Quickness is Key: Updates on FAST AST

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OBJECTIVES

- Understand the evolution of susceptibility testing for bacteria
- Describe current methodologies use for Rapid AST
- Explain considerations for incorporation of Rapid AST into laboratory workflow

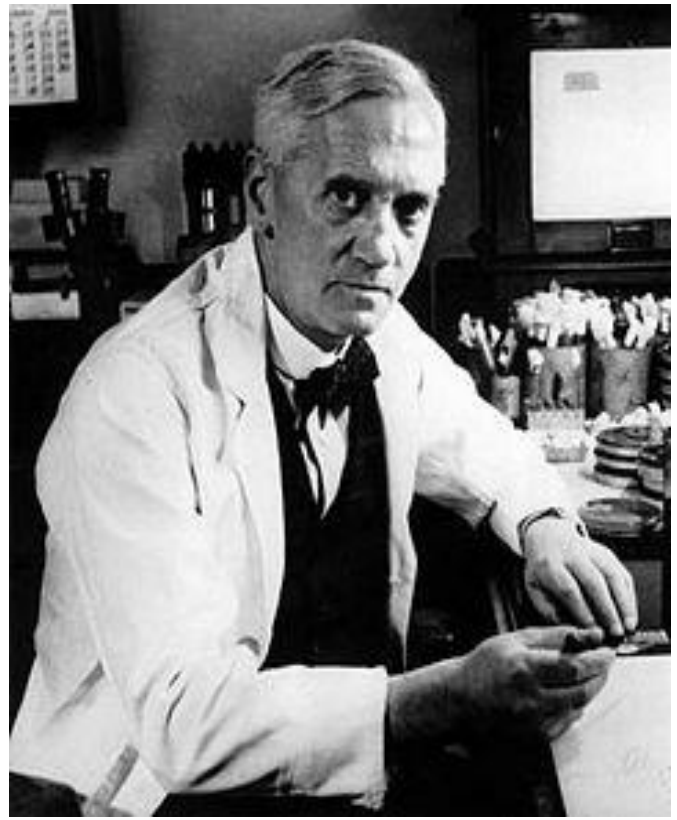
INTRODUCTION

A HISTORIC PERSPECTIVE

"But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient.

"There may be a danger, though, in underdosage. It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."

Nobel Lecture, December 11, 1945

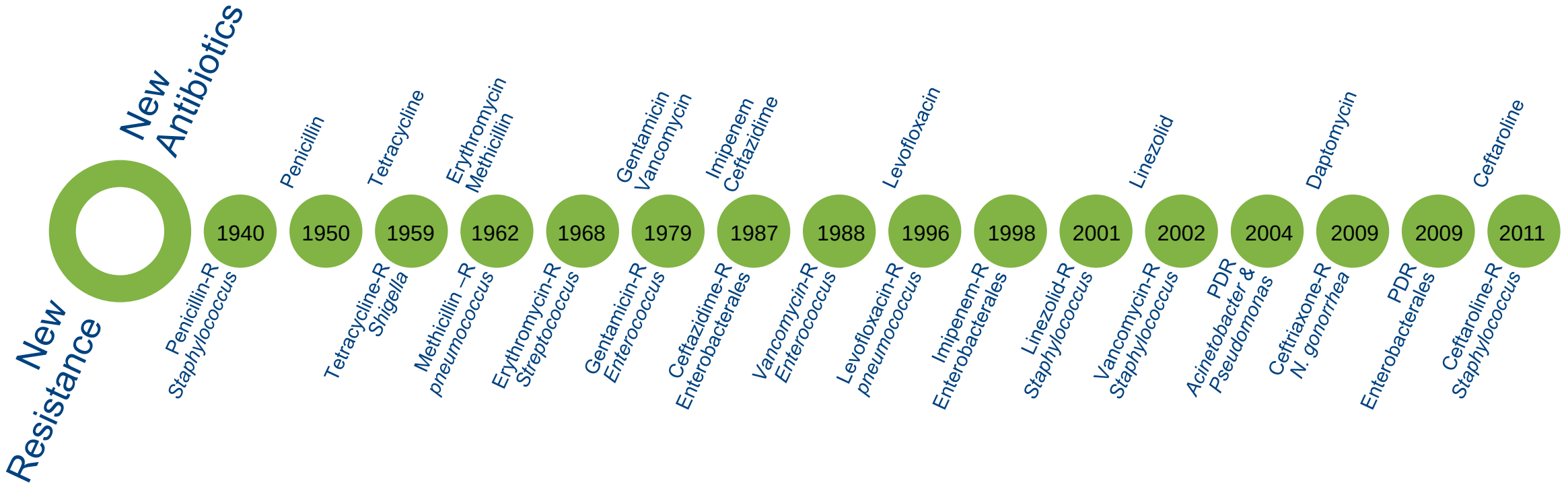


Alexander Fleming. New York Times.
26 June 1945

https://www.nobelprize.org/uploads/2018/06/fleming-lecture.pdf

ANTIMICROBIAL EXPOSURE & RESISTANCE

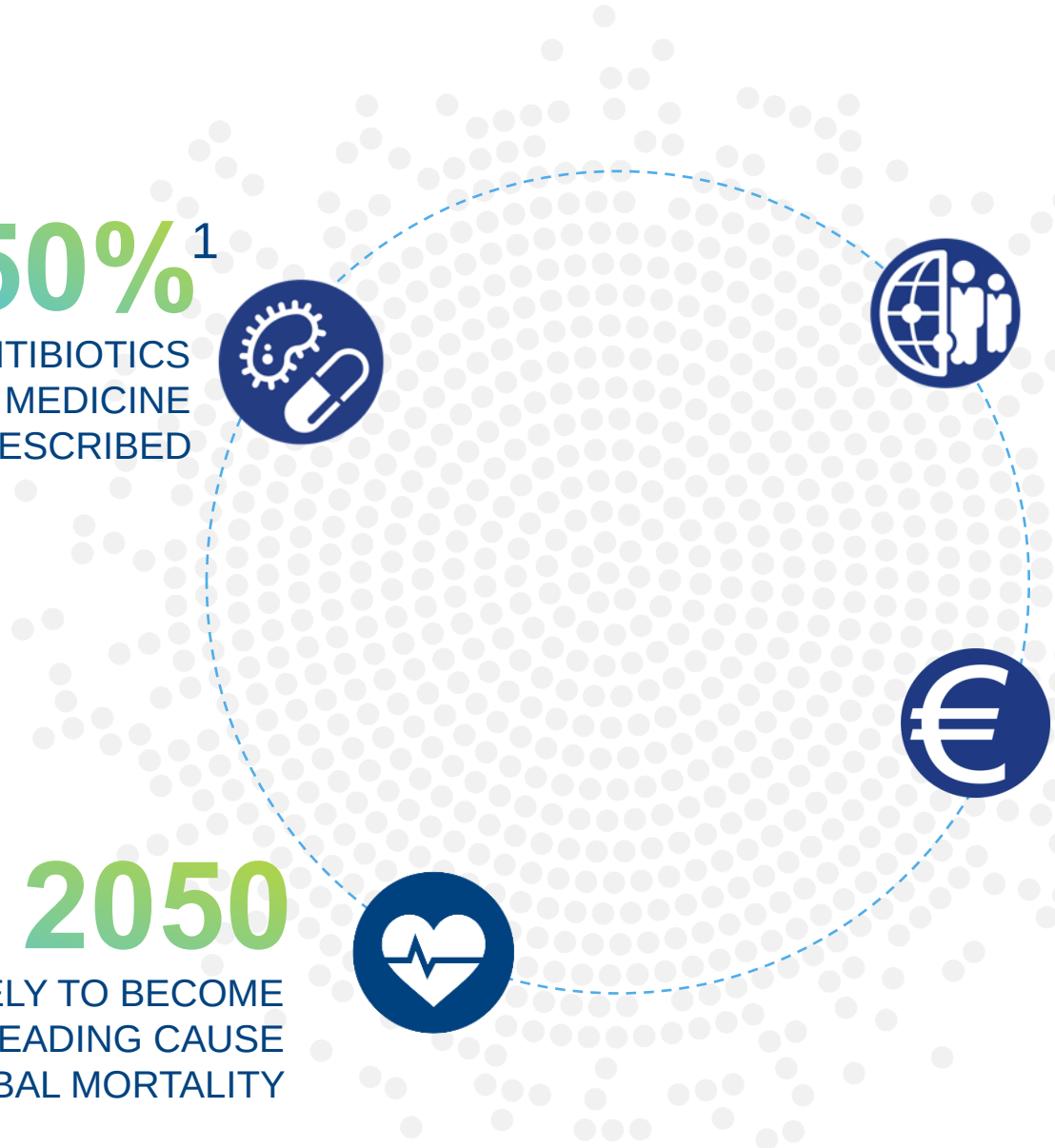
Primary Driver Behind Antimicrobial Resistance



PDR: pan drug-resistant

Adapted from "Antibiotic Resistance Threats in the United States. Centers for Disease Control and Prevention, 2013."

SO WHAT? AMR FACTS AND FIGURES



50%[1]

OF ALL ANTIBIOTICS
IN HUMAN MEDICINE
INAPPROPRIATELY PRESCRIBED

1.27M[2]

DEATHS DIRECTLY
ATTRIBUTABLE TO AMR
IN 2019

$100,000M[3]

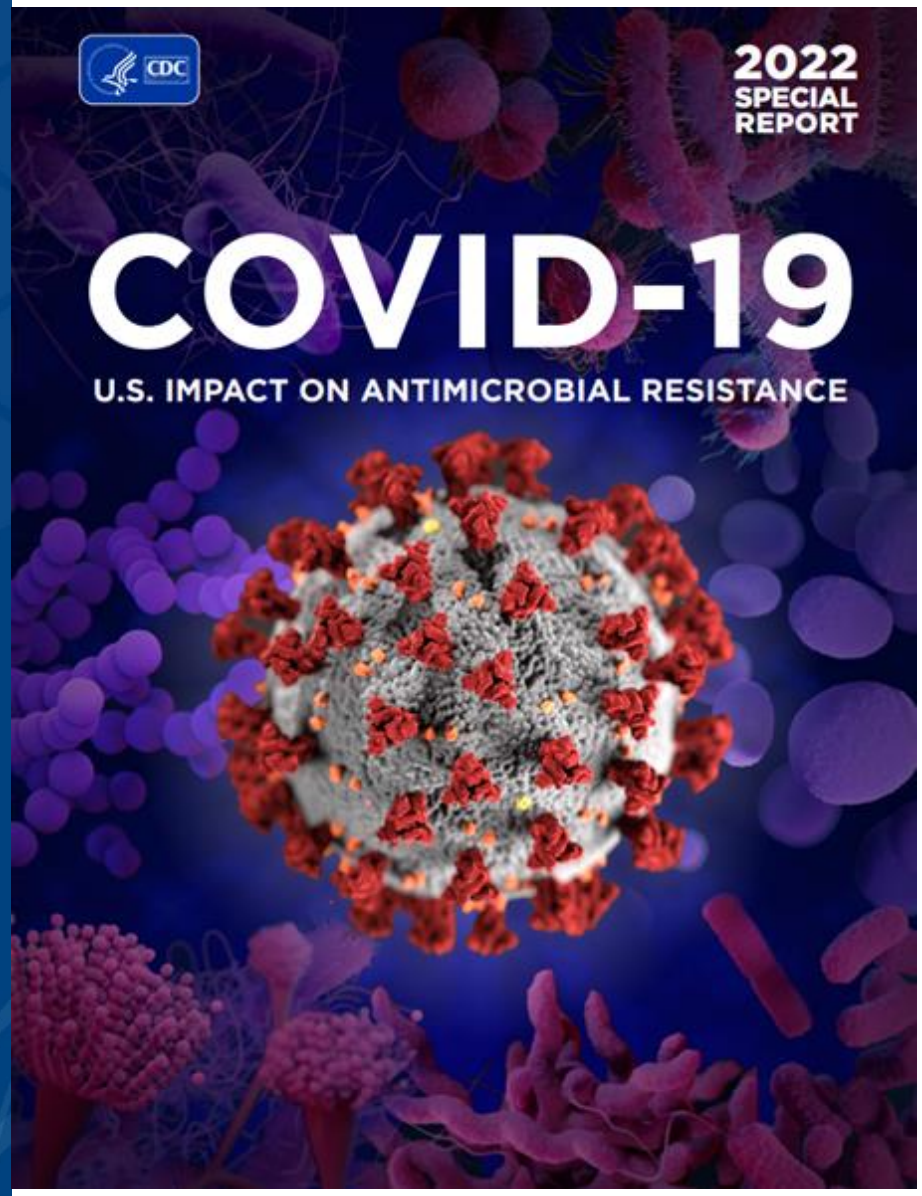
POTENTIAL LOSS FOR GLOBAL
ECONOMY BY 2050

BY 2050

AMR IS LIKELY TO BECOME
THE LEADING CAUSE
OF GLOBAL MORTALITY

1. World Bank Press release, “By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis”, September 20, 2016.
2. Lancet. 2022 Feb 12;399(10325):629-655.
3. Tackling drug-resistant infections globally: Final report and recommendations, The Review on Antimicrobial Resistance, Chaired by Jim O’Neill, May 2016.

PRN066757.01A



IMPACT OF COVID-19 ON AMR

- 2019 to 2020: 15% increase in resistant infections starting during hospitalization
  - Carbapenem-resistant *Acinetobacter* (↑78%)
  - Antifungal-resistant *Candida auris* (↑60%)*
  - Carbapenem-resistant Enterobacterales (↑35%)
  - Antifungal-resistant *Candida* (↑26%)
  - ESBL-producing Enterobacterales (↑32%)
  - Vancomycin-resistant Enterococcus (↑14%)
  - Multidrug-resistant *P. aeruginosa* (↑32%)
  - Methicillin-resistant *Staphylococcus aureus* (↑13%)

*Candida auris was not included in the hospital-onset rate calculation of 15%. See Data Table and Methods for more information on this pathogen

CDC. COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2022.

EFFECTS OF ANTIBIOTIC USE

Other classes of drugs do not lose their effectiveness over time[1]

- Antimicrobial exposure is the primary driver behind antimicrobial resistance[2]

Resistance will eventually develop to all antibiotics[1]

- Any previous exposure to antibiotics increases the risk of resistance[3]
- Every antibiotic exposure increases further risk of resistance[4]

Once a mechanism of resistance is established, it can be passed on to future generations of that specific bacteria[1]

- Translocation of plasmids *between* species amplifies resistance[1]

Antibiotics save lives, but can also be harmful without good stewardship

- Each additional day of antibiotic exposure increases the risk of resistance[5]

1. https://www.cdc.gov/drugresistance/about/how-resistance-happens.html
2. Antimicrob Agents Chemother. 2013; 51(10): 5131-3.
3. Infect Control Hosp Epidemiol. 2012;8: 817-30.
4. J Antimicrob Chemother 2011; 66(8): 1600-8.
5. Infect Control Hosp Epidemiol. 2013 Aug;34(8):809-17.

NEW CDC DATA

MORE THAN HALF OF ANTIBIOTIC PRESCRIBING FOR SELECTED EVENTS IN HOSPITALS WAS NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES

ANTIBIOTIC PRESCRIBING WAS NOT SUPPORTED IN:

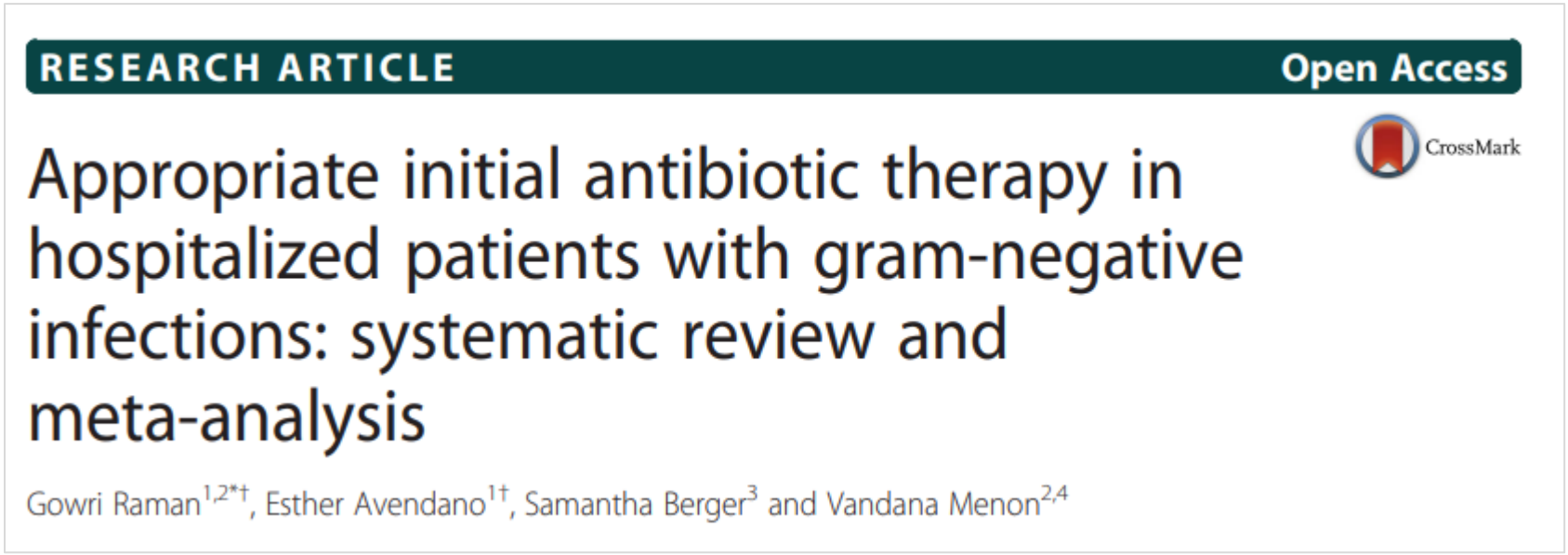
- **79%** OF PATIENTS — with community-acquired pneumonia
- **77%** OF PATIENTS — with urinary tract infections
- **47%** OF PATIENTS — prescribed fluoroquinolone treatment
- **27%** OF PATIENTS — prescribed intravenous vancomycin antibiotic

HOSPITAL PRESCRIBERS & PHARMACISTS CAN IMPROVE PRESCRIBING:

- Optimize antibiotic selection
- Re-assess antibiotic treatment when the results of diagnostic testing are available
- Use the shortest effective duration of therapy

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

WHY DOES APPROPRIATE THERAPY MATTER?



RESEARCH ARTICLE Open Access

CrossMark

Appropriate initial antibiotic therapy in hospitalized patients with gram-negative infections: systematic review and meta-analysis

Gowri Raman[1,2*†], Esther Avendano[1†], Samantha Berger[3] and Vandana Menon[2,4]

- Meta-analysis of 57 studies in 60 publications:
  - Appropriate antibiotic therapy (AAT) was associated with a lower risk of mortality and treatment failure
  - Inappropriate antibiotic therapy was associated with > 3 fold of increased risk of mortality in septic patients
  - “Technological advances for rapid diagnostics to facilitate AAT along with antimicrobial stewardship, surveillance, infection control, and prevention is needed.”

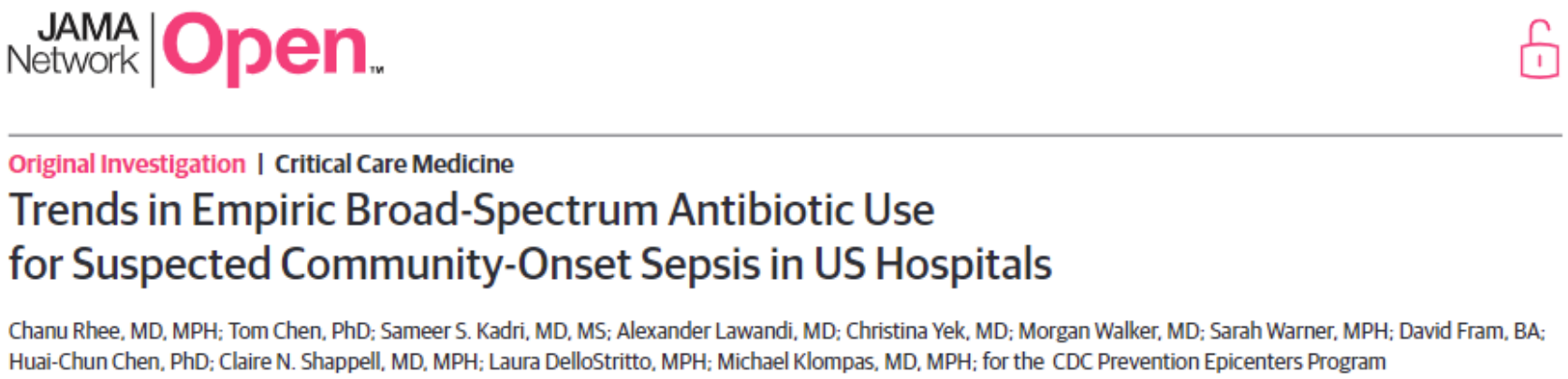
BMC Infect Dis. 2015 Sep 30;15:395.

IMPORTANCE OF APPROPRIATE THERAPY

- For patients with serious infections, such as bloodstream infections and sepsis, shortening time to effective antimicrobial therapy (TTET) has been associated with decreased mortality[1-7]
- Delay in TTET has been demonstrated to be one of the key modifiable risk factors for mortality in patients with bloodstream infections[7]
- Collaboration between the lab and antimicrobial stewardship intervention maximizes the impact on TTET[8,9]

1. Gutiérrez-Gutiérrez B. Lancet Infect Dis. 2017 Jul;17:726-34.
2. Bonine NGAm J Med Sci. 2019 Feb;357(2):103-110.
3. Perez KK. J Infect. 2014 Sep;69(3):216-25.
4. Babowicz F. AAC. 2021 May 18;65(6):e02364-20..
5. Lodise TP. Open Forum Infect Dis.2019 Jun; 6(6): ofz194.
6. Bassetti M. JAC Antimicrob Resist. 2022 Sep 13;4(5):dlac089.
7. Evans RN. BMC Infect Dis. 2020 Jul 25;20(1):545..
8. Timbrook TT. Clin Infect Dis. 2017;64:15-23.
9. Wenzler E. Am J Health Syst Pharm. 2018;75:1191-1202.

IMPORTANCE OF APPROPRIATE THERAPY


JAMA Network | Open

Original Investigation | Critical Care Medicine

Trends in Empiric Broad-Spectrum Antibiotic Use for Suspected Community-Onset Sepsis in US Hospitals

Chanu Rhee, MD, MPH; Tom Chen, PhD; Sameer S. Kadri, MD, MS; Alexander Lawandi, MD; Christina Yek, MD; Morgan Walker, MD; Sarah Warner, MPH; David Fram, BA; Huai-Chun Chen, PhD; Claire N. Shappell, MD, MPH; Laura DelloStritto, MPH; Michael Klompas, MD, MPH; for the CDC Prevention Epicenters Program

- Retrospective, cross-sectional study looking at over 6 million hospitalizations from PINC AI Healthcare Database (25% of US inpatient admissions) between Jan. 2017 and June 2021
- Among patients with suspected community acquired sepsis 65.1% received anti MRSA or antipseudomonal beta-lactam therapy.
- Resistant organisms were only identified in 9.5% of cases.

THE GENOTYPIC VERSUS PHENOTYPIC CHALLENGE

- Genotypic resistance mechanism detection is impactful when positive.
- Negative genotypic resistance mechanism testing can be misleading to clinicians, particularly for gram-negative organisms.
- Frequency of false susceptibility when relying on genotypic screening alone.

Census Region	CRO NS (n)	CRO % VME	MEM NS (n)	MEM % VME	TZP NS (n)	TZP % VME
New England	42	42.9	4	25.0	23	60.9
Mid-Atlantic	255	12.2	116	3.5	166	9.6
East North Central	80	25.0	13	7.7	31	41.9
West North Central	27	33.3	0	N/A	8	75.0
South Atlantic	38	29.0	5	0.0	21	47.6
East South Central	51	27.5	1	0.0	12	66.7
West South Central	131	18.3	23	30.4	56	23.2
Mountain	23	26.1	2	0.0	7	57.1
Pacific	55	21.8	1	0.0	19	47.4
Overall	702	20.7	165	7.3	343	27.1

CRO – ceftriaxone; MEM – meropenem; NS – non-susceptible; TZP – piperacillin/tazobactam; VME – very major error
CRO/TZP NS isolates screened for CTX-M, KPC and NDM
MEM NS isolates screen for KPC and NDM

Spafford K. J Clin Microbiol . 2019 Sep 24;57(10):e00674-19.

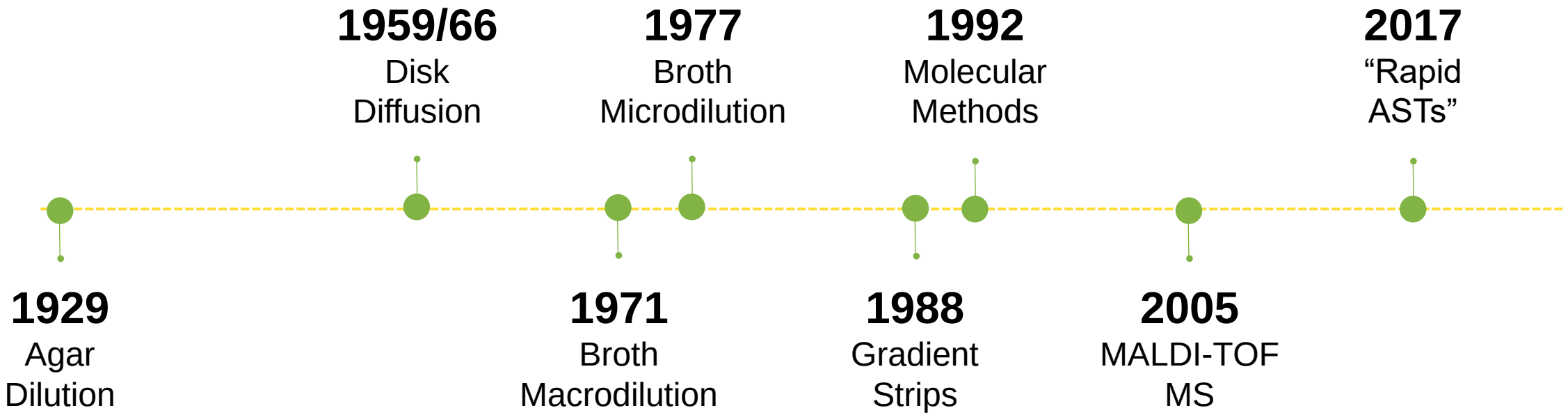
WHY DOES SPEED MATTER?

- 40 – 70% of patients with blood stream infections are on incorrect therapy prior to lab results
- Impacts:
  - Time to targeted therapy
  - Drug Toxicity
  - Mortality
  - Length of Stay
  - Hospital Cost

Bonine NG, et al. Am J Med Sci. 2019 Feb;357(2):103-110
Bassetti M, et al. JAC Antimicrob Resist. 2022 Sep 13;4(5):dlac089
Lodise TP, et al. Open Forum Infect Dis. 2019 Apr 23;6(6):ofz194
Perez KK, et al. J Infect. 2014 Sep;69(3):216-25.

THE METHODS

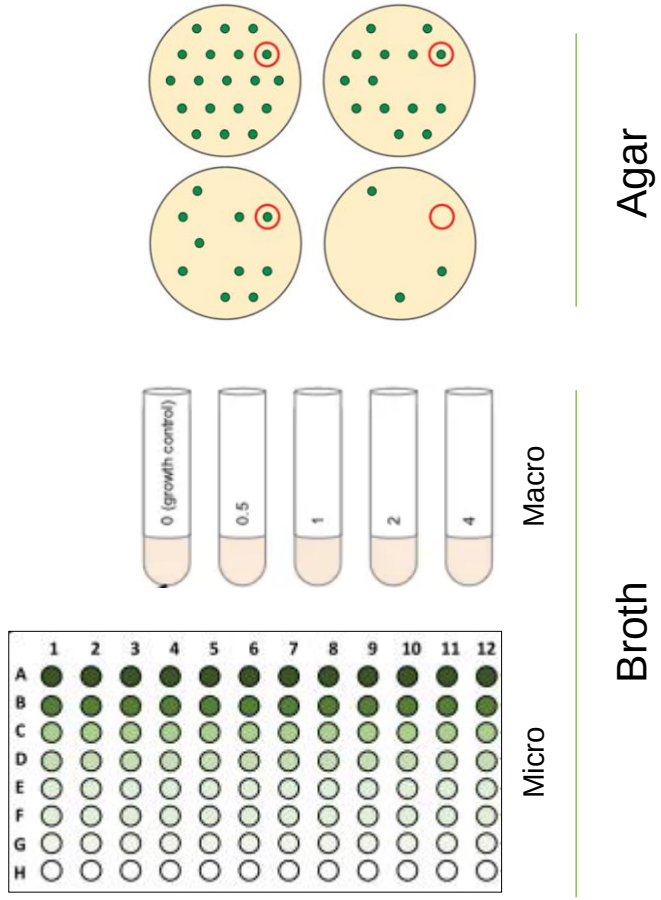
METHOD DEVELOPMENT TIMELINE



1. Schumacher et al. *Eur J Clin Microbiol Dis.* 2018

DILUTION GRADIENT

- Still considered the “Gold Standard”
- Very manual process
  - Automation available
- Requires pure culture
- Results ready in ~18 - 24 hours (organism dependent)
- Cost effective

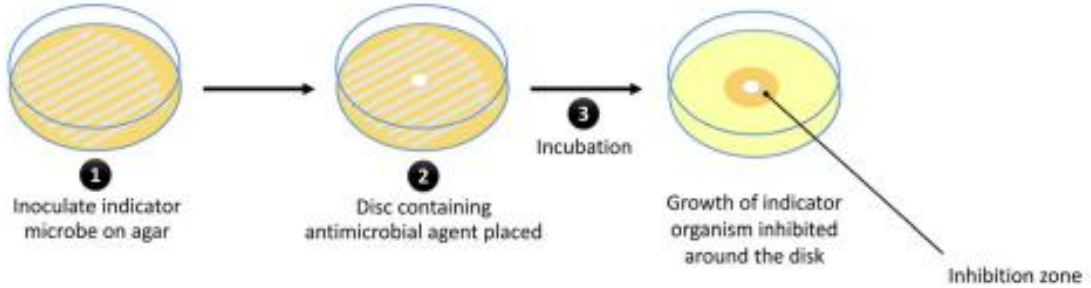


1. Schumacher et al. *Eur J Clin Microbiol Dis.* 2018
2. Reller et al. *Clinical Infectious Diseases*, 2009

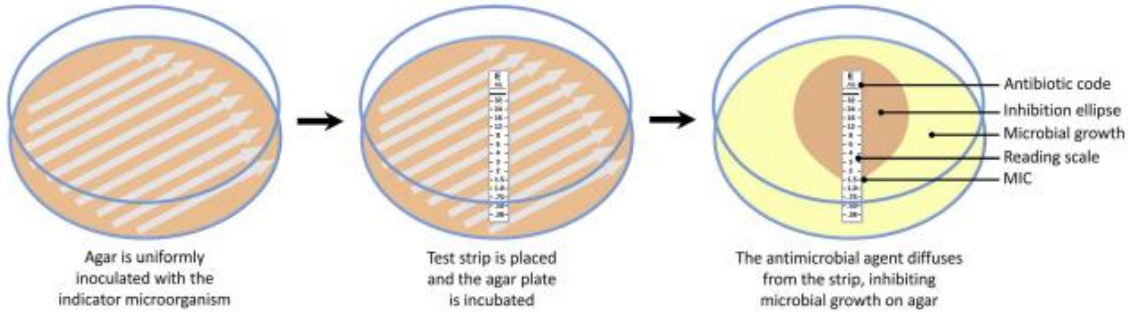
DIFFUSION GRADIENT

- Very manual process
  - Automation available
- Requires pure culture
- Results ready in ~18 - 24 hours (organism dependent)
- Cost effective
- Consider fastidious organisms, biochemistry of antibiotics

Disk Diffusion Assay



Gradient Strip Diffusion Assay



1. Schumacher et al. *Eur J Clin Microbiol Dis.* 2018
2. T. Hussain. *Eur J of Microbiol and Immun.* 2024

Methods for AST - Phenotypic Conventional

Positive blood culture

Isolation after 18-24hrs incubation

Calibrated suspension from isolated colonies

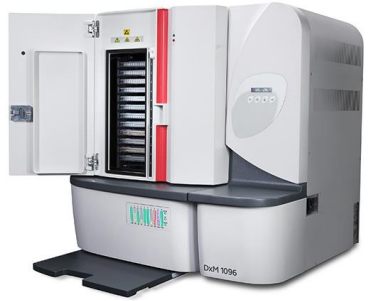
Manual (reading after 16-24 h incubation)

Gradient strips

Disk diffusion

Broth microdilution

Automated (8- 24h)

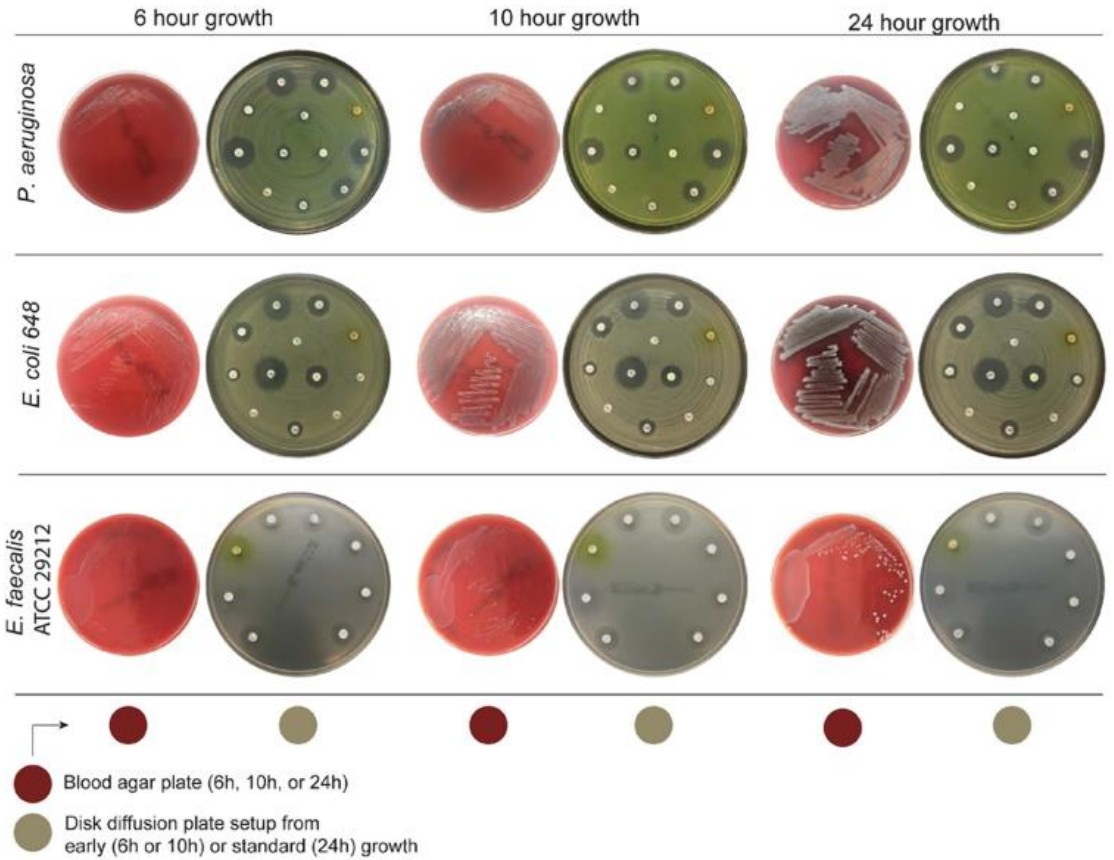


Day 0	Day 1	Day 2

Adapted from Gajic *et al*, Antibiotics 2022, Humphries *et al* JCM 2021

RETHINKING AN OLD FRIEND

- Can incubation methods/times be re-evaluated?
- Use ‘young’ cultures to set up KB
  - Results ready in 24-30h
  - Good categorical & quant agreement
  - Performed well across species and drugs
- Direct Disk Diffusion on Blood
  - M100 Ed. 24 – Table 3F



1. Schumacher et al. *Eur J Clin Microbiol Dis.* 2018
2. CLSI M100 Ed. 34

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  - M100 Ed. 24 – Table 3F
- Organism ID needed for interps

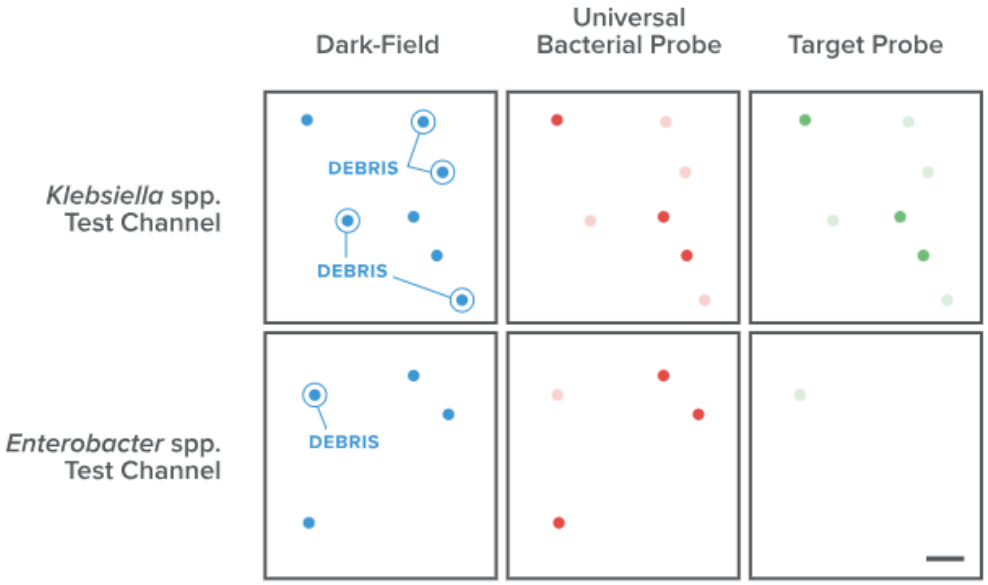
TABLE 4 Comparison of disk diffusion testing with optimized, 6-h early growth method (EDD6) versus standard 24-h growth method with 100 clinical isolates[a] (Table view)

					Discrepancies, *n*/*n* (%)		
Organism	R	S	Total	Agreement, *n*/*n* (%)[b]	Very major[c]	Major[d]	Minor[e]
A. baumannii	46	44	90	88/90 (97.8)	0/46 (0)	0/44 (0)	2/90 (2.2)
E. cloacae	33	87	120	114/120 (95)	0/33 (0)	0/87 (0)	6/120 (5)
E. coli	50	70	120	112/120 (93.3)	0/50 (0)	0/70 (0)	8/120 (6.7)
K. pneumoniae	49	71	120	119/120 (99.2)	0/49 (0)	0/71 (0)	1/120 (0.8)
MRSA	24	76	100	99/100 (99)	0/24 (0)	0/76 (0)	1/100 (1)
MSSA	10	90	100	100/100 (100)	0/10 (0)	0/90 (0)	0/100 (0)
P. aeruginosa	37	103	140	134/140 (95.7)	0/37 (0)	0/103 (0)	6/140 (4.3)
VRE	42	38	80	76/80 (95)	0/42 (0)	0/38 (0)	4/80 (5)
VSE	15	65	80	75/80 (93.8)	0/15 (0)	0/65 (0)	5/80 (6.2)
TOTAL	306	644	950	917/950 (96.5)	0/306 (0)	0/644 (0)	33/950 (3.5)

[a] R, resistant; S, susceptible.
[b] Categorical agreement between the early (EDD6) and standard growth methods.
[c] Number of very major discrepancies divided by total resistant organisms as determined by the standard growth method.
[d] Number of major discrepancies divided by total susceptible organisms as determined by the standard growth method.
[e] Number of minor discrepancies divided by total organisms tested.

1. Schumacher et al. *Eur J Clin Microbiol Dis.* 2018
2. CLSI M100 Ed. 34

FLUORESCENCE IN-SITU HYBRIDIZATION (FISH)



Comparison of dark-field, universal, and target signals informs organism detection and identification.

- ID and AST results

1. Acceleratediagnostics.com

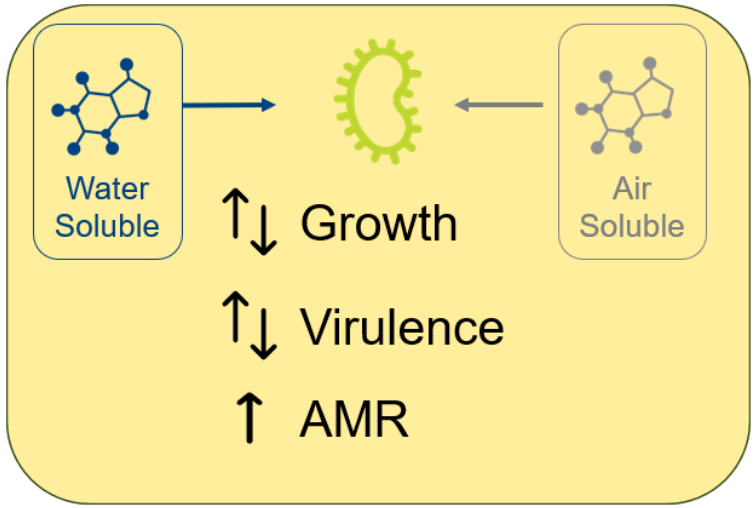
NEXT GENERATION PHENOTYPING (NGP)

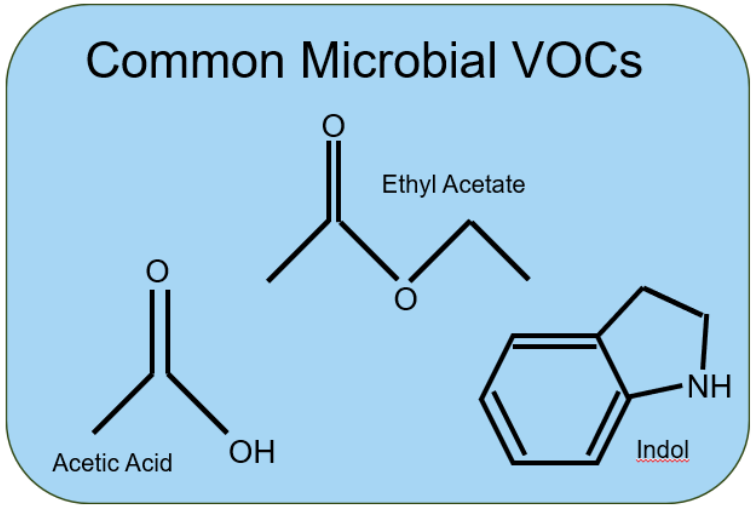
- Measures growth and viability through OD and fluorescence
- AST results only

1. Seluxdx.com

VOLATILE ORGANIC CHEMICAL DETECTION

VOCs are small metabolites produced during bacterial growth





1. Kuil SD. Antibiotics. 2022 *11*(6), 705
2. Weisskopf L. Nat Rev Microbiol. 2021 Jun;19(6):391-404.
3. bioMerieux.com

Methods for AST - Phenotypic Fast

Positive blood culture

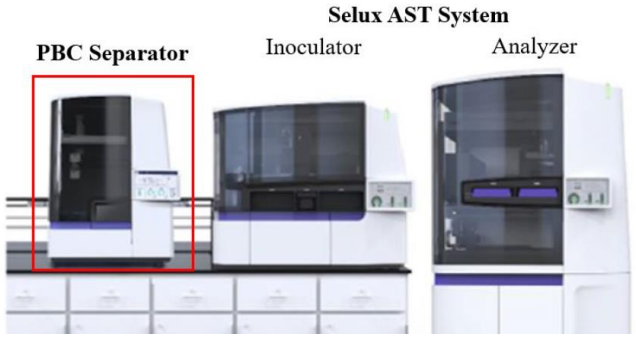
Manual

- Disk Diffusion Direct From Blood Culture CLSI M100 Ed. 34 (8 - 10 or 16-18 h)
- Short incubation

Interpretive categories S / I / R

Automated (4 - 8 h TTR)

MICs & Categories S / I / R



1. CLSI M100 Ed. 34
2. Acceleratediagnostics.com
3. Seluxdx.com
4. bioMerieux.com

Day 0 **Day 1**

COMMERCIALLY AVAILABLE RAPID PHENOTYPIC ANTIMICROBIAL SUSCEPTIBILITY TESTING METHODS

Test	Test Results	Sample Type	Average Time to Results (hours)	Regulatory status	
Alfred 60/AST (Alifax®, Polverara, Italy)	AST-only	Gram-negative BC Gram-positive BC	4-6	CE-IVD	Laser Light Scattering - Alifax S.r.l.
ASTar® system (Q-linea, Uppsala, Sweden)	AST-only	Gram-negative BC	6	**US FDA**, CE-IVD	ASTar in the lab | Q-linea (qlinea.com)
FASTinov (FASTinov SA, Porto, Portugal)	AST-only	Gram-negative BC Gram-positive BC	2	CE-IVD	FASTinov – ultra-rapid antibiotic susceptibility testing
LifeScale system (Affinity Biosensors, Santa Barbara, CA)	AST-only	Gram-negative BC	4.5	**US FDA**, CE-IVD	Rapid AST Test Results | LifeScale from Affinity Biosensors
★ Next-Generation Phenotyping (NGP) system (Selux, Charlestown, MA)	AST-only	Gram-negative isolated colonies Gram-positive isolated colonies Gram-negative BC	5.5	**US FDA**, CE-IVD	Precision diagnostics for infectious diseases - Selux Diagnostics (seluxdx.com)
★ Pheno® system (Accelerate Diagnostics, Tucson, AZ)	ID + AST	Gram-negative BC Gram-positive BC	7	**US FDA**, CE-IVD	Accelerate Pheno® system (acceleratediagnostics.com)
QMAC-dRAST™ (QuantaMatrix, Inc., Seoul, Republic of Korea)	AST-only	Gram-negative BC Gram-positive BC	6	CE-IVD, MDFS Korea	Sepsis Solution - dRAST | QuantaMatrix
★ VITEK® REVEAL™ (bioMérieux Marcy-l'Etoile, France)	AST-only	Gram-negative BC	5.5 - 6	**US FDA**, CE-IVD	VITEK REVEAL | bioMérieux, Inc. (biomerieux.com)

MacVane, et al., *Journal of Antimicrobial Chemotherapy*, 2024

CHALLENGES

CHALLENGES FOR IMPLEMENTATION

- Logistical
  - Trained staff
  - Shifts available
  - Verification (regulatory/compliance)
  - Training and validation of new system/workflow
  - LIS Integration

CHALLENGES FOR IMPLEMENTATION

- Need for rapid pathogen ID for most methods
- Cost considerations
- Implementation
  - Does it replace previous method?
  - How often is it performed on same patient?
  - How are results reported?
- Antimicrobial Stewardship
  - Indirect patient impact / actionability
- Limited real-word evidence
- Others?

COMPLEXITY OF RAPID AST ADOPTION

	Defining Characteristics		
	Patient	Laboratory	Hospital
LOW	High severity / Critical (e.g., ICU | Trauma)	Existing rapid ID (mol. or short culture MALDI)	Large Academic/Corporate hospitals (Tertiary/Quaternary care)
	High risk of MDR pathogen	24/7 microbiology lab coverage	24/7 Stewardship
	Elevated rates of MDR	Existing lab automation	Highly resourced IT/Reporting

COMPLEXITY OF RAPID AST ADOPTION

	Defining Characteristics		
	Patient	Laboratory	Hospital
MEDIUM	Transplant	Existing rapid ID | rapid AST (incl. LDT)	Small/Medium Academic/Community hospitals & State/County Facilities
	Pediatrics	Non-systematic Rapid ID usage	
	Oncology/ Haemato-oncology	Single shift workflow	Single shift Stewardship

COMPLEXITY OF RAPID AST ADOPTION

	Defining Characteristics		
	Patient	Laboratory	Hospital
HIGH	General Medicine / Surgery	Conventional ID Workflow	Low ASP Resources/expertise
	Non-critical	Centralized laboratory services	Send-out specialty testing
	Low rates of MDR	Reference laboratory services	Critical access hospitals

THANK YOU & QUESTIONS?

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