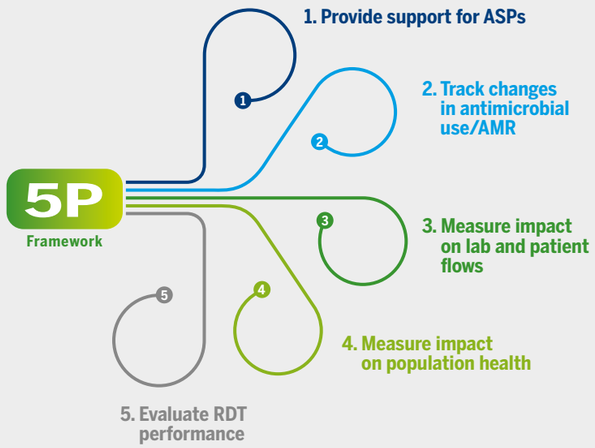


Figure 3. The 5P Value Framework
Adapted from Moore LSP, *et al. Infect Dis Therapy* 2023;12:1445–1463

The 5P Framework will allow future wider analysis of the value of rapid diagnostic tests (RDTs) in ASPs beyond per-patient outcome measures.

For a more detailed explanation of the 5P Framework see pages 22-23.



MEDICAL VALUE OF DIAGNOSTICS IN ANTIMICROBIAL STEWARDSHIP

Diagnostic tests are instrumental for Antimicrobial Stewardship Programs (ASPs), and have a decisive impact on clinical decision-making and patient care. They enable clinicians and pharmacists to more accurately tailor appropriate antibiotic therapy to maximize patient health outcomes.

To combat antimicrobial resistance and support antimicrobial stewardship efforts, diagnostics can play a key role on 2 different levels:

- 1. For the optimal diagnosis and appropriate management of a patient,
- 2. For the benefit and improvement of Public Health through screening and surveillance of antimicrobial resistance in order to maintain the effectiveness of existing antibiotics.

DETERMINING THE RIGHT TREATMENT FOR THE RIGHT PATIENT AT THE RIGHT TIME

To determine the most appropriate treatment for the patient, the clinician needs timely and accurate diagnostic test results.
The microbiology laboratory plays a crucial role in identifying precisely and rapidly the infectious agent, as well as ensuring its susceptibility to antibiotics, in order to help clinicians prescribe the right treatment at the right time **(Figure 1)**.

IMPROVED PATIENT OUTCOMES DEMAND FASTER RESULTS, REPORTING AND ACTION

Studies[1,2,3] have demonstrated that new, fast, accurate and reliable diagnostic technologies enable earlier prescription of responsible, appropriate antimicrobial therapy. Additionally, new digital tools, such as clinical decision support systems (CDSS), can efficiently support the work of the ASP teams.[4]
However, the optimal patient benefits of these new diagnostics can only be achieved if leveraged by an effective ASP team - with rapid reporting and translation of test results into actionable information for clinicians - through an optimized hospital workflow.

This requires a seamless partnership between clinical laboratories, pharmacists, and infectious disease clinicians, so that appropriate tests are ordered, appropriate samples are collected and diagnostic information is translated into appropriate patient management in real time (Figure 2).

The following summary (see page 26) of a publication by Pliakos *et al.*[2] illustrates how appropriate use and management of rapid diagnostics can positively impact appropriate therapy and patient outcomes, while being cost-effective.

In many low- and middle-income countries **(LMICs)**, however, diagnostic capabilities to support AMS initiatives are still severely lacking and there is an urgent need to develop simplified, affordable and rapid diagnostic tools. Diagnostics need to be better integrated into routine patient management, and clinical microbiologists have a central role to play in strengthening the role of diagnostic laboratories in these settings.[5]

A summary of a publication in Ethiopia (see page 58) reveals the cost-utility of a laboratory-supported pharmacist-led AMS intervention for inpatients in a low-resource setting in Africa[6]. The study results demonstrate improved health outcomes and substantial healthcare cost savings, despite greater upfront investments. Furthermore, a study in Brazil (see page 60) shows that an automated Identification/Antimicrobial Susceptibility Testing (ID/AST) method can provide early access to appropriate antimicrobial therapy for patients and have a positive clinical impact with a significant reduction in mortality and hospitalization time.[7]

The impact of rapid diagnostic tests (RDTs) appears to be gradually expanding in multiple directions, driving the conceptualization of a global value framework **(Figure 3).**

1. Timbrook TT, *et al*. *Clinical Infectious Diseases* 2017;64(1):15-23
2. Pliakos E, *et al. Clinical Microbiology Reviews* 2018;31(3):e00095-17
3. Beganovich M, *et al*. *Journal of Applied Laboratory Medicine* 2019;3(4):601-616
4. Nault V, *et al*. *Journal of Antimicrobial Chemotherapy* 2016;72:933-940
5. Yusuf E, *et al*. *Clinical Microbiology and Infection* 2019;25:6-9
6. Gebretekle GB, *et al. BMJ OPEN* 2021;11:e047515
7. Decarli A, *et al. Journal of Medical Microbiology* 2022;81(6):001543

CLICK TO ACCESS ARTICLE

INFECTIOUS DISEASE THERAPY
2023;12:1445–1463

Rapid Diagnostic Test Value and Implementation in Antimicrobial Stewardship Across Low-to-Middle and High-Income Countries: A Mixed-Methods Review.

Moore LSP, Villegas MV, Wenzler E, Rawson TM, Oladele RO, Doi Y, Apisarnthanarak A.

OBJECTIVE

The objective of the study was to assess the value of rapid diagnostic tests (RDTs) in antimicrobial stewardship programs (ASPs) across low-to-middle income and high-income countries.

STUDY DESIGN

The study utilized a mixed-methods approach, combining insights from a panel of seven infectious disease experts from Colombia, Japan, Nigeria, Thailand, the UK, and the USA, and evidence from a literature review.

RESULTS

- The experts propose an evaluation framework for RDTs, "The 5P (program support, preserve, practicable, population health, and precision) Value Framework" **(Figure 1)**, through which the value of RDTs in an ASP may be more optimally realized, beyond per-patient outcome measures.
- Optimally, RDTs should be used to facilitate decision-making throughout the clinical pathway, i.e. antimicrobial initiation, on-treatment, and de-escalation. Use of RDTs as part of bundled interventions that support decision-making is key. The experts acknowledged that molecular RDTs are most valuable in the initiation phase of the patient care pathway. Additionally, early, safe de-escalation of antimicrobials based on RDT results can also play an important role in ASPs by reducing antimicrobial consumption.
- A lack of setting-specific and robust clinical and economic outcome data is a key barrier to RDT uptake.
- Even when RDTs are not widely available, there is value in diagnostics as they aid surveillance and provide epidemiological data.
- Effective implementation across a range of resourcing, communication, education, logistic, and interfacing activities is key to realizing the value of RDTs within ASPs.
- Actionable advice for choosing an RDT is proposed.
- The experts advocate for the inclusion of RDTs in the World Health Organization Model List of essential *in vitro* diagnostics and in the iterative development of national action plans.

CONCLUSIONS

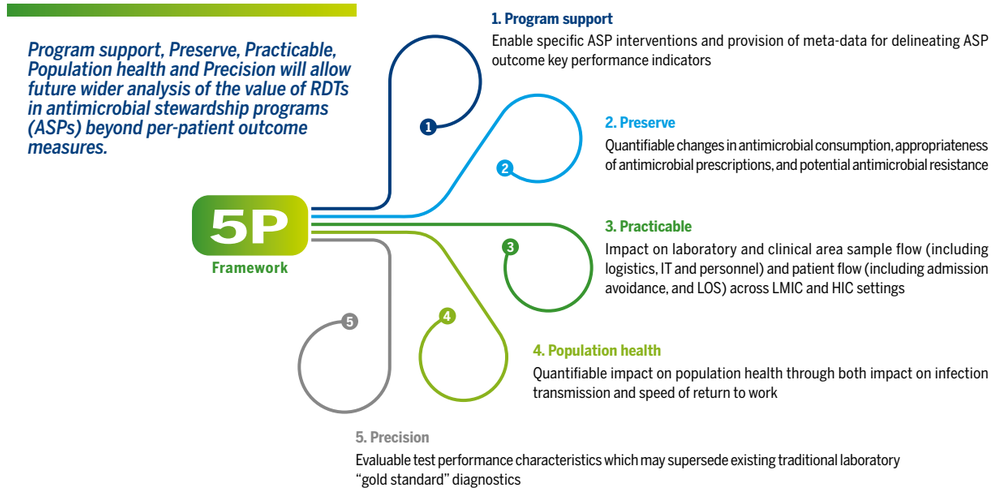
The study concluded that the utilization of RDTs in ASPs varies across low-to-middle income and high-income countries. In the USA, published evidence for the clinical and economic value of RDT use in ASPs is weighted towards bloodstream infections (BSIs) and more evidence generation is needed across other disease areas and regions.

To maximize the value of RDTs in ASPs, effective implementation and integration into global and national policies are essential.

"RDTs have significant potential to bring substantial value to patients, clinicians, ASPs, healthcare providers, and wider society."

RAPID DIAGNOSTICS FOR AMS IN LOW-TO-MIDDLE AND HIGH-INCOME COUNTRIES

Figure 1. The 5P Value Framework.
Adapted from Moore LSP, *et al. Infect Dis Therapy* 2023;12:1445–1463



ASP: antimicrobial stewardship program; HIC: high-income setting; IT: information technology; LMIC: lower-to-middle income countries; LOS: length of stay

KEY FINDINGS

- RDTs have far-reaching impact value in antimicrobial stewardship programs (ASPs) for hospitals, clinicians, patients and wider society.
- However, effective implementation is crucial for maximizing the benefits of RDTs in ASPs.
- Inclusion of RDTs in global and national policies is advocated for.

CLICK TO ACCESS ARTICLE

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY
2021;42:864–868 DOI:10.1017/ICE.2021.149

Rapid Diagnostic Testing for Antimicrobial Stewardship: Utility in Asia Pacific.

Apisarnthanarak A, Kim HB, Moore LSP, Xiao Y, Singh S, Doi Y, Kwa A L-H, Ponnampalavanar SS, Cao Q, Kim S-W, Lee HL and Santanirand P.

OBJECTIVE

The objective of this paper was to discuss the utility of rapid diagnostic testing (RDT) in antimicrobial stewardship (AMS) programs in the Asia Pacific region, as well as the challenges for their implementation, and to make recommendations.

STUDY DESIGN

In this narrative review, the authors discuss the challenges and opportunities associated with RDT use, including cost, logistics, and the need for further trials and data. The authors are experts in infectious disease, internal medicine, clinical microbiology, clinical pathology and pharmacy, originating from Asia-Pacific countries which have wide-ranging economic levels and many different infective pathogens.

RESULTS

Challenges:

- Insufficient funding of, and insufficient access to, some or all RDT technologies.
- Inability of some RDT platforms to accommodate the full range of relevant organisms, particularly where these differ from North America and Europe (e.g., tropical diseases).
- A lack of microbiology laboratories with sufficient internal expertise and/or external quality assurance.
- Suboptimal patient care pathways and reporting structures that hinder the process of obtaining rapid test results and subsequent implementation of findings.
- A lack of guideline recommendations and general guidance from professional societies, which compounds the lack of awareness and education among physicians regarding RDT and AMS outside of hospital intensive care and infectious disease departments.

Recommendations:

- Provide a working definition for RDT which will be appropriate to ASPAC settings.
- Recommend an inventory of RDTs appropriate for high, low and middle income countries in the region.
- Provide information on current barriers to the use of RDTs and possible solutions in various settings in ASPAC.
- Provide guidance on how to implement RDTs in current patient pathways **(Figure 1).**
- Provide advice on how to empower healthcare personnel to implement RDT.
- Target physicians from areas of medicine other than infectious diseases and other health care professionals such as nurses and pharmacists.

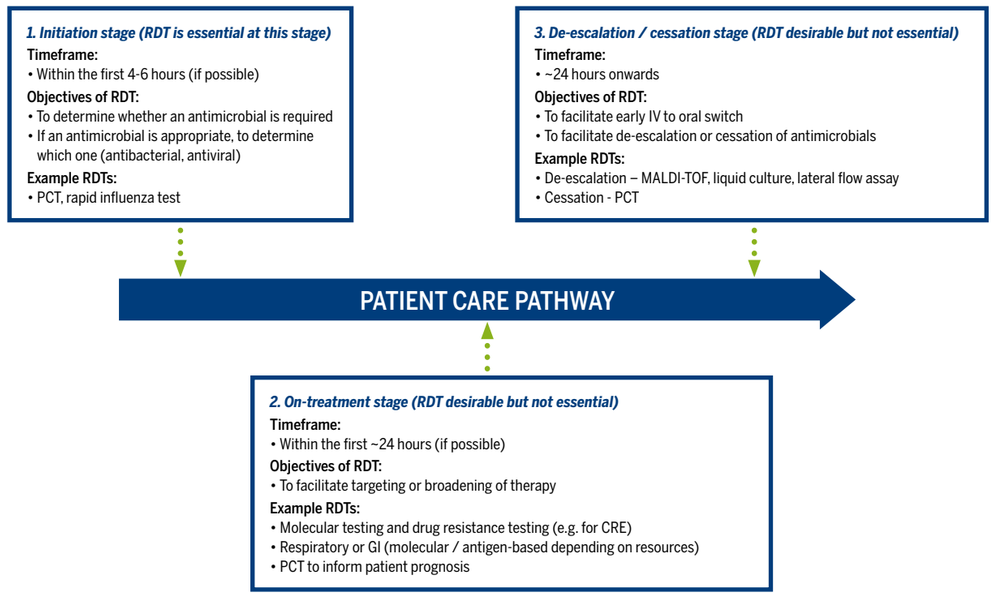
CONCLUSIONS

The authors conclude that RDT can be a valuable tool in AMS programs across the Asia Pacific region, but that more data are needed to optimize its use. They recommend a selective approach to RDT use, focusing on the initiation of antimicrobials, differentiating bacterial versus viral infections, and identifying locally relevant tropical diseases. In the absence of formal guidelines, regional consensus statements to guide clinical practice on the role of RDT in AMS are warranted and are currently being developed.

"... all stakeholders in Asia Pacific need to recognize the utility and potential benefits of RDT in AMS and take action to incorporate RDT to assist AMS efforts wherever it may be beneficial."

RAPID DIAGNOSTICS FOR AMS – ASIA-PACIFIC FOCUS

Figure 1. Impact of Rapid Diagnostic Testing at different time points during the patient journey.
Reproduced with permission from Oxford University Press. Apisarnthanarak A, *et al. Infection Control & Hospital Epidemiology* 2021;42:864–868



CRE: carbapenem-resistant Enterobacteriaceae; GI: gastrointestinal; IV: intravenous; MALDI-TOF: matrix-assisted laser desorption/ionization-time of flight; PCT: procalcitonin; RDT: rapid diagnostic testing

Moving from Utility to Application: Key actionable steps to integrate RDTs in AMS programs[1]:

- Identify an inventory of required RDTs at national and local levels.
- Establish AMS teams to interpret RDT reports and guide antimicrobial use.
- Develop institutional KPIs to measure effectiveness.
- Acquire high-quality data on RDT use in local trials.

1. Apisarnthanarak A, Kim HB, Moore L, *et al.* Utility and Applicability of Rapid Diagnostic Testing in Antimicrobial Stewardship in the Asia-Pacific Region: A Delphi Consensus. *Clin Infect Dis.* 2022;74(11):2067-2076. doi:10.1093/cid/ciab910

KEY FINDINGS

The recognized utility of rapid diagnostics for supporting antimicrobial stewardship need to be adapted and framed to the Asia Pacific context.

CLICK TO ACCESS ARTICLE

CLINICAL MICROBIOLOGY REVIEW
2018:31(3):E00095-17

The Cost-Effectiveness of Rapid Diagnostic Testing for the Diagnosis of Bloodstream Infections with or without Antimicrobial Stewardship.

Pliakos E, Andreatos N, Shehadeh F, Ziakas,PD, Mylonakis E.

OBJECTIVE

This study evaluated the cost-effectiveness of competing strategies for the diagnosis of patients with suspected bloodstream infection, when used alone or combined with an antimicrobial stewardship program (ASP).

STUDY DESIGN

A decision-analytic model comparing 12 strategies for the diagnosis of bloodstream infection was constructed with the main arms comparing the use of molecular rapid diagnostic tests (mRDTs) and conventional laboratory methods with or without an ASP.

Based on the availability of data in the literature, the cost-effectiveness of 7 mRDT* subcategories was assessed: PCR, MALDI-TOF, PNA-FISH, BC-GN, BC-GP with an ASP; PCR and PNA-FISH without an ASP.

The outcome for the analysis was the Incremental Cost-Effectiveness Ratio (ICER). The ICER numerator is the excess cost of a strategy over the reference conventional laboratory methods without an ASP, and the denominator is the incremental difference in effectiveness between the strategy in question and the baseline strategy. Effectiveness being defined as QALYs gained and death averted (QALY: Quality-Adjusted Life Years).

*PCR: Polymerase Chain Reaction; MALDI-TOF: Matrix Assisted Laser Desorption Ionization Time of Flight; PNA FISH: Peptide Nucleic Acid Fluorescent in situ Hybridization; BC GN/ BC GP: Blood Culture nanotechnology microarray system for Gram negative and positive bacteria

RESULTS

- In the base-case analysis, MALDI-TOF analysis with an ASP was the most cost-effective strategy, resulting in savings of $29,205 per quality-adjusted life year gained (ICER) and preventing 1 death per 14 patients with suspected bloodstream infection tested compared to conventional laboratory methods without an ASP.
- In the probabilistic analysis, mRDTs associated with an ASP had an 80.0% chance of being cost-effective, while mRDT without an ASP had only a 41.1% chance.

CONCLUSIONS

This study found that mRDTs are cost-effective for the diagnosis of patients with suspected bloodstream infection and can reduce health care expenditures **(Figure 1).**

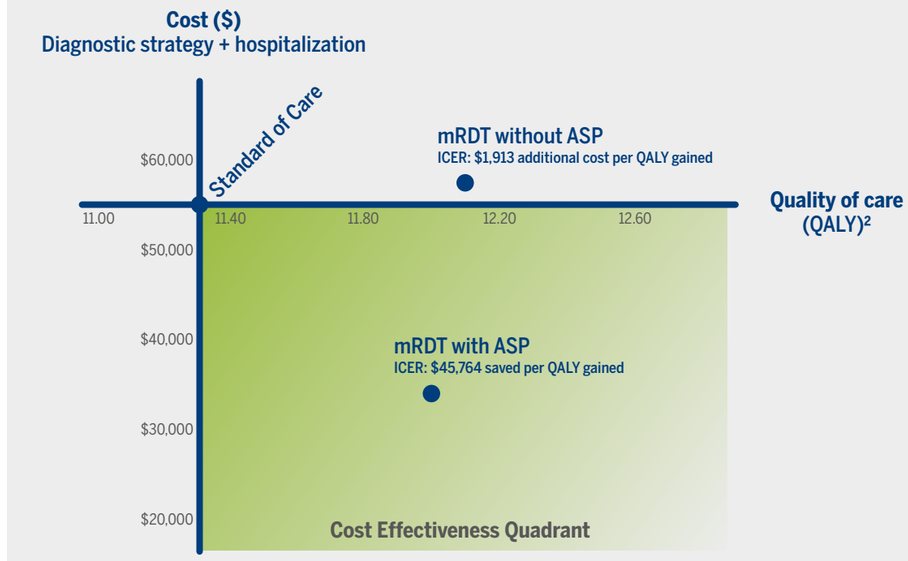
In addition, the ASP team is well placed to ensure that diagnostic tests are tailored to the clinical problem at hand, mRDT results are interpreted correctly, and antimicrobial agents are appropriately prescribed, thereby limiting the use of unnecessary empirical therapy.

"... the use of 'molecular' rapid diagnostic tests [...] was a cost-effective strategy that was associated with high therapeutic effectiveness and healthcare cost savings."

RAPID DIAGNOSTICS FOR AMS – COST-EFFECTIVENESS

Figure 1. Improving cost-effectiveness in the diagnosis of bloodstream Infections
Reproduced with permission from Elsevier. Pliakos E, *et al. Clinical Microbiology Review* 2018:31(3):e00095-17

Use of molecular rapid diagnostic tests (mRDTs), complemented by antimicrobial stewardship program (ASP) reduced the time to effective therapy and reduced healthcare costs.



ICER: Incremental Cost-Effectiveness Ratio; QALY: Quality Adjusted Life Years

KEY FINDINGS

- This study found that the use of 'molecular' rapid diagnostic tests for the diagnosis of patients with suspected bloodstream infection was cost-effective and associated with high therapeutic effectiveness and healthcare cost savings.
- MALDI-TOF analysis with an Antimicrobial Stewardship Program (ASP) was the most cost-effective strategy. The other cost-effective options were PCR and BC-GN, both with an ASP, and PNA-FISH without an ASP.
- Even though mRDT-based strategies appear to be less cost-effective in the absence of an ASP, they still remain more cost-effective than conventional laboratory methods without an ASP.

IMPACT OF INFORMATION DELAY ON PATIENT OUTCOMES

CLICK TO ACCESS ARTICLE

CLINICAL INFECTIOUS DISEASES
2023;77(5):680-686

Information Delay of Significant Bloodstream Isolates and Patient Mortality: A Retrospective Analysis of 6225 Adult Patients With Bloodstream Infections.

Fidalgo B, Morata L, Cardozo C, del Rio A, Morales J, Fernandez-Pittol M, Martinez JA, Mensa J, Vila J, Soriano A, Casals-Pascual C.

OBJECTIVE

This study evaluated the impact of real-time communication of microbiological information on the clinical and prognostic outcomes of adult patients with bloodstream infections (BSIs).

STUDY DESIGN

Observational, retrospective analysis of all clinical episodes of bacteremia in a teaching hospital in Barcelona, Spain, from January 2013 to December 2019. The study compared bacteremia-associated mortality when blood culture results were communicated to the infectious diseases specialist (IDS) in real-time (during daytime working hours) and when results were delayed by 8 hours or more (reported the following morning).

Primary outcome: impact on 30-day mortality of real-time vs delayed availability of blood culture results.

RESULTS

- A total of 6,225 BSI cases were included.
- 2,130 (34.2%) of BSIs became positive during daytime working hours; 4,095 (65.8%) became positive during night-time working hours. Overnight positivity was reported to the IDS the following morning and therefore not in real-time.
- Of the 6,225 patients included, 625 (10%) died at 30 days. Of the 625 deaths, 193 (30.8%) corresponded to blood cultures that became positive during daytime working hours and 432 (69.2%) became positive during night-time hours.
- Empirical antibiotic treatment was appropriate in 4,661 of 6,015 patients (77.4%).
- Initial analysis including all pathogens did not reveal an association between mortality and delayed information report (odds ratio [OR], 1.18; 95% confidence interval [CI, 0.99–1.42).
- However, information delay of BSIs caused by fast-growing microorganisms such as *Enterobacterales* was associated with a significant increase in the odds of death at 30 days in the univariate and the multivariate analysis (OR, 2.22; 95% CI, 1.50–3.30) and similar results were found with mortality at 14 days and 7 days.

CONCLUSIONS

Early identification of significant bacterial isolates is critical to effectively manage patients with BSIs. This study suggests that real-time reporting of clinically relevant microbiological results from blood culture isolates, particularly for rapidly growing bacteria (e.g., *Enterobacterales*), may impact clinical outcomes. In view of the important prognostic implications, the need for adequate resource allocation (microbiologist/IDS with 24/7 coverage) should be reconsidered, and investigated in future studies.

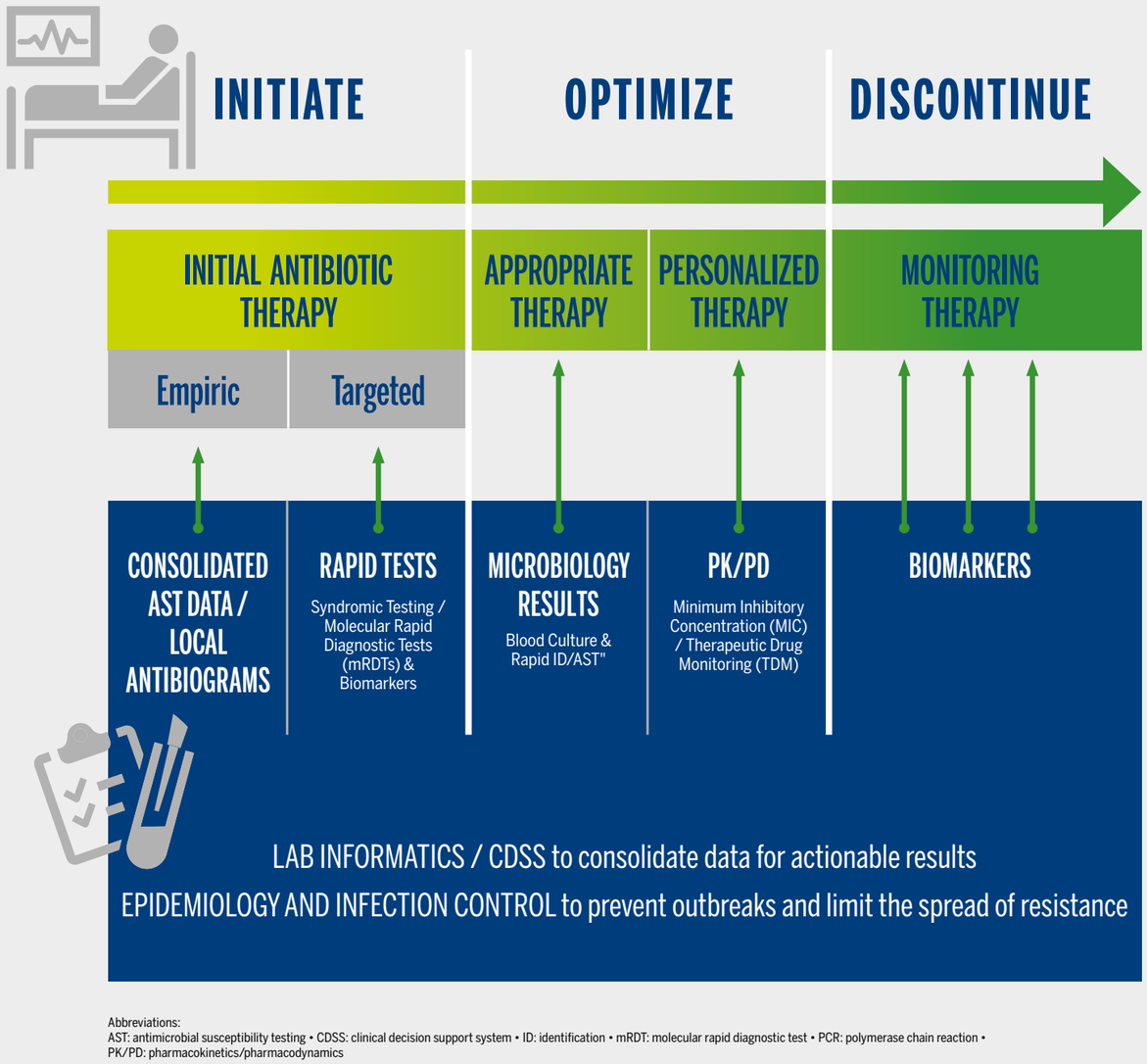
"Information delivered in real time has prognostic relevance and is likely to improve survival of patients with documented BSIs."

KEY FINDINGS

- Real-time reporting of blood culture results for BSI patients may impact clinical outcomes.
- Information delay of BSIs caused by fast-growing microorganisms such as *Enterobacterales* was associated with a significant increase in the odds of death at 30 days in the univariate and multivariate analysis.
- This study highlights the importance of a rapid collaboration between the microbiology laboratory and the IDS.
- The need for 24/7 hospital coverage by a clinical microbiologist and/or an IDS should be revisited in view of the important prognostic implications.

EVIDENCE-BASED IMPACT OF DIAGNOSTICS ON ANTIMICROBIAL THERAPY

Figure 1. How diagnostics support the antibiotic prescribing process and optimal patient care
Source: bioMérieux



Abbreviations:
AST: antimicrobial susceptibility testing • CDSS: clinical decision support system • ID: identification • mRDT: molecular rapid diagnostic test • PCR: polymerase chain reaction • PK/PD: pharmacokinetics/pharmacodynamics

EVIDENCE-BASED IMPACT OF DIAGNOSTICS ON ANTIMICROBIAL THERAPY

Diagnostics support clinical decision-making and appropriate antibiotic therapy prescribing along the continuum of patient care, from diagnosis to discharge and from antibiotic initiation to treatment optimization and discontinuation (Figure 1).

INITIATE ANTIBIOTIC THERAPY

KEY MEDICAL QUESTIONS

• Signs and symptoms suggestive of infection? • Is suspected infection likely viral or bacterial?	• What is the site of infection and which are the most common pathogens to be covered? • Are there severity signs/ organ failure?	• Are there severity signs/organ failure? • Are there risk factors for multidrug-resistant organisms (MDROs)? • Which antibiotic? Dose and duration?

➔ **Diagnostic test results help confirm bacterial origin of the infection and identify the causative pathogen** to avoid unnecessary antibiotic use and ensure optimal patient outcomes.

OPTIMIZE ANTIBIOTIC THERAPY

KEY MEDICAL QUESTIONS

• Can I safely de-escalate? • Should I add an antibiotic or an antifungal drug? • Can I stop the treatment?	• Is there a situation that requires: - a precise MIC? e.g. critical condition, challenging micro-organism, multidrug resistance, etc... - measuring drug concentration (TDM)?; high risk patients with altered pharmacokinetics, critical care, obese, organ transplantation, pediatrics and elderly populations	• How can I monitor emerging resistant strains in my ward? • How can I characterize them in order to take infection prevention actions?

➔ **Diagnostic test results determine a pathogen's susceptibility profile** to select the most appropriate treatment, limit use of broad-spectrum antibiotics and avoid adverse side effects.

DISCONTINUE ANTIBIOTIC THERAPY

KEY MEDICAL QUESTIONS

• Can I safely stop antibiotic therapy and reduce selection pressure?	• Should I reconsider my treatment?

➔ **Diagnostic test results help monitor the patient's response** to personalized treatment duration and support safe discontinuation of antibiotic therapy as early as possible.

The publications summarized in the following sections demonstrate the high medical value of diagnostics to reinforce clinical decision-making and support clinicians in their therapeutic choice.

INITIATION OF ANTIBIOTIC THERAPY

CLICK TO ACCESS ARTICLE

ANTIBIOTICS
2022;11(9):1192

Point-of-Care and Rapid Tests for the Etiological Diagnosis of Respiratory Tract Infections in Children: A Systematic Review and Meta-Analysis.

Brigadoi G, Gastaldi A, Moi M, Barbieri E, Rossin S, Biffi A, Cantarutti A, Giaquinto C, Da Dalt L, Donà D.

OBJECTIVE

The study objective was to systematically review the effects of point-of-care tests (POCTs) and rapid tests for respiratory tract infections in pediatric settings on changing antimicrobial prescription rate, length of stay, duration of therapy, and healthcare costs in high and low-middle income countries.

STUDY DESIGN

A systematic search of Embase, MEDLINE, and Cochrane Library databases was made. All randomized control trials (RCTs) and non-randomized observational studies meeting the study inclusion criteria were evaluated using the National Institute of Health (NIH) assessment tool.

A meta-analysis including 57 studies on pediatric populations (ED, inpatient, and outpatient) with RCTs (14.0%), non-randomized observational studies (47.4%) and quasi-experimental studies (38.6%) was then performed to assess the effects of rapid and point-of-care tests for respiratory tract infections, including the BIOFIRE® FILMARRAY® Respiratory (RP) Panel.

Primary outcome was the effect of POCTs and rapid tests on antibiotic prescriptions.

Secondary outcomes were the impact of the tests on the rate of prescriptions, days of therapy, length of stay, and reduction of cost.

RESULTS

- From a total of 6440 studies, 57 were eligible for the review. The analysis was stratified by setting and POCT/rapid test type.
- 93% of the studies were performed in high income countries (43.9% North America, 33.3% Europe, 14.0% Asia) and 82.5% were published after 2007.
- The most frequently studied tests were the rapid influenza tests (22/57, 38.6%) and the BIOFIRE RP Panel (22/57, 38.5%).
- Of the 49 studies that assessed antibiotic prescription rates after implementation of rapid tests or POCT, 65.3% found a statistically significant reduction.
- An overall reduction in antibiotic prescription was observed when comparing the BIOFIRE RP Panel to standard testing, but not when compared to clinical diagnosis.
- Of studies that reported impact on oseltamivir prescription, 12 of 20 (60%) reported a significant increase with POCT.
- The length of stay significantly decreased with POCT in 16 of the 34 studies (47.1%) which included this outcome.
- 11/18 studies (61%) measuring days of therapy reported a significant reduction after implementing rapid testing or POCT.
- A significant reduction in costs was found for three of the eight studies (37.5%) which included cost as an outcome.

CONCLUSIONS

The findings of this systematic review support the implementation of rapid tests and POCTs as valuable tools to improve antimicrobial prescribing, reducing unnecessary administration of antibiotics and duration of therapy and increasing appropriate use of oseltamivir. Their implementation would also seem to be useful in reducing turnaround time and length of stay, particularly in hospital settings.

"... implementation of rapid tests should be [...] combined within well-structured antimicrobial stewardship programs [...] to improve antimicrobial prescription."

KEY FINDINGS

- 1st systematic review evaluation of rapid tests and POCTs in pediatric setting worldwide and their impact on antimicrobial prescription, healthcare costs, and patient outcomes.
- Rapid tests and POCTs could be a valuable tool for the improvement of antimicrobial prescription rates.

CLICK TO ACCESS ARTICLE

CLINICAL INFECTIOUS DISEASES
2020;71(7):1684-1689

Use of Procalcitonin and a Respiratory Polymerase Chain Reaction Panel to Reduce Antibiotic Use via an Electronic Medical Record Alert.

Moradi T, Bennet N, Shemanski S, Kennedy K, Schlachter A, Boyd S.

OBJECTIVE

The objective of the study was to determine whether an automated electronic medical record (EMR) best practice alert (BPA) based on procalcitonin and respiratory polymerase chain reaction (PCR) results could help reduce inappropriate antibiotic use in patients with likely viral respiratory illness.

STUDY DESIGN

Quasi-experimental multicenter pre-post study conducted in 5 hospitals in the Saint Luke's health system (Missouri, US). Inclusion criteria included a positive viral detection from the BIOFIRE® FILMARRAY® Respiratory (RP) Panel and a procalcitonin level of <0.25 ng/mL within 48 hours of each other, as well as active use of systemic antibiotics. The study group received a BPA alerting providers of the diagnostic results suggesting viral infection and prompting them to reassess the need for antibiotics.

The primary outcome was total antibiotic-days of therapy.

RESULTS

- The study included 387 patients (226 in the prospective BPA group and 161 in the retrospective group without the alert).
- Viral detection rates varied between the groups. In the BPA group, influenza A (62 vs 19, $p<0.001$) and B viruses (20 vs 3, $p<0.004$) were more common, as was respiratory syncytial virus (RSV) (59 vs 25, $p=0.012$), whereas the number of rhinovirus cases was fewer (12 vs 36, $p<0.001$).
- The BPA group also had a lower mean ICU length of stay, 5.0 vs 6.9 days ($p=0.043$).
- There was a significant difference between the groups in the Charlson comorbidity index score, with a higher mean score for the BPA group (4.8 vs 4.0, $p<0.001$).
- In terms of primary outcome, the BPA group had significantly fewer antibiotic days of therapy, with a mean reduction of about 2.2 days (5.8 vs 8.0 days, $p<0.001$). After analysis of confounding factors, the reduction was about 1.48 days ($p=0.002$).
- The BPA group showed improved mean days of antibiotic therapy after the alert, 4.5 days vs 6.3. ($p<0.001$).
- The BPA group had a higher rate of antibiotic discontinuation within 24 hours of initiation, 37.8% vs 18.6% ($p<0.001$).
- The BPA group also had fewer patients discharged on antibiotics, with a reduction of nearly 28%.
- The rate of antibiotic re-initiation after discontinuation was similar in both groups, as were levels of *C. difficile* infection.

CONCLUSIONS

The automated antimicrobial stewardship BPA effectively reduced antibiotic use and discharge prescribing rates when diagnostics suggested viral respiratory tract infection, without a higher rate for reinitiation of antibiotics after discontinuation. This minimally invasive stewardship practice can easily be replicated by other institutions and represents a step forward in the fight against antibiotic misuse.

"By coupling temporally related PCT values [...] to viral PCR results, we were able to suggest to providers a subset of patients who were unlikely to have bacterial coinfection. The targeted stewardship alert enhanced the use of [RDTs] in determining infectious source."

KEY FINDINGS

- First study to implement automated clinician antimicrobial stewardship intervention by leveraging EMR-driven data for likely viral LRTIs.
- The introduction of the BIOFIRE RP Panel combined with PCT levels and electronic alert can significantly reduce antibiotic exposure for patients with LRTIs.
- The Best Practice Alert successfully identified LRTI patients eligible for antibiotic discontinuation.

CLICK TO ACCESS ARTICLE

DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
2021:99(3):115246

Enhanced Detection of Community-Acquired Pneumonia Pathogens with the BioFire® Pneumonia FilmArray® Panel.

Gilbert DN, Leggett JE, Wang L, Ferdosian S, Gelfer GD, Johnston ML, Footer BW, Hendrickson KW, Park HS, White EE, Heffner J.

OBJECTIVE

The objective of this study was to determine whether the BIOFIRE® FILMARRAY® Pneumonia Panel (BPP) multiplex PCR platform improved detection rates for potential viral and bacterial pathogens compared to the standard of practice multi-test bundle* (MTB) in patients with community-acquired pneumonia (CAP). The study also describes an approach for integrating BPP results as a basis for subsequent antibiotic stewardship (AMS) activities.

* MTB: multi-test bundle consisting of sputum and blood bacterial cultures, PCR testing of nasopharyngeal swab samples by the multiplex BIOFIRE® FILMARRAY® Respiratory Panel, anterior nasal swab PCR for *Staphylococcus aureus*, nasopharyngeal swab for *Streptococcus pneumoniae*, and urine antigen testing for *S. pneumoniae* and *Legionella pneumophila*.

STUDY DESIGN

Between January 2017 to March 2018, all patients admitted for CAP were enrolled. Patients were considered evaluable if all elements of the MTB and the BPP were completed, and they met other a priori inclusion criteria.

Blood and sputum cultures were performed on all patients. Two or more procalcitonin (PCT) levels were used to assist in the clinical decision as to whether detected bacteria were invading or colonizing.

Primary endpoint: percentage of potential pathogens detected using the BPP (8 viral and 18 bacterial targets) versus the MTB (8 viral and 6 bacterial targets).

RESULTS

- A total of 274 patients were evaluated, out of 585 enrolled patients.
- **A potential viral pathogen** was detected in more patients with BPP than with MTB (60.9% vs 40.5%) with an odds ratio (95% CI) of 9.00 (4.12 to 23.30) $p<0.001$ **(Figure 1)**.
- **A potential bacterial pathogen** was identified in more patients with BPP than with MTB (75.5% vs 66.4%) with an odds ratio (95% CI) of 2.09 (1.24 to 3.59), $p=0.003$ **(Figure 2)**.
- Significantly more patients were detected as having **any potential pathogen (bacterial, viral or both)** with BPP than with MTB (90.6% vs 80.9%, $p=0.001$).
- BPP showed superior performance in **detecting co-infections (Table 1)**.
- Low PCT levels helped identify detected bacteria as colonizers.

CONCLUSIONS

For hospitalized adult patients with CAP, the BPP detected significantly more common viral and bacterial potential pathogens compared to the current MTB. Furthermore, PCT levels helped determine whether detected bacteria were colonizing or causing infection.

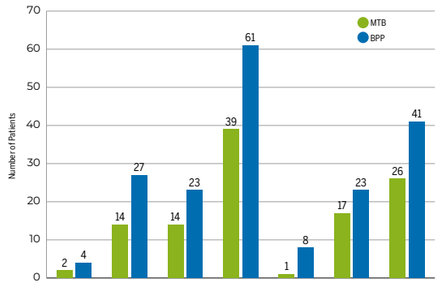
The increased diagnostic yield observed with BPP provides an opportunity to simplify the diagnostic testing for CAP. The new test bundle could potentially include BPP, sputum culture and sensitivity, blood cultures for the critically ill, and perhaps nasal *S. aureus* PCR, as well as 2 PCT levels taken 4-6 hours.

This new bundle, taking less than 2 hours to complete versus 1-2 days with the current MTB, could decrease the cost of testing **(Table 2)** by eliminating certain unnecessary tests and potentially contribute to antibiotic stewardship through reduced antibiotic consumption and shorter length of stay.

"... the BIOFIRE Pneumonia multiplex platform significantly increased the detection of potential viral and bacterial pathogens in hospitalized adult patients with community-acquired pneumonia, and thereby provided key data for AS activities."

Figure 1. Comparison of MTB vs. BPP for the detection of patients with potential viral pathogens, with or without detectable bacteria.*

Reproduced with permission from Elsevier. Gilbert GN, *et al. Diagnostic Microbiology and Infectious Disease* 2021:99(3):115246



Virus Detected P value (McNemar test)	Adenovirus ($p=0.5$)	Coronavirus ($p=0.002$)	hMPV ($p=0.004$)	Influenza ($p<0.001$)	HPIV ($p=0.016$)	RSV ($p=0.07$)	Rhinovirus ($p=0.001$)
Positive % Agreement	100	85.7	100	92.3	100	94.1	88.5
Negative % Agreement	99.3	94.2	96.5	89.4	97.4	97.3	92.7

*Some patients were detected with more than one viral species.
MTB: Multi-test bundle; BPP: BIOFIRE® FILMARRAY® Pneumonia Panel

Figure 2. Comparison of MTB vs. BPP for the detection of patients with potential bacterial pathogens, with or without detectable virus.*

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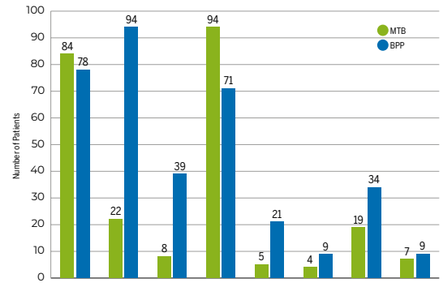

Bacteria Detected P value (McNemar test)	*S. pneumoniae* ($p=0.362$)	*H. influenzae* ($p<0.001$)	*M. catarrhalis* ($p<0.001$)	*S. aureus* ($p=0.002$)	*S. agalactiae* ($p<0.001$)	*S. pyogenes* ($p=0.18$)	Enterobacter ($p=0.001$)	Non-fermenters ($p=0.69$)
Positive % Agreement	78.6	100	87.5	58.3	100	50	84.2	71.4
Negative % Agreement	93.7	71.4	88	91.6	94.1	97.4	92.9	98.5

*Some patients were detected with more than one viral species.
MTB: Multi-test bundle; BPP: BIOFIRE® FILMARRAY® Pneumonia Panel

Table 1. Comparative detection of multiple bacterial and viral species with BPP vs. MTB.

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Type of Pathogen	Number of species	Number of patient with detected species	
		MTB*	BPP*
Only virus	1	24	25
	2	1	5
Only bacteria	1	43	37
	2	17	21
	>3	5	19
Virus (V) and Bacteria (B)	1(V) + 1(B)	54	62
	1(V) + 2(B)	10	30
	1(V) + >3 (B)	3	20
	2(V) + 3 (B)	5	12

+ Representative data. Less frequent combinations are not included
* MTB: Multi-test bundle; BPP: BIOFIRE® FILMARRAY® Pneumonia Panel

Table 2. Comparative laboratory cost of MTB vs. projected cost of BPP bundle.

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Test	MTB*, $	BPP*, $
Urine antigen		No need for urine antigens
Legionella	30.00	1
S. pneumoniae	19.00	43
Nasal swabs – PCRs	2	17
S. aureus	42.00	
S. pneumoniae	25.00	
PCR "resp panel"	91.00	
BIOFIRE® FILMARRAY® Respiratory Panel		180,000
Sputum C&S	8.23	8.23
Blood culture x 2	9.80	9.80
Tech x 1 hr @$36.50/hr	36.50	
Tech x ½ hr @36.50/hr		18.00
PCT @$23 ea x 2	46.00	46.00
SUBTOTAL	**307.53**	**262.03**
Overhead @ 30%	92.00	79.00
TOTAL	**399.53**	**341.03**

$ = US Dollars: represents estimated cost as per 2018
* MTB: Multi-test bundle; BPP: BIOFIRE® FILMARRAY® Pneumonia Panel

KEY FINDINGS

- More patients were identified with potential viral and bacterial pathogens using the BIOFIRE® FILMARRAY® Pneumonia Panel (BPP) than with the multi-test bundle (90.6% vs 80.9%).
- The BPP approach also demonstrated the potential to positively impact cost savings and antibiotic stewardship activities.

CLICK TO ACCESS ARTICLE

THE JOURNAL OF INFECTION
2022;85(6):625-633

Molecular Point-of-Care Testing for Lower Respiratory Tract Pathogens Improves Safe Antibiotic De-Escalation in Patients with Pneumonia in the ICU: Results of a Randomised Controlled Trial.

Poole S, Tanner AR, Naidu VV, Borca F, Phan H, Saeed K, Grocott MPW, Dushianthan A, Moyses H, Clark TW.

OBJECTIVE

This study aimed to assess the impact of syndromic molecular point-of-care testing (mPOCT) compared to conventional diagnostic testing, on antibiotic use in critically ill patients with pneumonia.

STUDY DESIGN

This monocentric randomized controlled trial was performed in the UK between 2019 and 2021. Critically ill adults in the intensive care unit (ICU) with a working diagnosis of community-acquired pneumonia (CAP), hospital acquired pneumonia (HAP), or ventilator associated pneumonia (VAP) were enrolled in this trial. 100 patients were randomly assigned to an intervention arm where the BIOFIRE® FILMARRAY® Pneumonia *plus* (PN*plus*) Panel[1] was used for testing and clinical advice including antimicrobial stewardship prescribing advice was given immediately based on test results (PN*plus* group). The 100 patients randomly assigned to the control arm received standard clinical care and microbiologic examinations.

The **primary outcome** was the proportion of patients who received results-directed antimicrobial therapy within 48 hours of a respiratory tract result.

The **secondary outcomes** were the proportion of patients with a causative organism identified and the time to result of microbiological investigations. Clinical and safety outcomes were also measured.

RESULTS

Samples collected and pneumonia types: 125 (63%) endotracheal aspirate, 57 (29%) sputum, 8 (4%) undirected bronchoalveolar lavage (BAL) and 7 (4%) directed BAL. The tests provided working diagnoses of the types of infections: 85 CAP, 69 HAP, and 46 VAP.

Primary outcome:

- 80 (80%) of the 100 patients in the PN*plus* group received results-directed therapy compared to 29 (29%) of the 99 patients in the control arm (difference of 51%, 95% CI 39 to 63, $p<0.0001$).

Secondary outcomes:

- **A credible pathogen identification** was obtained in 71 (71%) of 100 patients in the PN*plus* group, compared to 51 (51%) of 100 in the control group (difference of 20%, 95% CI 7 to 33; $p=0.004$).
- **Additional organisms** were detected in 43 (43%) of 100 patients who were intubated at recruitment and 29 (39%) of 75 patients who were not intubated.
- **The time to test result** was 1.7 hours [1.6 to 1.9] in the PN*plus* group vs 66.7 hours [56.7 to 88.5] in the control group (difference of -65.0 hours, 95% CI -68.0 to -62.0; $p<0.0001$). **The time to results-directed therapy** was 2.3 [1.8-7.2] hours in the PN*plus* group and 46.1 [23.0-51.5] hours in the control group (difference of -43.8 h, 95% CI -48.9 to -38.6; $p<0.0001$) **(Figure 1).**
- **Safety** was measured by the time to hospital and critical care discharge, the proportion of patients who received mechanical ventilation, and mortality. No differences between the groups were observed.

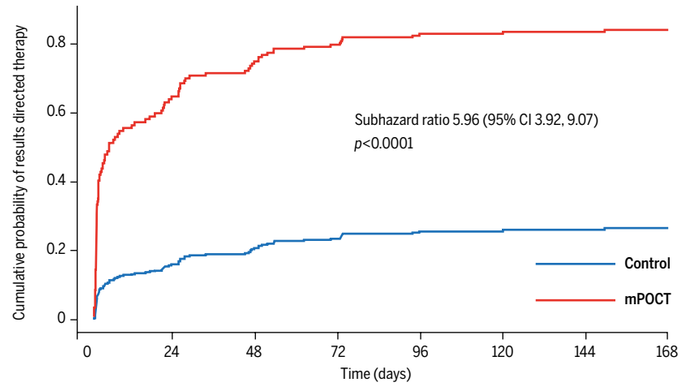
CONCLUSIONS

The study demonstrated that mPOCT led to the identification of a causative pathogen much more rapidly and in a greater proportion of critically ill patients with pneumonia than with current standard diagnostic testing. This was subsequently associated with more patients receiving diagnostic-directed antimicrobial treatment, and on average, almost 2 days earlier than with standard diagnostic testing.

[1] The BIOFIRE Pneumonia *plus* Panel is intended for use by trained medical and laboratory professionals in a laboratory setting or under the supervision of a trained laboratory professional.

"Embedding mPOCT within a stewardship intervention was associated with more patients rapidly receiving results-directed therapy and especially de-escalation of unnecessary broad-spectrum antimicrobial agents."

Figure 1. Time-to-event curve for results-directed antimicrobial therapy.
Reproduced with permission from Elsevier. Poole S, *et al. J Infect.* 2022;85(6):625-633



Number at Risk								
Control	97	89	78	68	60	57	55	53
mPOCT	99	30	25	24	21	20	17	17

KEY FINDINGS

- First randomized trial to report on the clinical impact of molecular POCT for pneumonia pathogens in a critical care setting.
- The mPOCT (BIOFIRE® FILMARRAY® Pneumonia *plus* Panel) led to increased diagnostic yield and generated more rapid actionable results than standard diagnostic testing.
- These actionable results impacted antimicrobial stewardship by enabling an earlier and appropriate treatment, and suggested a safe de-escalation.

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ANTIBIOTICS
2022;11(8):1028

Assessment of the Impact of a Meningitis/Encephalitis Panel on Hospital Length of Stay: A Systematic Review and Meta-Analysis.

Hueth K, Thompson-Leduc P, Totev T, Milbers K, Timbrook K, Kirson N, Hasbun R.

OBJECTIVE

This study aimed to review and summarize current literature on the association between the use of the multiplex BIOFIRE® FILMARRAY® Meningitis/Encephalitis (ME) Panel and length of hospital stay (LOS), days on antibiotic therapy, and length of acyclovir treatment.

STUDY DESIGN

A systematic review and meta-analysis of the current literature from 2015 onwards in the EMBASE and MEDLINE databases. A combination of terms were used to identify the multiplex BIOFIRE ME panel, meningitis and/or encephalitis, and length of stay.

Publications were retained if they met the following criteria:

- used the ME Panel to determine the etiology of suspected central nervous system (CNS) infections,
- reported on patients' length of hospital stay as the primary outcome,
- the study compared LOS of patients tested with the BIOFIRE ME panel to another cohort of patients.

RESULTS

- A total of 169 publications were identified and analyzed.
- After screening, 11 were retained for meta-analysis and 13 were retained for systematic review, which included a range of study designs: retrospective cohort (n=4), case-control (n=3), pre/post interventional (n=3), cross-sectional (n=1), combination designs (n=1), and randomized control trial (n=1).
- All 11 studies reported a reduction in the mean duration of hospital LOS using the BIOFIRE ME Panel compared to standard of care (SOC) **(Figure 1).** There was a statistically significant reduction in mean LOS by 1.2 days (95% CI [-1.96, -0.44]).
- 7 studies reported information on the duration of acyclovir therapy. Meta-analysis of the 7 studies demonstrated a statistically significant reduction in mean duration of acyclovir therapy in the BIOFIRE ME Panel cohorts by 1.14 days (95% CI [-1.78, -0.50), with the strongest effect observed in studies that exclusively included pediatric patients.
- Among the 6 studies which reported duration of antibiotic therapy, 3 studies demonstrated a statistically significant reduction in the mean duration of antibiotic therapy (all of which exclusively evaluated pediatric patients) of 1.85 days (95% CI [-2.50, -1.21]). The overall reduction in mean duration of antibiotic therapy across the 6 studies was not statistically significant, but showed a reduction of 1.01 days (95% CI [-2.39, 0.37]) **(Figure 2).**

CONCLUSIONS

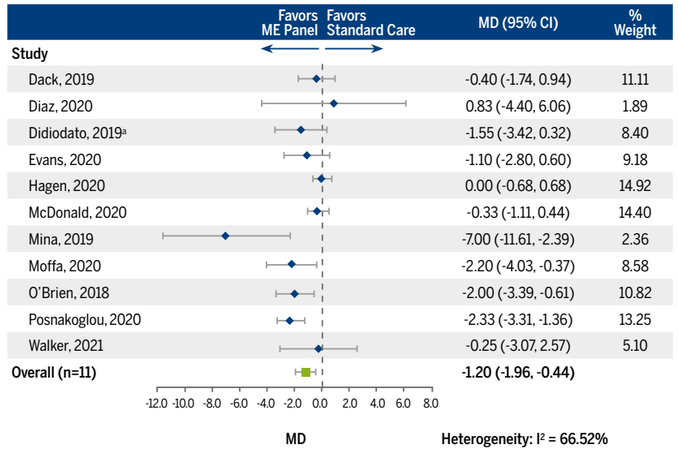
Rapid turnaround and diagnostic yield of the BIOFIRE ME panel is associated with a significant reduction in hospital LOS and length of acyclovir therapy, as well as a potential reduction in the number of days with antibiotic therapy.

Findings show that use of the BIOFIRE ME panel in clinical practice may contribute to more streamlined patient management (targeting therapy, discontinuing unnecessary therapy, avoiding additional testing and imaging, etc.).

"The multiplex ME panel has the potential to be an important component of antibiotic stewardship programs, and its clinical benefits may translate into more effective and targeted patient management."

Figure 1. Hospital Length of Stay.

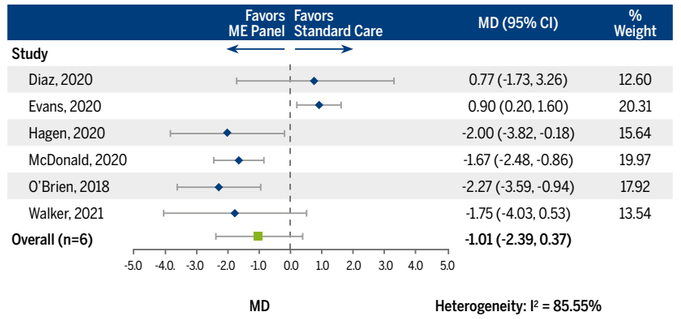
Reproduced from Hueth K, *et al. Antibiotics* 2022;11(8):1028. MDPI – Open Access



CI: confidence interval; MD: mean difference; ME: meningitis and/or encephalitis.
[a] Analysis was performed on the subgroup of patients whose time to discharge was <18 days, n=95.

Figure 2. Days of Treatment with Antibiotics.

Reproduced from Hueth K, *et al. Antibiotics* 2022;11(8):1028. MDPI – Open Access.



CI: confidence interval; MD: mean difference; ME: meningitis and/or encephalitis.

KEY FINDINGS

- BIOFIRE® FILMARRAY® ME Panel is associated with faster turnaround time and higher diagnostic yield.
- BIOFIRE ME Panel may lead to reduced unnecessary antimicrobial administration and optimize antiviral therapies among patients with suspected CNS infection.
- BIOFIRE ME Panel implementation is cost-effective, particularly if there is a reduction in length of hospitalization.

CLICK TO ACCESS ARTICLE

ANTIBIOTICS
2022;11:1732

Epidemiology and Economic Outcomes associated with Timely versus Delayed Receipt of Appropriate Antibiotic Therapy among US patients Hospitalized for Native Septic Arthritis: a Retrospective Cohort Study.

Balada-Llasat JM, Stamas N, Vincent T, Timbrook TT, Saiontz-Martinez C, Hemmert RB, Berger A.

OBJECTIVE

The objective of this study was to assess the magnitude and impact of delayed appropriate antibiotic therapy among patients hospitalized with septic arthritis (SA) using a large US hospital encounter database.

STUDY DESIGN

A retrospective observational cohort study using the National Premier Healthcare Database to evaluate the epidemiological and economic outcomes associated with timely versus delayed prescribing of appropriate antibiotic therapy (duration, de-escalation, length of stay (LOS), and costs) among hospitalized patients with a final diagnosis of SA from January 2017 to December 2019.

Timely appropriate therapy was defined as the receipt of antibiotic(s) with in vitro activity against identified pathogens within two days of admission; all other patients were assumed to have received delayed appropriate therapy.

RESULTS

- A total of 18,597 patients had at least one hospital admission for SA. After application of all inclusion criteria (culture results availability, same hospital stay and evidence of prescription of antibiotic therapy), the study sample size comprised 517 patients.
- For 93.8%, SA was monomicrobial; *S. aureus* (50.9%) was the most frequent organism identified at admission followed by *S. viridans* (5.8%), *S. epidermidis* (4.3%), *S. agalactiae* (3.3%) and *P. aeruginosa* (2.7%).
- Vancomycin and ceftriaxone were the most common initial therapies administered.
- Initial antibiotic therapy was deemed appropriate for 491/517 patients (95.0%).
- Patients with timely appropriate antibiotic therapy (receipt of appropriate antibiotic within 2 days of admission) were more likely to have antibiotic therapy de-escalation (36.3% vs 15.4% until 5 days or 54.8% vs 34.6% until discharge) and less likely to have antibiotic therapy escalation (4.3% vs 23.1% until 5 days or 9.6% vs 23.1% until discharge)
- After Inverse Probability Treatment Weighting (IPTW), 412 patients (94.1%) were allocated to timely appropriate therapy and 26 patients (5.9%) were allocated to delayed appropriate therapy.
- Twenty-six (5.9%) received delayed appropriate therapy which was associated with an additional (1) 1.1 days of antibiotic therapy, (2) 1.4 days in LOS, and (3) additional $3,531 in mean total in-hospital costs **(Table 1)**.

CONCLUSIONS

This study demonstrated that delayed appropriate antibiotic therapy was associated with longer average LOS, longer duration of in-hospital antibiotic exposure, higher likelihood of escalation, lower likelihood of de-escalation, and higher healthcare costs. The ability to rapidly identify pathogens and susceptibilities is likely to reduce LOS, duration of antibiotic exposure and care costs, while providing opportunities to enhance antimicrobial stewardship.

"Our findings indicate that receipt of timely appropriate antibiotic therapy for SA [septic arthritis] is associated with reduced exposure to antibiotics, shorter LOS, and an 18% reduction in costs to hospitals to render care."

Table 1: Inverse Probability Treatment Weighting (IPTW) Adjusted Utilization and Cost Outcomes.
Reproduced from Balada-Llasat JM, *et al. Antibiotics* 2022;11:1732. MDPI – Open Access.

Outcomes	Timely Appropriate Therapy (n=412)	Delayed Therapy (n=26)	*p*-value
Duration of in-hospital antibiotic therapy, days	7.3 (6.7-8.0)	8.4 (7.7-9.2)	0.02
Total in-hospital antibiotic exposure days, days	10.5 (9.7-11.5)	11.6 (10.6-12.6)	0.11
LOS, days	6.9 (6.3-7.6)	8.3 (7.6-9.0)	0.11
In-hospital cost, $			
Antibiotics	$624 ($515-$756)	$1,534 ($1,286-$1829)	<0.01
Other pharmacotherapies	$1,068 ($932-$1,223)	$1,639 ($1,438-$1,868)	<0.01
Medical care	$5,861 ($5,458-$6,294)	$6,521 ($6,085-$6988)	0.03
Room and board	$7,551 ($6,818-$8,362)	$7,975 ($7,223-$8,805)	0.44
Other costs	$659 ($535-$812)	$587 ($481-716)	0.44
Total in-hospital cost	$15,490 ($14,242-$16,846)	$19,021 ($17,528-$20,641)	<0.01

KEY FINDINGS

- Timely appropriate therapy was associated with a twofold increase in the likelihood of antibiotic de-escalation during the SA admission.
- Delayed appropriate therapy was associated with additional days of antibiotic therapy and LOS and an increase in hospital costs.
- Rapid pathogen detection is likely to reduce LOS, antibiotic exposure duration and healthcare costs, while supporting antimicrobial stewardship.

CLICK TO ACCESS ARTICLE

JOURNAL OF CLINICAL MICROBIOLOGY
2019;57(3):E01775-18

Impact of Gastrointestinal Panel Implementation on Healthcare Utilization and Outcomes.

Axelrad JE, Freedberg DE, Whittier S, Greendyke W, Lebwohl B, Green DA.

OBJECTIVE

The objectives of this study were to evaluate the clinical impact of the BIOFIRE® FILMARRAY® Gastrointestinal (GI) Panel, in comparison to conventional stool testing on endoscopy, abdominal radiology, and antibiotic prescribing.

STUDY DESIGN

This study was a retrospective comparative analysis of stool testing performed either with the GI Panel or with conventional stool testing on inpatients and outpatients from New York Presbyterian-Columbia University Medical Center, USA.

5,986 inpatients and outpatients had conventional stool culture performed with or without an ova and parasites exam or enzyme immunoassay for rotavirus and adenovirus 40/41 from December 2012 to February 2015.

9,402 inpatients and outpatients had BIOFIRE GI Panel testing from March 2015 to May 2017.

The patient medical records were used to collect data about all endoscopic procedures, all abdominal and common radiology done in the 30 days following the stool test. The information about antibiotic prescriptions in the 14 days following a stool test were also extracted.

RESULTS

- Out of 5,986 stool samples, 246 (4.1%) were positive by conventional stool testing and identified 38 viruses (15.4%), 202 bacteria (82.1%), and 9 parasites (4.3%).
- Campylobacter (n=110; 43.8%) and Salmonella (n=56; 22.3%) were the pathogens most commonly identified.
- The positivity rate with BIOFIRE GI Panel testing was 29.2% (2,746/9,402) with Enteropathogenic *E. coli* (EPEC) (n=530; 13.9%) and norovirus (n=613; 16.1%) the most commonly identified pathogens.
- The BIOFIRE GI Panel identified 1,073 viruses (39.1%), 1,792 bacteria (65.3%), and 226 parasites (8.2%). 28.5% (n=783) of the samples had multiple pathogens detected.
- Within 30 days following stool testing, patients who received the BIOFIRE GI Panel showed a lower utilization of endoscopic evaluation (8.4% vs 9.6% p=0.008) and of abdominal radiology (29.4% vs 31.7%, p=0.002) compared to patients who received conventional tests. This can be explained by the increased sensitivity and the higher positivity rate of the BIOFIRE GI Panel compared to conventional stool testing, as a positive stool test is seen as a definitive diagnosis, not requiring additional procedures.
- Additionally, there was a decrease in the number of patients being prescribed antibiotics in the 14 days following stool testing (36.2% compared to 40.9%, p<0.001) due to the increased ability of the BIOFIRE GI Panel to detect viral pathogens.

CONCLUSIONS

In this study, the implementation of multiplex PCR was associated with significant reductions in the utilization of endoscopy, abdominal radiography, and antibiotic prescribing compared with conventional stool testing. Offering a higher positivity rate, coupled with increased sensitivity and rapid turnaround, multiplex PCR stool testing has the potential to optimize health care utilization, reduce costs, and contribute to antibiotic stewardship.

"... the implementation of multiplex PCR was associated with a significant reduction in the risk of receiving endoscopy, abdominal radiography and antibiotics following a test."

KEY FINDINGS

- **The positivity rate increased from 4.1% with conventional stool testing to 29.2% with the BIOFIRE GI Panel.**
- **Implementation of BIOFIRE GI Panel led to a significant reduction in the utilization of endoscopic procedure and abdominal radiology, within 30 days following stool testing.**
- **Implementation of BIOFIRE GI Panel led to a significant reduction in antibiotic prescribing, within 14 days following stool testing.**

OPTIMIZATION OF ANTIBIOTIC THERAPY

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JAMA NETWORK OPEN
2022;5(4):E226136

Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients With Ventilator-Associated Pneumonia: The GRACE-VAP Randomized Clinical Trial.

Yoshimura J, Yamakawa K, Ohta Y, Nakamura K, Hashimoto H, Kawada M, Takahashi H, Yamagiwa T, Kodate A, Miyamoto K, Fujimi S, Morimoto T.

OBJECTIVE

Establishing methods to safely reduce overuse of broad-spectrum antibiotic agents for ventilator-associated pneumonia (VAP) is a pressing challenge. The effect of Gram staining on restricting the initial antibiotic choice has not been investigated in intensive care units (ICUs). The objective of this randomized clinical trial (RCT) was to compare the clinical response to Gram stain-guided restrictive antibiotic therapy versus guideline-based broad-spectrum antibiotic treatment in patients with VAP.

STUDY DESIGN **(FIGURE 1)**

This multicenter, open-label, noninferiority RCT with blinded end point assessment was conducted in the ICUs of 12 tertiary referral hospitals in Japan from April 1, 2018, through May 31, 2020. Patients aged 15 years or older with a VAP diagnosis and a modified Clinical Pulmonary Infection Score of 5 or higher were included. Patients were randomized to Gram stain-guided antibiotic therapy (stain performed directly on an endotracheal aspirate) or 2016 Infectious Diseases Society of America (IDSA) guideline-based antibiotic therapy.

Primary outcome was the clinical response rate, defined as completion of antibiotic therapy within 14 days, improvement or lack of progression of baseline radiographic findings, resolution of signs and symptoms of pneumonia, and lack of antibiotic agent re-administration, with a noninferiority margin of 20%.

Secondary outcomes were the proportions of antipseudomonal agents and anti–methicillin-resistant *Staphylococcus aureus* (MRSA) agents as initial antibiotic therapies; 28-day mortality, ICU-free days, ventilator-free days; and adverse events.

RESULTS **(TABLE 1)**

- In total, 206 patients were randomized to the Gram stain-guided group (n = 103) or guideline-based group (n = 103).
- Clinical response occurred in 79 patients (76.7%) in the Gram stain-guided group and 74 patients (71.8%) in the guideline-based group ($p<0.001$).
- There was no significant difference in coverage rates of initial antibiotic therapies between the groups (86.4% vs 92.2%; $p=0.18$). However, a reduced use of antipseudomonal agents (30.1%) and anti-MRSA agents (38.8%) was observed in the Gram stain-guided group vs guideline-based group.
- The 28-day cumulative incidence of mortality was 13.6% in the Gram stain-guided group vs 17.5% in the guideline-based group, with no statistical significance ($p=0.44$).

CONCLUSIONS

The GRACE-VAP trial studied the effectiveness of Gram staining to safely restrict overuse of broad-spectrum antibiotic agents in critically-ill patients with VAP. The findings show that Gram staining has the potential to reduce the spread of multidrug-resistant organisms in the critical care setting. Gram stain-guided antibiotic therapy was noninferior to guideline-based antibiotic therapy in terms of clinical response rate and led to a reduction in the use of antipseudomonal agents and anti-MRSA agents.

"The findings of this trial suggest that Gram staining can be used in the critical care setting to ameliorate the spread of multidrug-resistant pathogens."

Figure 1. Study design and key findings.
Adapted from Yoshimura J, *et al. JAMA Network Open* 2022;5(4):e226136. CC-BY License Permissions.

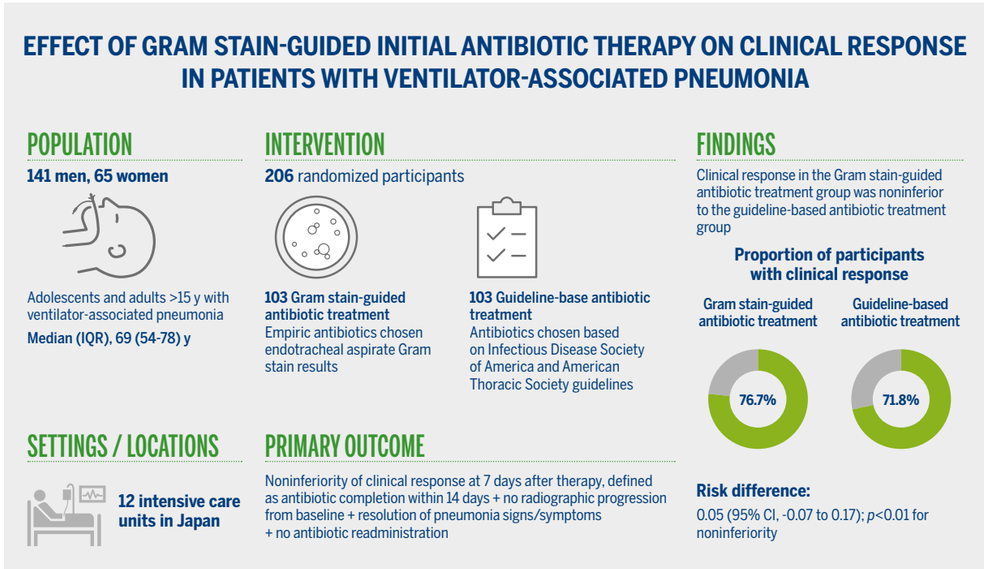

Table 1. Primary and Secondary Outcomes
Adapted from Yoshimura J, *et al. JAMA Network Open* 2022;5(4):e226136. CC-BY License Permissions.

Outcome	N. (%) Gram stain-guided group (n=103)	N. (%) Guideline-based group (n=103)#	*p* value
Primary outcome			
Clinical response rate	**79 (76.7)**	**74 (71.8)**	**<0.001**
Secondary outcomes			
28-d ventilator-free days, median (IQR)	14 (13.6)	18 (17.5)	0.44
28-d ICU-free days, median (IQR)	21 (0-24)	21 (4-25)	0.63
Administration of antibiotic therapy			
- Antipseudomonal agents	**72 (69.9)**	**103 (100)**	**<0.001**
- Anti-MRSA agents	**63 (61.2)**	**103 (100)**	**<0.001**
Coverage rate of initial antibiotic therapy	89 (86.4)	95 (92.2)	0.18
Escalation	7 (6.8)	1 (1.0)	0.03
De-escalation	67 (65.0)	79 (76.7)	0.07

#Antibiotic choice based on the 2016 VAP guidelines (Kalil AC, *et al. Clin Infect Dis*. 2016;63(5):e61-e111).
IQR: interquartile range; MRSA: methicillin-resistant *Staphylococcus aureus*.

KEY FINDINGS

- Gram stain-guided antibiotic therapy reduced the use of antipseudomonal agents and anti-MRSA agents.
- Gram stain-guided antibiotic therapy was noninferior to guideline-based antibiotic therapy in terms of clinical response rate.

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CLINICAL INFECTIOUS DISEASES
2022;75(12):2066-2075

Impact of a Rapid Molecular Test for *Klebsiella pneumoniae* Carbapenemase and Ceftazidime-Avibactam Use on Outcomes After Bacteremia Caused by Carbapenem-Resistant *Enterobacterales*.

Satlin MJ, Chen L, Gomez-Simmonds A, Marino J, Weston G, Bhowmick T, Seo SK, Sperber SJ, Kim AC, Eilertson B, Derti S, Jenkins SG, Levi MH, Weinstein MP, Tang Y-W, Hong T, Juretschko S, Hoffman KL, Walsh TJ, Westblade LF, Uhlemann A-C, Kreiswirth BN.

OBJECTIVE

The study investigated the impact of a rapid molecular test for the detection of the *Klebsiella pneumoniae* carbapenemase gene (*bla*$_{KPC}$) directly from positive blood cultures and the use of ceftazidime-avibactam to improve outcomes in patients with bloodstream infections caused by carbapenem-resistant *Enterobacterales* (CRE) in a KPC-endemic area.

STUDY DESIGN

Multicenter observational study conducted from January 2016 to June 2018 at 8 medical centers in New York and New Jersey. Patients with CRE bacteremia were enrolled based on carbapenem resistance detection using reference antibiotic susceptibility testing and whole genome sequencing.

The study assessed time to receipt of active antimicrobial therapy as well as 14-day and 30-day mortality in patients whose positive blood cultures underwent rapid molecular testing for *bla*$_{KPC}$ using the BIOFIRE® FILMARRAY® Blood Culture Identification Panel (BCID) compared to patients who did not undergo this test, in a context where almost all patients benefited from an infectious disease consult. Outcomes were also assessed with regards to the use of the new ß-lactam/ß-lactamase inhibitor (BLBLI), ceftazidime-avibactam, versus polymyxins when used as initial targeted therapies.

RESULTS

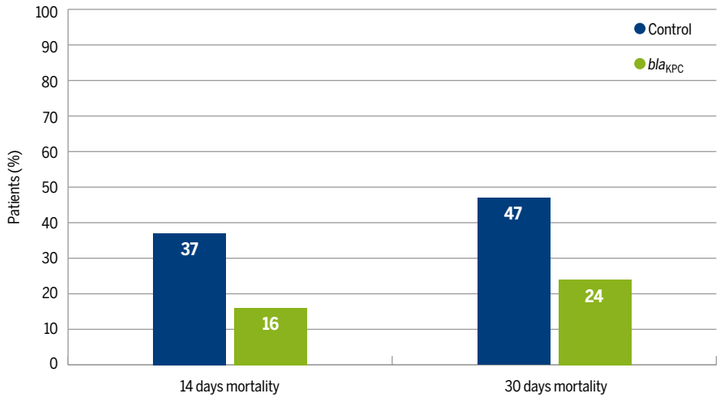
- Of 137 patients with CRE bacteremia, 106 (77%) were infected with carbapenemase-producing CRE (CP-CRE), including 89 (65%) with *bla*$_{KPC}$, 8 (6%) with *bla*$_{OXA-48}$, and 7 (5%) with *bla*$_{NDM}$.
- The 30-day mortality rate was 38% in patients infected with CP-CRE and 39% in patients with non-CP CRE.
- In the 51 patients whose blood cultures underwent *bla*$_{KPC}$ PCR testing (PCR patients), the time to active antibiotic therapy was reduced by half (median, 24 vs. 50 hours; p= .009) compared to the other 86 non-PCR patients. They were also more likely to receive initial targeted therapy with ceftazidime-avibactam (35% vs 16%; p= .011).
- The *bla*$_{KPC}$ gene rapid test was associated with a significant reduction in 30-day mortality (adjusted odds ratio, 0.37; 95% confidence interval [CI], 0.16–0.84) related to earlier initiation of targeted therapy **(Figure 1).**
- In addition, when compared with polymyxin monotherapy, patients who received ceftazidime-avibactam monotherapy had an absolute 30-day mortality reduction of 21% (31% vs. 10%, respectively). Although not statistically significant, the data is consistent with other studies' reports on decreased mortality with this new BLBLI.

CONCLUSIONS

This study demonstrated that, in a KPC-endemic area, *bla*$_{KPC}$ direct PCR testing of positive blood cultures was associated with decreased time to appropriate therapy as well as decreased mortality for CRE bacteremia. Ceftazidime-avibactam was found to lead to improved outcomes in patients with CRE bacteremia and is therefore a reasonable first-line therapy for these infections.

"bla$_{KPC}$ PCR testing of positive blood cultures was associated with decreased time until appropriate therapy and decreased mortality for CRE bacteremia."

Figure 1. Mortality rates of patients who received *bla*$_{KPC}$ PCR testing vs. the control group (p=0.007).
Adapted from Satlin JM, *et al. Clinical Infectious Diseases* 2022;75(12):2066-2075



KEY FINDINGS

- The first study indicating the association of *bla*$_{KPC}$ PCR testing and decreased mortality among patients with CRE bacteremia.
- According to the authors, this mortality reduction was attributed to the earlier initiation of active therapy in patients who received *bla*$_{KPC}$ PCR testing compared to non-PCR patients.
- This study adds to evidence supporting the role of rapid molecular diagnostic tests in antimicrobial stewardship, and more importantly, demonstrates improvement in patient outcomes.

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INTERNATIONAL JOURNAL OF ANTIMICROBIAL AGENTS
2022;59(2):106490

Impact of Early Antimicrobial Stewardship Intervention in Patients with Positive Blood Cultures: Results from a Randomized Comparative Study.

O'Donnell JN, Rhodes NJ, Miglis CM, Zembower TR, Qi C, Hoff BM, Barr VO, Gilbert EM, Bolon MK, Malczynski M, Gener J, Tran C, Catovic L, Postelnick MJ, Sutton SH, Scheetz MH.

OBJECTIVE

In this randomized comparative study, researchers aimed to compare clinical outcomes between rapid diagnostic technologies paired with early antimicrobial stewardship intervention (ASI) compared with the same rapid diagnostic technologies with standard of care (SOC) reporting in patients with positive blood cultures.

STUDY DESIGN

A single center, pragmatic, prospective cohort with randomized allocation study was performed between February 2015 and September 2015. Adult patients with positive blood cultures with organism identification to species via matrix assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF VITEK® MS), admitted for at least 48 hours following the positive blood culture (using BACT/ALERT® 3D) were included in the study.

ASI was defined as a clinical assessment by a stewardship team member with non-binding treatment recommendations offered to the primary team.

The same diagnostic techniques were used for both groups: following a positive blood culture and gram staining, MALDI-TOF MS was used for identification of organisms growing in blood culture, and antimicrobial susceptibilities were determined via VITEK® 2, Kirby Bauer disc diffusion, or ETEST®.

In the ASI group, antimicrobial stewardship pharmacists reviewed the records of patients, contacted the primary medical team and offered non-binding recommendations regarding the treatment regimen, dose, and duration. Follow up by stewardship pharmacists following antimicrobial sensitivity determination was conducted as necessary.

In the SOC group, following a positive blood culture, gram staining results were provided to the primary medical team and also reported in the electronic health record system. Identification and susceptibilities of organisms growing in blood cultures were reported in the electronic medical record. To promote appropriate antibiotic use, guidelines for use of broad spectrum agents at the hospital and formulary restrictions in the form of institutional guidelines were in place.

Primary outcome was time to definitive therapy after initial positive culture. **Secondary outcomes** included post-culture length of stay (LOS), time to first change in antibiotics, and in-hospital mortality.

RESULTS

- A total of 149 adult patients were enrolled in the study and randomized into an ASI group (n=76) and SOC group (n=73). Both groups were similar in age, sex, comorbidities, and severity of illness.
- Median time to definitive therapy was 67.5 hours in the ASI group vs. 86.3 hours in the control group (p = 0.01).
- Median time to first change in antibiotics was 67.3 hours in the ASI group vs. 84.6 hours in the control group (p = 0.02).
- Median hospital LOS post-positive culture was 8.7 days in the ASI group vs. 11.2 days in the control group (p = 0.049) **(Figure 1).**
- There was no difference in ICU LOS post-positive culture and in-hospital mortality between the two groups.

CONCLUSIONS

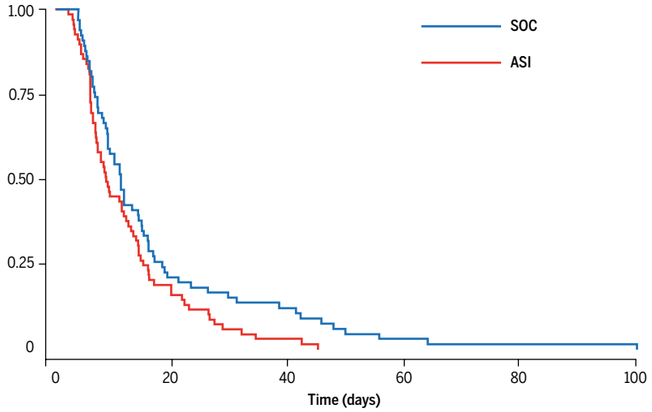
This study is one of the first pragmatic, prospective comparative studies with randomization to evaluate the effect of ASI in combination with rapid diagnostic technologies.

It demonstrated that the addition of ASI on top of the rapid diagnostic MALDI-TOF MS identification of BSIs contributed to significant decreases in time to definitive therapy (18.8 hours) and length of stay (2.5 days).

The relevance of these findings was increased by the pragmatic study design (real-life routine practice conditions) during normal business hours for antimicrobial stewardship pharmacist activities.

FAST MALDI-TOF/AUTOMATED AST – BLOODSTREAM INFECTIONS

Figure 1. Median hospital length-of-stay post-positive culture.
Reproduced with permission from Elsevier. O'Donnell JN, *et al. Int J Antimicrob Agents* 2022;59(2):106490



ASI: Antimicrobial Stewardship Intervention group; SOC: Standard of Care group

"The effect of ASI, in combination with MALDI TOF, appears to have multiple clinically relevant benefits and potential cost savings."

KEY FINDINGS

- Early antimicrobial stewardship intervention combined with rapid diagnostics in patients with positive blood cultures reduced time to definitive therapy by 18.8 hours on average.
- The consequence was a 2.5 day shorter length of stay following the first positive blood culture in the ASI group.

CLICK TO ACCESS ARTICLE

BMJ OPEN
2021;11:E047515

Cost-utility Analysis of Antimicrobial Stewardship Programme at a Tertiary Teaching Hospital in Ethiopia.

Gebretekle GB, Mariam DH , Mac S, Abebe W, Alemayehu T, Degu WA, Libman M, Yansouni CP, Fenta TG, Semret M, Sander B.

OBJECTIVE

The objective of this study was to assess the cost-utility of implementing a 2-step intervention, consisting of a strengthening of laboratory capacity with a concurrent pharmacist-led antimicrobial stewardship (AMS) program compared with usual care (empirical initiation of antibiotic therapy in the absence of strong laboratory and AMS) in a low-resource setting tertiary teaching hospital in Ethiopia*.

STUDY DESIGN

In this study, a major focus of the laboratory strengthening intervention was on performing blood culture testing routinely for all patients with fever or signs of sepsis hospitalized in medicine and pediatric wards, to enable reliable diagnoses of BSIs and detection of antimicrobial resistance. For this purpose, a newly donated BACT/ALERT® automated blood culture system was integrated in the laboratory.

The researchers developed a combination of a decision-tree with a Markov cohort model to assess the cost-utility of this 2-step intervention compared with usual care from a healthcare payer perspective. This perspective included all direct medical costs but not productivity loss or other costs. Direct medical costs include cost paid by any party, *e.g.*, medication cost, investigation/procedural cost, microbiology/culture and sensitivity test cost (including the total cost of the BACT/ALERT investment as well as consumables and technologist training costs, amounting to US$ 97,464), staff time cost, admission and other hospitalization costs. The team used a lifetime time horizon and discounted health outcomes and cost at 3% annually.

It is worth noting the bloodstream infection treatment cost per hospital stay is US$ 1,872 for the usual care versus US$ 289 for the intervention.[1,2] This large cost reduction during the AMS intervention was primarily due to the reduced use of very costly antibiotics (vancomycin, meropenem, third-generation and fourth-generation cephalosporins) by:

1. changing the large volume of broad-spectrum prescriptions to narrow-spectrum antibiotics (generally less costly);
2. significantly reducing treatment duration;
3. frequent discontinuation of incorrectly/unnecessarily prescribed antibiotics (*e.g.*, vancomycin, which accounted for 30% of the antibiotics budget recommended to be discontinued in 60% of cases with good acceptance).

Another contributor to this cost reduction was the reduced duration of hospitalization.

Outcome measures were expected life-years, quality-adjusted life-years (QALYs), direct medical costs (US$ 2018) and incremental cost-utility in terms of cost/QALY.

Deterministic and probabilistic sensitivity analyses were performed to assess parameter uncertainty and test robustness of the model.

RESULTS

- The study found that laboratory-supported pharmacist-led AMS was the dominant strategy, being more effective and less costly than usual care.
- Lab strengthening + AMS was associated with an expected incremental gain of 38.8 quality-adjusted life-years (QALYs) at lower expected cost (incremental cost savings: US$ 82,370) per 1000 patients compared with usual care **(Table 1).**
- Findings were robust to all assumptions made: sensitivity analysis to medication cost, infection-associated and AMS-associated mortality reduction did not change the dominance of this intervention (less costly and better health outcome).
- Probabilistic sensitivity analysis demonstrated that AMS program was likely to be cost-effective at 100% of the simulation compared with usual care at 1%–51% of gross domestic product/capita.

These large cost savings were obtained in the first year of the intervention. Considering potential objections that this economic benefit might not be sustainable over a longer time, two additional scenarios were assessed based on the following assumptions:

1. a strong microbiology capacity already exists,
2. AMS has no significant impact on mortality and a marginal impact on treatment duration.

Both scenarios were still shown to be cost-saving, *i.e.*, dominant, and sustainable.

* **Tikur Anbessa Specialised Hospital (TASH)** is Ethiopia's largest referral and teaching hospital with 800 beds and approximately 20,000 admissions annually

1. Yansouni CP, *et al.* **A Feasible Laboratory-Strengthening Intervention Yielding a Sustainable Clinical Bacteriology Sector to Support Antimicrobial Stewardship in a Large Referral Hospital in Ethiopia.** *Front. Public Health* 2020;8:258. doi: 10.3389/fpubh.2020.00258
2. Gebretekle GB, *et al.* **Half of Prescribed Antibiotics Are Not Needed: A Pharmacist-Led Antimicrobial Stewardship Intervention and Clinical Outcomes in a Referral Hospital in Ethiopia.** *Front. Public Health* 2020;8:109. doi: 10.3389/fpubh.2020.00109

LAB STRENGTHENING / AUTOMATED BLOOD CULTURE – COST-UTILITY IN LMIC

CONCLUSIONS

This is the first study to investigate the cost-utility of laboratory supported antimicrobial stewardship (AMS) intervention for inpatients in a low-resource setting in Africa. The study concludes that laboratory-supported pharmacist-led AMS can result in improved health outcomes and substantial healthcare cost savings, demonstrating its economic and medical advantage in a tertiary care hospital, despite greater upfront investments. These findings should guide improvements in the standards of healthcare for low-resource settings.

Table 1. Model costs estimate with values and ranges

Usual care	Base case US$		Sensitivity analysis range US$	Lab Strengthening + AMS Intervention
Daily hospitalization cost, per patient	5	5	1–35	
Bloodstream infection treatment cost per hospital stay per patient	1.872	289	255–2,821	
		8	6–24	Cost of blood culture test, per patient
		3	1–6	AMS staff time cost, per patient
		97.464	80,000-150,000	Total cost of automated blood culture platform investment including consumables and technologist, spread over 8 years of use

"Our analysis suggested that the implementation of a laboratory-supported pharmacist-led AMS programme at a tertiary care hospital in a low-resource setting was dominant (saving costs and improving health) compared with usual care. Our findings support implementation of AMS in similar settings."

KEY FINDINGS

- Laboratory-supported pharmacist-led AMS interventions in low-resource settings result not only in significant clinical benefits to individual patients but are economically advantageous.
- Substantial savings in healthcare costs can be achieved, even accounting for significant upfront investments in equipment and training.
- AMS was associated with an expected incremental gain of 38.8 QALYs at lower expected cost (incremental cost savings: US$ 82,370) per 1000 patients compared with usual care.

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JOURNAL OF MEDICAL MICROBIOLOGY
2022;71(6)

The Impact of VITEK 2 Implementation for Identification and Susceptibility Testing of Microbial Isolates in a Brazilian Public Hospital.

Decarli A, Vieira Nascimento L, Sayama Esteves LH, Arenas Rocha P, Midori V, Yuki G, Cieslinski J, Telles JP, Stadler V, Ribeiro T, Tuon FP.

OBJECTIVE

The objective of this study was to evaluate the clinical impact of an automated method for identification and susceptibility testing of microbial isolates in a Brazilian public hospital.

STUDY DESIGN

This retrospective cross-sectional study analyzed results before and after the implementation period of a VITEK® 2 system in a Brazilian university hospital used for trauma and general surgery. The standard of care consisted of manual biochemical testing of microscopical observations for identification (ID), and disc diffusion or ETEST® for antibiotic susceptibility testing (AST).

The study included patients with a positive culture of clinical samples from January to July 2017 (conventional method) and from August to December 2017 (automated method). The study evaluated demographic data, hospitalization time, time interval between culture collection and results, culture results and site, susceptibility profile, minimum inhibitory concentration, and outcome data.

RESULTS

- In total, 836 adult patients were included: 219 patients in the pre-VITEK 2 system implementation group and 545 in the post-implementation group.
- The comparison between the two periods showed:
  - a significant reduction of 25% of the time to results release (from a median 4 days down to 3 days, p=0.03);
  - a significant 50% decrease of the hospital length of stay (from 33.5 to 17.0 days, p<0.001);
  - a significant 30% reduction in mortality (from 44.3 to 31.0%, p<0.05).
- Reduced hands-on time and short incubation times for ID/AST contributed to the faster time-to-results with the automated method.
- Patient mortality in this study was high in both periods, which is a characteristic of a Brazilian public hospital. This meant that faster identification had a greater impact on reducing mortality. If mortality had been low, the impact of the automated method would have been smaller.

CONCLUSIONS

The study concluded that the use of automated systems in identification and susceptibility tests can improve antimicrobial therapy, and positively impact clinical outcomes with a decrease in antimicrobial resistance, hospitalization time, costs, and mortality.

"The VITEK 2 system provided early access to appropriate antimicrobial therapy for patients and effected a positive clinical impact with a reduction in mortality and hospitalization time."

KEY FINDINGS

- **The VITEK 2 system enabled early access to appropriate antimicrobial therapy for patients and had a significant positive clinical impact:**
  - **25% shorter time to results release**
  - **50% decrease in hospital length of stay**
  - **30% reduction in mortality.**

CLICK TO ACCESS ARTICLE

MICROBIOLOGY SPECTRUM
2023;11(1):E04673-22

Performance of the VITEK® 2 Advanced Expert System (AES) as a Rapid Tool for Reporting Antimicrobial Susceptibility Testing (AST) in *Enterobacterales* from North and Latin America.

Carvalhaes CG, Shortridge D, Woosley LN, Gurung N, Castanheira M.

OBJECTIVE

The objective of this study was to evaluate the performance of the VITEK® 2 Advanced Expert System (AES) confidence level report as a rapid tool for reporting antimicrobial susceptibility testing (AST) results for a challenging set of American *Enterobacterales* isolates.

STUDY DESIGN

The study evaluated 513 clinical isolates of *Enterobacterales* from 73 medical centers in 7 countries in North and Latin America (123 isolates [24.0% overall]). The isolates were assessed by VITEK 2 (N802 and XN15 AST cards) and CLSI broth microdilution (BMD). Included isolates were wild-type and those having acquired ß-lactamases, as characterized by whole genome sequencing. The VITEK 2 AES identified a phenotype to three confidence levels: (i) green, for consistent or typical (all minimum inhibitory concentrations [MICs] match with the phenotype); (ii) yellow, for consistent with correction or atypical (one MIC does not match with closest phenotype (s)); and (iii) red, indicating inconsistent (at least two MICs do not match with any phenotype or a phenotype cannot be identified with sufficient confidence). Comparison of AES assessment of confidence level was performed with BMD results and known genotypes. Review by an experienced microbiologist was conducted for accuracy.

RESULTS

Overall performance of VITEK 2 AES system and AES assessment:

- 148 (28.8%) isolates were wild-type, and 365 (71.2%) harbored carbapenemase (211 [41.1%]), extended-spectrum ß-lactamase (122 [23.8%]), and/or transferable *AmpC* (32 [6.2%]) genes.
- VITEK 2 displayed rates of essential agreement (EA) of >83% and categorical agreement (CA) of >81% in the 14,058 pathogen/antimicrobial combinations that were tested.
- For each ß-lactam antimicrobial, CA rates were <90% for cefepime (87.4%) and cefoxitin (86.9%), primarily due to minor errors.
- Cefepime very major errors (VMEs) were observed mainly in isolates with carbapenemase genes (14/16).
- Improving AES corrections based on organism phenotype can reduce cefepime VME from 5.8% to 1.8%.

AES assessment for rapid AST report:

- The AES confidence level was evaluated for 488 isolates, and the phenotype was identified for 447 (91.6%).
- AES reports were green, yellow, and red for 382 (78.3%), 65 (13.3%), and 41 (8.4%) isolates, respectively.
- As compared to BMD, 96.3% of green AES reports could be confidently and quickly auto-released, which enables rapid adjustments to antimicrobial therapy.
- 69.2% of yellow reports were acceptable; 16 (24.6%) isolates in yellow-labeled reports were consistent with BMD results.
- A red report was issued for 8.4% of isolates that were evaluated, and 80.5% displayed consistent results with BMD method.
- AES applies a red label in cases of technical problems or when the organism's phenotype is not present in AES knowledge base. Organism reidentification, additional testing, and/or retesting AST before reporting should be performed if the phenotype is not identified during AES assessment.

CONCLUSIONS

VITEK 2 displayed EA and CA rates of >90.0% for this challenging collection of *Enterobacterales*.

"VITEK 2 AES continues to provide accurate susceptibility testing for contemporaneous Enterobacterales isolates harboring diverse mechanisms of resistance to beta-lactams"

KEY FINDINGS

- **The AES confidence level report is a valuable tool for clinical laboratories, as 96.3% of consistent (i.e., green) AES reports could be confidently and quickly auto-released. This enables rapid adjustments to antimicrobial therapy when results are quickly communicated to an antimicrobial stewardship team.**
- **For contemporaneous *Enterobacterales* isolates with diverse ß-lactam resistance mechanisms, VITEK® 2 AES provides accurate susceptibility testing.**

DISCONTINUATION OF ANTIBIOTIC THERAPY

CLICK TO ACCESS ARTICLE

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE
2020; DOI.10.1164/RCCM.202004-1201OC

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis: A Randomized Trial.

Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, Panagaki A, Melachroinopoulos N, Drakou E, Marousis K, Chrysos G, Spyrou A, Alexiou N, Symbardi S, Alexiou Z, Lagou S, Kolonia V, Gkavogianni T, Kyprianou M, Anagnostopoulos I, Poulakou G, Lada M, Makkina A, Roulia E, Koupetori M, Apostolopoulos V, Petrou D, Nitsotolis T, Antoniadou A, Giamarellos-Bourboulis EJ.

OBJECTIVE

The objective of this study was to assess the impact of PCT-guided discontinuation of antimicrobials on the incidence of infection-associated adverse events in septic patients.

STUDY DESIGN

This multicenter randomized trial was designed as a real-world pragmatic study. Performed in 7 internal medicine departments in Athens, Greece, the study enrolled 266 patients with lower respiratory tract infections (LRTIs), acute pyelonephritis, primary bloodstream infection, and meeting the Sepsis-3 definitions.

After 24 hours of antimicrobial treatment, patients were randomized into two arms: PCT-guided discontinuation or standard of care (SOC). In the PCT-guided arm, antibiotics were discontinued if ≥80% decrease in PCT level or PCT level ≤0.5 µg/L at day 5 or later. In the SOC arm, duration of antimicrobial treatment followed international guidelines.

Primary outcome was the rate of infection-associated adverse events at day 180. Adverse events were defined as: new case of *C. difficile* infection; new case of multidrug-resistant organism (MDRO) infection; and death associated with either MDRO or *C. difficile* baseline infection. Secondary outcomes were: 28-day mortality, length of treatment (LOT) and hospitalization cost.

RESULTS

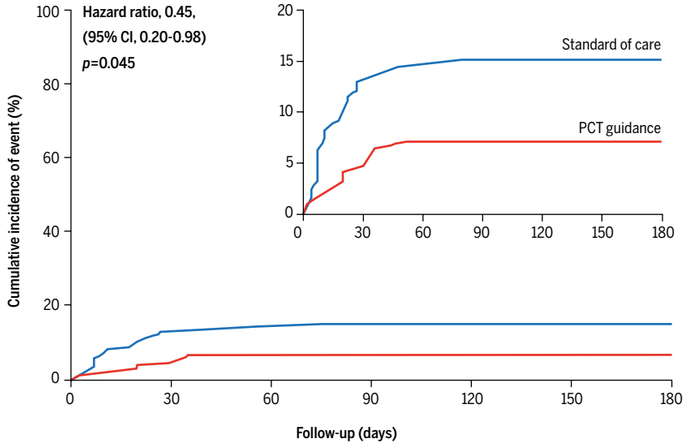
- The rate of infection-associated adverse events was 7.2% in the PCT-guidance arm vs 15.3% in SOC arm (p=0.045) **(Figure 1).**
- The 28-day mortality rate was 15.2% in PCT arm vs 28.2% in SOC arm (p=0.02).
- A trend for decreased mortality at day 180 was observed in the PCT arm (30.4%) compared to SOC arm (38.2%), but was not statistically significant.
- The median LOT was 5 days in PCT arm vs 10 in SOC arm (p<0.01).
- Costs were €956.99 in PCT arm vs €1,183.49 in SOC arm (p=0.05).

CONCLUSIONS

The PCT-guidance approach was shown to be effective in reducing the rate of infection-associated adverse events, as well as 28-day mortality, LOT and related cost of hospitalization. In countries with high antimicrobial consumption and high antimicrobial resistance rates, this strategy could be beneficial from a public health standpoint.

"In the PROGRESS trial, we demonstrate for the first time that PCT-guided early discontinuation of antimicrobials in patients with sepsis prevents infection caused by MDRO and/or C. difficile."

Figure 1: Kaplan-Meier curve for primary outcome: rate of infection-associated adverse events in the PCT-guidance group compared to the standard-of-care after 180 days.



KEY FINDINGS

- PROGRESS is the first multicenter randomized trial showing that early discontinuation of antimicrobials in patients with sepsis decreases the incidence of infection-associated adverse events.
- PCT-guided antimicrobial therapy was effective in reducing in-hospital and 28-day mortality.
- PCT-guidance could be a safe strategy with long-term benefits that may have substantial impact on public health.

ANTIMICROBIAL RESISTANCE SURVEILLANCE

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OPEN FORUM INFECTIOUS DISEASES
2022; 9(7):OFAC296

Epidemiology of Antimicrobial Resistance among Blood and Respiratory Specimens in the United States using Genotypic Analysis from a Cloud-Based Population Surveillance Network.

Timbrook T, Olin K, Spaulding U, Galvin B, Cox C.

OBJECTIVE

The objective of this study was to evaluate the epidemiology of antimicrobial resistance (AMR) genetic determinants from respiratory and blood specimens in the United States, using genotypic analysis of data collected by BIOFIRE® Syndromic Trends (Trend), and to demonstrate proof-of-concept of the AMR capabilities of the surveillance network. The Trend is a cloud-based population surveillance network with near real-time tracking of detections among BIOFIRE® FILMARRAY® Panels including those with AMR targets and allows for near real-time detection and tracking of AMR at the local, regional, and national level.

STUDY DESIGN

This retrospective study used BIOFIRE® FILMARRAY® Pneumonia (PN) Panel and BIOFIRE® FILMARRAY® Blood Culture Identification 2 (BCID2) Panel data from Trend. Data were utilized from 2019 to 2021 for both gram-positive and negative organisms along with their related AMR gene targets, as well as for detection of *Candida auris*. Detection rates were evaluated by panel and by region (Midwest, the South, and the West) **(Table 1)**. Selected codetection rates of AMR determinants and gram-negative and positive organisms were analyzed.

RESULTS

- In total, 26,912 BIOFIRE® FILMARRAY® tests were performed, primarily in the Midwest.
- The AMR detection rate was highest in the South and more common for respiratory specimens than blood.
- Methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* detection rates were 34.9% and 15.9%, respectively, whereas AMR for Gram-negative organisms was lower with 7.0% CTX-M and 2.9% carbapenemases.
- For Gram-negative organisms, *Klebsiella pneumoniae* and *Escherichia coli* were most likely to be detected with an AMR gene, and of Gram-negative organisms, *K pneumoniae* was most often associated with 2 or more AMR genes.
- Emerging AMR detections were observed with 10 *mcr*-1 and 4 *C. auris* positives occurring.

CONCLUSIONS

Surveillance of AMR is essential for infection control strategies to slow the spread of resistant organisms, as well as for antimicrobial stewardship. By providing near real-time surveillance of AMR, the Trend surveillance network used in this study provides an important in-depth evaluation of the epidemiology of AMR among respiratory and blood specimens for Gram-positive and -negative organism in the United States.

"The Syndromic Trends surveillance network data on AMR has important implications on national public health initiatives as well as informing antimicrobial stewardship and infection control actions through regional and institutional-level reporting."

ANTIMICROBIAL RESISTANCE SURVEILLANCE – GENOTYPING

Table 1. Detection rates of genotypic antimicrobial resistance detections per region overall and stratified by syndromic testing type.
Adapted from Timbrook T, *et al.* Open Forum Infect Dis. 2022; 9(7):ofac296

Panel	CTX-M detection rates (%) per region		
	Midwest	South	West
PN	5.4	10.8	8.3
BCID2	6.0	9.0	7.7
Combined	5.8	9.9	7.9

Panel	Carbapenemase detection rates (%) per region		
	Midwest	South	West
PN	3.8	4.9	1.8
BCID2	1.0	3.7	1.5
Combined	2.1	4.3	1.6

Panel	MRSA detection rates (%) per region		
	Midwest	South	West
PN	36.3	36.5	30.4
BCID2	36.5	48.9	22.0
Combined	36.4	42.3	25.3

Panel	VRE detection rates (%) per region		
	Midwest	South	West
BCID2	17.1	18.0	14.4

MRSA: methicillin-resistant *Staphylococcus aureus*; PN: BIOFIRE® FILMARRAY® Pneumonia Panel; VRE: vancomycin-resistant Enterococcus.

KEY FINDINGS

- Near real-time characterization of AMR is important for local guideline development and outbreak detection, regional benchmarking, and informing national public health initiatives.
- Nearly pandrug resistant detections (e.g. mcr-1 and blaNDM codetections) occurred, highlighting the importance of AMR surveillance.

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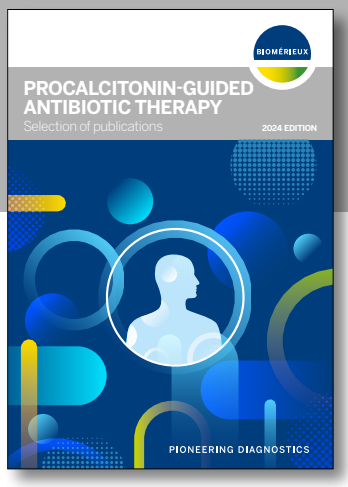

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