The Value of Diagnostics in Combating the Public Health Problem of Antimicrobial Resistance

Dr. Tristan Timbrook, PharmD, BCPS

Director of Health Economics and Outcomes Research, Global Medical Affairs, bioMérieux

Adjunct Assistant Professor, University of Utah College of Pharmacy, UT, USA

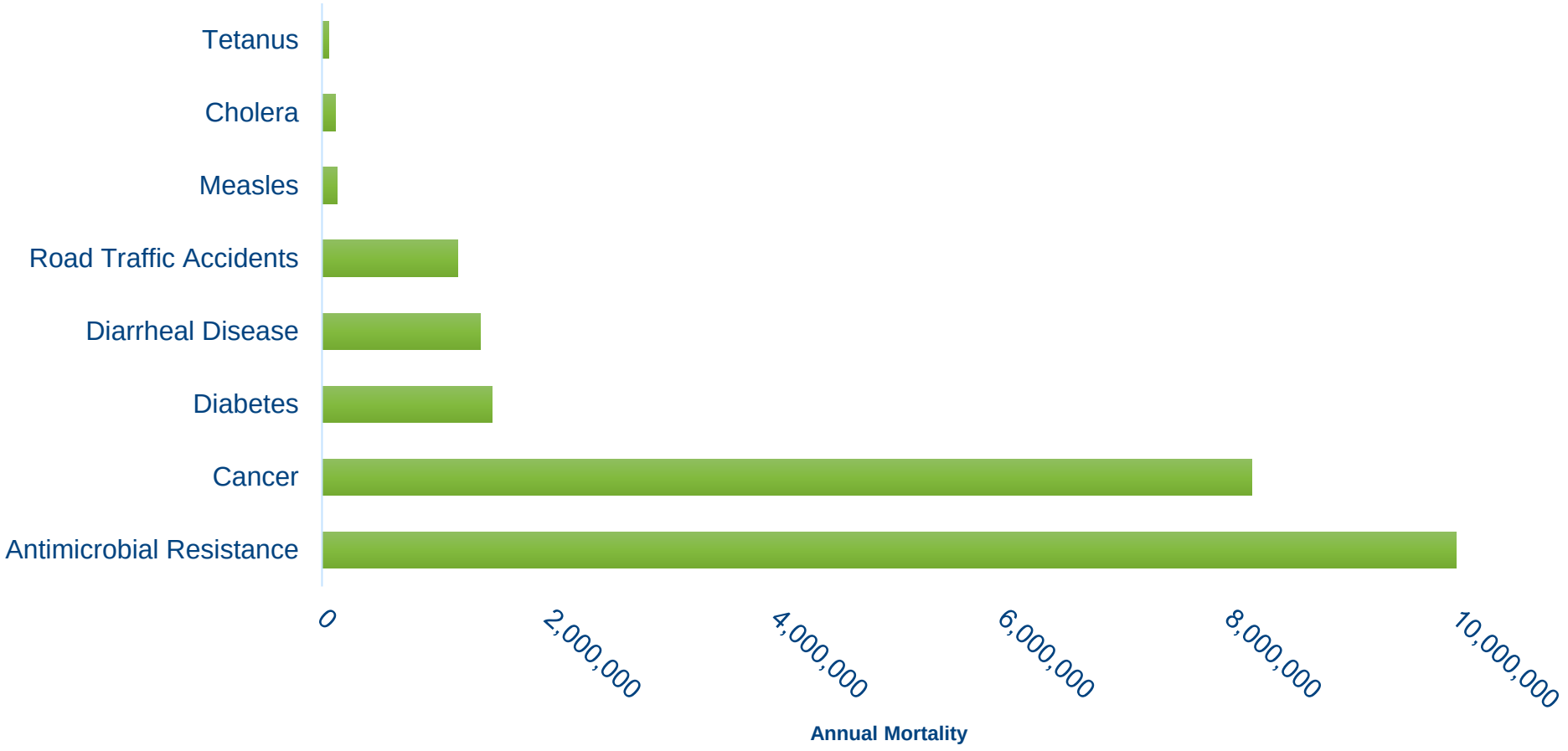
PIONEERING DIAGNOSTICS

700,000

global antimicrobial resistance (AMR) related deaths/year

O'Neil J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. 2014.

AMR ATTRIBUTED DEATHS IN 2050 COMPARED TO OTHER MAJOR CAUSES OF DEATH



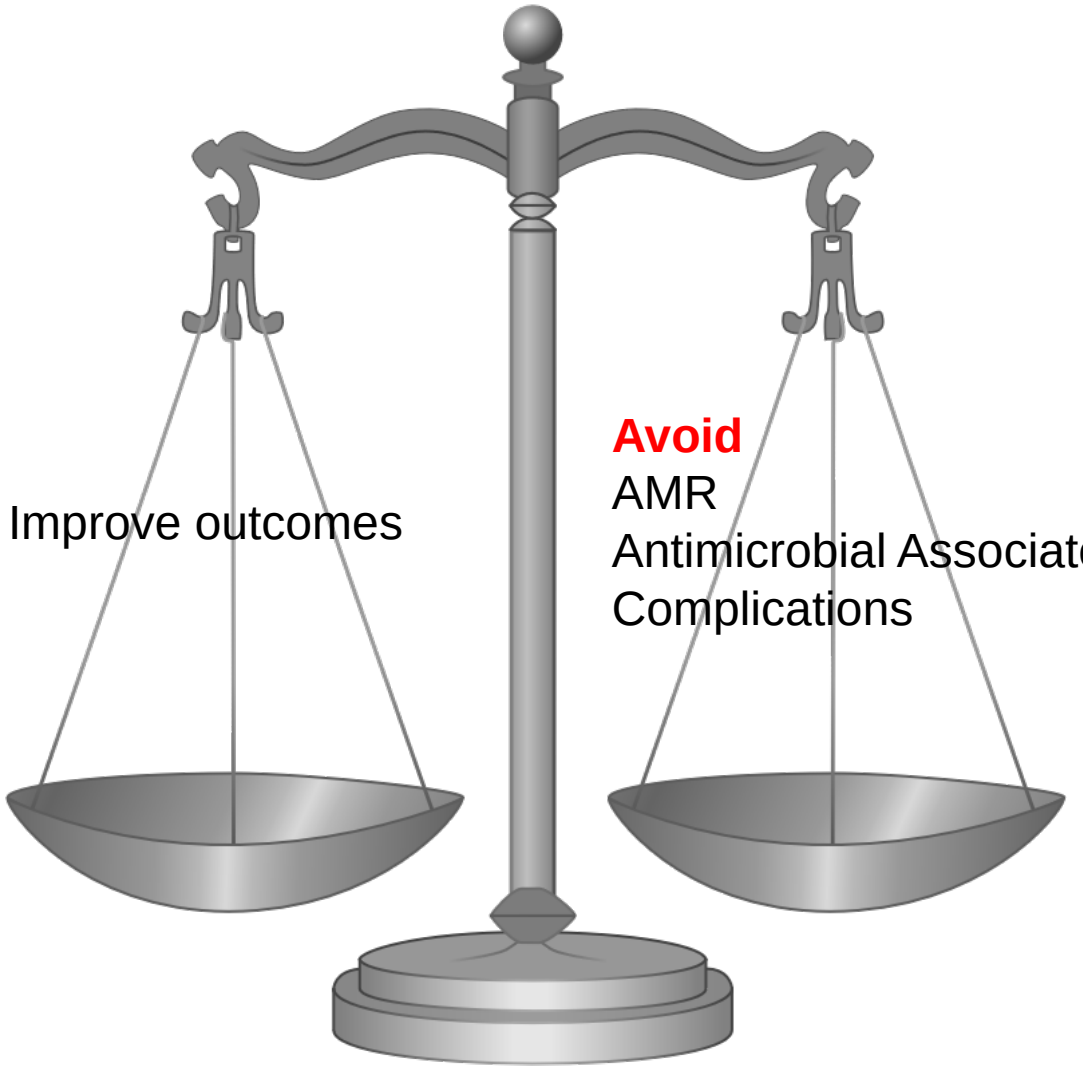
O'Neil J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. 2014.

STEWARDSHIP STARTS WITH DIAGNOSTICS

BALANCING EFFECTIVE ANTIBIOTICS WITH OVERUSE

Empiric Antimicrobial Therapy

- Initiate broad spectrum therapy ASAP
- Antimicrobial stewardship to ensure appropriate targeted therapy once pathogen identified
- Varies by patient, location, AMR



DIAGNOSTICS IMPACT ON AMR

Technical Efficacy ↔ Diagnostic Accuracy Efficacy

- Resource requirements
- Time to result
- Sensitivity and Specificity
- Positive and negative predictive value

Diagnostic Decision Efficacy

- Helpful in making diagnosis
- Changes probabilities in differential diagnosis

Therapeutic Efficacy

- Therapy initiation, change, or discontinuation after testing
- Procedure, imaging change after testing

Patient Outcome Efficacy

- Patients improved with test compared to without
- Morbidity and procedures avoided with testing
- Quality-adjusted life years impact

Societal Efficacy

Cost-benefit or cost effectiveness impact from societal perspective

AMR

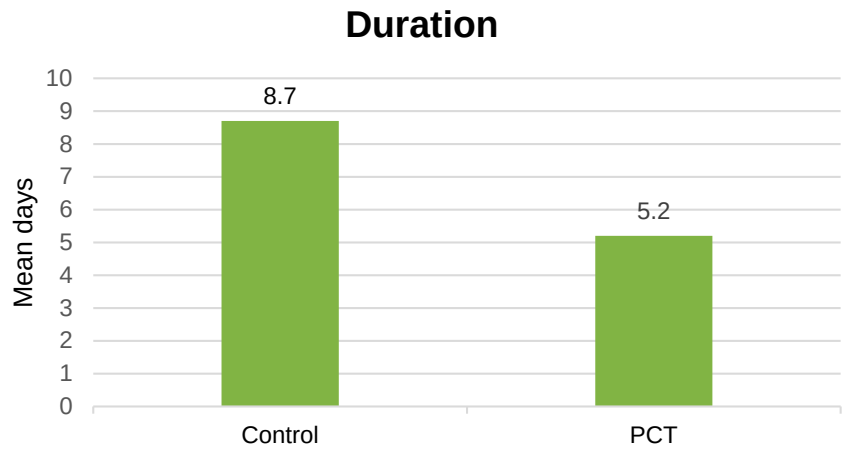
Hanson KE, Azar MM, Banerjee R, Chou A, Colgrove RC, Ginocchio CC, Hayden MK, Holodiny M, Jain S, Koo S, Levy J, Timbrook TT, Caliendo AM. Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations From the IDSA's Diagnostics Committee. Clin Infect Dis. 2020 Dec 17;71(10):2744-2751.
Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making. 1991 Apr-Jun;11(2):88-94.

PATIENT-LEVEL AMR

DECREASING ANTIBIOTIC EXPOSURE WITH PROCALCITONIN (PCT)

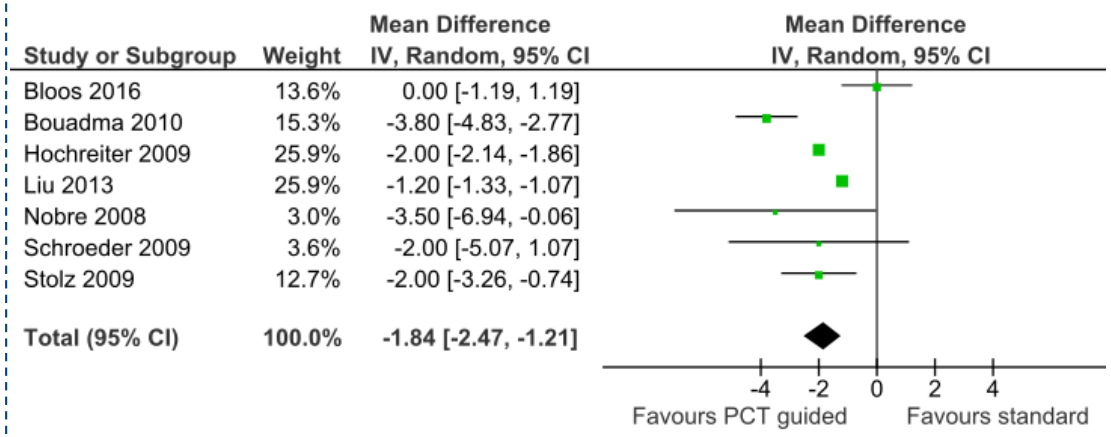
PCT-GUIDED THERAPY FOR ARTI

- N=14 RCT meta-analysis N=4221 patients
- Duration of antibiotic therapy ~4-day decrease



PCT-GUIDED THERAPY IN ICU

- N=15 RCT meta-analysis N=5486 patients
- Duration of antibiotic therapy for the first episode of infection ~2-day decrease



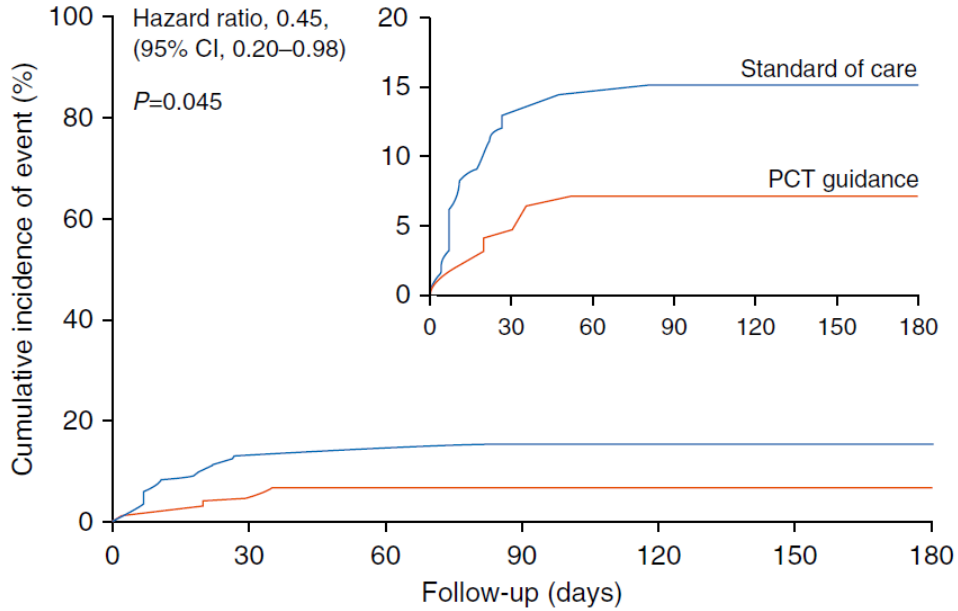
Zhang T, Wang Y, Yang Q, Dong Y. Procalcitonin-guided antibiotic therapy in critically ill adults: a meta-analysis. BMC Infect Dis. 2017;17(1):514.
Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to guide initiation and duration of antibiotic treatment in acute respiratory infections: an individual patient data meta-analysis. Clin Infect Dis. 2012;55(5):651-662.

DECREASING AMR WITH BIOMARKERS

Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis

- Multicenter RCT of sepsis patients randomized 1:1 to PCT-guided discontinuation of antimicrobials or standard of care
- Primary outcome infection-associated adverse events at Day 180
  - Composite of the incidence of any new infection by *C. difficile* or MDRO, or any death from either
- Infection-associated adverse events occurred in 7.2% (9/125) vs 15.3% (20/131) (P = 0.045)
- Median length of antibiotic therapy 5 vs 10 days (P < 0.001)

Infection-associated Adverse Events



No. at risk

Standard of care	131	87	81	78	77	76	76
PCT guidance	125	102	87	85	84	84	83

Kyriazopoulou E, et al. Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis. A Randomized Trial. Am J Respir Crit Care Med. 2021;203(2):202-210.

DECREASING ANTIBIOTIC EXPOSURE WITH MULTIPLEX PCR

POCT PCR RCT

- BioFire® FilmArray® Respiratory (RP) Panel vs Standard of Care Testing
- N=720 patients with acute respiratory illness or fever during respiratory season
- Antibiotic duration (days)
  - Overall 7.2 vs 7.7, p=0.17
  - IECOPD 6.1 vs 8.0, p<0.01
  - Asthma 3.9 vs 5.3, p=0.04

IMPACT OF EARLIER DIAGNOSTICS

- Post-hoc analysis of Brendish et al. RCT
- Patients with BioFire RP Panel divided into those with TAT ≤1.6 or >1.6 hours
- Antibiotic duration (days)
  - Overall 2.9 vs 6.5, p<0.01
- ROC curve analysis
  - ≤1.6h had optimal sens/spec for both early discharge and early antibiotic discontinuation

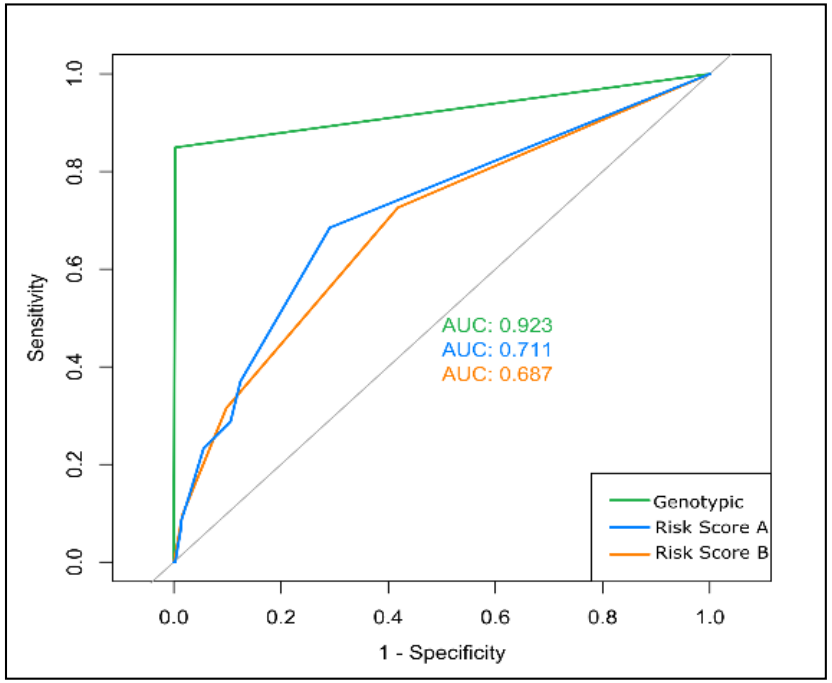
Brendish, N et. al., Eur Res Journal, 2018, 52(2) pii: 1800555
Brendish NJ. Lancet Respir Med. 2017;5(5):401–411.

USING DIAGNOSTICS TO MOVE BEYOND CLINICAL HEURISTICS FOR PREDICTING AMR

Minimizing Time to Optimal Antimicrobial Therapy

- Retrospective study of patients with Enterobacteriaceae bloodstream infections
- Comparing genotypic detections vs risk scores for predicting AMR
- Results
  - N=451; 16% resistance
  - 15% vs 63-71% CRO use in R cases
  - 0.3% vs 10-12% carbapenem use in CRO S cases

Genotypic vs Risk Scores for ESBL Prediction



Variables	ESBL Score
Nursing home resi nts	1
Events within 4 before bacter	
Antimicrobial t	
Invasive procedu	
Prior hospitalization	
Frequent ED visits wi before BSI	
Comorbidities	1
Urological dis s	1
Diabetes mellitus	1

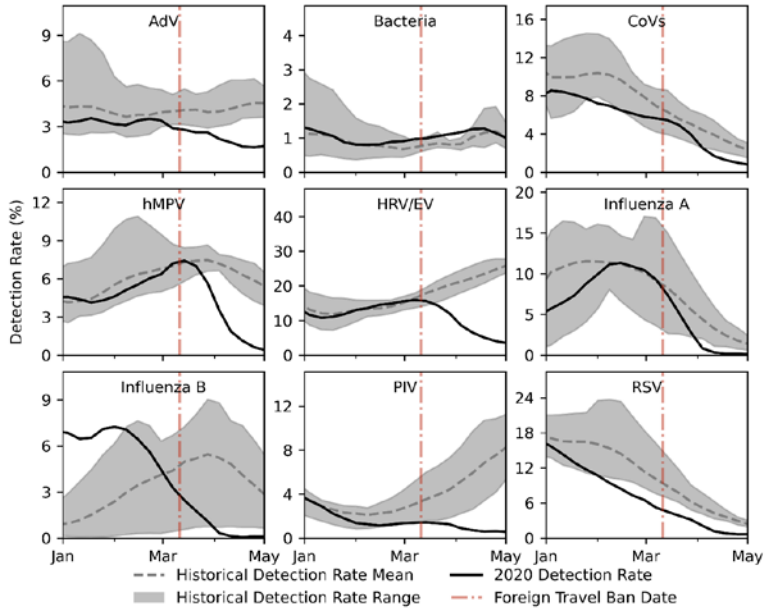
Cwengros LN, Mynatt RP, Timbrook TT, et al. *Open Forum Infect Dis*. 2020;7(8):ofaa278. Figure recreated and adapted by author.

POPULATION-LEVEL AMR

RAPID DIAGNOSTIC SURVEILLANCE

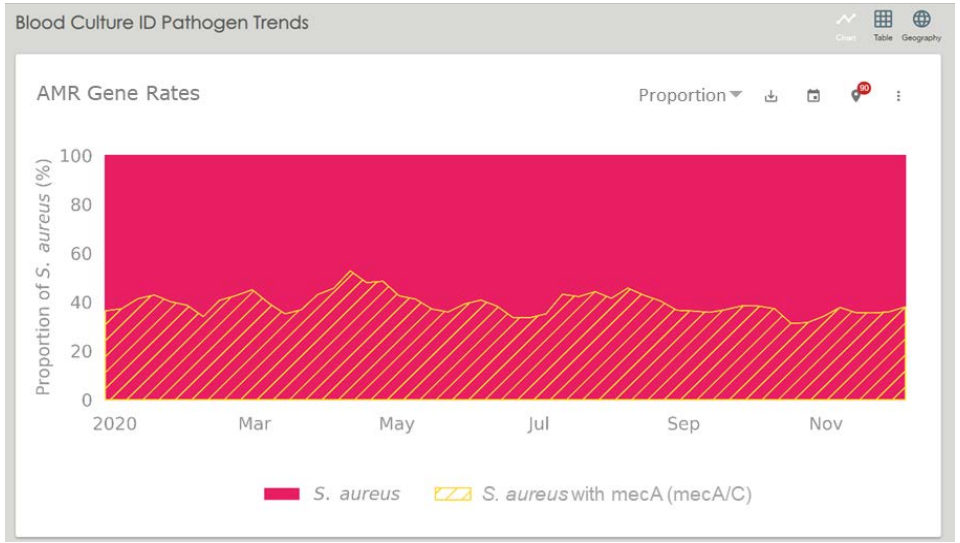
THE EFFECTS OF SOCIAL DISTANCING POLICIES ON NON-SARS-COV-2 RESPIRATORY PATHOGENS

- Detection rates were acquired from BioFire® Syndromic Trends across US facilities
- 15% reduction in total detection rate in March-April 2020
- Ability to monitor and report on public health measure impact in real-time

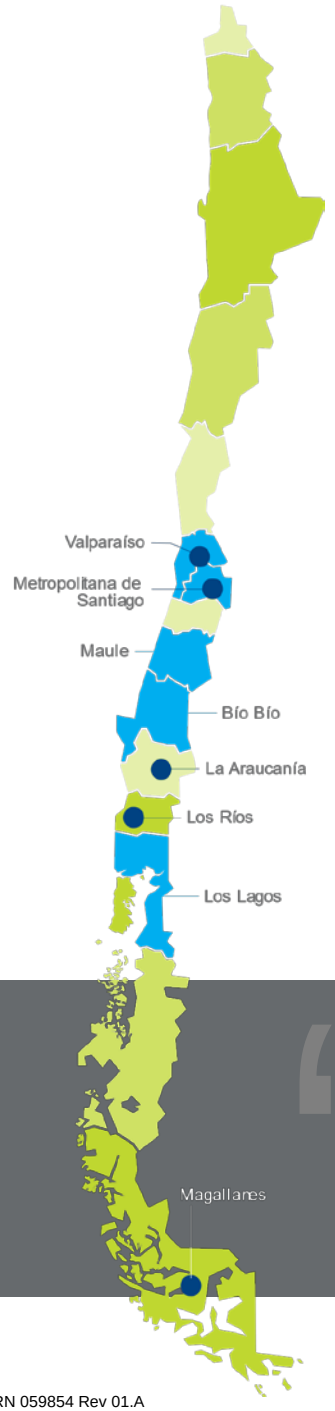


AMR SURVEILLANCE

- AMR tracking for may offer the same ability in monitoring and reporting public health measures impact in real-time



Nawrocki *et al.*, *Open Forum Infectious Diseases*, 2021;, ofab133.



ENABLED	UPCOMING
Metropolitana de Santiago	
9	8
La Araucanía	
1	-
Valparaíso	
2	1
Magallanes	
1	-
Los Rios	
1	-
Maule	
-	1
Bío Bío	
-	2
Los Lagos	
-	2

● Enabled
● Upcoming

AUTOMATION & ANALYTICS FOR SURVEILLANCE

Vendor-agnostic approach supports national AMR insights for Chile

CHALLENGE

- Collecting data from **any test or machine**, regardless of the manufacturer
- Consolidating data from **40+ hospitals** for surveillance of Antimicrobial Resistance
- **Months of work** in manual data aggregation and reporting in Excel

SOLUTION

- **Automatic** data collection and analysis
- Reports **accessible to all hospitals**
- Network-wide Antimicrobial Resistance reporting **more than just once a year**

IMPACT

- **Reduced workload** on staff
- Near **real-time insights** into the network's infectious disease landscape

"We believe that a platform like CLARION helps us get better data for AMR, and better data means better clinical decisions."

Francisco Silva, MD and Microbiologist at University of Chile Clinical Hospital

BIOMÉRIEUX

LOOKING FORWARD COMBATING AMR WITH DIAGNOSTICS

CHALLENGES IN DIAGNOSTICS OUTSIDE OF RESOURCE-RICH SETTINGS

Clinical Infectious Diseases
VIEWPOINT

Leveraging Existing and Soon-to-Be-Available Novel Diagnostics for Optimizing Outpatient Antibiotic Stewardship in Patients With Respiratory Tract Infections

Kelly A. Cawcutt,[1,©] Robin Patel,[2] Jeff Gerber,[3] Angela M. Caliendo,[4] Sara E. Cosgrove,[5] Elizabeth Dodds Ashley,[6] Piero Garzaro,[7] Melissa Miller,[8] and Ebbing Lautenbach[9]; for the IDSA Research Summit "Leveraging Existing and Novel Diagnostics for Optimizing Outpatient Antibiotic Stewardship in Patients with Respiratory Tract Infections" Group

- IDSA research summit of experts Oct 2019
- Up to 50% of outpatient prescribing in US is inappropriate
- Optimal stewardship structure in outpatient settings is unclear
- Diversity of settings: ED, UCC, PCC, pharmacies, school-based clinics, telemedicine, home testing

Challenges in Outpatient Care

Patient	Clinician	Organizational	Policy
Communication with clinician	Patient satisfaction scores and online reviews	Time-limited interactions	Prior authorizations
Capacity to carry out plan	Goal of good relationship with patients	Fast pace of clinic visits	Limited sick leave
Time away from school/work	**Fewer interactions with other clinicians on cases**	Limited ability to monitor patients after visit	Lack of dedicated resources
Expectations	Lack of availability and access to guidelines	Slow return of test results	**Relative paucity of data regarding problem and/or solutions**
Understanding of antibiotics	Communication with patients and families	**Unclear whether patients see their results**	Not required

Cawcutt KA, Patel R, Gerber J, Caliendo AM, Cosgrove SE, Ashley ED, Garzaro P, Miller M, Lautenbach E; IDSA Research Summit "Leveraging Existing and Novel Diagnostics for Optimizing Outpatient Antibiotic Stewardship in Patients with Respiratory Tract Infections" Group. Leveraging Existing and Soon-to-Be-Available Novel Diagnostics for Optimizing Outpatient Antibiotic Stewardship in Patients With Respiratory Tract Infections. Clin Infect Dis. 2021 Jun 15;72(12):e1115-e1121.

CHALLENGES IN DIAGNOSTICS OUTSIDE OF RESOURCE-RICH SETTINGS

The *Lancet* Commission on diagnostics: transforming access to diagnostics

Kenneth A Fleming, Susan Horton, Michael L Wilson, Rifat Atun, Kristen DeStigter, John Flanigan, Shahin Sayed, Pierrick Adam, Bertha Aguilar, Savvas Andronikou, Catharina Boehme, William Cherniak, Annie NY Cheung, Bernice Dahn, Lluis Donoso-Bach, Tania Douglas, Patricia Garcia, Sarwat Hussain, Hari S Iyer, Mikashmi Kohli, Alain B Labrique, Lai-Meng Looi, John G Meara, John Nkengasong, Madhukar Pai, Kara-Lee Pool, Kaushik Ramaiya, Lee Schroeder, Devanshi Shah, Richard Sullivan, Bien-Soo Tan, Kamini Walia

- Emergence of extensively drug-resistant tuberculosis has now been reported from 131 countries
- COVID-19 pandemic has highlighted the critical role of diagnostics in healthcare
  - Without access to diagnostics, delivery of universal health coverage, antimicrobial resistance mitigation, and pandemic preparedness cannot be achieved
- Addressing the challenges of antimicrobial resistance depends on good diagnostics
- Because of the importance of antimicrobial resistance to healthcare systems globally, providing access to the necessary diagnostic tests must be a component of any national essential diagnostics list

47% of the global population has little to no access to diagnostics

Fleming KA, Horton S, Wilson ML, Atun R, DeStigter K, Flanigan J, Sayed S, Adam P, Aguilar B, Andronikou S, Boehme C, Cherniak W, Cheung AN, Dahn B, Donoso-Bach L, Douglas T, Garcia P, Hussain S, Iyer HS, Kohli M, Labrique AB, Looi LM, Meara JG, Nkengasong J, Pai M, Pool KL, Ramaiya K, Schroeder L, Shah D, Sullivan R, Tan BS, Walia K. The Lancet Commission on diagnostics: transforming access to diagnostics. Lancet. 2021 Oct 5:S0140-6736(21)00673-5.

POPULATION LEVEL IMPACT THROUGH COORDINATED EFFORTS

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

MINIREVIEW

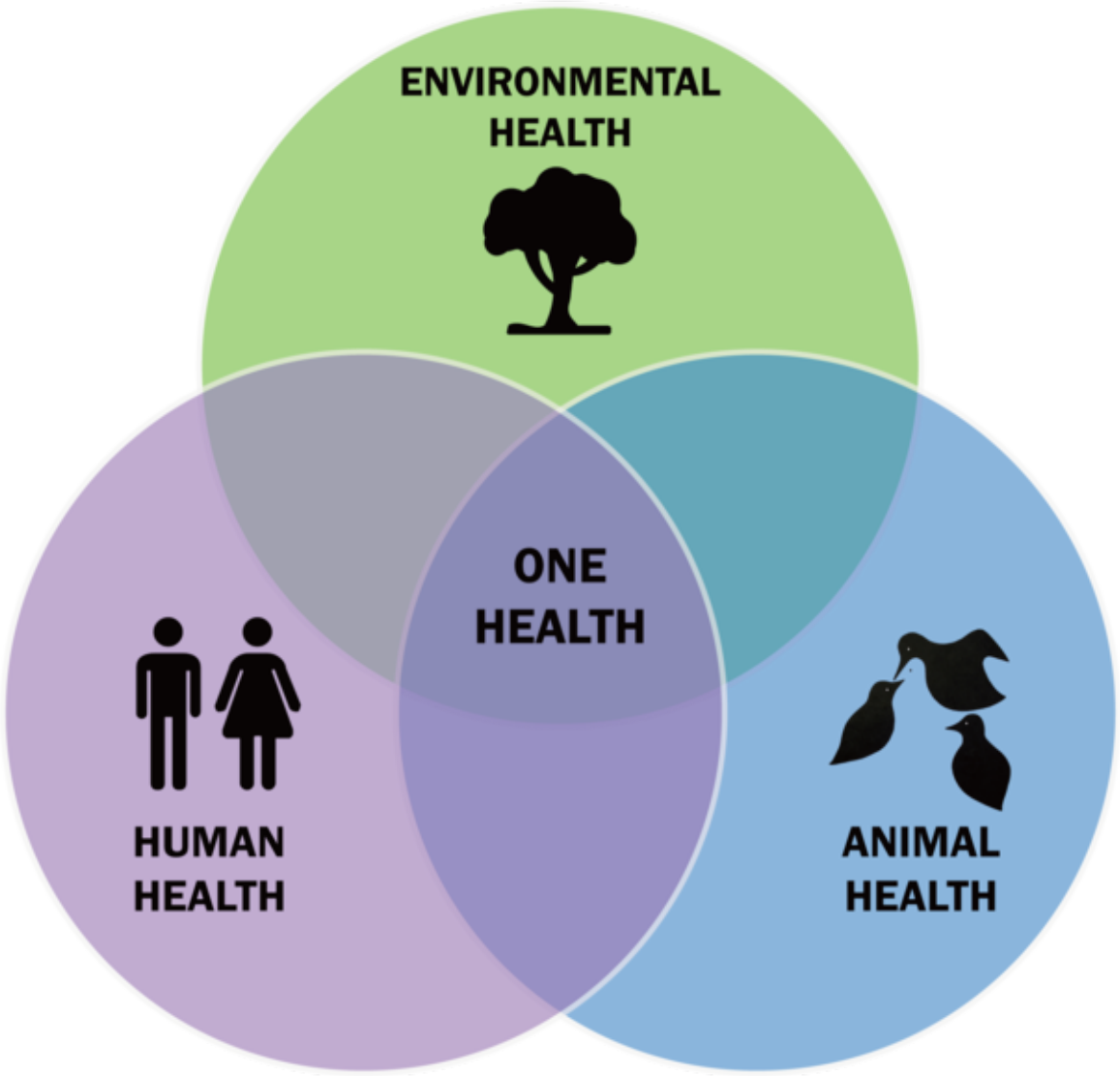
Clinical Utility of Advanced Microbiology Testing Tools

Melissa B. Miller,[a] Faranak Atrzadeh,[b] Carey-Ann D. Burnham,[c] Stephen Cavalieri,[d] James Dunn,[e] Stephen Jones,[f] Charles Mathews,[f] Peggy McNult,[g] John Meduri,[h] Chris Newhouse,[i] Duane Newton,[j] Michael Oberholzer,[k] John Osiecki,[i] David Pedersen,[f] Nicole Sweeney,[l] Natalie Whitfield,[m] Joe Campos,[n] on behalf of the ASM Clinical and Public Health Microbiology Committee and the ASM Corporate Council

- It may be **possible to eventually demonstrate outcomes** not only at the individual patient level but also **at the population level**.
- For example, there is potential to show that outcomes are improved via **public health benefits** that result **from better antibiotic selection and community-acquired resistance management** through **the regional applied use of advanced diagnostic technologies**.
- The **full benefits of these technologies** will only be **realized once antimicrobial stewardship and operational improvements** (e.g., strain tracking, hospital infection control surveillance, etc.) are **applied in aggregate**.
- This will **require a greater collaborative/coordinated effort** across multiple institutions potentially coordinated by a public health entity.

Miller MB, et al; ASM Clinical and Public Health Microbiology Committee and the ASM Corporate Council. *J Clin Microbiol*. 2019;57(9):e00495-19.

NEED UNITY IN ONE HEALTH APPROACH TO COMBAT AMR



OUR COLLABORATIVE APPROACH TO CONSULTING HELPS YOU ACHIEVE YOUR PROGRAM'S GOALS BY UNIFYING PEOPLE, PROCESS, AND TECHNOLOGY FOR BETTER OUTCOMES. CONTACT OUR INFECTIOUS DISEASE EXPERTS ABOUT OUR STEWARDSHIP CONSULTANCY PROGRAM.

HTTPS://GO.BIOMERIEUX.COM/STEWARDSHIP-CONSULTANCY-PROGRAM

PIONEERING DIAGNOSTICS